THE UPPER LIMBS AFTER STROKE: EXPLORING EFFECTS OF BILATERAL TRAINING AND DETERMINANTS OF RECOVERY

JACQUELINE H. MORRIS

A thesis submitted in partial fulfilment of the requirements of the degree of Doctor of Philosophy

QUEEN MARGARET UNIVERSITY 2009

ABSTRACT

The upper limbs after stroke: exploring effects of bilateral training and determinants of recovery

Background: Bilateral task training (BT) may improve upper limb (UL) recovery on the affected as well as non-affected side in longstanding stroke however for acute stroke its effects on physical and psychosocial outcomes compared to unilateral training (UT) has not been clearly established. Furthermore, clinical and demographic factors that influence UL training responses and predict UL recovery are also unclear for acute stroke.

PrimaryAims: To compare effects of BT and UT on:
- ipsilesional and contralesional UL outcomes
- anxiety, depression and health related quality of life (HRQOL)

Secondary Aims: To investigate:
- which clinical and demographic factors influence contralesional training responses
- predictors of UL activity limitation over time for the sample as a whole
- UL dysfunction as a predictor of HRQOL six months after stroke for the sample as a whole

Design: Single-blinded randomised controlled trial, with outcome assessment at baseline (T1), after 6 weeks training (T2), and 18 week follow-up (T3).

Participants: 106 in-patients randomised to receive BT (n=56) or UT (n=50) 2 to 4 weeks after stroke onset.

Intervention: Supervised BT or UT for 20 minutes on 5 weekdays, over 6 weeks, using a standardised programme developed for the study.

Outcome Measures: UL outcomes: Action Research Arm Test (ARAT), Rivermead Motor Assessment (UL scale), Nine-Hole Peg Test (9HPT).
Secondary measures: Modified Barthel Index, Hospital Anxiety and Depression Scale, and Nottingham Health Profile. Assessment was conducted by a blinded assessor.

Results: Between the two groups, there were no significant differences at T1 or T2 on any contralesional UL measure or on any psychosocial measure ($p>0.05$). At T3, 9HPT ($p=0.03$) and ARAT pinch section scores ($p=0.04$) in the UT group were significantly higher. None of the selected clinical or demographic factors significantly influenced training responses. BT significantly improved ipsilesional dexterity between T1 and T2 ($p=0.04$). For the sample as a whole, early ARAT and MBI scores significantly predicted contralesional ARAT scores at T2 and T3. Anxiety, depression and UL impairment significantly predicted overall HRQOL at T3.

Conclusions: BT was no more effective than UT for the affected arm – in fact UT was more effective for dexterity. BT was more effective than UT, however, for short-term recovery of ipsilesional dexterity. Future studies should determine optimal BT characteristics for contra- and ipsilesional recovery in stroke populations with differing levels of severity. Knowledge of predictors of UL activity limitation and HRQOL will enable therapists to target rehabilitation at factors that most influence these important outcomes.

Keywords: Upper extremity, bilateral, task training, rehabilitation, health related quality of life

ACKNOWLEDGEMENTS

AUTHOR'S CONTRIBUTION TO THE RESEARCH

The randomised controlled trial on which this thesis is based was supported by a grant of £129,000 from the Chief Scientist Office, project number CZH/4/80.

The project was designed by the author and funding secured through a research training secondment for Allied Health Professionals (AHPs) at the University of Dundee. The training was facilitated by Dr Brian Williams, Social Dimensions of Health Institute, Universities of Dundee and St Andrews. The aim of the secondment was to enable AHPs to develop a fundable research proposal. Funding was awarded in August 2002. The funded proposal, which addresses the primary research question of this thesis is attached as Appendix 15.

The author was the lead researcher on the project and she:

- Designed the study
- Obtained funding and ethical approval
- Brought the research team together and led the project steering group
- Developed and piloted the intervention
- Managed the project, the budget and the staff employed on the project from commencement to completion
- Undertook all data analysis and report writing for the Chief Scientist Office
- Screened and recruited participants
- Provided some of the physiotherapy intervention

Specific collaborations were as follows:

Dr Ron MacWalter, Stroke Physician, NHS Tayside
Grant holder and co-applicant, acted as Principal Investigator. The lead researcher was unable to do this as she had no pervious experience of funded research. Dr MacWalter also provided advice on various aspects of the study.

Dr Simon Ogston, Medical Statistician, University of Dundee
Grant holder and co-applicant. Provided statistical advice.

Drs Frederike van Wijck (Queen Margaret University) and Sara Joice (University of Dundee)
Steering group members who provided advice on various aspects of the project.

There are several publications from the project, and the author is the first author for all of these. Publications are attached in Appendices 16 and 17.

THANKS

My thanks go to my supervisors in the School of Health Sciences; to Fredrike van Wijck for her unfailing, cheerful and enthusiastic support and encouragement over many years, and to Marie Donaghy for her guidance in pulling all of this together.

Thanks too to Kath Fairgrieve and Brian Williams for starting this ball rolling all those years ago and for their ongoing mentorship and support.

I would like to also thank Ron Macwalter who put his faith in my ability to carry this off.

I would like to give a special thanks to Sara Joice for her endless ability to encourage me and for telling me frequently that I could do this. I would also like to thank her for her helpful advice on statistical matters.

Thanks also to Simon Ogston and Martyn Jones for their advice on statistical matters.

Thanks to Sally Wyke and Thilo Kroll from the Alliance for Self-Care Research for support in providing me with the time to finish this thesis.

I would like to thank all the patients who willingly participated in the study and made to process so enjoyable.

Thanks too to Rachel Mills, Ingrid Cole and Diane Johnstone who ran around the countryside to ensure that all of the patients were seen when they should be. Thanks go also to Gillian Crighton, Liz Beattie and all the other physiotherapists at Ninewells Hospital, Ashludie and Stracathro Hospitals without whose help this study could not have occurred.

Lastly and most importantly my thanks go to my family, to Jeremy, Andrew and Rebecca who have endured years of me sitting at the computer working on this project and without whose love and support I could not have done this.

CONTENTS

CHAPTER 1

CHAPTER 2

Page

CHAPTER 3

CHAPTER 4

Page

CHAPTER 5

Page

CHAPTER 6

Page

Chapter 7

LIST OF TABLES

CHAPTER 2

CHAPTER 4

CHAPTER 5

LIST OF FIGURES

CHAPTER 4

CHAPTER 5

LIST OF BOXES

CHAPTER 4

CHAPTER 1

INTRODUCTION

1.1. THE IMPACT OF STROKE

The World Health Organisation defines stroke as clinical signs of focal (at times global) disturbance of cerebral function which develop rapidly, last more than 24 hours or lead to death with no apparent cause other than that of vascular origin (Aho 1980). Stroke is the third most common cause of all UK deaths, approximately 24% of patients die within a month of onset (Wolfe 2000). For survivors, stroke is the largest cause of complex adult disability. At any time 300,000 individuals in the UK live with resultant moderate and severe disability (Adamson et al. 2004). Incidence of new stoke in the UK is around 150,000 per annum (National Audit Office, Department of Health. 2005). Epidemiological studies show that 52% of stroke survivors return home with lasting disability (Wolfe 2000) and 30-40% remain dependent in activities of daily living (ADL) (Dobkin 1995).

The economic burden of stroke is considerable. NHS costs are approximately £2.8 billion annually with costs from lost productivity, disability and informal care around £4.2 billion (National Audit Office, Department of Health 2005). Incidence and mortality rates have declined in recent years by approximately 30% because of faster and more effective acute treatment of stroke, and better quality rehabilitation (National Audit Office, Department of Health 2005). Projected demographic changes resulting in increases of 16% to 22% in the population aged 65 and over in the next 25 years means that stroke incidence will rise by approximately 30% (Malmgren et al. 1989), leading to increases of 4-8% in the number of disabled long-term survivors (National Audit Office, Department of Health 2005). Total stroke care costs will consequently rise in real terms by approximately 30% to 2031 (National Audit Office, Department of Health 2005).

Sequelae of stroke include upper and lower limb motor and sensory loss, language, communication and cognitive difficulties, perceptual difficulties, bowel and bladder dysfunction and dysphagia (Wolfe 2000). Stroke leads to limitations in activities including walking, feeding, dressing grooming and toileting, and more complex activities such as

cooking, shopping and functioning outdoors (Wolfe 2000). Dependence in ADL adversely influences quality of life for stroke sufferers (Kauhanen et al. 2000), and between 23 and 27% suffer from depression after stroke (Herrmann et al. 1998).

Upper limb (UL) dysfunction is an important and disabling consequence of stroke. Up to 85% of individuals initially demonstrate motor deficits (Nakayama et al. 1994) and functional recovery is often poor (Feys et al. 2000). Upper limb dysfunction also adversely influences perceived well-being at one year (Wyller et al. 1997). Furthermore, deficits - although subtle by comparison to the contralesional UL - also exist in the ipsilesional "unaffected" UL. These typically present as slowing in gross and fine dexterity tasks (Sunderland et al. 1999).

This thesis will focus firstly on physical aspects of upper limb dysfunction and rehabilitation. This will be followed by an examination of upper limb dysfunction and rehabilitation in relation to the psychosocial outcomes of anxiety, depression and health related quality of life.

1.1.2 THE IMPACT OF STROKE ON PHYSICAL OUTCOMES OF THE UPPER LIMB

1.1.2.1 Effects of stroke on the contralesional upper limb

Contralesional UL dysfunction is common after stroke. Impairments including paresis (Kwakkel et al. 2003) reduced muscle strength (Canning et al. 2004), impaired muscle activity co-ordination during task performance (Canning et al. 2004) sensory loss (Broeks et al. 1999), proprioceptive loss (Rand et al. 1999) and altered muscle tone (Pandyan et al. 2005) are common. These impairments may lead to secondary problems such as pain (Dromerick et al. 2008), loss or range of movement and muscle contracture which in turn cause functional limitations.

Functional UL recovery after stroke is typically poor, with 30 to 66% of individuals failing to achieve functional recovery after six months (Wade et al. 1983, Sunderland et al. 1989) and only 5-20% of individuals with stroke make full UL recovery (Nakayama et al. 1994, Heller et al. 1987) depending on initial severity. Studies show that individuals demonstrate

difficulties with functional activities (Wade et al. 1983) and dexterity (Heller et al. 1987) that persist into the chronic post-stroke phase (Broeks et al. 1999). Clearly, rehabilitation strategies to maximise contralesional UL functioning as soon after stroke onset as possible are of paramount importance and are discussed next

1.1.2.2 Approaches to contralesional upper limb rehabilitation in the acute post-stroke period

Natural UL recovery following stroke typically demonstrates rapid recovery in the first three months, and slowed recovery thereafter (Kwakkel et al. 2006). Various UL interventions have led to significantly improved motor performance and functioning in the chronic stage (Luft et al. 2004, Taub et al. 2006) when natural recovery has stabilised as a confounding effect. However the acute post-stroke period, when most natural recovery occurs, provides a window of opportunity to maximise recovery by modifying natural recovery processes. Studies demonstrate that intensive UL interventions soon after stroke can improve short term (Dromerick et al. 2000) and long-term UL impairment and activity limitation outcomes (Feys et al. 2004). Those studies focused on contralesional activities only, however bilateral training (BT), where identical activities are practised with both UL's simultaneously, may be an important strategy for UL recovery (Mudie and Matyas 2000). Few bilateral studies have however been undertaken in early rehabilitation. Bilateral training is discussed further in the next section

1.1.2.3 Bilateral training

Bilateral training (BT) has been described as practice of

> "spatiotemporally identical movements or tasks performed bilaterally but with each limb independently" (Mudie and Matyas 2000, pp. 24).

As a rehabilitation intervention in stroke, BT developed from converging evidence in motor control science and neuroscience. In healthy individuals the UL's demonstrate strong temporal and spatial coupling during bilaterally identical repetitive movement, making bilaterally different movements difficult to perform (Kelso et al. 1979). This phenomenon

exists in stroke, with observational studies demonstrating facilitation of hemiparetic UL movement when patients perform bilateral movements simultaneously (Cunningham et al. 2002). Concurrently, neuroscientific studies using transcranial magnetic stimulation (TMS) show that bilaterally identical movements modulate interhemispheric inhibition (Stinear and Byblow 2004) leading to increased motor cortex activation (Staines et al. 2001) and enhanced motor performance of the paretic UL (Summers et al. 2007).

Several BT paradigms have been investigated in stroke. These include functionally orientated task training (Mudie and Matyas 1996), simple movement function (Whitall et al. 2000) and interventions involving assistive technology (Hesse et al. 2005). Many BT studies suffer from methodological limitations however making conclusions about its effectiveness difficult. BT studies examining training paradigms such as functional electrical stimulation (Cauraugh and Kim 2002) and movement function training (Luft et al. 2004) have used randomised controlled designs which demonstrated important methodological limitations such as lack of adequate concealed randomisation, controls and blinding.

Functional task training involves training specific functionally or goal orientated activities. Widely used in physiotherapy and occupational therapy, functional task training is of particular importance because of its ecological validity for everyday functioning in normal life. At the time of writing this study proposal, several single case series studies have demonstrated benefits of bilateral task training over unilateral training on movement parameters in individuals in the chronic phase (Mudie and Matyas 1996, Mudie and Matyas 2000) however the methodological limitations of single case studies mean that findings cannot be generalised beyond case study participants. Evidence exists from a well-conducted randomised controlled trial that *unilateral* task training is effective for recovery of UL activity limitation (Winstein et al. 2004), but at the time of writing, these single case series were the only studies to directly compare unilateral and bilateral task training. Given that unilateral task training is typically used in physiotherapy and occupational therapy, it is important to establish if there is an advantage of bilateral over unilateral training before bilateral training should be considered for use in clinical practice. Further research using robust research methodology is clearly required to compare the effectiveness of bilateral task training with unilateral task training.

Finally, most BT studies have been conducted in the chronic phase after stroke (Mudie and Matyas 1996, Mudie and Matyas 2000) and little is known about effectiveness of BT in the

acute period. Patients receive most rehabilitation in the acute period and it is known that intensive UL rehabilitation at that time can influence later outcomes (Feys et al. 2004). It is clear that BT should be examined with patients in the acute phase of stroke. Investigation of effectiveness of bilateral task training compared to unilateral task training in acute stroke is the main purpose of this thesis.

1.1.2.4 Factors that influence contralesional upper limb training responses

Stroke is a heterogeneous condition, and not all patients have similar recovery potential. In testing effectiveness of an intervention such as bilateral task training, investigation of factors likely to influence responses to training is of key importance. Knowledge about clinical and demographic factors that influence training responses will lead to development of specifically tailored interventions appropriate to individual presentation. Information obtained from such analysis will also add to the body of knowledge about what influences UL recovery.

Numerous factors thought to influence UL recovery after stroke have been identified in the literature. Factors such as initial paresis or motor impairment (Hendricks et al. 2002) activity limitation (Higgins et al. 2005), muscle strength (Sunderland et al.1989), lesion site (Feys et al. 2000), sensation (Feys et al. 2000) age (Fritz et al. 2006) and gender (Wyller et al. 1996) have all been shown to influence UL recovery. Lesion side and hand dominance may influence BT outcomes however their effects have not been clearly established (McCombe Waller and Whitall 2005). Overall the impact of these factors on responses to rehabilitation interventions is unclear, with few rehabilitation studies, and in particular, BT studies including evaluation of these factors as part of their analyses. Lack of evidence regarding factors that may influence training responses means that it is unclear which patients might respond best to BT.

1.1.2.5 Ipsilesional effects of stroke on upper limb functioning and recovery

Effects of stroke are not confined to the contralesional limb. Although subtle in comparison to contralesional effects, ipsilesional deficits have been observed on clinical measures in the acute phase. Good evidence exists of slowed fine dexterity (Sunderland et al. 1999) and

more gross dexterity (Desrosiers et al. 1996) that persists into the chronic phase (Desrosiers et al. 1996). It is important to determine how ipsilesional dysfunction affects performance of activities of daily living, since after stroke patients frequently rely on the ipsilesional UL for performance of functional and self-care tasks. Furthermore limited evidence exists that BT may influence ipsilesional dysfunction (McCombe Waller and Whitall 2004), however again, methodological limitations mean that further research is required.

1.1.2.6 Predictors of upper limb activity limitation

Clinically, predicting UL recovery is important to therapists since it enables them to plan relevant treatment options, for example, care of the flaccid UL where no recovery is expected. It is important also to patients in their preparation for living with consequences of stroke. Since activity limitation is functionally the most important outcome for patients, it is critical that therapists understand its predictive strength in determining later activity limitation, so that rehabilitation efforts can be targeted appropriately. Although predictors of upper limb activity limitation have been examined (Kwakkel et al. 2003), early upper limb activity limitation has typically not been included as a *predictor* of later activity limitation. In order to fully understand clinically relevant predictors of this important outcome over time it is necessary to investigate early activity limitation relative to other UL, clinical and demographic factors as a predictor of later activity limitation over time.

Moving on from physical outcomes of the UL, the next section discusses the impact of UL outcomes after stroke on broader psychosocial health outcomes.

1.1.3 THE IMPACT OF STROKE ON PSYCHOSOCIAL OUTCOMES

Physiotherapy and rehabilitation has typically followed the biomedical model, focusing on impairment and disability outcomes after stroke. Stroke is a catastrophic event however that impacts on all aspects of an individual's life. Although the introduction of health models such as the International Classification of Functioning (World Health Organisation 2001) provide a more holistic biopsychosocial model of effects of health on the life of an individual, within rehabilitation research there has been little focus on how interventions intended to improve stroke outcomes influence the broader health outcomes of psychological

and general wellbeing. This section discusses the important psychosocial outcomes of anxiety, depression and health related quality of life in the context of UL rehabilitation.

1.1.3.1 Anxiety, depression and upper limb dysfunction

Anxiety and depression are common after stroke. Few rehabilitation intervention studies have examined these variables; however the emotional impact of stroke is important to patients and their carers and may impact on physical recovery and responses to rehabilitation (Chemerinski and Robinson. 2000). Post stroke depression has been associated in many studies with poor outcomes in ADL (Nannetti et al. 2005). Similarly, anxiety is another important psychological sequela of stroke that has been associated with poor physical outcome (Astrom 1996).

Relief of depression with anti-depressants has led to improvements in ADL and motor impairment (Chemerinski et al. 2001) however it is unclear whether improvements in physical outcomes influences depression. Since UL dysfunction is known to be the strongest predictor of psychological well-being at one year post stroke (Wyller et al. 1997), the question of whether improved UL recovery through a training intervention such as BT might then improve psychological outcomes is raised. Few studies appear to have examined the relationship between UL recovery or training responses and depression or anxiety therefore this is an area for further investigation within this thesis.

Moving from psychological well-being to general well-being, health related quality of life is a health outcome that provides a broader description of the disease and its outcomes.

1.1.3.2 Health related quality of life and upper limb dysfunction

Health related quality of life (HRQOL), as defined by the World Health Organisation (WHOQOL Group 1998) is a multidimensional measure of the impact of health and health outcomes on an individual's satisfaction with life and can therefore indicate the success of rehabilitation in improving perceived quality of life after stroke. Several UL rehabilitation intervention studies have included HRQOL measures, but findings have been equivocal with some demonstrating effects of improved UL functioning on HRQOL (Wolf et al. 2006), and

others demonstrated no effects despite improved UL outcomes (Kwakkel et al 1999). Clearly, findings may relate to the measures and nature and effectiveness of interventions, but they indicate that uncertainty exists about effects of improvements in UL impairment and activity on HRQOL that warrants further investigation.

Several studies have demonstrated that UL dysfunction is an important predictor of HRQOL six months or more after stroke relative to other demographic, social and clinical variables (McEwen et al. 2000, Nichols-Larsen et al. 2005) however each included only one measure of UL dysfunction. Conclusions about which aspects of UL dysfunction are most important in determining patients HRQOL are therefore difficult to discern. Clearly more work is required to determine how UL dysfunction influences HRQOL so that UL therapy can be appropriately targeted at those activities considered by patients to most influence their HRQOL.

1.2 AIMS OF THE THESIS

The main purpose of this thesis was firstly to compare effectiveness of bilateral UL task training and unilateral task training on physical and psychosocial outcomes in acute stroke. The second purpose was to contribute more broadly to the field of UL rehabilitation research in stroke by examining the importance of UL dysfunction in predicting the physical outcome of UL activity limitation and the psychosocial outcome HRQOL. The specific aims are discussed next.

1.2.1 PHYSICAL OUTCOMES

The **primary** aim of this thesis was:

- To compare the effects of bilateral UL task training and unilateral task training on physical outcomes of the hemiparetic, contralesional UL in patients with acute stroke.

Clinical and demographic factors may influence responses to UL rehabilitation interventions however little is known about which of those may influence BT outcomes compared to

unilateral training outcomes. To complement the primary aim of examining physical effects of BT, the first **secondary** aim within the physical outcomes theme was therefore:

- To explore clinical and demographic factors that may influence bilateral compared to unilateral UL task training responses

Little is known about the predictors of contralesional UL activity limitation and in particular regarding the strength of early activity limitation as a predictor of later activity limitation. The second **secondary** aim within the physical outcomes theme was therefore:

- To determine predictive strength of early UL activity limitation on UL activity limitation at different assessment points in time

Little is known about the nature of ipsilesional activity limitation, its recovery over time or its relationship to global functioning and in particular it is unclear whether it responds to bilateral task training. The final **secondary** study aims of the physical outcomes theme related to ipsilesional dysfunction:

- To determine if ipsilesional UL dysfunction can be detected on clinical measures
- To examine ipsilesional recovery over time
- To examine the relationship between ipsilesional dysfunction and activities of daily living
- To examine effects of bilateral task training compared to unilateral training on ipsilesional motor impairment and activity limitations

1.2.2 PSYCHOSOCIAL OUTCOMES

Given the psychosocial effects of stroke, and uncertainties regarding importance of UL recovery on psychosocial outcomes of anxiety, depression and health related quality of life, the **second** main thesis aim was:

- To compare effects of bilateral UL task training and unilateral task training on the psychosocial outcomes of anxiety, depression and health related quality of life in patients with acute stroke.

Uncertainties exist regarding the importance of UL dysfunction in predicting HRQOL, particularly after most patients have returned home at six months or more after stroke onset. The **secondary** and broader aim within the psychosocial outcomes theme was:

- To investigate the relative importance of several impairment and activity limitation constructs in predicting HRQOL.

The themes of physical and psychosocial outcomes provide a structure that will be followed throughout the thesis and explained in the next section.

1.3 STRUCTURE OF THE THESIS

The previous sections provided a background to the rest of the thesis in identifying the nature of UL dysfunction in stroke, by highlighting the importance of UL rehabilitation in acute stroke and by exploring BT as an emergent rehabilitation strategy for UL recovery. Arguments were presented for testing bilateral task training in an acute stroke population using a robust research design, and for examining its effects on physical UL outcomes and psychosocial outcomes. The case was presented for the exploration of factors likely to influence UL physical responses to BT and broadening the enquiry, to the examination of predictors of UL activity limitation. Finally, arguments were presented for examination of psychosocial outcomes, specifically effects of bilateral UL training on anxiety and depression and HRQOL, and the impact of UL dysfunction on HRQOL. To inform these investigation strands, a literature review was required, comprising the following topics:

The first chapter of the review (Chapter 2) relates to physical outcomes relevant to BT and UL recovery. The theoretical and neurophysiological basis for BT is firstly examined. Secondly, a literature review is reported which examines BT literature between 1996 and 2006 to determine the evidence supporting bilateral task training, bilateral movement function training and bilateral interventions involving assisted technology. The third strand broadens to review UL rehabilitation literature relating to factors likely to influence impairment and activity limitation training responses to UL interventions. A second purpose of this review strand is to determine, from current literature, what is known about predictors of UL activity and impairment outcomes, and how these vary over time. Finally, the nature of ipsilesional UL dysfunction is examined and the literature regarding the effects of BT on ipsilesional dysfunction is reviewed.

The next chapter (Chapter 3) reviews literature relating to psychological outcomes following stroke and specifically examines what is known about depression, anxiety (Chapter 3,

Section 3.1) and health related quality of life (Chapter 3, Section 3.2). Starting with a broad review of each, the review examines each topic in relation to stroke, followed by evaluation of the relationship between the psychosocial outcomes and UL recovery in general, and responses to rehabilitation interventions in particular.

These chapters inform the development of research questions addressed by a randomised controlled trial developed to investigate effects of bilateral compared to unilateral task training. The broader research questions intimated above will be addressed with data from that study.

Chapters 4 to 7 report the randomised controlled trial. The BT intervention was based on activities tested in previous bilateral task training studies (Mudie and Matyas 1996, Mudie and Matyas 2000) which were developed into a training programme based on principles of motor learning discussed in Chapter 4, and appropriate to severity of dysfunction. Chapter 5 reports the results and Chapter 6 discusses and interprets findings, compares them to previous studies, identifies study limitations and highlights areas for future research and clinical practice. The final chapter (Chapter 7) presents conclusions and provides suggestions for future directions of research emerging from the thesis.

1.4 CONCEPTUAL FRAMEWORK FOR THE THESIS: THE ICF

Throughout this thesis, the International Classification of Functioning, Disability and Health (ICF) (WHO 2001) provides a framework for categorising the intervention approaches and outcome measures emerging from the literature and later informs the selection of outcome measures in the clinical trial. The ICF is a conceptual framework that aims to provide a standardised language and conceptual framework for the classification of the impact of health conditions. The framework describes human functioning and disability as the product of a dynamic interaction between various health conditions and environmental and personal contextual factors and aims to build a coherent and consistent body of scientific knowledge that will inform rehabilitation research (Institute of Medicine 2007).

The ICF describes multiple levels of human functioning – from the level of the body or body parts through to the level of the whole person functioning is his or her environment. It is useful here to describe some of the key terminology used in the ICF, since the terms are

mentioned throughout the thesis. The ICF describes *body functions* as physiological functions of body systems whilst *body structures* are anatomical parts of the body such as organs, limbs and their components. *Impairments* are problems in body function or structure such as a significant deviation or loss. *Activity* is the execution of a task or action by an individual and *Activity Limitations* are difficulties an individual may have in executing activities. *Participation* is involvement in a life situation whilst *Participation Restrictions* are problems an individual may experience in involvement in life situations. Life situations include domains such as domestic life, education and employment and community, civic and social aspects of life. Each of these levels of the health condition may be influenced by extrinsic environmental factors which are defined as physical, social or attitudinal circumstances; or by personal factors such as education, gender, race lifestyle.

The ICF has been widely accepted by the rehabilitation community (Stuki et al. 2008). As such it was considered the most appropriate framework to guide the reporting of some of the findings from the literature review in this thesis and for selection of outcome measures for the randomised controlled trial, and will be referred to throughout the thesis.

CHAPTER 2

LITERATURE REVIEW

PHYSICAL OUTCOMES: BILATERAL UPPER LIMB TRAINING AND FACTORS INFLUENCING TRAINING RESPONSES AND RECOVERY

2.0 INTRODUCTION

This chapter starts with a review of neurophysiological mechanisms of stroke recovery and examines how these may be influenced by rehabilitation. The first section starts with a review of the impact of stroke on motor control, followed by a discussion of the physiological mechanisms underpinning recovery and rehabilitation responses. Theoretical and scientific rationale for BT as a rehabilitation strategy are then discussed, followed by an examination of how they might be effective in stroke. This is followed in section 2.2 by a critical review of the literature relating to the use of BT as a rehabilitation intervention for the contralesional upper limb (UL) in stroke. Section 2.3 reviews the clinical and demographic factors that influence contralesional UL recovery and responses to therapeutic interventions, with a view to determining which might be important to bilateral training interventions. The final physical outcomes section (2.4) reviews the nature of ipsilesional UL dysfunction after stroke and examines what is known about bilateral training in this context.

2.1 THE THEORETICAL BASIS FOR CONTRALESIONAL BILATERAL TASK TRAINING AS A THERAPEUTIC INTERVENTION

This section explores the theoretical basis for bilateral training as a rehabilitation intervention for the contralesional upper limb in stroke. The section starts by examining how stroke influences motor control and cortical activation patterns and how recovery occurs through neuroplasticity naturally and with rehabilitation. This is followed by a review of interlimb coupling in healthy individuals and in stroke and discusses the motor control models underpinning the phenomenon and how these relate to bilateral training. Finally, possible mechanisms of how bilateral training might lead to improved recovery are discussed.

2.1.1 EFFECTS OF STROKE AND RECOVERY MECHANISMS AT A NEURAL LEVEL

2.1.1.1 How does stroke affect motor control?

Cortico-motoneuronal activity during movement is task-specific. Populations of interconnected neurones are arranged in neural networks distributed across the motor cortex. These are selectively activated in response to task requirements (Kandel et al. 2000, Rossini et al. 2003) suggesting overlapping functions of some motor cortical areas. Motor cortex damage from stroke depletes cortico-motoneurones pools within the networks leading to diminished excitatory influences on limb motor neurones (Turton et al. 1996). Reduced motor system capacity to modulate excitatory influences in response to task requirements consequently leads to inefficient and stereotypical motor patterns often seen in stroke (Turton et al. 1994). The topological arrangement of the system that allows co-operation of multiple cortical areas may however be important in stroke recovery.

2.1.1.2. Cortical activation patterns after stroke

In line with the overlapping functions of motor cortical areas, stroke recovery is characterised by complex reorganisation of cortical activation patterns, which change over

time. In healthy individuals, movement is controlled mainly by the contralateral hemisphere although with some activation of bilateral motor and supplementary motor areas with increased movement complexity (Catalan et al. 1998). Functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) studies demonstrate that in cortical and non-cortical stroke, intact areas of the damaged hemisphere around the lesion reorganise and become more active than usual during hemiparetic UL movement (Rossini et al. 2003, Cramer 2004). Additionally, sensorimotor and secondary motor areas not usually involved in motor tasks, such as cingulate and premotor cortices are also activated alongside increased bilateral activation of motor areas and ipsilateral corticospinal pathways (Rossini et al. 2003, Calautti and Baron 2003, Cramer 2004). These activation patterns reflect the overlapping and flexibly responsive nature of components of the motor system. Motor control appears to occur through multiple, selectively activated neural networks in which some functions are shared by different groups of neurones (Rossini et al. 2003, Calautti and Baron 2003, Nelles 2004). This shared and often bilateral functioning becomes active to compensate for damage during stroke recovery.

Debate exists around the role of increased bilateral cortical activation during paretic UL movement. Bilateral activation patterns appear to shift over time towards more normal contralateral hemisphere activation, depending on lesion site and size (Feydy et al. 2002). Additionally, corticospinal tract and sensorimotor cortex sparing appears predictive of more normal activation patterns (Feydy et al. 2002). Persistent bilateral over-activity appears associated with poorer recovery (Turton et al. 1996, Netz et al. 1997, Caramia et al. 2000, Calautti et al. 2001) suggesting that it may be an ineffective response to stroke. However TMS studies demonstrate that activation of the intact hemisphere may be compensatory in response to loss of function (Johansen-Berg et al. 2002, Serrien et al. 2004). Bilateral activation of both hemispheres during movement may therefore represent a recovery mechanism. Where poor recovery exists, bilateral activation may be the central nervous system's response to extensive motor cortex damage with all available resources, and not simply a marker of poor recovery. Research in this field is currently in its infancy and an understanding of the role of bilateral cortical activation patterns in stroke recovery will no doubt increase with time. Currently all that can be concluded is that bilateral cortical activation is an early response to attempts to move the affected UL after stroke that normalises over time in all but the most severely affected participants.

In healthy individuals, during movement, interhemispheric inhibition of the motor cortex controlling the limb that is not moving occurs via the corpus callosum (Schnitzler et al. 1996). This is thought to prevent simultaneous activation of ipsilateral uncrossed and contralateral crossed pathways from competing and interfering with control of unilateral movement. It also prevents simultaneous mirror movement of both limbs (synkinesis) (Mayston et al. 1999) and modulates contralateral movement in bimanual non-symmetrical movements (Schnitzler et al. 1996). In stroke however, over-activation of the unaffected motor cortex during paretic UL movement may represent abnormally high interhemispheric inhibition directed towards the damaged hemisphere. This may suppress motor output from the affected cortex, adversely influencing recovery (Murase et al. 2004, Cauraugh and Summers 2005). Return to contralateral activation patterns thus appears desirable and predictive of better recovery. Clearly, rehabilitation strategies that augment activity of depleted cortico-motorneurone networks promote more normal cortical activation and address abnormally high interhemispheric inhibition warrant investigation.

2.1.1.3 Evidence of rehabilitation-induced neural plasticity in stroke

Stroke recovery appears to occur through reorganisation of spared neuronal tissue local or remote to the injury (Matthews et al. 2004). Recovery may occur spontaneously, *or* in response to activity, however relationships between spontaneous and activity induced recovery remains unclear (Rossini and Forno 2004). Recovery occurs firstly through blood flow restoration around the infarct (Turton and Pomeroy 2002) followed by reduction in inhibitory transmitters such as gamma butyric acid (GABA). That probably enhances synaptic transmission, leading to rapid, widespread but transient increases in excitation. Unmasking, of functionally silent synapses, or disinhibition of the overlapping neural networks around the lesion then ensues (Dobkin 1998, Asanuma and Pavlides 1997, Matthews et al. 2004). The exact role and interactions between these mechanisms and motor recovery however remains debatable (Rossini et al. 2003). This process, known as neuroplasticity, is not necessarily conducive to recovery. Nudo (2000, pp 190) stated that long-term neuroplastic changes may be “adaptive, maladaptive or epiphenomenal”. Spasticity is one consequence of maladaptive plasticity that may interfere, rather than support recovery of function (Bach-y-Rita 2000).

Gradual but more permanent plasticity over days and weeks probably results from both spontaneous reorganisation and relearning through practice, probably analogous to some extent to changes that occur during skill learning throughout adult life. Enhanced synaptic efficiency, mediated via activity, facilitates long-term potentiation (Dobkin 1998). Long-term potentiation is sustained nerve cell depolarisation following stimulation, and leads eventually to permanent motor learning via genetically mediated dendritic growth and synaptogenesis (Rossini et al. 2003). These long-term changes eventually lead to cortical activation pattern reorganisation potentially beneficial to recovery (Dobkin 1998, Turton and Pomeroy 2002). They probably involve modification of existing pathways, rather than development of completely new neuronal circuits (Matthews et al. 2004). Studies using TMS, functional MRI (fMRI) and positron emission tomography (PET) have demonstrated shifts from bilateral and contralesional activation to more normal ipsilesional activation with enhanced perilesional activity during paretic UL movement following intensive training. In these studies, the non-paretic UL was constrained, forcing participants with chronic stroke to use the paretic limb for task performance (Miltner et al. 1998, Liepert et al. 2000, Liepert et al. 2001, Nelles et al. 2001, Johansen Berg et al., 2002 Rossini et al. 2003). The studies provide evidence that training-induced plasticity is possible, even many months or even years after stroke.

Given this evidence, researchers developing and testing rehabilitation interventions must determine optimal practice characteristics to stimulate and refine post-stroke cortical reorganisation to drive motor and functional recovery. Bilateral training involving simultaneous UL movements may be an alternative approach to the unilateral approaches already examined. Bilateral training has emerged from converging neuroscientific evidence about stroke recovery mechanisms and from motor control science (Mudie and Matyas 1996, Mudie and Matyas 2000, Cauraugh and Summers 2005). Bimanual coupling studies suggest that the less affected UL may facilitate paretic UL performance, a potentially effective approach to UL rehabilitation. Theoretical and scientific rationale for this are examined next.

2.1.2. INTERLIMB COUPLING IN HEALTHY INDIVIDUALS AND IN STROKE

2.1.2.1 Interlimb Coupling

During bimanually identical movements, in healthy individuals, the ULs demonstrate strong temporal and spatial coupling (Kelso et al. 1979, Swinnen 2002, Serrien and Swinnen 1999). Whilst bilaterally identical and unilateral tasks are easily performed, performing bimanually different tasks simultaneously results in interference, with each UL tending to adopt movement characteristics of the other (Franz et al. 1991, Swinnen 2002, Fontaine et al. 1997). One to one in-phase movements where homologous muscles are active and anti-phase movements, where opposite muscle groups are simultaneously active, appear easiest to perform, are most stable and accurate, and require least attention (Kelso et al. 1979, Swinnen 2002). Other co-ordination patterns are less stable, and revert towards the in-phase, mirror movement pattern in a phase transition, as parameters such as speed and frequency are increased (Kelso et al. 1979). These findings suggest the existence of centrally shared control mechanisms that may mediate interlimb coupling during rhythmically repeated movement. Dynamic systems theory (Haken 1975, Haken et al. 1985, Kelso 1979) has been used to explain the phenomenon of a common control mechanism during bimanual movements. The theory models rhythmic symmetrical movements as coupled oscillators and in this way describes, explains and predicts the co-ordination patterns between the limbs mathematically. The stability of the co-ordination pattern depends on the relative phasing of the angle between limb segments involved in the cyclic movements. As motor control parameters are adjusted, for example when speed is increased, asymmetrical co-ordination provides less stability between the oscillators. Eventually, the system self-organises into the more stable symmetrical pattern which emerges as a result of the physical properties of the system. The stability and strength of interlimb coupling during symmetrical rhythmic movement provides one theoretical rationale for BT as a therapeutic intervention in stroke. Dynamic systems theory predicts that the contralesional (i.e. most affected) limb will couple to the ipsilesional (i.e. less affected) limb and that the movement parameters of both limbs will be influenced towards the most stable pattern. This clearly affords therapeutic possibilities *if* the less affected ipsilesional limb enhances movement of the contralesional hemiparetic limb.

2.1.2.2 Normal neural mechanisms for interlimb coupling

The rationale for BT in stroke emerges from suggestions that control of bimanual co-ordination is centrally organised. The supplementary motor area (SMA) has been considered a locus for bimanual control (Swinnen 2002) but recent evidence suggests that distributed task-specific neural networks may be responsible, involving the primary motor cortex (Donchin et al. 1998), premotor cortex, cingulate area, SMA and cerebellum (Debaere et al. 2001, Gerloff and Andres 2002, Swinnen and Wenderoth 2004). The corpus callosum is particularly involved in spatial parameters of bimanual co-ordination (Eliassen et al. 2000), whilst temporal movement parameters appear to be controlled sub-cortically (Franz and Eliassen 1996). The small portion of the corticospinal tract that remains uncrossed may also mediate interlimb coupling during bilateral movement, given that descending commands to crossed and uncrossed fibres are identical (Carson and Swinnen 2002). It thus appears that control of bilateral movement involves bilaterally distributed neural network interactions at cortical and sub-cortical level and across both hemispheres, which change as a function of task complexity (Debaere et al. 2001). The bilaterally organised, shared nature of these networks suggests that in stroke, it may be possible for the unaffected UL to influence movement of the paretic UL when both ULs are moving together.

2.1.2.3 Interlimb coupling in stroke

Evidence of interlimb coupling in stroke emerges from several single-session observational studies; however findings have not been wholly conclusive. Supporting evidence was found by Cunningham et al. (2002), who demonstrated improved smoothness and velocity of elbow movement during bilateral compared to unilateral movement, in five chronic stroke participants, particularly with added inertial loading. However, Harris-Love (2005) demonstrated higher peak velocity, acceleration time and movement time of unilateral compared to bilateral movement in 32 participants with chronic stroke during a reaching task. In contrast to Cunningham, this was not enhanced with inertial loading. Furthermore, movement time increased in the non-paretic UL during bilateral movement. Similarly, Rose (2005) demonstrated higher mean paretic UL peak velocity in bilateral compared to unilateral aiming in 30 participants with chronic stroke, however prolonged non-paretic UL movement time and lower peak velocity in the bilateral condition was also demonstrated. Rice (2001) demonstrated no beneficial effect on frequency and velocity of elbow

oscillations of the paretic limb in 18 subacute and chronic participants, but unaffected limb slowing was demonstrated during bilateral compared to unilateral performance. Mudie (Mudie and Matyas 2001) did not find an effect on EMG output in densely affected participants who practised bilateral compared to unilateral shoulder movements in a single session, nor was there a difference between acute and chronic participants.

In summary, these findings suggest that benefits of bilateral training to paretic UL movement may exist depending on task constraints, but possibly at the expense of non-paretic UL movement parameters. Slowing of the non-paretic UL to match paretic UL movements supports the idea that the limbs are constrained as a single unit. Trials examining effects of therapeutic programmes of BT on clinical outcomes are reviewed in Section 2.2. It is important first to discuss neural mechanisms that may underpin BT in stroke in the context of neural mechanisms for bimanual coordination and neuroplasticity.

2.1.2.4 Neural crosstalk model

The neural crosstalk model is another theoretical motor control model that may explain the observed facilitatory effects of bilateral movement in stroke (Marteniuk and Mackenzie 1980, Cardoso de Oliveira 2002, Cauraugh et al. 2005). This model, which is based on a motor programming approach to motor control, supports what is known about anatomical correlates of bimanual movement and suggests that crosstalk, or intermingling of motor signals between hemispheres, occurs when motor parameters for each UL are specified. High-level transfer of motor signals between hemispheres occurs via the corpus callosum, SMA, motor cortices and premotor areas (Cardoso de Oliveira 2002, Cauraugh et al. 2005, Carson 2005). A lower level of transfer is also thought to occur at the execution level, for which uncrossed ipsilateral corticospinal fibres are considered the primary candidate (Cardoso de Oliveira 2002, Cauraugh et al. 2005). The role of these motor fibres in movement control is not fully understood, however they are thought to “leak” motor commands to each UL from the ipsilateral hemisphere and have been implicated in congenital mirror movements (Mayston et al. 1999). These fibres may be responsible for observations that during bimanually different movements, performance of both ULs becomes similar (Cardoso de Oliveira 2002). Inhibitory crosstalk, probably at callosal level between cortical motor areas (Carson 2005) exists to mediate ipsilateral activity in the normal CNS. It suppresses ipsilateral pathways from allowing identical mirror movements to interfere with unilateral movement and to allow selection and control of bimanually different movements

(Cardoso de Oliveira 2002). Clearly, when bilaterally identical movement commands are specified, as demonstrated in the coupling studies in stroke, the need for interhemispheric inhibitory influences to prevent mirror movement is diminished because excitatory influences from each hemisphere are congruent. Intracortical inhibition during bilateral movement performed by healthy individuals is supported in a TMS study (Stinear and Byblow 2002). There, suppression of intra-cortical inhibition during simultaneous wrist flexor contraction compared to asynchronous contractions was demonstrated supporting the idea that crosstalk exists and can be modulated by bilateral movement.

2.1.2.5 Neural cross-talk after stroke

The neural crosstalk model is also congruent with BT following stroke. The abnormally high interhemispheric inhibition during paretic UL movement (Murase et al. 2004) discussed above may be modified by shared, bilaterally identical motor commands. Shared identical motor commands may promote more normal interhemispheric inhibition to rebalance excitatory and inhibitory influences towards normal, reinforcing and facilitating output from the damaged hemisphere (Cauraugh and Summers 2005). This idea is supported by evidence from functional MRI (Staines et al. 2001). Activation of homologous muscles appears to provide crossed facilitation between the symmetrically organised motor cortices (Rossini et al. 2003, Rossini and Forno 2004, Stinear and Byblow 2004a), probably mediated by the corpus callosum, that increases excitability of spared motor pathways to the paretic limb.

Furthermore, during bilateral symmetrical movement, and at the lower or execution level of crosstalk, ipsilateral corticospinal excitatory influences from the undamaged hemisphere, freed from inhibition because of the shared identical motor command to each hemisphere, are enhanced. These may summate with spared excitatory impulses from the damaged hemisphere to reinforce interlimb coupling and facilitate movement recovery in the hemiplegic UL (Mudie and Matyas 2000, Cauraugh et al. 2005, Stinear et al. 2001). Although evidence is emerging to confirm these theories (Staines et al. 2001) further research is required to fully understand mechanisms underpinning BT.

Other proposed mechanisms, in line with neural crosstalk, by which bilateral movement may influence paretic UL performance in stroke are via spared indirect corticospinal pathways, such as the corticopropriospinal system, a system of spinal interneurones that receive

bilateral input from bilaterally projecting reticulospinal and rubrospinal pathways and whose responses are known to be upregulated following stroke (Mazevet et al. 2003). These pathways mainly influence proximal musculature but may account partly for effects of bilateral movement on the paretic UL (Mudie and Matyas 2000). Proximal effects of bilateral coupling have been demonstrated (Cunningham et al. 2002, Harris-Love et al. 2005) supporting the theory that indirect corticospinal pathways may be involved in facilitating bilateral control. Conversely, using TMS, diminished facilitation of C3/4 propriospinal activity with bilateral movement in normal subjects has been demonstrated (Stinear and Byblow 2004a) suggesting that bilateral facilitatory effects may not be mediated via this system. The role of indirect corticospinal pathways in bilateral facilitation in stroke therefore requires further investigation.

Congruent with the neural crosstalk model therefore, several mechanisms exist to explain how bilaterally activating both ULs simultaneously may influence movement of the paretic limbs, providing a neurophysiological basis for BT as a therapeutic approach.

2.1.3 NEUROPLASTICITY AND BILATERAL TRAINING AFTER STROKE

Studies demonstrating immediate effects of BT on paretic UL movement suggest rapid CNS reorganisation (Mudie and Matyas 2000). Shared motor commands to each hemisphere, recruitment in the damaged and undamaged hemispheres of normally inhibited uncrossed ipsilaterally projecting corticospinal pathways or indirect corticospinal influences may cause increased neuronal excitability in adjacent and overlapping networks to the lesion. In turn this may lead to unmasking of new neural networks and connections for UL control within the damaged hemisphere (Mudie and Matyas 2000). Over time and with repeated practice, excitatory influences of BT may lead to long-term potentiation, synaptogenesis, and cortical reorganisation of damaged hemisphere neural networks associated with long-term retention of motor learning for unilateral movement of the paretic UL.

BT studies provide some evidence of sustained effects on cortical reorganisation. One study (Stinear and Byblow 2004b) demonstrated decreased ipsilesional cortical excitation using TMS after BT but no significant increase in contralesional activation. Conversely, another study (Luft et al. 2004) demonstrated increased contralesional activation on fMRI following BT. Differences in populations, training paradigms, and assessment techniques may account for these diverse findings. More work is required to investigate effects of BT on neural reorganisation associated with recovery before exact mechanisms can be determined. Further empirical testing is required before mechanisms for short and long-term facilitatory effects of BT can be elucidated, but potential mechanisms exist whereby BT may influence post-stroke recovery of the hemiparetic UL.

2.1.4 DISCUSSION OF MOTOR CONTROL THEORIES

The sections above presented two contrasting models of motor control that aim to describe and explain the coordination of coupled movement of the upper limbs, and as they underpin approaches to BT, it is relevant to briefly discuss how these relate. The first model discussed was dynamic systems theory. That model, which postulates the notion of self-organisation in complex systems (Haken and Wunderlin, 1990) assumes that movement patterns emerge from the physical properties of the system, and can be described in terms of mathematical non-linear relationships between the various subsystems. Rather than assuming an "executive" that is responsible for the coordination of movement in a top-down fashion,

coordination is governed from *within* the system. According to this model, a mode of activity can be described by so-called order-parameters such as phase relationships between linked segments (e.g. the phase relationship between thorax and pelvis rotation during gait) that compress information about individual degrees of freedom (e.g. individual vertebrae). Changes in so-called control parameters (e.g. walking speed) may bring about dramatic changes in the order parameters (e.g. an increase in walking speed changes the phase relationship between thorax and trunk from in-phase at low speed to out-of-phase at higher speeds). A typical research paradigm, based on this model, is to investigate a mode of activity (e.g. gait, or coupled upper limb movement) under different conditions of the control parameter, which is varied systematically to uncover possible critical fluctuations, slowing down and phase transitions – the hallmarks of self-organising systems. As such, this model lends itself most directly to the study of cyclical movements which are characterised by a distinct order. In line with this, the model has been mainly used in therapeutic application to gait, e.g. in individuals with cerebral palsy (Engsberg et al. 2008), elderly fallers (Wagenaar et al. 2003) and stroke (Ford et al. 2009) to explain how changes in gait stability and co-ordination occur. Such application for the model is logical, clear given that gait is a repetitive, cyclical activity. Dynamic systems theory has, as described in the previous sections, been applied to the study of upper limb coupling in stroke, as a basis for upper limb rehabilitation (Rice and Newall 2001). There is however a tension between the goal orientated, discrete unilateral or bimanually different UL tasks that are mostly performed in functional activity and which are the focus of most rehabilitation interventions, versus the largely automatic, cyclical movements that have no construct of intention (Schmidt 2005). Given the specificity of learning hypothesis (see Chapter 4, Section 4.1.5.5) , it is not clear how UL movements practised in a cyclical fashion, in line with this theory, might translate to improved performance of discrete functional tasks.

In contrast, the neural crosstalk model assumes a top-down information processing model of motor control rather than an emergent approach determined by the physical properties of the system. In the neural crosstalk model, hierarchically organised motor programmes are thought to exist that specify classes of movement in abstract terms (Schmidt 1975). These programmes contain the broad rules (i.e. the order of actions, relative timing and relative force), which, together with the specific parameters (i.e. specific muscles, absolute timing and force production) are responsible for the execution of the movement. The motor programme is then relayed to the so-called comparator in the form of a feedforward reference of correctness, generated as an anticipatory comparator standard of the desired

movement. The actual movement is compared against the comparator standard which specifies the sensory qualities of a motor goal (Schmidt and Lee 2005). During movement execution - if time permits - feedback from sensory organs such as proprioceptors and vision provide information from which errors are computed compared to the reference of correctness. The system receives and processes the feedback and corrects the motor output. This is a process that is undertaken continuously as movement progresses to process, correct and refine movement. Considering the accuracy and precision requirements for the coordination of goal-directed, functional upper limb movement, this model may explain the execution of discrete UL tasks better than dynamic systems theory (Schmidt and Lee 2005).

This is in contrast to the dynamic systems theory which predicts that interlimb coupling may be used to entrain the affected UL but in which the movement patterns are emergent, continuous and not necessarily related to functional tasks.

In this study, the primary aim was to develop a training intervention to improve functional activity of the affected upper limb in stroke. Having considered the contribution of two contrasting models of motor control above, it would appear more appropriate to consider that the information processing model is a more appropriate basis for development of such tasks than dynamic systems theory.

2.2 A CRITICAL REVIEW OF BILATERAL TRAINING INTERVENTION STUDIES FOR UPPER LIMB REHABILITATION FOLLOWING STROKE

Interest in BT as a therapeutic approach to UL recovery in stroke has led to a growing body of research examining a range of BT paradigms. The aim of this section was to critically review published BT studies to determine the strength of evidence for BT, highlighting aspects relevant to the present study.

The review question was set as: “What is the quantity and quality of the evidence supporting BT as a strategy for management of UL activity limitation, impairment, and psychosocial outcomes in participants with acute and chronic stroke?” The review was conducted by the author alone.

2.2.1 METHODS OF CRITICAL REVIEW

2.2.1.1 Criteria for included studies

Inclusion criteria

PARTICIPANTS

Studies involving participants with a clinical diagnosis of stroke were included, regardless of time from onset, severity of UL impairment and site of lesion.

INTERVENTIONS

Studies had to involve evaluation of practice with both UL's simultaneously performing identical movements or tasks to induce a change in UL motor performance and could involve assistive devices for example, functional electrical stimulation or robotic devices.

The main area of interest for this thesis was the effect of bilateral therapeutic programmes on UL outcomes. Trials of interest were those examining therapeutic interventions aimed at improving UL recovery in stroke. Although several studies examining the effects of a single session of bilateral activities on interlimb coupling and co-ordination in stroke exist, these were considered to be observational studies that were not specifically evaluative of therapeutic programmes and were not included in this review.

DETERMINING INTERVENTION CATEGORIES

Evidence suggests that task complexity may influence effectiveness of BT (Cauraugh and Summers 2005). Studies varied considerably in terms of the nature of the interventions. Three broad categories of intervention were identified, aligning the primary aim of the intervention with the ICF concepts impairment and activity limitation: Bilateral Interventions Addressing Activity (BIA); Bilateral Interventions Addressing Movement Function (BIMF) An additional category, in this case not based on the ICF was also added, comprising interventions using assistive technology - Bilateral Interventions Involving Activity or Function Assisted by Technology (BIAT).

STUDY DESIGNS AND METHODOLOGY

Because of the developmental nature of this field of study, trials of any design were considered, whether random allocation or blinding was conducted or not, and whether there was a control comparison or not. Single group design and single case study design with n=1 were included.

OUTCOME MEASURES

Primary outcomes of interest were a) UL activity limitation, including task performance, daily use, manual dexterity, manipulation b) UL impairment including measures of active and passive movement, or motor performance, movement profiles such as quality and speed of movement, movement patterns, muscle tone, co-ordination, strength or range of movement. Secondary outcomes were global activity limitation or disability, measured in terms of activities of daily living (ADL) or extended activities of daily living (EADL), and psychosocial outcomes including quality of life, well-being or measures of mood or depression. Additional outcomes were those indicating neuroplasticity and included measures recorded with functional magnetic resonance imaging (fMRI) and Transcranial Magnetic Stimulation (TMS).

Exclusion criteria

Papers not in English and not related to humans were excluded.

2.2.1.2 Search strategy

Searches were conducted using OVID, CINAHL, MEDLINE, EMBASE and PsychINFO databases. Using key words (i.e. cerebrovascular disease, cerebrovascular accident, stroke, hemiplegia, upper extremity, UL, hand, wrist, rehabilitation, physical therapy, physiotherapy occupational therapy, exercise, motor activity, task performance, motor skills, motor learning bilateral, bimanual), papers published between 1996 and 2006 were identified. Full details of the search terms are in Appendix 2.

Studies were identified and abstracts reviewed for relevance. Studies of relevance were described and critically appraised on the basis of participants, methodology, interventions,

outcomes, type of comparison and results. This was followed by synthesis of evidence for each type of intervention.

2.2.1.3 Methodological quality

Study quality was determined using guidelines and criteria for levels of evidence from the Scottish Intercollegiate Guidelines Network (SIGN 2006) for grading of trial quality (Harbour and Miller 2001). The criteria were used for the identification of aspects of study design known to influence validity of results and conclusions. The SIGN checklists were used to evaluate the quality of each study (SIGN 2004).

SIGN evidence levels are shown in Table 2.1 and the SIGN checklist used to rate individual trials is included in Appendix 1.

Table 2.1 SIGN Grading System (SIGN 2004)

SIGN Levels of Evidence	
1++	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 -	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

2.2.2 RESULTS OF LITERATURE SEARCH

Because of the diversity of study designs, it was not appropriate to conduct a meta-analysis of study results therefore reporting of results is descriptive.

A total of 523 citations were produced. Excluding those not in English and not related to humans led to 446 potentially relevant studies. When duplicates were removed, 320 studies remained. Examining the abstracts indicated that of those, 79 were studies unrelated to stroke. Of the remaining 241 studies, 18 trials met inclusion criteria and were reviewed.

1. BILATERAL INTERVENTIONS ADDRESSING ACTIVITIES

These were interventions addressing the activity level of the International Classification of Function (World Health Organisation 2001) equating to the task training approach often described in the rehabilitation literature. Tasks were defined as involving co-ordinated UL movements to achieve specific functional or simulated functional goals. Simulated functional goals could involve completion of tasks similar to everyday tasks in the home or community, for example, grasping, reaching to, moving or using an object.

2. BILATERAL INTERVENTIONS ADDRESSING MOVEMENT FUNCTION.

These were BT interventions addressing the body function/impairment level of the International Classification of Function (ICF) (World Health Organisation 2001). These typically involved simple movement sequences performed using voluntary movement, but without a specific functional goal. These were proximal, distal single joint or whole UL movements and could be component movements of functional tasks.

3. BILATERAL INTERVENTIONS INVOLVING ACTIVITY OR FUNCTION ASSISTED BY TECHNOLOGY

This was defined as any assistive or rehabilitative device involving artificial augmentation of voluntary movement or task performance during UL bilateral training, for example functional electrical stimulation or robotic devices.

Studies falling into each intervention category are presented and discussed, followed by a general discussion of all of the studies, highlighting gaps in the evidence to date and requirements for future research.

2.2.3 Bilateral interventions addressing activities (BIA)

Four of the 18 studies investigated BT involving tasks classified as activities (ICF classification) (Table 2.2). A total of 67 participants were involved. Three used multiple baseline single case series design (Mudie and Matyas 1996, Mudie and Matyas 2000, Lewis and Byblow 2004) the fourth (Desrosiers et al. 2005) was a randomised controlled trial (RCT). Two studies (Mudie and Matyas 1996, Mudie and Matyas 2000) demonstrated positive effects of BIA, however others demonstrated contrasting findings. Studies are summarised in Table 2.2.

Table 2.2 Summary of studies examining bilateral interventions addressing activities

Study	Design	Participants	Intervention	Comparison	Outcome measures	Results	SIGN Evidence Level
Mudie and Matayas (1996)	Two single case multiple baseline time series Blinded assessors	6 right hemisphere stroke 2 left hemisphere stroke Mean age 69.4 7 Male, 1 Female; 3 -78 weeks post stroke, mean 17.8 Able to perform most components of movement Concurrent rehabilitation	*Study 1*: n=4 unilateral practice of 3 tasks vs bilaterally practice *Study 2*: n=4 unilateral block placement, peg targeting and simulated drinking. Hands linked vs. bilaterally identical practice 5 days per week over 8 weeks	Baseline unilateral phase compared to bilateral intervention phase	**Visual rating kinematic scales** of spatial co-ordinates, speed, rhythm, direction, deceleration towards target of each task relative to normal movement; end point location and joint position. Raters blinded to test sequence. Graphical visual analysis by panel of judges.	**Visual rating kinematic scales**: spatial co-ordinates, speed, rhythm, direction, deceleration towards target, end point location and joint position significantly improvement in all three tasks relative to normal movement in both studies for 7 participants with the introduction of BT ($p<0.05$). Improvements maintained at 6 month follow up.	3
Mudie and Matayas (2000)	Same data for first two series, (above) plus data from third series Blinded assessor	8 right hemisphere stroke 4 left hemisphere stroke Mean age 69.6 years 9 Male; 3Female 4 -78 weeks post stroke Undergoing or completed rehabilitation Able to perform most components of movement	Study 1 and 2 as above. Study 3: 4 participants - baseline bimanually different task practice followed by bilaterally identical practice Study 3: 5 days per week over 6 weeks	Baseline phase of bimanually different practice compared to bilaterally identical practice	**Visual rating kinematic scales** of spatial co-ordinates, speed, rhythm, direction, deceleration towards target of each task relative to normal movement; end point location and joint position. Raters blinded to sequence of testing. Graphical visual analysis by panel of judges.	**Visual rating kinematic scales:** significant improvement in spatial co-ordinates, speed, rhythm, direction, deceleration towards target, end point location and joint position for most participants in most tasks relative to normal movement ($p<0.05$). In studies 2 and 3, participants had greater impairment and demonstrated improvements in nearly all tasks. Improvements maintained at 6 month follow- up.	3

Table 2.2 Summary of studies examining bilateral interventions addressing activities

Study	Design	Participants	Intervention	Comparison	Outcome Measures	Results	SIGN Evidence Level
Lewis (2004)	Single case series with multiple baseline design. Blinded assessor.	5 right hemisphere stroke 1 left hemisphere stroke Age range 42-84 4 Male, 2 Female 1-47 months post-stroke First ever stroke, evidenced on CT.	Three tasks trained for 5 days over 4 weeks. 11 repetitions of each task. Baseline unilateral phase followed by bilateral phase.	Time series analysis before and after introduction of BT	**Visual analogue scale :** Movement Performance **FuglMeyer Upper Limb scores.** Motor Impairment: **Transcranial magnetic stimulation (TMS);** excitability of contralateral and ipsilateral pathways from both hemispheres measured using electromyography (EMG)	**Movement performance and Impairment**: No significant difference across tests (p=0.05). **TMS** only completed for 3 participants. Contralateral responses: Increased affected hemisphere cortical map n=2; reduced map area n=1. Ipsilateral responses: no significant differences No follow-up	3
Desrosiers (2005)	RCT Blinded assessor	23 right hemisphere stroke; 18 left hemisphere stroke. Mean age 73.2± 10.4 years 19 Male, 22 Female 10 days-2 months post-stroke 8 dropouts	*Intervention:* bilateral symmetrical and asymmetrical functional tasks graded according to impairment. Some unilateral tasks included. *Control*: "conventional" Occupational Therapy activities. 4 x 45minutes x 5 weeks	Change between control group and intervention groups in pre and post intervention test scores	**UL Fugl-Meyer Scale**: Motor Impairment **Grip Strength** **Box and Block Test:** Gross manual dexterity. **Purdue Peg Test**: Fine manual dexterity Finger to Nose Test: Motor co-ordination**. TEMPA**: UL activity limitation. **Functional Independence Measure**: ADL independence.	Significant improvement from baseline; no significant effects of BT over control intervention (p>0.05). No follow-up	1+

TRIALS DESCRIPTION

Three single case series involving 12 participants (Mudie and Matyas 1996, Mudie and Matyas 2000) (Table 2.2) demonstrated improved unilateral task performance with bilateral practice compared to unilateral and bimanually different practice of three tasks. Improvements were maintained at six-month follow-up (Table 2.2). Using similar tasks and study design, Lewis (2004) (Table 2.2) found similar effects in one of six participants. Furthermore, no significant alterations in contralateral or ipsilateral TMS cortical maps were found.

One RCT examined 41 participants with sub-acute stroke (Desrosiers et al 2005). The intervention comprised bilateral symmetrical and asymmetrical tasks, with some unilateral tasks. Control activities also involved unilateral and symmetrical bilateral tasks. No differences were found between groups on a range of standardised UL impairment and activity limitation measures.

2.2.3.1 Discussion of bilateral interventions addressing activities

PARTICIPANTS

Age was fairly homogeneous across the studies ranging from 69.4 to 73.2 years. Time post-stroke was however heterogeneous across the single case studies, ranging from one to 47 months making chronicity effects on outcome difficult to discern. Although one study (Lewis and Byblow 2004) grouped acute and chronic participant data for analysis, the small sample (n=6) precluded clear conclusions. One study (Desrosiers et al. 2005) recruited a homologous sample, including only participants less than eight weeks post-stroke. Heterogeneity of time post-stroke may therefore affect the diversity in findings across BIA studies suggesting that more research is required to determine optimal timing for such interventions.

Initial motor impairment may influence UL recovery (Katrak et al. 1998; Feys et al. 2000a). Mudie and Matyas (1996, 2000) provided no initial impairment measure. Descriptive statements suggested that, at baseline participants could perform UL movements but not functional tasks, whereas in the other case series (Lewis and Byblow 2004) initial motor impairment scores ranged from mild to severe. Conversely, in the RCT (Desrosiers et al. 2005) *all* participants demonstrated minimal UL function, therefore findings apply to that

homogeneous population. Furthermore, UL performance, stroke side, type and location, co-morbidities and psychosocial factors were equivalent between study groups at baseline. These important covariates, likely to influence training responses, were not addressed in the single case designs and may have influenced outcomes. All studies excluded participants with cognitive deficits and neglect, limiting generalisability of findings. Variations in population characteristics across studies may thus explain their contrasting findings, making conclusions about clinical application of BIA difficult.

DESIGN AND RANDOMISATION

Single case methodology proposes, in line with clinical practice, that individual responses to interventions are important. The individualised approach however makes comparison with other studies *and* generalising findings beyond individual participants difficult. The method does not control for other factors, such as clinical and demographic characteristics or selection bias that may influence outcomes. Single case series findings should therefore be interpreted cautiously as evidence supportive of BIA (Table 2.2).

The RCT design minimises potential bias, accounts for confounding variables, and should provide good internal validity. The RCT (Desrosiers et al. 2005) addressed these factors through concealed random group allocation. Groups were comparable at baseline for time post-stroke, initial severity, socio-demographic and clinical variables. Thus compared to the single case series, potentially confounding variables were controlled.

BLINDING

Assessor blinding avoids unconscious expectations or biases influencing findings (Bowling 2000). All studies reported this.

SAMPLE SIZE

For an RCT it is critical that the study sample is sufficiently large to detect significant intervention effects (Bland 1995). Desrosiers et al. (2005) reported no power calculation, and attrition after randomisation was 19.5% (n=8). It is unclear whether missing data were dealt with. Thus the study was possibly underpowered to detect significant differences (Desrosiers et al. 2005).

RECRUITMENT

To avoid recruitment bias, participants should be randomly recruited from a study population (Bowling 2000). Where this is not possible, a defined population should be screened for

inclusion. Single case series are therefore prone to recruitment bias. Insufficient detail about inclusion criteria was provided to determine selection biases in the BIA single case series (Mudie and Matyas 1996, Mudie and Matyas 2000, Lewis and Byblow 2004). Conversely, only individuals from a cohort of potential participants meeting specified inclusion criteria were recruited to the RCT thereby addressing potential recruitment bias (Desrosiers et al. 2005).

DROPOUTS/ADVERSE EVENTS

A range of clinical reasons were provided to explain dropouts from the RCT (Desrosiers et al. 2005). Other studies did not report drop-outs, and no adverse events were reported.

FOLLOW-UP

Mudie (1996, 2000) reported maintenance of improved movement patterns and increased UL use at six months, but no standardised measure assessed UL use. Further research is clearly required to investigate longstanding effects of BIA on a range of outcomes.

CONCURRENT REHABILITATION

Three single case series (Mudie and Matyas 1996, Mudie and Matyas 2000, Lewis and Byblow 2004) reported, but did not account for, concurrent rehabilitation, which may have been a confounding factor. The RCT (Desrosiers et al. 2005) did not report rehabilitation status therefore its impact as a potential source of bias is unclear.

COMPARISONS

In each single case series, BIA was compared to unilateral or bimanually different practice. In contrast, experimental activities in the RCT included bilaterally identical, bimanually different, and some unilateral tasks. The control group undertook conventional OT, including bilateral activities which were poorly described. The independent variable appeared to be structured motor learning, not bilateral compared to UT, making conclusions about effectiveness of bilateral components of training difficult to draw.

INTERVENTIONS

Clearly intervention content may influence effectiveness. Transfer of acquired motor skills to targeted functional tasks occurs where practice task components approximate closely to components and environmental conditions of targeted tasks, a phenomenon described as training specificity (Schmidt and Wrisberg 2004). Thus, effectiveness of BT may depend on whether practice tasks reflect requirements of targeted tasks. Another consideration is whether BT effects transfer to unilateral performance, since most functional tasks involve

unilateral or bimanually different UL performance, rather than bilaterally identical performance. The BIA studies were examined to address these considerations.

The single case series (Mudie and Matyas 1996, Mudie and Matyas 2000, Lewis and Byblow 2004) used three tasks commonly found difficult by stroke participants: block placement on a shelf; simulated drinking and peg targeting to a shelf arranged at shoulder height. Lewis and Byblow (2004) broadened those activities to include peg and cup inversion and transfer of containers from one box to another. Selection of simple tasks easily performed unilaterally or bilaterally meant that effects of bilateral practice on unilateral performance were easily observed. However, as described, training effects are specific to the conditions of the trained tasks. Transfer of effects of BT from the selected tasks to other unilateral functional tasks was not examined, suggesting that task variation should be incorporated to reflect the breadth of skills required for normal UL use. In contrast, ecological validity of the RCT tasks (Desrosiers et al. 2005) was higher, incorporating graded progression and variability. Tasks simulated comprised everyday unilateral UL activities, raising questions about skill transfer from bilateral practice to unilateral performance, given that there was no impact of the intervention compared to the control intervention.

In terms of dose, intervention duration ranged between four and eight weeks. All BIA trials involved 4 or 5 days training weekly. Individual sessions varied comprising 11 (Lewis and Byblow 2004), or 16 trials per session (Mudie and Matyas 1996, Mudie and Matyas 2000) or 45 minutes daily, a total of 15 hours (Desrosiers et al. 2005). Variation in intervention intensity may have influenced outcomes and it is unclear what constitutes an effective therapy dose. More research is clearly required to identify optimal training characteristics, duration and dose-response relationship of BIA.

OUTCOMES: CLINICAL RELEVANCE, VALIDITY AND RELIABILITY

Activity Outcomes

Desrosiers (2005) used several standardised impairment and UL activity limitation outcomes (Table 2.2), providing a more complete picture of UL outcomes than other studies. Notwithstanding the mixed unilateral and bilateral intervention characteristics, the end-point assessment and relatively crude clinical measures may have missed subtle kinematic effect demonstrated by Mudie (1996, 2000). The differences in outcomes on the measures challenge the level, nature and selection of therapy outcome measures and ecological validity of kinematic measures and raise questions about what measures are clinically important.

Impairment Outcomes

The case series (Mudie and Matyas 1996, Mudie and Matyas 2000, Lewis and Byblow 2004) examined UL movement impairment using subjectively rated observations; therefore measurement validity for impairment may be challenged. Videotaped task performance was rated using ordinal scales based on photogoniometry and visual observation (Mudie and Matyas 1996, Mudie and Matyas 2000). Scoring methods were piloted (Bernhardt et al. 1998) and high inter-rater reliability reported. Although face validity for comparison to normal performance is clear; criterion validity is unclear compared to clinically relevant activity or impairment measures. Similarly, Lewis (2004) subjectively rated movement qualities (Table2.2) compared to unaffected UL movement using a visual analogue scale. Reliability and validity of that scale were not reported thus psychometric robustness of the tool is unclear, which may explain contrasting study outcomes compared to Mudie (1996, 2000).

Lewis (2004) also examined motor impairment using the Fugl Meyer Test (a motor performance test with high reliability and validity), which supported their kinematic findings (Table 2.2), however Mudie (1996, 2000) included no standardised motor performance measure. The relationship between kinematic performance and impairment and activity measures and BT is therefore unclear. Further investigation of effects of BIA on a range of UL outcomes is necessary to determine its effectiveness.

Activity-induced neuroplastic changes may occur with UL rehabilitation (Liepert 2006) and assessment of these changes may provide information about how behavioural interventions work at neural level. One study (Lewis and Byblow 2004) examined neurophysiological outcomes (Table 2.2). Only three participants could complete the TMS measures, and findings were inconclusive. Two participants demonstrated enlarged cortical maps, suggesting increased excitation whilst one demonstrated a reduced cortical map suggesting reduced excitation. From that study, the physiological effects of BIA are unclear. Clearly more study of neurophysiological effects of BIA is required.

RESULTS

The primary outcome of interest of this review was UL activity limitation (Page 3). The only study to examine activity limitation found no effects (Desrosiers et al. 2005). The mixed bilateral *and* unilateral nature of the experimental activities provided little information about BIA, however. This study also found no effect on ADL and instrumental activities of daily living (IADL).

Impairment was another relevant outcome to this review. The RCT again demonstrated no effect on motor impairment and UL strength (Desrosiers et al 2005). Significantly improved movement patterns were demonstrated in two case series studies (Mudie and Matyas 1996, Mudie and Matyas 2000) immediately following introduction of BIA that were retained at six months. Contrastingly, Lewis (2004) found no effects of BIA on movement patterns (Table 2.2); however differences in measurement method compared to Mudie (1996, 2000) may explain contrasting findings. Additionally, Lewis (2004) found neither conclusive neurophysiological effects of BIA using TMS, nor improvements in motor impairment (Table 2.2), supporting the study's kinematic findings.

LEVELS OF EVIDENCE

Evidence levels determined by SIGN grading for the single case series was low (Table 2.2) reflecting methodological limitations of the eligible study designs. The more robust RCT suggests that BIA is no more effective for UL recovery than a control intervention. The mixed bilateral and unilateral intervention and control activities mean that conclusion regarding *exclusively* bilateral compared to unilateral task training still requires to be conducted.

2.2.3.2 Summary

Limited evidence from two single case series studies suggests that BIA may improve UL movement patterns in participants with mainly chronic stroke who demonstrate moderate impairment severity. This evidence is not conclusive since contradictory findings were demonstrated in a third single case series. The only RCT found no difference between BIA and conventional therapy on UL activity and limitation outcomes and ADL and IADL, but the intervention and control groups mixed bilateral and unilateral activities which may have influenced outcomes. Evidence about effectiveness of bilateral training of activities or functionally-related tasks, therefore is unclear. Interventions in the single case series were described in detail, however like many rehabilitation trials, the RCT intervention was poorly described. More detail of tasks and task progression should be provided to facilitate replication.

One study measured ADL independence (Desrosiers et al. 2005) and none examined clinical or demographic factors that may have influenced outcomes, such as sensory impairment,

handedness or side and site of lesion. Furthermore, psychosocial outcomes such as quality of life (McEwen et al. 2000) were not assessed in any study. Clearly, effects of BIA on activity and participant perceived outcomes should be evaluated more fully.

Before BIA effectiveness can be established, further studies using robust trial design are required. These should determine effects of BIA on UL activity limitation, impairment, ADL and psychosocial factors over time whilst controlling for severity of dysfunction and time post-stroke and investigating effects of demographic and clinical factors on outcome.

Given that UT is the conventional approach in physiotherapy, BT and UT should be directly compared. Upper limb interventions soon after stroke are known to influence immediate and long-term outcomes (Feys et al. 1998, Winstein et al. 2004, Feys et al. 2004). Little is known about effects of BIA in this phase, therefore effects should be examined. Furthermore, whilst limited evidence exists of lasting facilitatory effects of BIA on movement patterns, effects of BIA on other measures of UL impairment and activity over time are unknown and should be determined.

2.2.4 Bilateral interventions addressing movement function (BIMF)

Bilateral interventions involving movement function (BIMF) were defined as movements or movement sequences performed using voluntary movement, but without specific functional goals. These were proximal, distal or whole UL movements and could be component movements of functional tasks. This intervention category was considered separately from BIA since ecological validity of such functions is potentially lower. It was important to evaluate evidence relating to BIMF and if possible, evaluate effects of BIMF on functional UL performance and global disability. BIMF studies are summarised in Table 2.3.

Table 2.3 Summary of studies examining bilateral interventions involving movement function

Study	Design	Participant characteristics	Intervention	Comparison	Outcome measures	Results	SIGN Evidence Level
Whitall (2000)	Single cohort pre/post test design. No blinding.	7 Left hemisphere stroke 7 Right hemisphere stroke 8 Male, 8 Female Age 44-89 yrs 14 - 360 months post-stroke Proximal movement n=14, good distal movement n=3 Dropouts n=2	Bilateral UL training with rhythmic cueing (BATRAC). Push/pull 5 minutesx4 per day x3 per week x 6 weeks	Pre-test, post-test and retention comparison. Retention 2 months after end of intervention	UL Motricity: **Fugl Meyer** UL Functional Ability: **Wolf Motor Function test** Daily use: **Maryland UL Questionnaire (UMAQ). Strength**: isotonic shoulder/ elbow/wrist dynamometry **Range of Movement (ROM)**: standard goniometry.	**Fugl Meyer**; Significant improvements, $p<0.004$) **Wolf**: no significant difference **UMAQ**: significant improvement ($p<0.002$) **Strength**: elbow flex, wrist flexion ($p<0.05$) **ROM**: active shoulder extension, thumb opposition, active and passive wrist flexion ($p<0.05$) Gains retained at 8 week follow-up.	2-
Platz (2001)	RCT Random allocation of participants to bilateral or unilateral practice. No blinding reported.	7 left middle cerebral artery stroke, 7 right middle cerebral artery stroke. Mean age 55.9 years 9 Male, 5 Female. Subacute phase. Almost complete or complete UL recovery. 14 Healthy matched ontrols.	Three training tasks: aiming to target, index finger tapping 30 minutes on 5 consecutive weekdays. Unilateral, bilateral or dual task conditions	Participants to controls; participant performance pre-to post-training; unilateral to bilateral practice	3D measures of spatial accuracy and movement time	**Accuracy:** No effect of training type, or task condition ($p>0.05$). **Movement time**: decreased with training ($p<0.05$), type of training did not influence effects. No significant effect of UT or bilateral training on any outcome ($p<0.05$). Follow-up: None	1-

Table 2.3 (cont) Summary of studies examining bilateral interventions involving movement function

Study	Design	Participant characteristics	Intervention	Comparison	Outcome Measures	Results	SIGN Evidence Level
Stinear (2004)	Single cohort pre-test/post-test design.	6 left hemisphere stroke, 3 right hemisphere stroke Mean age 62, range 48-84 yrs. 7Male, 2Female Time post-stroke: 2-84 months. Range of baseline Fugl Meyer scores at from low to high.	Auto assisted rhythmical wrist flexion/extension. 6x10min/day x 4 weeks. Synchronous or asynchronous pattern.	Two baseline assessments (T1 and T2) 7 days apart, post training. Retention 1 month after end of intervention	Motricity: **Fugl Meyer**: Grip & wrist strength: **Strain gauge** **Cortical Maps**: EMG hand muscles during TMS stimulation	**Fugl Meyer**: significant improvement between baseline tests (p=0.04). Further improvement between T2 and post training (p=0.02). **Strength**: no significant changes. **Cortical Maps**: **Unaffected hemisphere:** No change at baseline (p >0.2). Reduced cortical map T1 to post-training (p=0.04). Significant reduction unaffected cortical maps of participants with greatest Fugl Meyer (p=0.03). **Affected hemisphere**: motor evoked potentials only in 3 participants; no significant change in maps. Participants with acute stroke lost gains at retention whilst chronic stroke retained gains.	2-

Table 2.3 (cont) Summary of studies examining bilateral interventions involving movement function

Study	Design	Participant characteristics	Intervention	Comparison	Outcome Measures	Results	SIGN Evidence Level
McCombe Waller (2004)	Single cohort pre/post test design. No blinding reported.	**Participants:** Side of lesion not given 5 Male, 5Female, age not given. >12 months post-stroke; minimal antigravity shoulder and UL movement; 4 mild, 5 moderate, 1 severe. **Controls**: 10 healthy age and sex matched. 1 dropout	Bilateral BATRAC Push/pull in phase and antiphase 5 minutes x4 per day x 3 per week x 6 weeks	1) Baseline hemiparetic participants vs. healthy controls 2) Pre and post training comparison of hemiplegic participants	Finger co-ordination and timing during bilateral tapping Motricity**: Fugl Meyer** Functional Ability: **Wolf Motor Function test.** Daily use: **Maryland UL Questionnaire (UMAQ)**	1) Only 3 hemiparetic participants could tap with paretic UL. No statistical difference between participants and controls on non-paretic baseline performance 2) Tapping rate and consistency: 1 additional participant could tap post-training, performance declined in one participant. Non-paretic UL performances improved ($p<0.05$). Significant hemiparetic improvements other measures ($p<0.01$) No follow-up.	2-

Table 2.3 (cont) Summary of studies examining bilateral interventions involving movement function

Study	Design	Participant characteristics	Intervention	Comparison	Outcome Measures	Results	SIGN Evidence Level
Luft (2004)	RCT No blinding reported	**Intervention group:** 3 left hemisphere stroke; 6 right hemisphere stroke 7Male, 2Female; Mean age 63.3+/-15.3; years Time post stroke: 75 months. Mean Fugl Meyer scores 29.6+/-3.5. **Control Group:** 4 left hemisphere stroke; 8 right hemisphere stroke 5 Male, 7 Female. Mean age 59.6± 10.5. 45.5 months post stroke. Mean FM scores 28.3+/-2.1	Random allocation to (BATRAC), 5 minutes x 4 per day x 3 per week x 6 weeks *or* dose matched therapeutic exercise	Pre and post training assessments for each group	Brain activation: **fMRI** during elbow movement Motricity: **Fugl Meyer** Functional Ability**: Wolf Motor Function Test** Daily use**: Maryland UL Questionnaire (UMAQ)**	**fMRI: A**ctivation increases with BATRAC: cerebellum, post and precentral gyri (p=0.06), contralesional hemisphere (p=0.009). Increased ipsilesional activation but not significant. Control group: no significant changes. No synkinesis. **Motor performance and function:** significant improvement BATRAC group on Fugl Meyer *only when 3 participants with no improvement removed* (p=0.02). Overall, improvement not statistically different to control (p<0.26). No follow-up.	1-

Table 2.3 (cont) Summary of studies examining bilateral interventions involving movement function

Study	Design	Participant characteristics	Intervention	Comparison	Outcome Measures	Results	SIGN Evidence Level
Mccombe Waller (2005)	Pre and post training Blinded assessor	11 left hemisphere stroke, 11 right hemisphere stroke. 17 Male, 5 Female. Right handed Mean age 61.4. Median 60 months post-stroke; Minimal antigravity movement at shoulder.	(BATRAC), 5 minutesx4 per day x3 per week x 6 weeks, in-phase and antiphase training.	Training responses between right and left hemispheric stroke; pre to post test scores.	Motricity: **Fugl Meyer** ROM**: Goniometry** Strength: **Dynamometry** Functional Ability**: Wolf Motor Function Test** Daily use**: Maryland UL Questionnaire (UMAQ)**	**Change pre to post testing**: Significant improvement left hemisphere stroke all measures except shoulder extension ($p<0.06$). Right hemisphere stroke significant improvement Fugl Meyer ($p<0.01$) and UMAQ ($p<0.03$). **Between group difference in change**: Significant advantage for left group all measures except Fugl Meyer ($p<0.22$) and shoulder extension ($p<0.23$). No follow-up.	1-

DESCRIPTION OF TRIALS

Six BIMF trials were found (Table 2.3). Interventions involved aiming and tapping movements (Platz et al. 2001), patient assisted wrist flexion/extension, bilateral UL training with auditory cueing (BATRAC) (Whitall et al. 2000, McCombe-Waller and Whitall 2004, Luft et al. 2004, McCombe-Waller and Whitall 2005) and auto-assisted bilateral wrist flexion/extension (Stinear and Byblow 2004b).

Platz (2001) compared unilateral to BT of three rapidly executed tasks on movement accuracy and timing in 14 recovered sub-acute participants. No benefit of BT was demonstrated. In a small single group study, Stinear (2004b) tested auto-assisted bilateral wrist flexion/extension in nine sub-acute and chronic stroke participants. Significant motor performance effects were demonstrated immediately following intervention. Reduced contralesional hemispheric cortical maps were also demonstrated in participants with enhanced movement, suggesting decreased corticomotor-neurone excitability (Stinear and Byblow 2004b).

Other studies examined bilateral UL training with auditory cueing (BATRAC) in chronic stroke, finding significant effects on activity limitation, motor impairment, range of movement, strength and daily use (Whitall et al. 2000, McCombe-Waller and Whitall 2004), with one study demonstrating significantly increased contralesional cortical activation patterns (Luft et al. 2004). The meaning of changed cortical activation patterns remains under debate, but changes were associated with improved motor outcomes resulting from BT. Another study demonstrated effects on fine motor control in participants with right compared to left hemispheric lesions (McCombe-Waller and Whitall 2005).

2.2.4.1 Discussion of bilateral interventions involving movement function

PARTICIPANTS

Samples appeared fairly homogeneous in terms of age (mean age 55.9 to 63.3 years) however wide variation existed in chronicity. With the exception of two studies (Platz et al. 2001, Stinear and Byblow 2004b), participants ranged between six months and 12 years post-stroke (Whitall et al. 2000). Platz (2001) examined sub-acute participants, but did not define timescales whilst Stinear (2004b) included three participants two months post-stroke and six participants at six months or more post-stroke. Loss of effects at one month

follow-up existed in acute, but not chronic participants, suggesting time related training responses that varied with chronicity.

Severity ranged from almost full recovery (Platz et al. 2001), to moderately severe impairment (Whitall et al. 2000, Luft et al. 2004, McCombe-Waller and Whitall 2004, McCombe-Waller and Whitall 2005). Another study demonstrated diverse baseline motor scores (Stinear and Byblow 2004b), making conclusions about effects of severity on training responses difficult.

DESIGN AND RANDOMISATION

Study groups should be equivalent on potentially confounding variables (Bowling 1999), or any differences should be described and accounted for. Two studies (Platz 2001, Luft et al. 2004) randomised to intervention and control groups, but provided no details of randomisation methods. Lack of concealment of randomisation may influence outcome (Bowling 1999). Other studies (Whitall et al. 2000, McCombe-Waller and Whitall 2004, Stinear and Byblow 2004b, McCombe-Waller and Whitall 2005), compared pre and post intervention outcomes in single cohorts. Alternative explanations for improvement, such as attention provided by participating, or ongoing rehabilitation, cannot therefore be rejected. Bilateral intervention alone was provided, without comparison to unilateral or other interventions, thus effects of bilateral training components versus intervention participation per se cannot be determined.

BLINDING

Lack of blinding renders studies prone to observer bias. In rehabilitation studies, double blinding is difficult. Only two studies reported even single blinding of assessors (Platz et al. 2001, McCombe-Waller and Whitall 2005) therefore effects of observer bias on outcomes of other studies cannot be discounted.

SAMPLE SIZE

One study (Luft et al. 2004) calculated sample size based on likely between group changes in fMRI activation patterns. Group numbers were small, however (n=9 and n=12) and sample size calculation based on fMRI challenges the power of tests examining motor and functional outcomes.

RECRUITMENT

Details of recruitment were in general scant, making recruitment bias difficult to determine. One study recruited through advertisement, rendering it susceptible to self-selection bias (McCombe-Waller and Whitall 2005).

DROPOUTS/ ADVERSE EVENTS

Two studies reported dropouts during intervention, (Whitall et al. 2000, Luft et al. 2004), but only Luft (2004) compared dropouts to completers to assess whether factors other than chance influenced attrition. No studies reported intention to treat analysis, or indicated how missing data were dealt with, another limitation suggestive of low methodological quality.

FOLLOW-UP

Two studies reported follow-up assessment (Whitall et al. 2000, Stinear and Byblow 2004b), however losses to follow-up and reasons for them, which may influence generalisability of findings, were not reported. Follow-up periods were short, at one month (Stinear and Byblow 2004b) and eight weeks (Whitall et al. 2000) indicating a requirement for longer-term retention testing.

CONCURRENT REHABILITATION

Concurrent therapy may confound findings. In four studies (Whitall et al. 2000, McCombe-Waller and Whitall 2004, Luft et al. 2004, McCombe-Waller and Whitall 2005), conventional rehabilitation had been completed. Other studies did not report rehabilitation status (Stinear and Byblow 2004b, Platz et al. 2001) thus concurrent therapy may have influenced results.

COMPARISONS

Most BIMF studies (Whitall et al. 2000, Stinear and Byblow 2004b, McCombe-Waller and Whitall 2004) compared pre and post treatment outcomes and did not control extraneous variables such as age, severity of impairment, lesion location or handedness that may have influenced findings.

Both RCTs (Platz et al. 2001, Luft et al. 2004) randomised participants to different intervention groups. Platz (2001) compared unilateral to BT of matched duration and intensity, an important design feature since the intervention differed only in respect to practice mode, whilst Luft (2004) compared BATRAC to the same duration of neuro-

developmental therapy. That control intervention, involving spinal and scapular mobilisation, was passive in nature which may have exaggerated between group differences than if a more active intervention focussed on active UL movement was employed.

Exploration of factors that might influence BIMF has been scant. McCombe-Waller (2005) demonstrated a dominant side advantage for 11 right handed participants with left hemispheric stroke participating in BATRAC compared to 11 with right hemispheric stroke, in terms of UL function, range of movement and strength. Like all BIMF studies, the study was small and conclusions therefore limited. Effects of side and site of lesion and hand dominance on BT outcomes may be important but require further investigation with other clinical and demographic factors in larger studies to enhance understanding of the effects of BIMF in clinical populations.

INTERVENTIONS

Intervention activities (Table 2.3) varied in complexity. Platz (2001) trained rapid, fine finger movements with almost fully recovered participants. In contrast, other studies involved simpler movements (Table 2.3). Stinear (2004b) trained wrist flexion/extension using the unaffected hand to assist, and BATRAC studies (Whitall et al. 2000, Luft, McCombe-Waller and Whitall 2004, McCombe-Waller and Whitall 2005) trained push-pull activity with auditory cueing. The rationale for that intervention was to provide spatiotemporal UL control during bilaterally synchronous in- or antiphase movements, enhancing interlimb coupling using limited degrees of freedom of movement.

Activities of daily living involve numerous degrees of freedom, whilst these studies trained limited degrees of freedom, raising the question of how successfully training effects transfer to ADL performance. All studies except one (Platz et al. 2001) which demonstrated no effect of BT on the kinematics of performance, demonstrated transfer of training effects beyond trained tasks. Effects were demonstrated on the Fugl Meyer test, a measure of motor impairment (Whitall et al. 2000, Stinear and Byblow 2004b, Luft et al. 2004, McCombe-Waller and Whitall 2004) whilst three studies demonstrated improvements on activity measures (Whitall et al. 2000, McCombe-Waller and Whitall 2004, McCombe Waller and Whitall 2005), suggesting that training effects may indeed have transferred to more everyday activities.

Treatment dose ranged from 2.5 to 20 hours in total and was delivered between three and five times per week (Table 2.3.). Interestingly, the study that delivered most training (Stinear and Byblow 2004b), failed to demonstrate differences in motor performances in some participants. The passive nature of that intervention compared to more active interventions in other studies may explain differences. Determination of optimum training characteristics for BT is clearly required.

OUTCOMES: CLINICAL RELEVANCE, VALIDITY AND RELIABILITY

Activity Outcomes

UL activity, the primary outcome of interest of this review, was examined in several studies using the timed Wolf Motor Function Test (Wolf et al. 2001) and a questionnaire of UL use, the University of Maryland UL Questionnaire which included assessment of everyday unilateral and bilateral UL use (Whitall et al. 2000, Luft et al. 2004, McCombe-Waller and Whitall 2004, McCombe-Waller and Whitall 2005) (Table 1.3). Daily UL use reflects ecological validity of interventions for everyday functional use however the selected questionnaire has been shown to demonstrate poor concurrent validity with other UL measures (Bovend'Eerdt et al. 2004).

Impairment Outcomes

One study (Platz et al. 2001) measured movement time and targeting accuracy; another included computerised finger tapping rate and timing (McCombe-Waller and Whitall 2004) as outcomes. Although significant training effects were demonstrated providing information about motor control, interlimb coupling and co-ordination, clinical and functional relevance of kinematic measures of performance remains unclear. Measurement validity and reliability were not reported.

More clinically relevant impairment outcomes were strength and range of movement (Stinear and Byblow 2004b, Whitall et al. 2000, McCombe-Waller and Whitall 2004, Luft et al. 2004). Measurement reliability was not provided, making measurement error difficult to judge. All studies except one (Platz et al. 2001) used the Fugl Meyer test, which primarily examines control of joint movements. This test has been extensively validated (Platz et al. 2005a) and its use across BIMF studies means study findings are comparable.

No study reported sensory impairment, an important factor which may influence motor outcome (Broeks et al. 1999). Effects on global disability and psychosocial effects such as quality of life, well-being or mood, outcomes relevant to participants that may be influenced by UL dysfunction (McEwen et al. 2000) were also not examined.

TMS (Stinear and Byblow 2004b) and fMRI (Luft et al. 2004) were other measures used in two studies to examine effects of training on neurological activation patterns. Such measures support clinical findings and provide physiological principles for intervention. One limitation of TMS is that it appears difficult to elicit motor evoked potentials from many stroke participants, limiting generalisability of findings to those in whom evoked responses are possible (Stinear and Byblow 2004b). A caveat is that although training-induced neuroplastic changes may be demonstrated, the meaning and importance of these changes and mechanisms underlying them remain under debate (Rossini et al. 2003).

RESULTS

Study results are summarised in Table 2.3.

Motor performance improved significantly from baseline in the single group studies, which were conducted with moderately impaired participants (Stinear and Byblow 2004b, Whitall et al. 2000, McCombe-Waller and Whitall 2004, McCombe-Waller and Whitall 2005). The BATRAC studies also report significantly improved UL activity limitation and daily use, strength and range of movement. Effectiveness of the bilateral characteristic of the intervention cannot be conclusively determined however, since no study compared BT to UT (UT) or another intervention.

One RCT examined BATRAC in participants with moderate to severe impairment (Luft et al. 2004) (Table 2.3) and found significant improvements in motor performance compared to controls. Critically, the difference was significant only when three participants of nine who had not improved, were removed from analysis. This method is questionable and provides a highly selective perspective of effectiveness of BATRAC for motor impairment. Since no significant training effects were found for strength, activity or daily use, with or without those who had improved, effectiveness of BATRAC can be seriously challenged. Given that this was the only RCT to investigate BATRAC, evidence supporting this intervention is rather weak.

Investigating another aspect of motor impairment, Platz (2001) found that UT of rapid, fine motor and aiming tasks was more effective than BT for movement time and movement accuracy. McCombe-Waller (2004) found inconsistent results for tapping rate, consistency and bilateral in-phase and anti-phase finger co-ordination following BATRAC in three participants with chronic stroke with moderate impairment, although motor performance and activity limitation measures significantly improved. The small sample precludes conclusions in relation to motor control, impairment or activity. This study also included comparison of baseline tapping and interlimb co-ordination to matched controls, but because only three participants could perform the test with the paretic UL, conclusions were limited. Study aims were somewhat unclear, and together with the study by Platz (2001) provide little convincing evidence in support of BIMF training.

Two studies investigated cortical activity before and after training. Using TMS with electromyography (EMG) Stinear (Stinear and Byblow 2004b) demonstrated significantly reduced unaffected hemisphere cortical map volume in participants with motor improvement, suggesting normalisation of hemispheric excitability, but found no corresponding increase in affected hemisphere map volume. Motor evoked potentials were only elicited in the hemiplegic UL of three of nine participants however. Conversely, using fMRI, Luft (2004) demonstrated increased unaffected hemisphere motor area activity in participants undertaking BATRAC training, compared to controls, suggesting increased areas of activity although no significant functional or motor improvements were demonstrated (see above). Interpretation must be cautious regarding BT group effects given the apparently passive nature of control activities in that study. Differing test methods and small samples across studies may explain the equivocal findings. Effects of BIMF on cortical activation and interhemispheric excitation remain unclear, and further work is required to determine neurological mechanisms for BIMF.

Few studies conducted follow-up. One study (Whitall et al. 2000) demonstrated retained performance at eight weeks across selected impairment and functional measures, suggesting enduring improvements in motor performance. Stinear (2004b) assessed performance one month after intervention, but only with participants who had improved with intervention. Given that some participants improved during a non-intervention baseline phase, important data may have been missed by not testing all at follow-up. Clearly more work is necessary to ascertain the duration of effects following BIMF.

LEVELS OF EVIDENCE FOR BIMF TRIALS

Study quality was low (Table 2.3). Only two low quality RCTs involving 35 participants examined BIMF. One demonstrated no effect of BIMF on impairment or activity outcomes (Platz et al. 2001), the other only did so - but only when participants were removed from the analysis (Luft et al. 2004), a procedure that seriously challenges the validity of the results. Other studies were pretest/post-test design without control, where biasing factors were not controlled; therefore evidence levels assigned were low.

2.2.4.2 Summary

Evidence for BIMF for UL recovery in stroke is limited and contradictory. Studies suffer from considerable methodological weaknesses that preclude definitive conclusions about effectiveness. Issues such as lack of comparison groups and, where they existed, inadequate comparison interventions, suggest that evidence supporting the intervention is weak. Although single group studies demonstrated post-treatment effects on UL impairment and activity limitation outcomes in chronic stroke, lack of control groups mean that conclusions about bilateral training components cannot be determined. The two RCTs (Platz et al. 2001, Luft et al. 2004) demonstrated no effect on functional outcomes and motor performance.

Responses to BIMF at different post-stroke stages remain unclear. Two studies examined acute/ subacute participants, one demonstrated no effect in well-recovered participants (Platz et al. 2001); the other, which examined only two acute participants (Stinear and Byblow 2004b), suggested that responses may differ from more chronic participants in terms of retention of effects. Although research in the chronic stage diminishes spontaneous recovery as a confounding variable, responses to BT in the acute stage should also be examined. Most neuroplastic changes as well as physiotherapy intervention occurs then, and recent studies show that intervention in the acute stage may influence later outcomes (Feys et al. 2004).

Effectiveness of BIMF with participants of differing levels of severity of UL dysfunction is unclear. No benefit of bilateral compared to UT existed with well-recovered participants, whilst studies involving moderate to severely affected participants must be regarded cautiously because of methodological limitations. A properly conducted RCT to examine how participants with differing severity respond to BT is required.

Across studies, BIMF activities were simple, repetitive pre-functional movements. Common variations in intervention included duration and intensity of intervention and distal or whole UL movement. These require further investigation if optimal training characteristics are to be established.

Outcomes ranged from kinematics to clinical impairment measures, motor and functional performance and everyday use. Some measures, such as tapping rate and movement profiles represented limited relevance to functional UL performance. No study examined effects of sensory impairment on outcome, an important potential covariate of recovery (Wade 1989). Effects of training on global disability measures such as ADL and IADL and on broader concepts of health-related well being or mood were again not examined. Importantly, one study identified that participants with left hemisphere damage recovered better than those with right hemisphere damage, a finding that requires further investigation to determine clinical applicability of BT. Two studies examined follow-up but follow-up periods were short-term. The impact of BIMF on a broad range of short and longer term outcomes over requires to be investigated fully.

2.2.5 Bilateral interventions involving assistive technologies (BIAT)

Bilateral interventions involving assistive technologies were defined as any assistive or rehabilitative device involving artificial augmentation of voluntary movement or task performance during BT. Although BIAT interventions are not yet routine in physiotherapy practice in stroke rehabilitation, it was considered important to examine evidence relating to BIAT, which might inform the physiotherapy research questions being developed for this thesis. Studies are summarised in Table 2.4.

Table 2.4 Summary of studies examining bilateral interventions involving assistive technology

Study	Design	Participant characteristics	Intervention	Comparison	Outcome Measures	Results	SIGN Level
Caraugh (2002)	RCT No details of randomis-ation No blinding. No details of dropouts.	13 left hemisphere stroke; 12 right hemisphere stroke. 4 female, 21 male. Mean age 63.7 years. >1year post stroke; mean time = 39.1 months. Mild to moderate paresis. No other rehab	**Unilateral Group** (n=10): EMG triggered functional electrical stimulation wrist/finger extension. **Bilateral Group** (n=10): FES plus simultaneous movement non-paretic UL. Control Group (n=5): wrist/finger extension no augmented stimulation. Training 3x30min per day x 4 days x 2 weeks	Comparison between groups and pre and post test unilateral performances.	Dexterity: **Box and Block** Reaction Time **Sustained muscle contraction** wrist/finger extensors	**Functional manual dexterity**: significant effect of BT ($p<0.04$) over other conditions. Reaction Time: BT significantly faster ($p<0.01$). **Sustained Muscle Contraction**: Significant improvement BT ($p<0.05$) No follow-up.	1-
Lum (2002)	RCT	**Robot:** 9 right hemisphere stroke, 4 left hemisphere stroke. 12 Male 1Female **Control:** 10 right hemisphere stroke 4 left hemisphere stroke. 8 Male, 6 Female Mean age=64.6 years. Mean 39.5 months post-stroke. Moderate impairment, continued usual rehab.	**Robotic Group**: Targeted reaching movements - bimanual, passive, active constrained. **Control Group**: conventional therapy and 5 minutes robotic 1 hour x 24 sessions over 2 months.	Between group differences in scores at pre and post-test and follow-up.	Motor performance: **Fugl Meyer** ADL: **Barthel**, **Functional Independence Measure** Strength: **torque sensors** Reach**: hand position and orientation**	**Motor and sensory performance**: Proximal tests: significant advantage robot group 1 and 2 months not maintained at 6 months. Not significant for distal test, Barthel Index. Robot group significant advantage in FIM at 6 months. **Strength**: Robot group significantly greater improvements at 2 months. **Reach**: data only available for 19 subjects. Robot group significantly greater improvements at 2 months ($p<0.01$). 6-month follow-up: gains for robot group in function lost at 6 months. Other measures not reported.	1++

Table 2.4 (cont) Summary of studies examining bilateral interventions involving assistive technology

Study	Design	Participant Characteristics	Intervention	Comparison	Outcome Measures	Results	SIGN Level
Cauraugh (2003a)	RCT 5 second and 10 second functional electrical stimulation, 2 (FES) groups and control group.	Volunteers 11 left hemisphere stroke; 15 right hemisphere stroke 4 Female, 21Male Mean age 66.4 years Mean 2.8 years post-stroke Mild to moderate paresis. No other rehabilitation.	5 Second Stimulation Group: EMG triggered FES stimulation paretic wrist/finger extension and simultaneous movement of non-paretic UL. 10 second stimulation group: EMG triggered 10 second FES stimulation paretic wrist/finger extension and simultaneous movement of non-paretic UL. Control group (n=6): voluntary bilateral wrist flexion/extension 3x30min x 4 days x 2 weeks.	Test session x stimulation duration	Dexterity: **Box and Block** **Reaction Time** & Reaction times **Sustained muscle contraction:** Force and EMG Signals wrist/finger extensors	**Dexterity**: Significant improvement for 10s stimulation group between pre and post-test ($p<0.02$) compared to the other groups. **Reaction Times**: Stimulation groups improved compared to control group ($p<0.05$). No differential effect of stimulation group. **Sustained Muscle Contraction:** Both stimulation groups improved compared to no stimulation group. No differential effect of stimulation group. No follow-up.	1-

Table 2.4 (cont) Summary of studies examining bilateral interventions involving assistive technology

Study	Design	Participant Characteristics	Intervention	Comparison	Outcome Measures	Results	SIGN Level
Cauraugh (2003 b)	RCT Unilateral and Bilateral groups	Volunteers. 11 left hemisphere stroke; 9 right hemisphere stroke. 4 Female, 16 Male Mean age 66.4 years. Mean 33.9 months. post-stroke. Mild to moderate paresis. No other rehab.	Unilateral Group (n=10): EMG triggered FES stimulation of paretic wrist/finger extension. Bilateral Group (n=10): EMG triggered FES stimulation of paretic wrist/finger extension and simultaneous movement of non-paretic UL. Both groups 3x30min per day for 4 days over 2 weeks.	EMG activation threshold levels across trials and between training protocols.	**EMG Activation** thresholds during training trials	**Higher EMG thresholds** for bilateral group than unilateral group ($p<0.03$). **Higher activation thresholds** last 6 trials compared to first six trials ($p<0.001$) indicating increased voluntary activity following training. No follow-up.	1-

Table 2.4. (Cont) Summary of studies examining bilateral interventions involving assistive technology

Study	Design	Participant Characteristics	Intervention	Comparison	Outcome Measures	Results	SIGN Level
Hesse (2003)	Cohort study. Single group pre and post training design.	5 left hemisphere stroke; 7 right hemisphere stroke; 8 Male 4 Female, Mean age 63.6 years. Mean 9.3 months post-stroke Proximal movement only. Continued rehabilitation.	15 minutes robotic UL training daily x 3 weeks. Maximum of 250 repetitions of wrist flex/ext and pro/supination. Passive/ active with non-paretic UL assistance/ active with paretic UL activity also 45 minutes rehabilitation daily over 4 weeks.	Pre training compared to post training	Motor control: **Rivermead Motor Assessment** UL section Tone: **Modified Ashworth** Patient impressions: **Visual Analogue Scale** Blinded raters	**Motor control:** 7 participants no change, no overall improvement RMA. **Tone:** Significantly reduced at wrist and fingers. Patient impressions: Tone improved, no functional gains . **3 month follow-up**: **RMA:** 3 participants maintained improvement. **Tone**: declined to pre intervention level.	2-
Lum (2004)	PreTest/ Post-test no controls	9 right hemisphere stroke, 4 left hemisphere stroke; 12 Male, 1Female Mean age 63.2 years. Mean post-stroke time 30.2 months. Outpatient therapy completed; continued with any community therapies.	Robot targeted reaching tabletop and shoulder level. Passive and active constrained mode 50 minutes robot practice 5 min tone normalising and limb positioning before and after 1 hourx24 sessions x 2 months. 8 movement patterns practised in passive mode x3 and in active mode 2-6 times per session.	Across subject comparison of averaged weekly performances for kinematic data and force data. Between first and last two sessions for EMG. Low and high level participants	**Interaction forces Kinematics**, force directional error, **EMG** during active constrained training mode. Motor Performance: **Fugl Meyer**	Increase in **work** output ($p<0.05$) active not passive constrained mode. No correlation between work improvements and **Fugl Meyer.** Sub group of low level participants increased extent of **reach** in 5/8 patterns ($p<0.02$); high level participants increased reaching speed ($p<0.05$). **Force directional error** reduced $p<0.05$. **EMG** increased amplitude shoulder agonists ($p<0.05$) not in tabletop activities. No follow-up.	2-

Table 2.4 (cont) Summary of studies examining bilateral interventions involving assistive technology

Study	Design	Participant Characteristics	Intervention	Comparison	Outcome measures	Results	SIGN Level
Cauraugh (2005)	RCT Unilateral Bilateral Control groups	Stroke Participants: 6 left hemisphere stroke; 15 right hemisphere stroke 10 Female; 11 Male. Mean age 66.4 years. Mean 4.15 years post-stroke. Mild to moderate paresis. No other rehab. Healthy Controls: 3 Female, 2 Male, mean age 54.5 years.	Unilateral Group (n=10): EMG triggered FES stimulation of paretic wrist/finger extension. Bilateral Group (n=11): EMG triggered FES stimulation of paretic wrist/finger extension and simultaneous movement of non-paretic UL. 3x30min per x 4 days over 2 weeks	Pre and post intervention within group assessments. Between group baseline comparisons.	**Hand Kinematics** during aiming task measured by electromagnetic data acquisition system	**Reaction time**: No reliable training effect. **Movement time**: significant improvement bilateral group but not other groups pre to post test (0<0.01). **Peak limb Velocity**: bilateral group improved only during bilateral movement (p<0.04). **Deceleration time**: shorter deceleration time during bilateral movement (p<0.03) Concluded that training of distal movement transferred to proximal joint control. No follow-up	1-

Table 2.4 (cont) Summary of studies examining bilateral interventions involving assistive technology

Study	Design	Participant Characteristics	Intervention	Comparison	Outcome measures	Results	SIGN Level
Hesse (2005)	RCT Blinded outcome assessment	Computerised UL trainer . 8 right hemisphere stroke, 14 left hemisphere stroke. 10 Male 12 Female.. Mean Age 65.4 years Mean 5.3 weeks post stroke. Electrical stimulation group: 11 right hemisphere stroke 11 left hemisphere stroke 10 Male 12 Female. Mean age 64 years. All severely affected, continued usual rehab.	Computerised UL trainer: Mirror training alternate wrist flex/ext and pro/supination with robotic device. Three modes: Passive/ active with non-paretic UL assistance/ active with resisted paretic UL activity 200 reps each activity per session. Electrical Stimulation Group: EMG triggered FES of wrist extensors, 60-80 reps per session 20 minutes daily x 6 weeks Usual therapy continued.	Baseline group comparison, post intervention and 3 month follow-up	Motor performance: **Fugl Meyer Test** Muscle Power: **MRC Scale** Muscle tone: **Modified Ashworth scale**	**Motor performance** Significantly greater improvement UL trainer group ($p<0.0001$). **Muscle Power:** Significant improvement UL trainer group ($p<0.001$). **Muscle tone**: no difference between groups. Follow-up: gains in FM and power retained.	1++

DESCRIPTION OF TRIALS

Four studies applied electromyography threshold triggered functional electrical stimulation (EFES) to wrist and finger extensors (Cauraugh and Kim 2002, Cauraugh and Kim 2003a, Cauraugh and Kim 2003b, Cauraugh et al. 2005) (Table 2.4). EFES was triggered by electromyographic (EMG) thresholds. One study (Cauraugh and Kim 2002) demonstrated significantly better manual dexterity, reaction time and sustained muscle contraction with combined paretic wrist EFES and voluntary non-paretic wrist extension compared to unilateral stimulation or movement without stimulation (Table 2.4). A follow-up study (Cauraugh and Kim 2003a) demonstrated significantly better dexterity with 10 second compared to five second bilateral EFES stimuli compared to no stimulation. In a third investigation, higher muscle activation thresholds in bilateral compared to unilateral conditions were demonstrated after training (Cauraugh and Kim 2003b), suggesting that bilateral movement coupled with stimulation leads to improved voluntarily wrist extensor activation. A final study (Cauraugh et al. 2005) demonstrated bilateral advantages for transfer of effects from stimulated distal muscles to proximal muscles.

Four studies examined bilateral robotic therapy (Table 2.4.). Robotic devices trained either individual joint movements (Hesse et al. 2003, Hesse et al. 2005), or targeted reaching (Lum et al. 2002, Lum et al. 2004). No significant improvement in motor performance following bilateral wrist flexion/extension and forearm pro/supination was demonstrated using one robotic trainer (Hesse et al. 2003). An RCT involving the same intervention (Hesse et al. 2005) however demonstrated improved motor performance and strength with bilateral robotic training compared to unilateral wrist extensor FES in early rehabilitation. In that study however the robotic group received a much greater treatment dose than the FES group however which probably influenced results. Another RCT demonstrated significantly improved motor performance, strength and reach distance with robotic training compared to conventional therapy (Lum et al. 2002). Fewer force production errors, work, directional error, and greater shoulder muscle activation were reported in severely affected participants following the intervention (Lum et al. 2004).

2.2.5.1 Discussion of bilateral interventions involving assistive technologies (BIAT)

PARTICIPANTS

The BIAT trials were conducted with participants aged between 63 and 66 years with mild to moderate impairment (Table 2.4). One robotic training study demonstrated effects on motor impairment measures in participants 5 weeks post-stroke (Hesse et al. 2005); otherwise participants were more than one year post-stroke.

Severity is difficult to judge because of diversity in assessment methods. EFES studies examined moderately affected participants with some active movement to trigger electrical stimulation. Other studies examined severely affected participants. Given the assistive nature of robotic therapy, participants were more severely affected with limited active movement. The diverse interventions and inclusion criteria mean that it is not possible to be clear about effectiveness of the interventions for different patient populations.

DESIGN AND RANDOMISATION

Two studies (Lum et al. 2004, Hesse et al. 2003) used a single group design, all others were RCTs. All but one RCT included concealed random allocation (Lum et al. 2002). In that study, details of randomisation were not provided, making allocation bias a possibility.

BLINDING

Blinding of therapists treating patients is very difficult in this type of trial; however raters undertaking assessments can be blinded. One study reported blinded outcome assessment (Lum et al. 2002) whilst in another (Hesse et al. 2005) unblinded therapists who treated the participants conducted assessments which may have led to effect bias because of their knowledge of allocation to the intervention groups. Other studies (Cauraugh and Kim 2002, Cauraugh and Kim 2003a, Cauraugh and Kim 2003b, Cauraugh et al. 2005) did not report blinding.

SAMPLE SIZE

One study (Hesse et al. 2005) reported a sample size calculation. Results of other studies should be regarded cautiously therefore, since non-significant findings may reflect inadequate power to detect differences.

RECRUITMENT

One study provided recruitment details (Hesse et al. 2005); others provided no screening or recruitment details therefore recruitment bias may be a confounding factor. The EFES studies recruited volunteers, without describing recruitment methods, another potential source of bias.

DROPOUTS/ADVERSE EVENTS

One study reported dropouts, intention to treat analysis and absence of adverse events (Hesse et al. 2005). Other studies reported neither of these important methodological issues, and loss to follow-up may have influenced results. Only one study (Hesse et al. 2003) reported patient impressions of the training, therefore acceptability of the other interventions in unknown.

FOLLOW UP

Three trials conducted follow up assessments (Lum et al. 2002, Hesse et al. 2003, Hesse et al. 2005) at three and six months after intervention, which can be considered adequate time to assess retention of effects. EFES studies did not conduct follow-up assessment. Effects of FES are known to disappear at follow-up (Powell et al. 1999) therefore absence of follow-up assessment represents a considerable limitation.

CONCURRENT REHABILITATION

Participants in three studies concurrently received other rehabilitation (Hesse et al. 2003, Lum et al. 2004, Hesse et al. 2005). One study reported details of usual therapy, which comprised 45 minutes of neurodevelopmental occupational and physiotherapy per day (Hesse et al. 2003). Only one trial (Hesse et al. 2005) randomised participants to intervention or control therapy to control for usual therapy as a confounding effect.

COMPARISONS

The EFES studies compared groups differing only by key independent variables of no EFES and EFES and bilateral or unilateral practice, thus directly investigating bilateral characteristics of training, whilst Hesse compared bilateral robotic arm training to EFES (Hesse et al. 2005). Conversely Lum (2002) did not discriminate the bilateral component, combining bilateral, unilateral, passive and resisted modes of robotic practice compared to usual therapy. Other studies compared pre to post training scores without controlling for confounding variables.

INTERVENTIONS

Due to severity of participant impairment, and restrictions imposed by devices, the number of degrees of freedom involved in the movements practised in these interventions were low. Consequently, trained movements were typically neither functional nor goal orientated in nature, focusing on single joint movement. One intervention (Lum et al. 2002, Lum et al. 2004) involved goal attainment with targeted reaching which, although more functionally relevant than activities in other BIAT studies, range and choice of movement was limited by machine constraints. Furthermore, the uniform nature of those movements precludes development of problem-solving motor strategies necessary for everyday functional tasks, raising questions about potential transfer of skill acquisition to everyday UL use.

Cortical imaging suggests that motor learning requires active participation to elicit neuroplastic changes (Liepert 2006). All BIAT interventions involved some active participation. EFES intervention (Cauraugh and Kim 2002, Cauraugh and Kim 2003a, Cauraugh and Kim 2003b, Cauraugh et al. 2005) involved augmented *voluntary* movement, whilst robotic training involved passive *and* active training (Lum et al. 2002, Lum et al. 2004, Hesse et al. 2003, Hesse et al. 2005). The robotic studies did not describe ratios of active to passive activity making differentiation between influences of passive and active training difficult. Furthermore, whilst Hesse (2005) compared exclusively bilateral assisted activity to unilateral control activities, Lum (2002, 2004) included unilateral *and* bilateral activity, making conclusions about the specific contribution of *bilateral* robotic therapy difficult.

Training dose ranged from 3.75 to 24 hours for robotic training, and 24 hours across EFES studies, distributed across two weeks to two months (Table 2.4). The study with lowest training dose (Hesse et al. 2003) demonstrated no effect on motor performance, suggesting a possible link between dose and outcome. Optimal training doses are unclear, however higher doses of intervention may be most effective, but require further investigation.

OUTCOMES: CLINICAL RELEVANCE, VALIDITY AND RELIABILITY

Impairment Outcomes

Outcomes included reaction time; movement and muscle activation profiles; and sustained muscle contraction, but reliability and validity were not reported. Effects on several outcomes were measured in milliseconds (Lum et al. 2002, Cauraugh and Kim 2002, Cauraugh and Kim 2003a), a scale of questionable clinical significance. Strength, examined in several studies, (Lum et al. 2002, Hesse et al. 2005) is of greater functional and clinical relevance (Canning et al. 2004) and may be a more valid clinical outcome.

The Fugl Meyer test of motor impairment, which has established reliability and validity (Poole and Whitney 2001, Croarkin et al. 2004, Platz et al. 2005a) was used in two studies (Lum et al. 2002, Hesse et al. 2005) but it primarily measures movement, not UL activity limitation, therefore conclusions about intervention effects on UL function is limited. The Rivermead Motor Assessment, a valid, reliable impairment-orientated measure of greater clinical relevance was used in another study (Hesse et al. 2003).

Activity Outcomes

The only activity measure used was the box and block test (BBT) (Cauraugh and Kim 2002, Cauraugh and Kim 2003a). The BBT measures timed manual dexterity (Mathiowetz et al. 1985) is reliable and demonstrates concurrent validity with other activity measures (Platz, et al. 2005b). However the BBT is a narrow measure of UL functional activity involving cube placement, and of limited ecological validity therefore clinical conclusions about BIAT efficacy for activity limitation should be drawn cautiously.

RESULTS

Results of BIAT studies are summarised in Table 2.4.

Two RCTs testing EFES (Cauraugh and Kim 2002, Cauraugh and Kim 2003a) demonstrated improvement in the BBT measure, a dexterity activity limitation measure. The study design was high quality therefore findings can be regarded as fairly robust suggesting that impairment orientated training may improve activity limitation outcomes.

Two RCTs (Lum et al. 2002, Hesse et al. 2005,) demonstrated significantly improved motor impairment on the FM test with robotic training. Effective elements of those interventions

are unclear however may result from strength training in the two robotic group compared to controls. Training dose may also have influenced findings. Whilst well matched in the EFES studies, participants in the robotic group in one study had 24,000 practice trials compared to 2400 in the EFES control group (Hesse et al. 2005). This is less easy to judge in the other RCT (Lum et al. 2002), where time per session and not repetitions were matched. Clearly results should be regarded cautiously until further work has established the optimum dose of training.

The EFES studies suggest that bilateral wrist extension accompanied by EFES is effective for kinematic parameters, such as reaction time and sustained muscle contraction compared to unilateral stimulation (Cauraugh and Kim 2002, Cauraugh and Kim 2003a, Cauraugh and Kim 2003b). Small sample sizes and statistical methods challenge robustness of findings. Similarly, Lum (2002) demonstrated improved reach distance using robotic training. Given that training targeted proximal movements, outcomes are unsurprising. That experimental intervention involved unilateral and bilateral activity, thus conclusions relating to *bilateral training* cannot be drawn.

Muscle strength was influenced by robotic training (Hesse et al. 2005, Lum et al. 2002) probably reflecting resistance applied during training. Results should be regarded cautiously, since in one study (Hesse et al. 2005) the intervention group demonstrated higher baseline ADL performance. Results also suggest that bilateral EFES influences sustained muscle contraction (Cauraugh and Kim 2002, Cauraugh and Kim 2003a), a component necessary for muscle force generation.

One pre-test/ post-test study demonstrated significantly reduced muscle tone at the elbow (Hesse et al. 2003) however this was not replicated in the RCT (Hesse et al. 2005) therefore no convincing evidence of reduction in muscle tone exists.

Using the Barthel Index and the Functional Independence Measure (FIM), one study (Lum et al. 2002) found no effect of robotic intervention on ADL independence; however at 6-month follow-up significantly greater improvement on the FIM was demonstrated. Given that no UL improvement was demonstrated, the finding may reflect development of compensatory strategies for function, unrelated to hemiparetic UL performance, since the FIM allows performance of function with the unaffected UL (Granger et al 1993).

One study demonstrated that sensation influenced improvements in strength and reach (Lum et al. 2002) whereas no difference in motor performance between severe, moderate, and mild categories of impairment was demonstrated. The impact of sensation requires further investigation since other studies suggest that strength of interlimb coupling is negatively affected by sensory deficit (Jackson et al. 2000). Effects of sensation and initial severity on outcomes will be reviewed in section 2.3.

The EFES studies included no follow-up assessment, therefore learning effects of this intervention are difficult to determine. The robotic studies provided conflicting findings. The single group study (Hesse et al. 2003) found that effects on motor performance and tone were lost at 3-month follow-up, whilst the RCT of the same intervention demonstrated retained motor performance and strength effects at 18 weeks, probably related to the higher treatment dose of the intervention group compared to the control group in that study. The other robotic study (Lum et al. 2002) found that benefits for proximal motor performance were lost at 6 months.

EVIDENCE LEVELS

Generally evidence levels for BIAT interventions were higher than for other types of intervention and strongest evidence exists to support use of robotic training. EFES trials were methodologically weaker, with potential biases that could influence results.

2.2.5.2 Summary

In summary, this group of studies involved six RCTs and 171 participants.

Overall, methodological quality was higher than for other bilateral interventions, however studies were small, and only one demonstrated use of adequate sample size calculation, casting doubt on statistical power in some studies. More work with larger samples is required before results can considered sufficiently robust. Interventions involved either EFES with bilateral movement, or bilaterally arranged robotic devices. Because of low degrees of freedom of movement afforded by devices, interventions focused on single joint movements or restricted movement combinations, therefore ecological validity of interventions in relation to everyday UL use may be sub-optimal. One study (Lum et al. 2002) incorporated both bilateral and unilateral practice into the intervention, making effects of BT *per se* difficult to discriminate.

Most studies examined participants in the chronic period, however one study demonstrated positive findings in acute stroke participants (Hesse et al. 2005) suggesting that intervention soon after stroke may be warranted. Robotic studies were conducted mainly with participants with moderate to severe impairment whereas the EFES studies included participants with mild to moderate severity. One study found no differences in response between participants with differing severity, however investigation across interventions is required to determine relationships between severity and magnitude of responses.

Follow-up periods in one single cohort study (Hesse et al. 2003) and two RCTs (Hesse et al. 2005, Lum et al. 2002) were conducted to assess retention at three and six months respectively. Only one RCT (Lum et al. 2002) demonstrated retention effects. For other interventions, the retention of effects is unknown.

Optimal therapy doses remain unclear. Authors of the EFES series demonstrated a systematic approach to development of intervention parameters. Having established an effect of the intervention, they explored optimal intervention parameters, such as stimulation duration and EMG thresholds. New bilateral paradigms should be explored in this way, to determine optimal intervention parameters for participants with different characteristics.

Overall, results suggest that BIAT positively influences impairment, including movement parameters such as reaction time, strength, dexterity and movement performance, however effects on functional UL performance are unclear and need to be determined if these relatively expensive interventions are to be adopted into rehabilitative practice. One study (Lum et al. 2002) suggested that BIAT influenced long-term ADL performance, but given that some UL parameters had worsened, compensatory tactics rather than UL improvement may explain findings. Impact on ADL requires further investigation. Impact of intervention on psychosocial parameters such as mood and quality of life were not examined. Furthermore, although one study examined effects of sensory impairment, more work is required to map out the impact on outcomes of sensation and other clinical and demographic factors.

2.2.6 CONCLUSIONS

In total, ten RCTs involving 269 participants and eight other studies involving 78 participants were conducted to examine the effects of BT. The median level of evidence for the RCTs was 1- (range = 1- to 1++). The median level of evidence for the other studies was 2- (range = 2- to 3). Most trials were small and of poor methodological quality. Intervention and outcome measures diversity means that few robust conclusions about effectiveness of BT, compared with UT as a therapeutic approach to UL rehabilitation can be made. Trial quality and evidence levels were strongest for BIAT trials. The few other trials demonstrating high level of evidence examined diverse interventions, making conclusions based on effects of BT in general difficult to determine.

The imited evidence that exists from several RCTs suggests that bilateral robotic UL training and EFES may be effective in improving motor impairment in participants with moderate to severe hemiparesis compared to conventional unilateral approaches. Effects are apparent in participants with chronic and acute stroke. A paucity of good, adequately powered RCTs means that the picture is less clear for movement function, although there is some evidence from one RCT that BATRAC may improve motor impairment but methodological limitations make definitive conclusions difficult. Of greatest clinical relevance is carry-over into the domain of activity however few studies have examined whether bilateral functional task training is superior to conventional unilateral task training. Studies have mainly been single case series and have examined participants in the chronic post-stroke stage. Given the important role of early rehabilitation in determining long-term recovery, delayed as well as immediate effects of bilateral compared to unilateral training should be determined for participants with acute stroke using a randomised controlled trial design. Evidence of effects of BT on UL activity limitation and ADL performance is scant and effects on psychosocial outcomes have not yet been examined. Effects of impairment severity on responses across a range of outcomes remain to be determined, and influences of important covariates, such as sensory impairment, hand dominance, and side of lesion remain unclear.

There is therefore a need to conduct an adequately powered randomised controlled trial to compare the effects of bilateral with unilateral task training in terms of UL activity limitation including ADL independence, impairment, psychosocial outcomes such as mood and health related quality of life. Furthermore, critical clinical and demographic factors that may

influence training responses should be determined, along with the effects of severity of impairment.

It is clear that:

- Bilateral robotic UL training and EFES are effective in improving motor impairment in individuals with acute and chronic stroke with moderate to severe hemiparesis compared to conventional unilateral approaches
- Bilateral movement function training may improve impairment and activity outcomes compared to conventional therapy in individuals with moderate severity

It is less clear:

- Whether BT involving functional task training is effective compared to UT in the acute post-stroke period
- How effective BT involving functional task training in the acute post-stroke period is in terms of short and long-term activity limitation and impairment outcomes compared to UT
- Whether BT compared to UT in the acute post-stroke period influences ADL independence, impairment and psychosocial outcomes such as anxiety, depression and health related quality of life
- Whether demographic and clinical factors including severity of initial UL dysfunction, sensory impairment and hand dominance influence responses to bilateral task training undertaken in the acute post-stroke period

To determine which factors may influence contralesional UL recovery in general and responses to bilateral training in particular, literature related these factors is reviewed in Section 2.3.

2.3 FACTORS INFLUENCING UPPER LIMB RECOVERY AND RESPONSES TO THERAPY

Continuing with the physical outcomes theme of the thesis, to ensure that rehabilitation interventions target clinical populations appropriately, it is critical to identify and understand clinical and demographic factors that influence UL recovery and responses to therapy. Patients and therapists also need good information to plan for eventual outcomes. Section 2.2 showed that only a few BT studies have examined which demographic or clinical factors influence responses to therapy and UL recovery. The literature examining predictors of upper limb impairment and activity limitation and responses to therapy is reviewed in this section.

To maintain continuity with previous sections, UL outcomes and recovery variables were categorised as motor impairment or activity limitation, according to ICF definitions (WHO 2001). Both motor impairment and activity limitation are represented as primary outcomes in most studies of therapeutic UL interventions and therefore form the main focus of this review section. Motor impairment refers to control of simple voluntary movements, complex voluntary movements or coordination of voluntary movements. Upper limb activity refers to execution of tasks or actions, and relates to ability to function. Upper limb impairment and activity limitation were the outcomes of interest. An examination of effects of variables that may influence activity and impairment outcomes was conducted. These included severity of initial impairment and activity limitation, effects of site and side of hemiplegia, hand dominance, age and gender and proprioception on responses to therapy. Whilst the potential importance of muscle strength and muscle tone is acknowledged here, they were not included as predictors as the main focus of interest was activity limitation.

Searches for papers published between 1996 and 2007 were conducted in CINAHL, MEDLINE, EMBASE and PSYCHINFO. Search strategies were conducted with a combination of terms that are shown in Appendix 2. Older relevant studies were identified from reference lists of these studies and reviewed where appropriate.

Where relevant throughout this review, studies were summarised in tables. Where several outcomes and predictors were examined in an individual study, the study was reported in the first relevant table and the reader referred back to that table if required.

2.3.1 EFFECTS OF SEVERITY OF INITIAL MOTOR IMPAIRMENT

2.3.1.1 Upper limb motor impairment outcomes

Motor impairment is relevant to UL recovery because it reflects severity of underlying neurological damage. Studies examining predictors of motor impairment are summarised in Table 1, Appendix 3. Studies included consecutive cohorts of patients diagnosed with stroke demonstrating a range of upper limb impairments or activity limitations.

Early motor impairment predicts or correlates with later impairment outcome (Table 1, Appendix 3). In one study (Katrak et al. 1998) early shoulder shrug or abduction predicted hand movement at three months. However, the purpose designed measure, failure to report reliability between seven raters and scant statistical reporting affect the robustness of the study. In a descriptive study (Nakayama et al 1994), 56% of patients with initial severe paresis showed no reduction in UL paresis by discharge. Predictive modelling was not conducted however and times to discharge varied. The Barthel Index measured outcome, but is not a sensitive measure of UL function since patients can score maximally without using the hemiparetic UL (Platz et al. 2005a). Thus some evidence, limited by methodological flaws, suggests that early paresis determines later impairment.

Similar evidence emerges regarding motor impairment. Duncan (1992) (Table 1, Appendix 3) demonstrated that Fugl Meyer (FM) scores at 30 days versus 5 days post-onset best predicted six month scores, suggesting that strength of prediction depends on its timing. Sub-groups for analysis were small, however, potentially limiting study power. Confirming that time is important, Feys (2000a) demonstrated stronger prediction of FM outcome at two months than at six months from baseline assessment 2-5 weeks post-onset. Data came from an RCT testing UL training; which may have influenced outcomes. Broeks (1999) demonstrated a significant and strong correlation ($r=0.83$) between FM scores 2-8 weeks and four years post-stroke (Table 1, Appendix 3) but lack of predictive modelling limits comparability with other studies. Variations in time of initial assessment may have skewed findings, given that rapid recovery occurs in the first two months (Duncan et al. 1992).

The Motor Assessment Scale UL sections mix motor impairment and activity, but most items relate to motor impairment. One week and one month scores strongly predicted UL

discharge scores (Loewen and Anderson 1990) but one month scores were most predictive, again suggesting effects of timing.

In summary, evidence exists that severity of early motor impairment determines impairment outcomes and recovery up to twelve months post-onset. Several studies were poorly designed or conducted (Nakayama et al 1994, Katrak et al. 1998, Broeks et al. 1999) however evidence from three more methodologically robust studies (Loewen and Anderson 1990, Duncan et al. 1992, Feys et al. 2000a) – perhaps unsurprisingly - shows that early impairment predicts later impairment. One month assessment has stronger predictive strength than assessment at one week, suggesting timing for optimal prediction is critical. Since therapists and patients need to accurately predict outcomes for treatment planning and discharge, further investigation is required to confirm these findings, address study limitations, and explore assessment timing further. The next section examines impairment as a predictor of activity limitation.

2.3.1.2 Severity of initial motor impairment on upper limb activity outcomes

Several studies show relationships between motor impairment and UL activity outcomes (Table 2, Appendix 3 summarises these). Early impairment appears to predict activity outcomes. Katrak (1998) (Table 1, Appendix 3) demonstrated that early shoulder movement predicted hand function at three months. Assessment items were however limited in functional ecological validity, with no justification for their selection. Another study (Rand et al. 1999) (Table 2, Appendix 3) demonstrated a significant correlation (Table 2, Appendix 3) between initial FM score and six week Frenchay Arm Test, suggesting a relationship between motor impairment and activity outcome. Sample size justification and measurement procedures were not reported however. Similarly, initial impairment predicted Frenchay Arm Test score at 18 months in a study involving 92 participants (Wade et al. 1983); however details of data, analysis and results were scant. Limited assessor training and numerous assessors probably also influenced findings. A cohort study (Kwakkel et al. 2003) (Table 2, Appendix 3) of participants with UL flaccidity showed that four week FM UL scores optimally predicted six month Action Research Arm Test (ARAT) scores with 94% probability. Data was from an RCT involving UL and lower limb (LL) training which may have influenced findings. This otherwise carefully conducted study demonstrated that even with initial flaccidity, motor impairment strongly predicts UL activity outcome, and optimum predictive timing is around 4 weeks. Limited validity of the Barthel Index to

measure UL activity outcomes (Platz et al. 2005a) means that another study provides little information about UL activity limitation (Olsen 1990). Authors found correlations between paresis and Barthel grooming and dressing items (Table 2, Appendix 3) suggesting that severely paretic patients recover lower levels of UL activity performance; however correlations were low and ability to score high on the Barthel without using the paretic UL (Platz et al. 2005a) means that findings add little to determining factors likely to influence UL impairment.

Generally, evidence from these studies is affected by methodological limitations related to selected measures. Overall, evidence exists that UL motor impairment 2-4 weeks post-stroke predicts, or is associated with, 4-6 week and longer-term functional UL recovery. Strength of these relationships was generally high with correlation coefficients greater than 0.65 and predictive probability greater than 85%. Unsurprisingly, studies indicate a relationship between ability to move, and ability to perform functional tasks.

2.3.1.3 Severity of initial motor impairment and responses to therapeutic interventions

Four studies examined effects of motor impairment on responses to therapy (Table 3, Appendix 3). In one study (Fritz et al. 2006) patients had to be able to extend wrist and fingers, otherwise participants demonstrated a range of initial impairment. To address whether differential effects existed for initial impairment, sub-analyses were conducted. Studies provide some evidence that initial impairment influences therapy responses but unsurprisingly, effects depend on intervention characteristics. Strength of evidence varies across studies because of variations in method, as will be discussed below.

Overall, poorer intervention responses in patients with more severe initial impairment were demonstrated. One RCT (Parry et al. 1999) (Table 3, Appendix 3) demonstrated greatest improvement in activity limitation and impairment with increased therapy dose in participants with less initial UL impairment. Only participants who completed the intervention *or* demonstrated improvement were included in sub-analysis, an approach likely to introduce bias, since only 50% of participants completed the intervention. Also groups were created using median split where the data was divided into two sub-groups comprising those scoring less or more than the median score. This is a fairly arbitrary approach to sub-group generation. Winstein (2004) (Table 3, Appendix 3) also demonstrated in an RCT that

less severe initial motor impairment led to greatest improvement in impairment and activity following task and strength training. Neither of these studies addressed the power of sub-group analyses which may have influenced findings.

Examining constraint induced movement therapy (CIMT) in a pre and post intervention study, Fritz (2005) (Table 3, Appendix 3) demonstrated predictive effects of active finger extension and grasp-release on post-training and follow-up activity limitation. Responses were greatest with better initial motor control. No comparison group was used; therefore findings should be treated cautiously. Post-hoc power calculations and intention to treat analysis however made analysis more robust. This study was conducted in longstanding stroke; therefore extrapolation to more acute patients needs to be cautious.

Conversely, Feys (1998) (Table 3, Appendix 3) demonstrated greatest motor recovery following sensorimotor stimulation for participants with *most severe* initial impairment. Impairment severity was an a priori predictor and included in planned factorial analysis. Differences still existed at five years (Feys et al. 2004). The intervention required little active movement, and severely affected participants possibly responsed better *because* of their limited motor control whilst less severely affected participants probably benefit from meaningful and varied tasks for motor learning.

Interestingly, no study was found to examine effects of initial severity on responses to BT.

In summary, interventions, outcomes and timing of training across studies were diverse; however initial motor impairment does affect responses to experimental interventions. Unsurprisingly, intervention characteristics also determine benefits, so predicting therapy responses is complex. Study limitations, particularly analysis using underpowered sub-groups, the lack of controls and relatively arbitrary definitions of severity, means that more work is required to provide good evidence to inform practice. The body of work suggests however that examination of effects of impairment severity on responses to therapy is important, to determine clinical groups most likely to benefit. This is particularly relevant to BT, where effects of initial motor impairment on outcome have not been examined.

2.3.2 EFFECTS OF SEVERITY OF INITIAL ACTIVITY LIMITATION

Activity limitation, representing functional UL use, is probably the most important outcome for patients. In this section the influence of initial activity limitation on UL outcomes was reviewed, followed by an examination of effects on rehabilitation outcomes.

2.3.2.1 Motor impairment

No study examined activity limitation as a predictor of motor impairment.

2.3.2.2 Activity limitation

One study of consecutively admitted patients with UL impairment (n=55) (Higgins et al. 2005) investigated predictive strength of initial UL activity limitation for activity outcomes. Box and block dexterity test scores (BBT) at one week post-stroke explained 92% of the variance in BBT at five weeks. Removing the BBT as a predictor, the Frenchay Arm Test (FAT) measuring general UL activity, explained 84% of BBT variance. Unsurprisingly, initial dexterity predicted outcome dexterity, but congruence existed between gross dexterity and more general arm function. The Nine Hole Peg Test, measuring fine dexterity, was less predictive of BBT than the FAT, suggesting gross dexterity and general UL function are more closely related than fine and gross dexterity. The short follow-up period means conclusions apply only to early post-stroke recovery; however the study identifies factors potentially relevant to early rehabilitation. This study had clear aims and was well-conducted however lack of sample size calculation means that findings should be treated cautiously.

2.3.2.3 Severity of initial activity limitation in the context of rehabilitation interventions

Initial activity limitation may also influence therapy responses, however evidence is scant and only two studies examined activity limitation in respect to responses to therapeutic interventions. Studies were conducted in the acute (Sunderland et al. 1994) and sub-acute periods (Platz 2002) (Table 4, Appendix 3). One RCT compared enhanced and conventional UL therapy (Sunderland et al. 1994). A power calculation to determine sample size was conducted but not for severity sub-groups that were later defined. Statistical methods were

poorly described. The rationale for determining severity sub-groups was not provided. Methodological limitations reduced the strength of the evidence, but greatest treatment effects in a range of impairment and activity outcomes were demonstrated in patients with least initial activity limitation determined by the FAT (Table 4, Appendix 3).

The other study (Platz 2002) (Table 4, Appendix 3) found greater recovery following Arm Ability Training in participants with more severe baseline activity limitation which explained 70% of variance in post-training activity limitation. However study aims were relatively ill defined and lack of controls mean that evidence for the effectiveness of the intervention and consequently effects of initial activity outcomes is limited. Platz (2002) studied participants with mild to moderate severity with preserved precision grip, whereas Sunderland (1994) examined participants with no precision movements, and some without functional activity which may explain the contrasting impact of activity limitation on outcomes between studies.

2.3.2.4 Severity of initial activity limitation and responses to bilateral training

None of the bilateral training studies reviewed in Chapter 1 examined the impact of initial activity limitation on responses to bilateral training, an important gap in the evidence base that requires to be addressed.

Summarising, these studies suggest firstly that baseline dexterity soon after stroke predicts outcome within 5 weeks, but the predictive strength of UL dexterity and activity limitation measures differs in this context. Little is known about the predictive strength of initial activity limitation over longer periods. Whilst patients with severe activity limitation demonstrate limited therapy responses, those with some recovery tend to respond better, with smallest gains for those with most recovery. Findings again suggest that the nature of experimental intervention influences outcomes. Given methodological limitations of these studies, more research is required to examine effects of initial activity limitation on long and short-term activity outcomes *and* in the context of intervention studies to enhance understanding about the impact of activity limitation on responses to therapy.

Severity of impairment and activity limitation are clearly the most important most widely studied predictors and outcomes of UL recovery and responses to therapy. The next section focuses briefly and more narrowly on the evidence relating to a range of other factors which

may influence responses to therapy. These factors were more difficult to identify in the literature because many were embedded as secondary analyses in reports.

2.3.3 EFFECTS OF OTHER CLINICAL AND DEMOGRAPHIC FACTORS ON RESPONSES TO UPPER LIMB REHABILITATION INTERVENTIONS

In this section the lesion site, lesion side and hand dominance, proprioception, age and gender are reviewed as factors that might influence responses to rehabilitation interventions.

2.3.3.1 Lesion site

Several studies have demonstrated that lesion site influences overall stroke outcome. For example, Barber et al. (2000) used a scoring system (ASPECTS) to quantify ischaemic change on CT at baseline in the context of a thrombolysis trial. In a sample of 156 participants with anterior-circulation ischaemia, the ASPECTS score of scans taken within 3 hour of stroke onset was a significant predictor of functional outcome at three months measured on the Rankin Scale with sensitivity of 0.78 and specificity of 0.96. The Rankin Scale is a fairly crude measure of function, so conclusions with respect to more complex ADL functioning must be drawn cautiously. Relatively few potential predictor variables were included in the logistic regression analysis so the relative impact of variables such as gender, urinary incontinence, and ADL functioning is not accounted for in the model. The study does nonetheless indicate that lesion location on CT can be quantified for clinical decisions and that it may be predictive of crude functional outcome.

Other studies have found similar results. For example Ng et al. (2007) delineated seven lesion locations from CT and MRI and examined the relative predictive importance of vascular territory in prediction of outcome on the Functional Independence Measure at discharge from rehabilitation in 2213 patients. The study demonstrated a hierarchy of outcome, with patients whose scans showed stroke in more than one hemispheric area with poorest outcome, whilst those with posterior cerebral artery stroke demonstrating best outcome. They also found that admission scores were more predictive of discharge score than vascular area, and that change in functional outcome did not vary between the stroke types. However, the study demonstrated selection bias since only patients admitted to rehabilitation were included. Discharge date was used as the point of assessment for

prediction, however that may depend on multiple factors pertinent to individual patients, not necessarily just related to physical stroke recovery. In spite of these limitations, the study demonstrated that although scan findings are important in discriminating patient sub-groups they do not necessarily predict overall functional outcome.

However another study (Schiemanck et al. 2006) showed in 75 participants that MRI scan classification at 11 days based on cortical/subcortical; white/gray matter and lesion volume did not add predictive value in determining functional outcome measured on the Barthel Index at one year. In that study, age and ADL independence were most predictive of ADL at one year. The sample was a selected group determined by admission to stroke unit, and the number of variables that could be included in regression analysis was limited by the small number of cases. The authors therefore had to be selective about which variables to select as predictors and some important variables may have been excluded from the analysis. Taken together these studies demonstrate some but not conclusive predictive strength of lesion location.

Fewer studies have investigated relationships between neuroanatomical lesion site and upper limb impairment (Stinear et al. 2007). Feys et al. (2000a) found in 45 participants that the combination of admission motor performance and sub-cortical lesions and severity of disability was most predictive of UL recovery at 2 months (74.6%) with sub-cortical lesions adding 5.3% of variance as a significant negative predictor of poorer UL motor impairment outcome. Between 2 and 12 months subcortical lesions predicted 60% of variance of recovery, indicating their importance. However all participants demonstrated severe UL dysfunction, limiting generalisability of findings to those with more moderate dysfunction. Furthermore, baseline assessment occurred two to five weeks after stroke onset therefore very early recovery was not captured in the regression models. The assessments were part of a randomised controlled trial of an UL intervention where participants were randomised to a treatment or control group. Although the dichotomous factor “group” included in regression as a potential independent variable, intervention responses may nonetheless have influenced predictive strength of the variables.

Similarly, Shelton (Shelton and Reding 2001) found that of 41 patients with severe motor impairment, those with subcortical or mixed lesions recovered less by time of hospital discharge than those with cortical damage. Lesions involving the posterior limb of the internal capsule were significantly associated with poorest scores on the UL FM test, whilst patients with purely cortical involvement fared best. However the types of neuroimaging

tests used were not specified, making study replication difficult and raising the possibility that findings might vary across the different neuroimaging approaches. Furthermore, follow-up was only at two months and focused on the shoulder and elbow but not the hand.

These findings support a consensus (Knopman and Rubens 1986, Werring et al. 1998) that UL recovery is dependent on an intact corticospinal tract, with patients who have subcortical stroke demonstrating poorer outcomes. Together these studies suggest that use of assessment of lesion site *may* add value to prediction of later outcome, but whether it does or not may depend on how lesion site is assessed, timescales over which prediction occurs, and the combination of variables included in regression analysis.

Only one study was found to investigate lesion site and responses to UL rehabilitation (Sonde 2001), and showed that of 14 participants, those without damage of the peri-ventricular white matter assessed by MRI scan (n=5) demonstrated best responses to transcutaneous electrical nerve stimulation in terms of FM scores at three year follow-up. However details of recruitment procedures and inclusion criteria were not provided therefore characterisation of the study population and likely biases are difficult to discern. The unilateral, passive and afferent nature of that intervention also means that findings are unlikely to apply to a bilateral training intervention, however this study indicates that lesion site may determine responses to specific types of post-stroke training and is worth investigating.

2.3.3.2 Lesion side and hand dominance

Known hemispheric differences exist in terms of executive control of the motor system (Haaland and Harrington 1989, Harrington and Haaland 1992, Haaland and Harrington 1994, Haaland et al. 2004) with each hemisphere exerting different control on movement phases and sequencing. Investigation of effects of lesion side and hand dominance on UL responses to therapy may be important.

The effects of side of lesion side and hand dominance on impairment outcomes are unclear. Two studies examined this, one with patients in the acute stage and one with those in the more chronic stage. Katrak (1998) (Table 1, Appendix 3) found that in 71 patients, side of hemiparesis was not significantly predictive of later hand movement 3 months after stroke, however data supporting this effect was not presented. Harris (2006) (Table 5, Appendix 3)

demonstrated that strength, grip and tone in 93 patients with chronic stroke were significantly affected by dominance, indicating less impairment where the dominant hand was affected (Table 2.1.6). Participants were volunteers, a source of potential bias, and there was no sample size calculation, however the study was otherwise carefully conducted. Clearly, the outcomes investigated in these studies were diverse, and the quality of one study was poor (Katrak et al 1998) therefore the evidence is very limited, however it does suggest that hand dominance and not side of lesion may influence motor impairment.

Lesion side and hand dominance appear not to influence UL activity outcomes. Katrack et al. (1998) found no effect of lesion side on recovery of hand function, although as earlier reported the selected measure in that study had limited validity and unreported reliability. Kwakkel et al. (2003) (Table 2, Appendix 3) did find an *association* of lesion side with dexterity outcomes at six months in 102 patients with flaccid upper limbs. Here the odds ratio for that variable was low therefore side was not included in the multivariate modelling for prediction indicating that it had potentially little influence on outcome. In that study, patients had participated in a trial of an UL intervention which may have influenced recovery variables and their predictive strength. The strict trial inclusion criteria also mean that the findings can only be generalised to populations similar to that sample.

No effect of lesion side or dominance on UL activity measured on the Chedoke Arm and Hand Activity Inventory and the Motor Assessment Log (MAL) was found in a study of 93 patients with chronic stroke (Harris et al. 2006) (Table 5 Appendix 3). However in that study patients may have used compensatory strategies for functional activities, with increased use of the affected UL to perform the tasks on the Chedoke Arm and Hand Activity Inventory where both hands perform tasks, and in the MAL where general UL ADL activities are measured. This may be why the impact of dominant hemiplegia on ADL performance appears less in that study than that was shown for impairment (see paragraph above).

Lesion side does not appear to influence responses to treatment intervention however methodological limitations, limited populations and diverse outcomes mean that evidence is very specific to certain interventions. Four studies were conducted with participants who were all volunteers with persistent UL impairment in the chronic post-stroke phase. Byl (2003) (Table 6, Appendix 3) demonstrated no overall effect of lesion side on recovery of UL functional activity with motor and sensory training in a sample of participants with

chronic stroke (n=18). There was however a small advantage on some more complex items of the selected test for patients with right side dominant hemiparesis. Feys (1998) (Table 3, Appendix 3) also found no effect of lesion side on impairment and activity outcomes in a large RCT study of a sensorimotor training intervention (n=100). Similarly, Miltner (1999), who examined 15 participants and Fritz (2006), who examined 55 participants both demonstrated no main or interaction effects of side of lesion or dominance on responses to constraint-induced therapy in single group studies.

Methodologically these studies were limited. Mainly conducted with patients in the chronic stage, only two were RCT designs, (Feys et al. 1998) (Table 3, Appendix 3), (Byl et al. 2003) (Table 6, Appendix 3). Only one study reported randomisation method and blinded measurement (Byl et al. 2003) whilst only one other, a single group design, reported intention to treat analysis (Fritz et al 2006). All except one study (Feys et al. 1998) used the WMFT as a measure of outcome, allowing for comparison between the studies, however none reported use of a measure of handedness, so it is not clear how the studies standardised assessment of handedness. Three studies (Fritz et al 2006; Byl et al. 2003, Miltner et al. 1999) examined constraint therapy, again providing a body of evidence relevant to that intervention. Some strong evidence is therefore emerging that side of lesion and dominance do not influence activity outcomes for constraint therapy in the chronic stage in patients with some recovery. There is however a clear need for further work to examine the effects of lesion side and dominance on a range of outcomes in more acute patients, patients with more severe deficits and undertaking different interventions in robustly designed randomised controlled trials.

In contrast, different responses to bilateral training have been reported depending on lesion side and dominance (McCombe-Waller and Whitall 2005). Significantly greater improvements in a range of UL impairment and activity measures was reported for 11 patients in the chronic stage with right hand dominant, left hemisphere damage compared with 11 patients with non-dominant left hand, right hemisphere damage following six weeks of BATRAC training. The patients demonstrated no baseline differences. All patients were right hand dominant therefore effects may not apply to patients with left hand dominance. The response may reflect greater motivation in right hand dominant patients with right hemiparesis to recover, greater interhemispheric inhibition for the dominant arm, or fewer perceptual or visuospatial impairments with left hemisphere damage (McCombe-Waller and Whitall 2005). However the sample was small, there was no control group or reported

blinding which may have magnified effects. The methodological limitations of this study therefore mean that it should be repeated to confirm these findings and to investigate if they apply to more acute patients. Side of lesion and dominance are therefore key factors to investigate in the context of bilateral training.

2.3.3.3 Proprioception

Proprioceptive feedback is thought to be critical to motor control and movement execution, particularly for skilled movements that require feedback and adjustment for error detection and accurate execution (Schmidt and Wrisberg 2004). The spatial information obtained through intact proprioception may be critical to normalising movement control and recovery after stroke (Rand et al. 1999). It is also thought to be particularly critical in synchronization of the upper limbs during bimanually identical movements (Jackson et al. 2000), particularly during reach to grasp movements. Therefore two issues emerge relevant to bilateral training in acute stroke. Firstly, after stroke, impaired proprioceptive sense may influence motor control and contribute to motor impairment, and secondly, given its importance in bimanual synchrony, it is important to understand if impaired proprioception influences bilateral training outcomes in stroke. This is particularly important since evidence regarding the role of proprioception in UL recovery in general is inconclusive.

The exact role of proprioception in upper limb recovery is however unclear. Four longitudinal cohort studies examined effects of proprioceptive impairment on motor impairment outcomes. These all used baseline measures collected from consecutive cohorts of patients with UL impairment within the first month except for one (Broeks et al. 1999) (Table 1, Appendix 3), in which data was collected up to 2 months post-onset. Three studies also examined activity outcomes.

Katrak (Katrak et al. 1998) (Table 1, Appendix 3) found no predictive value of proprioception for recovery of hand movement. The authors did not report how the measure was conducted however, or how proprioception was operationalised, nor did they present data relating to sensory loss and therefore the findings should be regarded very cautiously. Rand (Rand et al. 1999) (Table 2, Appendix 3) compared FM scores of patients with initial proprioceptive deficits to patients with pure motor stroke at baseline and six weeks post-onset (n=40) and although patients with proprioceptive deficit demonstrated higher scores on impairment and activity limitation measures there were no statistical differences, suggesting

that proprioception does not significantly influence motor impairment recovery. Similarly, Gowland (1982) (Table 7, Appendix 3) using chi squared tests, demonstrated that there was no difference in proportions of patients with good FM scores and poor FM scores between those with sensory impairment including proprioception, and those without (n=233). Those with best recovery however tended to demonstrate normal sensation. No details of the tests were provided, and since time to discharge was not reported the timescale during which sensory impairment might be important as a predictor is unclear.

Other studies suggest that proprioception may influence UL impairment outcomes. Broeks (Broeks et al. 1999) (Table 1, Appendix 3) demonstrated that patients with initial cutaneous and proprioceptive loss showed poorer UL FM scores at 4 years (n=54) however, no valid or reliable scoring system for sensation was reported and the relationship between sensation and motor impairment was not tested statistically. Feys (Feys et al. 2000a) (Table 1, Appendix 3) demonstrated that initial and two months post-stroke proprioception was a significant predictor of motor recovery measured on the FM test at 12 months post stroke in 100 patients, however this was part of an RCT investigating a sensorimotor intervention that may have influenced findings. Meldrum (Meldrum et al 2004) (Table 7, Appendix 3) also demonstrated that early sensation significantly predicted motor outcome on the RMA at six months (n=114). No discrimination was made between effects of limited proprioception and cutaneous sensation, in that study however. Thus some evidence suggests that proprioception relates to UL motor impairment, whilst other evidence suggests that sensation is not important.

Reliability of sensory tests is generally poor (Lincoln et al. 1998). Furthermore in many studies the range of tests were often not clearly described. It is likely that the subjective and interpretive nature of patient accounts of proprioception probably explain discrepancies between study findings. Furthermore, some studies (Broeks et al. 1999, Meldrum et al. 2004, Gowland 1992) did not discriminate between proprioception and cutaneous or tactile sensation in reporting findings, making the role of each difficult to discriminate. Additionally, reporting of the statistical methods in some studies was poor There is therefore a need to investigate the relationship between proprioceptive impairment and recovery of motor impairment using reliable and valid sensory tests, adequate samples and appropriate statistical techniques.

EFFECTS OF PROPRIOCEPTION ON ACTIVITY OUTCOMES AND RECOVERY

There was some evidence suggesting a relationship between proprioceptive impairment and UL activity. Kwakkel (Kwakkel 2003) (Table 2, Appendix 3) demonstrated a significant correlation between initial proprioception and dexterity at six months in 102 patients with initial flaccidity. In line with this, Wade (1983) (Table 2, Appendix 3) demonstrated an association between initial position sense deficit and UL activity at 18 months in 92 participants. Rand (Rand et al. 1999) however, (Table 2, Appendix 3) demonstrated no significant effects of initial proprioceptive loss on activity limitation at baseline or six weeks. Similarly, Katrak et al. (1998) (Table 1, Appendix 3) found no association of sensation to hand function at three months (n=71). Thus the long and short term effects of proprioceptive loss on UL activity remain unclear, and since details of measurement in some studies were scant (Wade et al. 1983, Katrak et al.1998), results may relate to the methods and measures used, rather than the true effects of sensation. The two most methodologically robust studies (Rand et al. 1999, Kwakkel et al. 2003) demonstrated conflicting results, whilst the lack of detail about measurement and methods of the two other studies may have influenced findings to an unquantifiable extent. More investigation is therefore required to determine the effects of proprioceptive loss on UL activity outcomes.

EFFECTS OF PROPRIOCEPTION ON RESPONSES TO THERAPEUTIC INTERVENTIONS

No study investigated the impact of proprioceptive impairment on responses to therapeutic interventions.

EFFECTS OF SENSATION ON RESPONSES TO BILATERAL THERAPEUTIC INTERVENTIONS

Only one study of relevance to bilateral training was found. Jackson et al. (2000) demonstrated directional errors and spatiotemporal irregularities during bimanually identical and bimanually different movement compared to unimanual movement and performance of control subjects in a deafferenated patient with hemianaesthesia, loss of light touch and proprioception. Unsurprisingly, control of bilateral co-ordination appears mediated by proprioceptive signals. Although findings from a single case study should be regarded cautiously, it appears that loss of intact proprioception may be detrimental to bimanual coupling. Given that effects of bilateral training are thought to depend on the ability to generate tight interlimb coupling (Caraugh et al. 2005), proprioception should be examined

as an important and potentially influential factor when investigating outcomes of bilateral training.

2.3.3.4 Age and gender

Few studies have examined effects of age and gender on UL recovery. The study by Katrack et al. (1998) (Table 1, Appendix 3) and reported above, claimed that neither age nor gender predicted hand impairment or functional activity at three months (n=71), however the methodological limitations discussed above suggest this study must be cautiously interpreted. However neither factor was a significant predictor of activity at six months in patients with an initially flaccid limb (n=106), in the well-conducted study reported by Kwakkel et al. (2003) (Table 1, Appendix 3). In contrast Wyller et al. (1996) demonstrated significantly higher scores for men on an arm subsection of the Sodring Motor Evaluation of Stroke Patients, a measure of activity, in 87 patients during an unspecified subacute phase that had resolved by one year post stroke. Details of recruitment and measurement procedures were scant in that study, however, making study replication difficult and raising questions about the representativeness of the sample. There appears to be little evidence of the impact of age on UL recovery and evidence is mixed for gender. The impact of gender and age on UL recovery therefore requires more investigation.

Few intervention studies have examined the impact of these factors on training responses. Age was the only significant predictor of the amount of use of the affected arm on the MAL, in a study examining constraint therapy in participants with longstanding stroke (n=55) (Fritz et al. 2006) (Table 6, Appendix 3). Here, greater age was associated with less UL use, but not with capability to use the arm as measured by the WMFT. Again training effects must be regarded cautiously since lack of a control group suggests potential bias of effects. This finding is however in line with studies of more general functional outcomes after stroke (Bagg et al. 2002), which suggests that age accounts for only a small proportion of variance (1.3%) in functional outcome. No studies demonstrated that gender was a factor that might influence training responses, however given that gender may influence recovery (Wyller et al. 1996) it is clear that it should be examined further in the context of therapy responses. Clearly more work is required to investigate whether age and gender influence therapy outcomes generally, but BT outcomes in particular.

2.3.4 CONCLUSIONS

Overall, studies suffered from methodological limitations including convenient samples and scant details of eligibility requirements, lack of power calculations, broad and non-specific aims and in some studies, measurement validity could be questioned. Furthermore, statistical methods were generally not well reported. The use of hospital discharge as an end-point in several studies does not account for optimal UL recovery, which may continue to recover over months and years (Taub et al. 2006) and depends on many factors such as housing, services and social circumstances. Overall, the mixed quality of the studies means that evidence for factors influencing recovery and responses to training is limited and research using well defined populations, adequately powered samples and robust statistical approaches is required.

However in conclusion the review demonstrated that:

- Initial severity of impairment influences UL impairment and activity outcomes. Optimal predictive strength for later outcome occurs 4-6 weeks after stroke
- Initial severity of impairment influences responses to therapy, but the way in which this occurs depends on the nature of the intervention.
- Side of hemiplegia and hand dominance may influence UL outcomes.
- Hemiplegia of the dominant right hand may lead to better BT than hemiplegia of the non-dominant left hand in patients with chronic stroke, but it is not clear whether this applies to other BT paradigms in the acute phase
- Having sub-cortical stroke leads to poorer UL impairment outcomes but it is not known if lesion site influences responses to BT
- The role of proprioception, gender, and age on UL impairment and activity outcomes is not yet clear

It is not known:

- To what extent initial activity limitation predicts later activity limitation and what timing is optimal for prediction of outcome
- To what extent initial severity of activity limitations influences responses to bilateral training inpatients with acute stroke
- Whether proprioception, gender and lesion site influence BT responses in patients with acute stroke

- Whether effects of lesion side and hand dominance influence BT in patients with acute stroke

The next section moves from examination of the contralesional UL to examine the effects of stroke on the ipsilesional UL.

2.4 EFFECTS OF STROKE ON IPSILESIONAL UPPER LIMB PERFORMANCE

Evidence suggests that effects of stroke are not only experienced contralesionally, but that ipsilesional dysfunction also occurs. Brodal, a neuroanatomist, first reported altered ipsilesional skilled movement and handwriting after his own right internal capsule stroke (Brodal 1973). Subsequent research shows that - although subtle compared to contralateral effects - stroke causes ipsilesional UL motor performance deficits that vary depending on side of hemispheric damage (Desrosiers et al. 1996, Prigatano and Wong 1997, Sunderland et al. 1999, Sunderland 2000). Deficits may result from damage to bilaterally organised neural networks that respond to BT (McCombe-Waller and Whitall 2004). It was appropriate therefore to review the nature of ipsilesional dysfunction, to review its clinical relevance, and to examine the case for BT in that context. In this section, studies demonstrating the existence of ipsilesional deficits were evaluated followed by a review of behavioural and neural mechanisms underlying the phenomenon. Finally, evidence relating to recovery and training approaches was reviewed and the potential role of BT discussed.

One point of note should be made regarding the breadth of this part of the review. There is a large literature in the field of motor control science evaluating ipsilesional performance using kinematic measures. The purpose of much of that literature is to investigate differences between right and left hemispheric control of movement, and to develop and evaluate motor control models of different movement phases during ballistic and targeted movement e.g. (Winstein and Pohl 1995, Hermsdorfer et al. 1999, Farne et al. 2003). That literature - whilst of interest - is not of direct relevance to the clinical focus of this thesis and was therefore not reported and reviewed here. In this review, only papers of clinical relevance were included.

The search strategy for this part of the review is described in Appendix 2.

2.4.1 THE NATURE OF IPSILESIONAL DYSFUNCTION

Although many studies have used sensitive kinematic assessment of movement parameters to investigate ipsilesional performance, the main focus of this thesis is clinical outcomes; therefore the review was limited to clinically detectable deficits. The nature of ipsilesional

impairments are examined first, followed by activity limitations. Clinically detectable ipsilesional activity limitations relevant to UL task performance are reviewed first, in section 2.4.1.1. Evidence for ipsilesional motor and sensory impairments is evaluated in sections 2.4.1.2 and 2.4.1.3, followed by a discussion of the neural and behavioural mechanisms underlying ipsilesional dysfunction.

2.4.1.1 Ipsilesional activity limitation

Studies investigating UL ipsilesional activity limitations are described in Table 10, Appendix 3. Ipsilesional activity limitations documented in the literature can be categorised as dexterity and gross UL activity limitation. The relationship between UL activity limitation and global activity limitation has also been explored and will be discussed.

DEXTERITY

Dexterity deficits following stroke appear to vary depending on lesion side, however their functional relevance is not yet clear. Ipsilesional activity limitation has primarily been explored using timed dexterity tasks (Table 8, Appendix 3) because these are sensitive enough to detect relatively subtle ipisilesional performance deficits, mainly expressed in slowed performance compared to normal. Tests using everyday objects to evaluate gross dexterity will be discussed first.

Several studies used the timed Jebsen Hand Function Test (JHFT) which times performance of everyday dexterity tasks. (Bovend'Eerdt et al. 2004). Sunderland (Sunderland et al. 1999) demonstrated ipsilesional slowing in 15 acute participants with left hemisphere damage (LHD), five of whom were apraxic, compared to controls. In most participants the difference was resolved by six months (Sunderland 2000) but 30% of LHD participants demonstrated persistent slowing not exclusively related to apraxia. Similarly, Spaulding (Spaulding et al. 1988) found slowed performance in participants with LHD compared to right hemisphere damage (RHD); and LHD apraxic participants were slower than non-apraxic. Diverse participant aetiology in that study means that conclusions can only be tentatively applied to stroke. Furthermore, heterogeneity of time since onset, numerous assessors, scant procedural details and use of published norms for comparison rather than matched controls limit the robustness of findings (Spaulding et al. 1988). Both the above studies also demonstrated slowed RHD performance on the JHFT compared to controls, but in each, participants with LHD were persistently slower.

Similarly, slowed performance in participants with chronic stroke compared to controls has also been found on the JHFT (Wetter et al. 2005) but only 37% of 59 participants demonstrated contralateral deficit, so this sample may have been unrepresentative of the hemiplegic population. There was no difference in that study between RHD and LHD. Furthermore, sub-groups were very small for the conducted statistical procedures therefore findings must be cautiously interpreted. Another study (Desrosiers et al. 1996) demonstrated slowed dexterity compared to controls in participants with longstanding stroke on the timed TEMPA UL test and the box and block test (Table 8, Appendix 3), but no significant difference between participants with LHD and RHD. In contrast to the study by Sunderland discussed above (Sunderland 2000), these studies suggest that dexterity deficits may persist more than one year after stroke. Differences in test sensitivity between studies for detection of subtle hemispheric differences in dexterity, or population differences such as age and time post-stroke between studies, may explain contrasting results. Furthermore, participants self-selected by responding to mailing for one study (Desrosiers et al. 1996) which may have created a sample that was less likely to be impaired than in those in which population screening was conducted (Sunderland et al. 1999), whilst other studies reported no details of recruitment. Overall, it seems that ipsilesional deficits in gross dexterity exist and may persist into the chronic stage more than six months after onset. It is unclear whether individuals with LHD and RHD experience differing degrees of dysfunction, however there is some evidence that LHD leads to slower performance.

Fine dexterity or finger dexterity appears to be affected in a similar fashion to gross dexterity. Slowed dexterity existed on a nine hole peg placement test (9HPT) in individuals 60 days post-onset with RHD and LHD (Yelnik et al. 1996). For the LHD group, significant deficits persisted even after apraxic participants were removed from analysis. Similarly, Marque (Marque et al. 1997) demonstrated significant slowing on that test in 15 participants with LHD compared to controls at 90 days post-onset. Furthermore, in a small pilot study, Morris (2003) observed slowed 9HPT performance in 7 participants with LHD in the acute post-stroke period compared to 7 with RHD, although data was not tested statistically. Conversely, although Desrosiers (1996) demonstrated poorer dexterity on the Purdue peg test compared to controls, no difference between LHD and RHD was found. Small sub-groups may have influenced findings and compared to other studies, while participants were in a more chronic stage. Although the weight of evidence suggests that LHD influences ipsilesional fine dexterity more than RHD, the lack of consistent findings suggests that the

impact of side of hemispheric damage on ipsilesional fine dexterity requires further investigation.

In summary, compared to matched controls, participants with LHD and RHD appear to demonstrate clinically detectable dexterity deficits in tasks involving both everyday objects and in timed peg and block placement tests. Participants with both LHD and RHD appear affected, however some studies suggests that participants with LHD may be more severely affected particularly where participants are apraxic. Several studies have however found no effect of side. Differences in outcome may be a result of methodological limitations and differences in timing, test methods and analyses, and there is a need to further examine the nature of ipsilesional dexterity impairment in an adequately powered study.

GROSS UPPER LIMB ACTIVITY LIMITATION

Ipsilesional deficits in gross UL activities have also been demonstrated. Broeks (1999) found ipsilesional deficits in 11 of 54 participants on the Action Research Arm Test four years after stroke onset. All participants completed the test, but some scored submaximally because of slowness. Details of the data, scoring methods and reliability were scant however and neither hemispheric differences nor apraxia were examined. Sub-maximal scores however indicate potentially important deficits relevant to UL activity in everyday life, and this is an area for further research.

CHANGE IN UPPER LIMB ACTIVITY LIMITATION OVER TIME

Most ipsilesional studies were cross-sectional and conducted with participants in the chronic stage; therefore little evidence exists about the recovery pattern and timescales of ipsilesional activity limitation. Significant recovery of timed dexterity at six months (Sunderland 2000) and 90 days (Marque et al. 1997) respectively was shown in two studies, however participants remained impaired at follow-up compared to controls in both, suggesting long-term deficit. In one study (Sunderland 2000), this only concerned participants with LHD. No other studies examined recovery of ipsilesional activity or the differential recovery of participants with LHD and RHD, although several studies with participants in the chronic stage demonstrate persistent deficits even years after stroke (Desrosiers et al. 1996, Wetter et al. 2005). There is therefore a need to examine more closely timing of recovery of ipsilesional activity limitation from the acute stage in order to better understand its potential impact post-stroke.

2.4.1.2 Ipsilesional motor impairment

FINGER TAPPING

Finger tapping speed, like fine dexterity, may also be influenced by stroke and related to overall functional performance. Less task-related than the dexterity tasks described above, slowed finger tapping speed may signify bilateral cerebral hemispheric dysfunction (Prigatano and Wong 1997), disruption to systems that subserve planning, timing and speed (Haaland and Harrington 1994), or disruption to motor pathways (Desrosiers et al. 1996) however exact mechanisms have not been determined. Furthermore, findings from the literature examining this phenomenon are not consistent. Studies are summarised in Table 9, Appendix 3. Several studies of participants with acute (Marque et al. 1997, de Groot-Driessen et al. 2006) and chronic stroke (Hermsdorfer and Goldenberg 2002, McCombe-Waller and Whitall 2004) demonstrated no ipsilesional finger tapping deficits compared to healthy controls. Other studies however have demonstrated that finger tapping is slower in patients than controls (Harrington and Haaland 1992, Ietswaart et al. 2006). Assessment methods included a variety of computerised measures of tapping (Marque et al. 1997, McCombe-Waller and Whitall 2004, de Groot-Driessen et al. 2006) or kinematic measurement (Hermsdorfer and Goldenberg 2002, Ietswaart et al. 2006) and variation in sensitivity of the measurement approaches to detect differences might explain the contrasting findings. Chronicity may also be a factor however findings from patients at different time points are mixed, with some demonstrating deficits in the acute stage and others in the chronic stage.

Apraxia, a deficit of movement execution, may be an explanatory factor for reduced tapping speed. One study found no difference in finger tapping speed between apraxic and non-apraxic participants (Harrington and Haaland 1992). Conversely, Ietswaart (2006) found slowing compared to matched controls in participants with LHD and apraxia, suggesting that these factors may influence tapping speed. Only seven individuals of varied chronicity participated in that study however, and no comparison was made to participants with RHD so it is not clear from that study if the deficit applied only with LHD. Thus evidence is not conclusive about the impact of apraxia on tapping speed.

It appears that ipsilesional finger tapping deficits may depend on time post-stroke, the presence of apraxia, interhemispheric differences in motor control, or simply measurement

sensitivity, however collectively the evidence suggests that finger tapping speed may be an important clinical tool for predicting recovery.

GRIP STRENGTH

Diminished ipsilesional grip strength has been demonstrated soon after stroke, but appears to resolve within the first year post onset. Three studies (Jones et al. 1989, Marque et al. 1997, Sunderland et al. 1999) (Table 10, Appendix 2) demonstrated significantly diminished ipsilesional grip or UL strength in acute and sub-acute participants compared to matched controls. Improvements were found at follow-up assessments between 90 days and 12 months, suggesting that deficits mainly resolved within a year. One study found that participants with left hemisphere damage (LHD) performed more poorly than those with RHD (right hemisphere damage) and controls, but this was not significant and had resolved at 6 months, however the study sample (n=24) was small for that sub-group analysis (Sunderland 2000) (Table 8, Appendix 3). Resolution within one year concurs with another study (Desrosiers et al. 1996) where no grip strength deficit was found in participants with longstanding stroke.

Sample size varied and in some studies was very small (Marque et al. 1997, Jones et al. 1989) making generalisation of findings difficult. However, all compared participants to matched healthy controls, accounting for other confounding variables. All studies used instrumented hand dynamometry to measure strength, rather than clinical scales, however none reported measurement reliability and in one, reporting of research questions and measurement procedures was scant (Jones et al. 1989). Despite methodological limitations, it can be concluded with some certainty that ipsilesional grip strength is reduced following stroke, but resolves between three months and one year, irrespective of side of damage.

Grip requires comparatively low sensorimotor control and feedback for accuracy with low levels of interhemispheric interaction for its execution (Jones et al. 1989) and consequently is probably minimally influenced by damage to bilaterally organised neural networks. The rapid recovery may thus relate to task simplicity. The timescale may also reflect general recovery. Strength deficits may be addressed through increased ipsilesional use for functional tasks to compensate for contralesional effects of hemiplegia (Desrosiers et al. 1996).

2.4.1.3 Relationship between ipsilesional motor dysfunction and global activity limitation

Although the subtle ipsilesional activity limitations and impairments described above are of academic interest in providing information about performance and hemispheric functioning, an important question arises about the clinical relevance of the findings. There is some evidence that they might be indicators of global functioning. Relationships between rehabilitation outcomes and admission finger tapping speed have been demonstrated, suggesting that it may be a useful predictor of recovery. One study (Prigatano and Wong 1997) (Table 9, Appendix 3) demonstrated a relationship between admission tapping speed and achievement of rehabilitation goals; however goal achievement was not standardised or well described. Another study (de GrootDriessen et al. 2006) (Table 9, Appendix 3) demonstrated that admission tapping speed and Barthel Index scores were significantly correlated and that together they predicted 49% of variance in Barthel Index at discharge. However measurement was conducted by several raters, which may have influenced findings since there was no reported rater reliability. Also, the Barthel Index predicted 44% of variance, unsurprisingly suggesting that it is much more important to later outcome than finger tapping. Together these studies show that there may be a predictive relationship between global functioning and a simple, rapid finger test.

Similarly, fine dexterity on a peg test correlated with functional independence in one study of individuals in the chronic stage (Desrosiers et al. 1996) (Table 8, Appendix 3) whilst gross dexterity and proprioception were related to self-perceived activity levels, again suggesting relationships between ipsilesional impairment and global activity. However the findings were not replicated in another study in the acute stage (Sunderland 2000) (Table 9, Appendix 3) where no significant correlation between ipsilesional dexterity and a measure of extended ADL at six months was found. The contrasting findings might be explained by differences in sample size across studies and use of different measures of dexterity and functioning. Extended ADL and ADL measure different constructs. ADL is a physically focused outcome that may be more closely related to ipsilesional dexterity than extended ADL which may involve more cognitive and communication skills with weaker relationships to physical indicators like finger control.

Thus there is some evidence of a link between ipsilesional fine finger control and global activity limitation, however evidence of the link is not is not entirely conclusive. Ipsilesional performance on a simple finger test may be predictive of global functioning and has clinical potential as a simple bedside test of global cortical functioning. However as the studies

demonstrate, further investigation is required to confirm the relationship and clarify how the variables interact to determine the clinical importance of ipsilesional dysfunction.

2.4.1.4 Ipsilesional sensory impairment

Intact somaesthesia appears important for UL function (Leonard 1998) therefore ipsilesional sensory deficits may contribute to diminished UL and global functioning following stroke (Kim and Choi-Kwon 1996). It was relevant therefore to examine what is known about ipsilesional sensory deficits after stroke. Studies are summarised in Table 11, Appendix 3.

TACTILE SENSATION

The impact of ipsilesional tactile sensory dysfunction on ipsilesional motor performance is unclear. Studies are summarised in Table 11, Appendix 3. Two early studies (Boll 1974, Fontenot and Benton 1971) demonstrated poorer ipsilesional tactile perception in participants with RHD compared to LHD. Participants in both were poorly described with mixed aetiology, making inferences for stroke difficult. Inclusion criteria were poorly defined and only Fontenot (1971) compared participants to controls. Boll (1974) aggregated results from three different sensory tests making inferences about particular tactile domains difficult. In another study (Essing et al. 1980) which described populations and procedures clearly, higher ipsilesional light touch thresholds in stroke participants compared to controls were demonstrated however no hemispheric differences were detected. The diverse range of participant chronicity in the study may have influenced results, given that recovery might not be complete in participants in the earlier post-stroke periods. Conversely, Derosiers (1996) found unimpaired touch thresholds and no hemispheric differences in participants with chronic stroke compared to controls. In the only study in the acute stage, Kim (1996) demonstrated intact ipsilesional texture discrimination but impaired point localisation and stereognosis, suggesting that there might be variation in deficits depending on the domains under assessment. No study examined the relationship between tactile impairment and functional recovery. Clearly uncertainty exists about the existence and nature of ipsilesional touch impairment and hemispheric differences relating to it. This is an area that requires further investigation with participants with homogeneous aetiology.

DISCRIMINATIVE SENSORY FUNCTIONING

The nature and importance of ipsilesional discriminative sensory functioning is also unclear. Two studies found no two-point discrimination (2PD) deficits (Desrosiers et al. 1996, Kim and Choi-Kwon 1996) in individuals with acute and chronic stroke respectively, but the study by Kim demonstrated point localisation deficit in 17 of 57 participants that was not related to lesion side. Morris (2003) however demonstrated no deficits in 2PD in a small pilot study (Table 11, Appendix 3), but did find a higher frequency of impaired tactile localisation using the Nottingham Sensory Assessment in RHD (n=4 of 5 participants) compared to LHD (n=1 of 5 participants), suggesting hemispheric differences might exist in ipsilesional tactile discrimination. Clear conclusions cannot be made from such a small sample however. From this literature, evidence of impact of stroke on ipsilesional tactile discrimination impairment and effects of side of stroke is inconclusive. Findings may reflect differences in tests, timing and sample size and require further investigation to determine the nature of tactile localisation and its impact on ipsilesional performance.

PROPRIOCEPTION

Proprioception is an integrative sensory modality important for multi-joint control during complex movement (Leonard 1998) that may be affected ipsilesionally. Two studies found impaired ipsilesional thumb and elbow proprioception in individuals with chronic stroke compared to controls, using conventional clinical tests (Desrosiers et al. 1996, Sartor-Glittenberg and Powers 1993) (Table 11, Appendix 3). No hemispheric differences were found. Similarly, proprioception scores between participants with RHD and LHD did not differ in acute (Morris 2003) or chronic stroke (Desrosiers et al. 1996) although in one study no statistical comparison was possible because of the small sample (Morris 2003). Conversely, no position sense impairment was reported in a sample of 67 acute stroke participants (Kim and Choi-Kwon 1996). Tests across studies were diverse, measuring movement (Desrosiers et al. 1996, Sartor-Glittenberg and Powers 1993) or position sense (Morris 2003, Kim and Choi-Kwon 1996) and study samples varied in size and chronicity, making comparison difficult. Findings suggest that impaired ipsilesional proprioception may exist but the diversity of measures and findings mean that it requires further investigation before definitive conclusions can be drawn. Effects of lesion side also require confirmation because differences in measurement approach make conclusions unclear. Change over time and effects on functional outcomes have not been examined.

No studies tracked change in ipsilesional sensory impairment over time.

In summary, for ipsilesional tactile sensation, discriminative sensory functioning and proprioception, the literature is unclear about whether deficits exist and whether they relate to side of hemispheric damage. The most likely explanation for this is the diversity of approaches to measurement of sensory function in which some studies used clinical tests (Desrosiers et al. 1996, Sartor-Glittenberg and Powers 1993) and others used more sophisticated, standardised measures of sensation (Kim and Choi-Kwon 1996). Timing of assessment may also have influenced findings, but no clear pattern of findings related to chronicity was apparent. To fully understand ipsilesional dysfunction and to determine its clinical importance, further investigation of ipsilesional sensory dysfunction at a clinical level should be conducted, and change over time should be examined.

Having explored what is known about clinically relevant ipsilesional dysfunction, it was appropriate next to explore what is known about neural and behavioural mechanisms underpinning it.

2.4.2 NEURAL AND BEHAVIOURAL MECHANISMS UNDERLYING IPSILESIONAL DYSFUNCTION

Although mechanisms for ipsilesional motor deficits are not fully understood, there are several explanations that may underpin the deficits. Disrupted neural pathways (Spaulding et al. 1988, Jones et al. 1989) and disruption to hemispheric executive functioning (Haaland and Harrington 1994, Winstein and Pohl 1995) including apraxia (Harrington and Haaland 1992, Ietswaart et al. 2006) have been proposed as possible explanations for ipsilesional impairment (Sunderland et al. 1999) and it is probable that impairment arises from a complex combination of these factors.

2.4.2.1 Neural mechanisms

Physiological mechanisms underlying ipsilesional deficits probably involve multiple interrelated neural substrates, reflecting descending bilateral hemispheric control of UL movement. Although movement is predominantly controlled by the contralateral hemisphere, evidence suggests bilateral cortical activation during unilateral movement. The corticospinal tract originates from the primary motor cortex and associated premotor areas.

Although most fibres cross and terminate contralaterally in the spinal cord, between 10 and 15% of fibres descend ipsilaterally to the ventral spinal cord (Brinkman and Kuypers 1973). These probably contribute to bilateral control of unilateral movements (Lacroix et al. 2004, Debaere et al. 2001), although most influence is probably on proximal musculature with limited distal influences (Brinkman and Kuypers 1973). Direct cortical motor area damage through stroke may therefore damage the uncrossed as well as crossed pathways, resulting in subtle ipsilesional motor deficits (Pohl et al. 2000).

Damage to the integrity of bilaterally distributed neural networks may also lead to ipsilesional dysfunction. Healthy subjects demonstrate bilateral cortical network activation during unilateral UL tasks, involving ipsilateral primary motor, sensory and premotor cortices as well as supplementary motor areas, which become increasingly active with task complexity (Shibasaki et al. 1993, Winstein and Pohl 1995, Chen et al. 1997, Catalan et al. 1998). Stroke results in changes that may damage the functioning of these networks resulting in ipsilesional performance deficits, despite predominant contralateral motor control (Cramer 2004, Calautti and Baron 2003, Caramia et al. 2000). The fact that ipsilesional dysfunction is mainly seen in complex, rapid tasks such as fine dexterity and rapid finger tapping supports this explanation, however supporting evidence from functional imaging is scant.

Evidence of altered bilateral networks in stroke comes from only one fMRI study where ipsilesional UL movement demonstrated activation patterns more usually associated with hemiplegic UL movement (Hanlon et al. 2005). Damaged hemisphere motor, sensory and anterior cingulate cortex areas in seven sub-acute stroke participants were more active than controls on ipsilateral UL movement. This suggested that bilaterally distributed neural network activation for ipsilesional UL control was significantly altered, possibly representing beneficial recovery mechanisms, but alternatively suggesting abnormal responses that may interfere with normal ipsilesional movement. Findings should be regarded carefully however. Although no synkinesis was observed during testing, researchers did not measure or control for it, thus subtle contralesional UL activity may have occurred during scanning and have confounded findings. Clearly more research is required to establish ipsilesional neural activation patterns and their relevance to ipsilesional impairment and global functioning.

Disrupted transcallosal interactions and interhemispheric inhibition may also underpin altered ipsilesional motor control. The damaged hemisphere receives abnormally high interhemispheric inhibition from the undamaged hemisphere following stroke (Cauraugh and Summers 2005). The non-damaged primary motor cortex receives low interhemispheric inhibition from the damaged hemisphere (Butefisch et al. 2003, Liepert et al. 2000). The reduced hemispheric inhibition from the damaged hemisphere probably changes the excitability pattern of the undamaged hemisphere and may lead to ipsilesional limb performance deficits (Yarosh et al. 2004), but this theory is currently speculative, and requires further investigation.

Summarising, investigations into neural mechanisms responsible for ipsilesional deficits in stroke are scant. Theoretically however, disruption to ipsilateral neural pathways, bilaterally distributed neural networks or abnormal interhemispheric inhibition may be implicated. It is likely that a combination of these mechanisms is responsible; however exact neural mechanisms have yet to be comprehensively examined.

2.4.2.2 Behavioural mechanisms

Examination of the nature and role of apraxia and other cognitive deficits in ipsilesional impairment is beyond the scope of this thesis, however given that apraxia has been implicated in some studies as a possible cause of some ipsilesional deficits, a brief definition of the nature of the phenomenon is warranted here. The left hemisphere is thought to have an executive role in planning and sequencing movement and hemispheric damage may result in the global deficit of apraxia that in stroke may in part explain deficits in ipsilesional performance. Poizner (1998) page 163, defined apraxia as:

> "an impairment of the execution of learned, skilled, purposeful movements when the incorrect performance cannot be explained by weakness, impaired perceptual systems or lack of co-ordination"

Apraxia is particularly associated with left hemisphere damage (LHD) in right hand dominant participants (Kimura 1977). Thought to be caused by loss of learned kinaesthetic and spatial representation of movement from the left parietal cortex, or translation of those representations to motor programmes (Poizner et al. 1998), in its most overt presentations apraxia presents as inability to co-ordinate spatial and temporal characteristics of movement

in gesture imitation (Poizner et al. 1998), motor sequences (Harrington and Haaland 1992, Kimura 1977), skill acquisition (Kimura 1977) and finger tapping (Ietswaart et al. 2006).

Several clinical studies have demonstrated association between ipsilesional dexterity impairment and apraxia. In these studies, participants with LHD and apraxia performed more poorly than controls, participants with RHD and participants with LHD without apraxia, (Ietswaart et al. 2006, Sunderland et al. 1999). Findings have not all been equivocal however and other studies have demonstrated no associations between timed pegboard performance (Harrington and Haaland 1992) or reaction time (Spatt and Goldenberg 1997) and apraxia. Deficits caused by apraxia may be more apparent in error rate rather than speed therefore effects may be more apparent in tests assessing accuracy (Sunderland et al. 1999) than speed (Harrington and Haaland 1992). Clearly the impact of apraxia on ipsilesional performance should be considered as a possible cause of deficits, particularly in LHD, however ipsilesional deficits also exist in the absence of apraxia and may vary in nature depending on lesion side.

HEMISPHERIC FUNCTIONS

Other specific hemispheric executive functions relating to motor control may explain hemispheric differences in clinically detectable deficits. These have emerged from studies examining motor control using sensitive tests to determine kinematic profiles and movement parameters during ipsilesional aiming and prehension tasks. Several studies examining these functions are reviewed below. Because the main focus of the present study was on clinical outcomes, this section was not intended to be comprehensive, but used a few key studies to illustrate the main findings relating to hemispheric differences.

Comparing kinematic trajectories of 20 participants with chronic stroke exhibiting RHD and LHD to controls, Winstein (Winstein and Pohl 1995) demonstrated that participants with LHD were slower than controls during the initial transportation phase of a rapid aiming task whilst those with RHD demonstrated slowing and reduced velocity smoothness during target impact, particularly with increased accuracy demands. Similarly, Hermsdorfer (1999) demonstrated that 21 participants with LHD were slower reaching maximum velocity and decelerating in the transport phase of movement of a pinch grip movement than 19 participants with RHD, who were slower in the terminal movement phase where accuracy adjustments were required. There was no association between apraxia and kinematic parameters in participants with LHD. Similarly two early studies (Haaland and Harrington

1989, Haaland and Harrington 1994), showed slower ipsilesional reaction times, prolonged movement and more errors when reaching to targets of differing sizes in participants with longstanding LHD compared to controls. This was observed particularly as accuracy demands decreased, suggesting an executive left hemispheric role in controlling the early, ballistic phase of movement. During this phase, rapid, pre-programmed movement that does not require accuracy adjustment occurs, and in the studies, participants with RHD were not significantly different to controls. These findings were supported by Pohl (Pohl et al. 2000) who, using a similar task, demonstrated longer ipsilesional dwell times and movement times in ten well-recovered participants with LHD compared to ten with RHD and ten age matched controls. Participants with RHD did not differ from controls.

The selected studies are only a small sample of this body of literature. The studies were small and measures and tasks varied, however findings support clinical studies which overall tend to suggest that LHD causes more slowing than RHD. The difference appears to occur in the first phase of movement suggesting an executive role for the left hemisphere in movement planning and sequencing in the initial phase of pre-programmed ballistic movement. These studies support findings from clinical research, in suggesting that slowing caused by LHD may be independent of apraxia. Findings are less consistent for RHD. The right hemisphere appears to exert visuo-spatial movement control and on-line sensory-motor adjustment for accuracy during the terminal phase of precision movement (Haaland and Harrington 1989) but findings across studies have not been completely unequivocal. Findings may have been influenced by differing accuracy demands of task characteristics, a finding reflected in the clinical studies. Whilst all these ipsilesional deficits are subtle, the slowing of movement caused by LHD appears most likely to be apparent and detectable using clinical measures.

In summary, hemispheric differences in executive functioning may explain some of the differences in ipsilesional functioning between individuals with LHD and RHD. Some but not all differences may be related to presence of apraxia with LHD, but LHD can cause slowing in the absence of apraxia. The type of task may also influence whether slowing is detected or not, since the left hemisphere has control of ballistic, pre-programmed movements whereas the right hemisphere controls tasks requiring accuracy and on-line adjustment.

2.4.3 EFFECTS OF TRAINING

The impact of training on ipsilesional impairment has not been extensively examined although some studies suggest that with practice, ipsilesional performance may improve. One study demonstrated improved ipsilesional performances between a first and second trial in a single session on a tracking test, particularly with LHD (Yelnik et al. 1996) however learning effects and retention beyond the single test session were not examined. Similarly, Pohl (Pohl et al. 2000) examined training effects on a Fitts tapping test in 10 participants with chronic stroke and 10 age-matched controls. With practice in a two hour training session, movement time, acceleration, deceleration, dwell time and peak horizontal velocity significantly improved, however participants with LHD demonstrated persistently higher dwell times than controls and participants with RHD. The sample small size, and lack of follow-up assessment preclude definite conclusions about sustained effectiveness of such training, however. In spite of the above limitations, these studies provide some evidence that ipsilesional performance on relatively complex tasks may improve with practice. Although there is some evidence that side of stroke may influence learning, further investigation is required to confirm this.

BT also affords possibilities for training of the ipsilesional UL. In a study examining ipsilesional and contralesional finger tapping rate and consistency of 10 participants with longstanding stroke, McCombe (2004) demonstrated no deficits in ipsilesional rate or consistency in unilateral tapping compared to controls; however ipsilesional deficits during bilateral tapping were demonstrated. Participants subsequently underwent six weeks of UL training involving rhythmic repetitive reaching (BATRAC) not involving specific finger training, and using an intervention designed to influence *contralesional* UL recovery. Following training, consistency of inter-trial intervals during bilateral in and anti-phase tapping improved to a level that did not differ from baseline scores of healthy controls. This was a very small study, and only four participants of ten were able to tap bilaterally. It provides some evidence however that BT may influence certain ipsilesional movement parameters and suggests that further investigation of the effects of BT on ipsilesional deficits is warranted. It is however of clinical importance and relevance to the current thesis to examine effects of BT on ipsilesional performance of more functional outcomes, such as dexterity and activity limitation.

2.4.4 CONCLUSIONS

A range of ipsilesional impairment and activity limitation have been demonstrated in the literature, and although subtle compared to contralateral effects of stroke, the balance of evidence suggests that deficits exist. The full nature of deficits in right and left hemisphere stroke and their functional implications have yet to be determined however. Therapists must fully understand the nature of these deficits to be able to fully address the whole breadth of rehabilitation challenges presented by contralesional *and* ipsilesional dysfunction and this review has highlighted many areas for further research.

Overall, findings from this section of the literature review show it is clear that:

- Ipsilesional slowing, detectable on clinical tests of gross and fine dexterity exists after stroke and may persist into the chronic stage
- In some cases slowed dexterity is associated with apraxia
- Grip strength is reduced after stroke but tends to recover by three to six months post-stroke
- There is a relationship between ipsilesional finger tapping speed and global functioning
- Bilateral movement function training may influence ipsilesional UL co-ordination patterns

It is less clear:

- Whether ipsilesional gross UL activity limitation, or impaired tactile sensation, discriminative sensory function and proprioception exist after stroke
- Whether ipsilesional deficits in dexterity, gross UL activity limitation, tactile sensation, discriminative sensory function and proprioception recover over time
- Whether scores in timed ipsilesional dexterity, gross UL activity limitation, tactile sensation, discriminative sensory function and proprioception differ depending on side of hemispheric damage
- Whether ipsilesional dexterity and gross UL activity limitation are related to global functioning
- Whether a programme of bilateral task training influences ipsilesional outcomes on clinical measures.

2.5 CHAPTER SUMMARY AND CONCLUSIONS

In this chapter, the evidence relevant to physical outcomes of bilateral training targeting the contralesional UL has been reviewed, and demonstrates that evidence for effectiveness of bilateral task training is scant. Given its ecological relevance to everyday UL function, the intervention requires comparison to unilateral task training in an acute stroke population.

Little is known about the patient populations that might benefit most from BT therefore demographic and physical factors that might influence these BT outcomes were also reviewed. The role that the factors may play in prediction of UL recovery was additionally evaluated. A number of factors were identified that require investigation in the context of BT and, of relevance to rehabilitation as a whole; these will also be examined as overall predictors of UL recovery.

Evidence for the existence of ipsilesional dysfunction was examined next and the nature of this dysfunction was explored, followed by review of training interventions that might influence ipsilesional recovery. The section concluded that there is a small amount of evidence suggesting that BT may influence ipsilesional performance even when the intervention is targeted at the contralesional limb. Therefore after establishing that ipsilesional dysfunction may be apparent on selected clinical measures, and evaluating effects of side of hemispheric damage and its relationship to global functioning, effects of BT on clinical ipsilesional outcomes should be investigated.

Research questions relating to all of these points will be presented in Chapter 4, the methods section. But first, Chapter 3 moves from examination of physical outcomes of BT to determine the evidence for examination of psychosocial outcomes in the context of BT, which will yield a set of additional questions to be addressed.

CHAPTER 3

LITERATURE REVIEW

PSYCHOSOCIAL OUTCOMES: BILATERAL UPPER LIMB TRAINING, ANXIETY, DEPRESSION AND HEALTH RELATED QUALITY OF LIFE

3.0 INTRODUCTION

The previous chapter focused on physical upper limb (UL) outcomes in the context of bilateral training (BT) and UL recovery. However given the catastrophic impact of stroke on the life of an individual it is relevant in this final review chapter to examine the literature relating to the psychosocial impact of stroke in general, and BT and UL recovery in particular. This is important since the rehabilitation literature has typically and narrowly focused on physical outcomes, often ignoring the wider implications of rehabilitation interventions on the lives of survivors beyond impairment and disability outcomes. The emotional impact of stroke is of key concern to patients and their carers and impacts on their recovery and rehabilitation (Gainotti et al. 2001, Chemerinski and Robinson 2000). Anxiety and depression are important emotional sequelae of stroke. Whilst it is known that relief of depression is associated with improved activities of daily living (ADL), much less is known about the impact of physical improvements through rehabilitation on anxiety and depression outcomes. Upper limb dysfunction is known to adversely influence general psychological well-being one year after stroke (Wyller et al. 1997), but the impact of UL training on psychological outcomes has not received much interest to date. The purpose of Section 3.1 was to focus on how UL interventions intended to improve stroke outcomes -and UL recovery in particular - may influence an individual's psychological wellbeing.

Health related quality of life is a multidimensional measure of the impact of health and health outcomes on an individual's satisfaction with life. Little is known about the impact of UL rehabilitation interventions on HRQOL. Also, it is not clear which aspects of UL dysfunction most influence HRQOL. This chapter therefore discusses the important psychosocial outcomes of anxiety, depression and health related quality of life in the context of UL rehabilitation. Section 3.1 addresses anxiety and depression and section 3.2 addresses

health related quality of life. Each topic is first examined in the context of stroke in general before focusing on UL recovery and BT in particular.

3.1 ANXIETY, DEPRESSION AND UPPER LIMB DYSFUNCTION IN STROKE

Neuropsychiatric complications such as depression, anxiety, apathy and pathological affect are common following stroke (Chemerinski and Robinson 2000). Of these, depression and anxiety are the most common and may impact on recovery and responses to rehabilitation (Gainotti et al. 2001, Chemerinski and Robinson 2000). Depression has been described by Watson (1995, pp3) as "the emotion of sadness associated with feelings of sorrow, hopelessness and gloom" whilst anxiety "is centred on the emotion of fear, and involves feelings of worry, apprehension and dread". The relationship between functional performance and anxiety and depression remains unclear, however (Chemerinski and Robinson 2000, Chemerinski and Levine 2006). In this section, the relationship between post-stroke depression (PSD), anxiety, functional recovery and responses to rehabilitation is examined, and implications for UL recovery are reviewed.

3.1.1 POST-STROKE DEPRESSION

3.1.1.1 Incidence of post-stroke depression

Between 18 and 61% of individuals with stroke experience PSD (Chemerinski and Levine 2006, Gainotti and Marra 2002). Reported incidence depends on timing and location of assessment, diagnostic criteria, existence of pre-stroke depression, and lesion location (Gainotti and Marra 2002, Kim and Choi-Kwon 2000). For more acute patients, within three months of onset, reported incidence was between 18% (Kim and Choi-Kwon 2000) and 30% (Dennis et al. 2000). Some studies excluded individuals with pre-stroke depression (Kim and Choi-Kwon 2000) thus providing a more accurate estimation of *post-stroke* depression. One review (Chemerinski and Levine 2006) suggested that in acute stroke incidence is 25-30%. It is thus clear that diagnosis of depression is difficult in stroke and that approaches to diagnosis vary and may influence recorded incidence. Many individuals experience

cognitive and communication difficulties making diagnosis difficult and contributing to the wide range of incidences described.

The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2000) is the gold standard for diagnostic criteria for PSD. Depression is usually identified in structured interview using these criteria; however this method is difficult for many patients with stroke. Many studies therefore extract the criteria from standardised measures of depression, a method criticised for inclusion of features that may reflect the stroke itself, rather than PSD (Turner-Stokes and Hassan 2002). Validity of these questionnaires for depression diagnosis in stroke has often not been evaluated, a factor that may influence reported incidence (Turner-Stokes and Hassan 2002) making it difficult to accurately determine from the literature how common PSD is.

3.1.1.2 Causes of post-stroke depression

Mechanisms underlying PSD are complex and exact mechanisms unclear. Physical *and* psychological determinants have been proposed (Gainotti and Marra 2002, Chemerinski and Levine 2006). Lesion site, specifically left sided anterior lesions has been associated in some studies with PSD (Robinson et al. 1975, Carson et al. 2000). Bias and methodological limitations inherent in individual studies, such as highly selective samples, small sample sizes and exclusion of aphasic patients may have exaggerated effects of lesion site (Carson et al. 2000) and several systematic reviews found no evidence of links between lesion site and depression from pooled analyses (Singh et al. 1998, Carson et al. 2000, Gainotti and Marra 2002).

In a proposed psychological model, PSD results as a reaction to the physical consequences of stroke and is not anatomically defined (Gainotti and Marra 2002, Nannetti et al. 2005, Whyte and Mulsant 2002). Here, depression is linked to functional impairment but only in so much as it is mediated by perceived meaning ascribed by the patient to their disability or impairment (Gainotti and Marra 2002).

Stroke severity and physical disability are consistently associated with PSD however, with cognitive impairment a third important factor (Hackett and Anderson 2005). Social factors, such as hospitalisation, presence of a spouse, and other social support add to the complexity of the condition (Hackett and Anderson 2005). In that review, depression was defined by

DSM criteria in 7 studies using information from six different mood scales, and in the other studies by structured interviews and in several studies by a single question. The authors report that the heterogeneity of the measures and the poor statistical methods made the ability to draw conclusions difficult.

It is clear that PSD is complex and the likelihood of an individual developing PSD depends on many interlinked but individually relevant physical, psychological and social factors relating to stroke and the consequences of stroke. Irrespective of the cause, it is clear that PSD is common after stroke and its relationship with physical outcomes of rehabilitation requires exploration.

3.1.1.3 Post stroke depression and physical outcomes

Post-stroke depression is associated with post-stroke ADL performance. Many studies (Nannetti et al. 2005, Pohjasvaara et al. 2001, van de Weg et al. 1999, Sinyor et al. 1986, Paolucci et al. 1999) (Table 12, Appendix 3) showed that PSD is associated with poorer initial and outcome ADL independence. Several studies suffered from considerable numbers of dropouts at follow-up that may have influenced the results (Pohjasvaara et al. 2001, Sinyor et al. 1986). Whilst initial and final scores on functional indices were lower for patients with depression, gains in ADL recovery during rehabilitation in some studies were similar for patients with and without depression (van de Weg et al. 1999, Sinyor et al. 1986), suggesting that although depression influences ADL status, it may not undermine responses to rehabilitation interventions. Another study demonstrated that although motor impairment and ADL performances were lower with PSD (Nannetti et al. 2005) motor impairment recovery was not influenced by PSD. In contrast, ADL recovery *was* lower with PSD particularly after hospital discharge, suggesting a differential effect of depression on ADL and impairment. This important study suggested that ADL and motor performance are affected by PSD, but effects on recovery may depend on timing of assessments and environment.

In line with the observations that PSD influences physical outcomes, three studies demonstrated that improving PSD with antidepressant treatment led to better ADL and motor impairment outcomes (van de Weg et al. 1999, Chemerinski et al. 2001). The studies are summarised in Table 13, Appendix 3.

Methodologically, one study was limited by non-standardised use of antidepressants by physicians and retrospective data collection and analysis (Gainotti et al. 2001) (Table 13, Appendix 3), whilst in another (van de Weg et al. 1999) (Table 12, Appendix 3) no baseline comparison of function between the groups was reported. The other study which was more methodologically robust, used a small sample (n=23) (Chemerinski et al. 2001) (Table 13, Appendix 3) therefore findings should be cautiously interpreted. Overall the study supports the idea that PSD influences outcome and recovery of ADL and motor impairment.

Studies used a range of measures for depression and ADL, and assessment points varied widely making clear conclusions difficult. Despite this it is clear that PSD is associated with initial ADL performance and ADL outcomes. The influence of PSD on recovery of ADL is less clear, and may depend on timing and the environment in which assessment is conducted. Little is known about effects of PSD on motor impairment, however one fairly robust cohort study suggested that impairment outcome but not recovery i.e. change in outcomes - was affected suggesting that PSD influences initial impairment but not natural recovery. More robust cohort studies are required to determine the relationship between PSD, motor impairment and activity outcomes and recovery. Conversely, the impact of natural recovery or rehabilitation on PSD appears not to have been previously explored.

3.1.2 POST-STROKE ANXIETY

Fewer studies have examined the role of anxiety in physical recovery from stroke, but some suggest that it occurs in approximately 20% - 27% of patients, depending on time of assessment (Chemerinski and Levine 2006).

3.1.2.1 Causes of post-stroke anxiety

Like depression, the causes of post stroke anxiety are unclear. In one longitudinal study by Astrom (1996) patients with post-stroke anxiety also exhibited generalized cerebral cortical and subcortical atrophy, at three year follow-up. The authors suggested that that atrophy might be a factor leading to post-stroke anxiety, however like depression other factors may play a role, such as aging, pre-existing Alzheimer's disease, impaired cerebral blood flow and comorbid conditions. Morrison (Morrison et al. 2005) found that post-stroke anxiety was best explained by previous anxiety, and female gender. It can be concluded that like

depression, post-stroke anxiety may be explained by a broad range of aetiological, social and demographic factors.

3.1.2.2 Post-stroke anxiety and physical outcomes

Like depression, anxiety appears to be associated with poorer physical outcomes. One study (Shimoda and Robinson 1998) demonstrated that anxiety was negatively associated with post-stroke recovery of ADL performance on the John Hopkins Functioning Inventory at 12 months, through interaction with depressive symptoms. Findings must be regarded cautiously since they were based on only 15 patients with anxiety only, nine with depression only and 18 with a mixture of anxiety and depression. Another study (Leppavuori, Pohjasvaara et al. 2003) demonstrated lower ADL performance in 57 (20%) of patients with anxiety diagnosed using the Zung Self-Rating Scale, from a sample of 277 patients 3-4 months post-stroke. Reduced ADL performance occurred most frequently in patients with post-stroke anxiety compared to primary generalised anxiety. Similarly, lower ADL performance measured on the Barthel Index was associated with generalised anxiety at hospital admission and until three year follow-up (Anstrom 1996). All studies used DSM diagnostic criteria to diagnose anxiety therefore assessment was fairly standardised and robust. Although some of these conclusions were based on small samples, there is convincing evidence that anxiety is associated with poor ADL performance. No studies examined effects of anxiety on ADL recovery, motor performance or recovery, or UL performance and recovery, an important gap in the evidence.

3.1.3 UPPER LIMB INTERVENTIONS AND ANXIETY AND DEPRESSION

Although there is clear evidence that anxiety and depression influence physical outcomes, little is known about whether improvements in physical outcomes, as a result of rehabilitation interventions improve anxiety and depression outcomes. This is an important area of investigation given that there is a large body of work demonstrating for example that participation in physical activity improves depression in healthy individuals (Mead et al. 2008). In the context of an UL rehabilitation intervention, it is therefore relevant to examine whether the physical outcomes of the intervention influence anxiety and depression outcomes.

Literature relating to the relationship between UL recovery, rehabilitation outcomes and the more specific psychological variables of anxiety and depression is however scant. One study showed that depression predicted 12% of variance in UL responses to a sensori-motor training intervention, suggesting that relationship between depression and UL recovery is weak (Platz and Denzler 2002). However the trial was conducted with 33 patients who had mild paresis and very low initial depression scores. Furthermore, for eight patients, the origin of hemiplegia was traumatic brain injury whose psychological issues may differ from stroke and may therefore not be representative of the typical stroke population. Conclusions applicable to stroke are therefore very limited from this study, and little is known about the relationship between anxiety and depression and UL training responses.

Upper limb dysfunction is known to detrimentally influence psychological well-being measured on the General Health Questionnaire, (Wyller et al. 1997) at one year. It is logical to ask then that if UL dysfunction is improved through an intervention, such as BT, which will be tested for effectiveness in this thesis, will it influence anxiety and depression which inevitably are constructs of psychological well-being.

3.1.4 DISCUSSION

Depression and anxiety are important sequelae of stroke. However, the causes of PSD are unclear. Lesion site is probably not a predictor of depression however and PSD probably results from complex interactions between physical, social and emotional consequences of stroke. PSD is associated with poorer ADL outcomes however the link is complex and it is unclear whether depression is the cause or effect of poor recovery. The relationship is probably bi-directional, however improved ADL independence with anti-depressant therapy suggests that relief of depression improves ADL outcomes. The impact of PSD on motor impairment is less clear. Few studies have examined it and one study suggested that motor impairment is not influenced by PSD. Less is known about the impact of anxiety on motor and functional recovery, but there is evidence from three studies that post-stroke anxiety negatively influences ADL recovery.

Observational and intervention studies used standardised depression or anxiety scales to diagnose PSD and anxiety, rather than clinical interviews, however the validity and sensitivity of these checklists for diagnosis of depression in stroke has been challenged (Turner-Stokes and Hassan 2002), particularly where patients demonstrate communication

difficulties. The diversity of measures used makes assimilation of findings difficult, and many studies excluded patients with aphasia because of inability to use the measures with these patients. In many studies, sub-groups of depressed or anxious participants in larger cohorts were small, and several demonstrated very small numbers at follow-up (van de Weg et al. 1999, Sinyor et al. 1986), limiting the strength and generalisability of the findings. Measures of function and impairment were general, not focussing specifically on UL or lower limb recovery.

There is some evidence that depression has a small impact on UL responses to training however methodological limitations limit the strength of that evidence (Platz and Denzler 2002). Thus little is known about the impact of UL dysfunction and recovery on psychological outcomes in the acute and sub-acute post-stroke period and studies should be conducted to investigate whether any relationship exists between post-stroke depression and anxiety and UL recovery. The relationship between PSD and anxiety and physical functioning *may* however be bi-directional. The most important question relevant to this thesis that emerges from the literature is whether improved motor and functional performance resulting from a specific intervention such as bilateral training for the UL can improve these psychological states.

3.1.5 CONCLUSIONS

It is known that:

- Approximately one quarter of stroke patients suffer from PSD, anxiety or both
- Post-stroke anxiety and depression influence motor and functional performance and recovery in the short and long-term period following stroke
- Remission of post-stroke depression is associated with improved functional outcomes
- Post-stroke depression has a small influence on UL responses to rehabilitation

It is less clear:

- What impact anxiety and depression have on UL recovery
- Whether better UL recovery as a result of a specific UL training programme influences post-stroke anxiety and depression

Having examined the psychological variables anxiety and depression in stroke and their relationship to physical recovery in general and UL recovery in particular, the next section examines health related quality of life in stroke in a similar fashion.

3.2 HEALTH RELATED QUALITY OF LIFE AND UPPER LIMB DYSFUNCTION

Although the postulated purpose of rehabilitation is restoration of quality of life (Renwick et al. 1996), reflecting the biomedical model context of much care, outcomes of rehabilitation have however mostly focused on narrow measures of impairment and activity limitation without considering the impact on patients' lives beyond impairment and function. One article title suggested: "There's more to life than putting on your pants" (Radomski 1995), which implies that for therapists there is an obligation to examine the impact of rehabilitation interventions beyond physical recovery towards the perceived experience of the individual within his or her environment, as recovery takes place.

The traditional biomedical model, in which physiotherapists typically operate, has viewed health as an absence or presence of disease in terms of pathology and physical functioning (Bowling 2005). It is clear however that this narrow model is insufficient to encompass the range of factors that determine experience and perceptions of health or ill-health. The psychological factors discussed in section 3.1 and social factors such as social networks, motivation, adherence, coping strategies and many other factors influence health experiences and perceived health outcomes and require a much broader model of health than the purely biomedical model.

The introduction of the concept of health related quality of life (HRQOL) to healthcare reflects a paradigm shift in what is understood by health outcomes and represents an attempt to operationalise an holistic concept of what is meant by health outcomes (Bowling 2005). The importance now placed on this more holistic perspective of health is reflected firstly in the development of the International Classification of Functioning (ICF) (World Health Organisation 2001) which is a biopsychosocial model to address and classify health and the consequences of disease in relation to the individual as a whole functioning in his environment. This is in contrast to the medical model which has traditionally regarded health as the absence of disease. Secondly, the holistic perspective of health is also reflected in the prominence of health related quality of life in government health policy documents (Scottish Government, 2007). Here quality of life is seen as a key outcome of improved healthcare delivery. The shift towards a biopsychosocial model of health outcomes has not always been reflected in physiotherapy practice however and the current paradigm shift

reflected in policy drivers suggest that examining HRQOL as an outcome of an intervention to improve outcomes after stroke in the context of this thesis is timely.

In this chapter definitions of quality of life and health-related quality of life (HRQOL) will be examined before going on to examine how HRQOL has been operationalised and used in stroke research. Factors that influence HRQOL in stroke are reviewed, followed by an examination of the impact of upper limb impairments and activity limitations on HRQOL within the context of upper limb rehabilitation in general and bilateral training in particular.

Search strategies are detailed in Appendix 2.

3.2.1 DEFINING HEALTH RELATED QUALITY OF LIFE

Historically, quality of life (QOL) has been characterised by life satisfaction or happiness. It conceptualises individual aspirations and expectations and how well these have been fulfilled (Renwick et al. 1996, Anderson and Burckhardt 1999). Quality of life as a concept is very broad and encompasses a range of often overlapping constructs and models. These range from objective indicators of standards of living to psychological and health indicators as well as models encompassing social involvement and social cohesion. A brief description of several of these models will be provided here to examine where HRQOL fits within the overarching concept of QOL, and to identify how these fit with the ICF.

Quality of life has been defined in many ways. Models have been described at the macro level - concerned with objective indicators at the level of society; or at the micro level - concerned with subjective indicators at the level of the individual (Bowling and Windsor 2001, Brown et al. 2004). Macro approaches to defining QOL are concerned with environmental factors such as income, employment, housing and education. Micro approaches are more concerned with perceptions of overall quality of life, encompass individuals' experiences and values at the level of the individual, and may include related, proxy indicators such as well-being, happiness and life satisfaction (Brown 2001). Quality of life is a complex collection of interacting objectively and subjectively observed dimensions ranging from fulfilment of basic needs, psychological constructs of well-being, happiness and morale and life satisfaction, social expectations, health and individual perceptions (Brown et al. 2004). Within the ICF, macro approaches to defining QOL as objective indicators at the level of society have congruence with environmental factors that

may influence functioning and participation. The micro, subjective approach to defining QOL is less obviously positioned within the ICF, and has been noted as a missing component of the framework (Institute of Medicine, 2007). The relationship between QOL and the ICF concepts has been highlighted as an area for future conceptual development (Institute of Medicine, 2007). Objective and subjective indicators are discussed further below.

Objective indicators of quality of life have typically included income, schools and education, housing, public transport, political and social environment, availability of medical and health services, resources and crime levels amongst other constructs (Brown et al. 2004). The validity of using these factors alone to indicate QOL is questionable however, given that studies have consistently shown only moderate links between objective indicators, including socio-demographic characteristics, and satisfaction with life (Campbell et al. 1976; Leman 1983). Surveys indicate that only 6 to 8% of variance in well-being and happiness is typically predicted by variables such as age, gender, income, education and occupation, whereas most variance is explained by subjective variables (Inglehart and Rabier 1986). The ICF includes indicators of participation in education, employment and a range of social and community roles and therefore assesses them as objective indicators but does not set out to link them to QOL in any way. It does assess how participation in education, social activities and roles is influenced by environment and personal factors, thus providing an indication of how objective factors might influence participation in these areas but it does not place any quality assessment upon them.

Subjective indicators have also been extensively used to determine QOL (Brown et al. 2004). These indicators ask individuals about their perceptions and satisfaction in life. They have included domains such as life satisfaction, psychological well-being, individual fulfilment and self-worth. It has been argued that this approach to determining QOL may be biased since responses may be clouded by social desirability and emotional state regarding issues such as income, social prestige and happiness (Brown 2004), however it is now accepted that both subjective and objective indicators are necessary to determine what QOL, taking into account their perceptions, expectations and values (Hudler and Richter 2002). Regarding the ICF, this mixed approach to determining QOL is not explicitly represented in the framework, and values and perceptions are not addressed.

Needs satisfaction and needs pereceptions models of QOL have also been proposed by researchers. Basic needs such as personal care food, shelter and safety are a prerequisite to quality of life and have been identified as priorities by vulnerable groups in society (Brown et al. 2004). Maslow's hierarchy of needs (1968) goes on to propose that once basic needs are satisfied, human beings pursue higher needs such as self-actualisation, happiness and esteem. In this philosophical approach, the fulfilment of needs is seen as a the foundation for quality of life (Hörnquist 1982). Studies have shown a high correlation between fulfilment of higher needs and QOL (Hyde et al. (2003). In relation to the link between the ICF and Maslow's needs based model of QOL, the lowest level of need in Maslow's model, physiological needs leading to homeostasis, is addressed in the ICF constructs of body structures and functioning. Some aspects of social engagement proposed by Maslow are captured in the activity and participation constructs of the ICF, however it is more difficult to see how concepts such as self-esteem, confidence, respect, morality and creativity link to the ICF. They may be addressed in the "personal factors" construct of the ICF however that model is mainly concerned about how personal factors address functioning. Thus whilst some concepts are common to both models, Maslow's model is a philosophical model that deals with high level ways of being and thinking and of expression of attributes that probably transcend the more functional "doing" model of the ICF that is concerned with the health condition.

Adding to the debate about a needs fulfilment model of QOL is the argument that fulfilment of basic or welfare needs is insufficient to determine life satisfaction, or quality of life (Brown et al. 2004). Satisfaction is a subjective concept that can be influenced by social comparisons and expectations. This has led to the additional concept of perceptual needs - subjective evaluation of objective circumstances, which moves beyond basic need to individual perceptions of how well the needs are being addressed (Brown 2004). Again, the ICF does not appear to explicitly address satisfaction within its model of functioning making its congruence with these models limited.

Where basic human needs have been met, QOL is thought to equate to well-being – the extent to which pleasure, happiness and satisfaction needs have been met (Brown et al.2004). These constructs are typically operationalised as components of psychological well-being and measured using scales of life satisfaction, well-being, morale or affect and may be supplemented by measures of psychological morbidity such as anxiety and depression (Bowling 2004). Other psychological constructs that have been attached to quality of life or

life satisfaction are happiness, life satisfaction, morale, self-esteem, self-mastery, autonomy and control, optimism and pessimism (Brown et al. 2004). Detailed examination of how these models that are related to QOL is beyond the scope of this thesis.

In conclusion, there is an ongoing debate within the literature about what is meant by well-being, life satisfaction and QOL and how these constructs relate. There is also debate about whether the psychological constructs described are outcomes of life quality or satisfaction themselves, or whether they are mediators, constituents or influences of QOL (Brown et al. 2004). Again, some of these complex psychological constructs go beyond the "health condition" focus of the ICF, and given the complexity of their relationship to QOL, much work is required to clearly determine the theoretical relationships between psychological indicators and QOL before their relationship with the ICF can be determined with certainty.

Health, or ill health, may affect individual capacity to achieve satisfaction in QOL therefore the impact of health cannot be viewed as an entirely separate concept to general QOL, but rather as a contributory factor to overall QOL (Dijkers 2007, Moons et al. 2006). Indeed studies with elderly people have shown that health status – mental or physical health - predicts between 55 and 60% of variance in life satisfaction, happiness and standard of living (Michalos et al. 2001, Bowling and Windsor 2002), suggesting that health is a considered by that population as a key component of QOL. Depending on the perspective of the individual, and the philosophical and theoretical approach taken to conceptualising QOL, the construct of health and the construct of QOL, may to some extent be interdependent. Physical independence in activities of daily living and social participation are examples of domains of QOL that are partly dependent on health, since each may be influenced by change in health (Bowling 2005, Dijkers 2007, Moons et al. 2006). Thus whilst there is overlap with QOL, QOL relating to health is simply a narrow construct of QOL. Acknowledging the relationship and distinctions between health and QOL, the notion of health related quality of life (HRQOL) has been advanced (Wood-Dauphinee 1999). Definitions of HRQOL have typically focused on negative aspects of disease, ill-health and dependency (Brown 2004). However the move towards use of the ICF and incorporation of activity, participation environmental and personal factors into that model has seen a shift towards functioning and ability. This reflects the earlier World Health Organisation definition of health as "a state of complete physical, mental and social well-being" (WHO 1948).

HRQOL has been defined in a fairly narrow biomedical perspective as the impact of health related status on disability and activities of daily living Kaplan (1985) and more broadly as the impact of perceived health on an individual's ability to live a fulfilling life (Bullinger et al 1993). Some authors believe that it also incorporates patients' satisfaction with healthcare treatments and outcomes, as well as future outcomes and the value an individual attaches to living (Wood-Dauphinee 1999). The breadth of these definitions makes it easy to understand why debate and confusion exits regarding definitions of HRQOL.

This confusion is also reflected in lack of clarity regarding theoretical constructs underpinning HRQOL and about how it should be measured (Wood-Dauphinee 1999). Despite the debate about HRQOL, it is vital that clinicians capture the impact of illness and healthcare interventions on the lives of individuals whom they treat, from the perspective of that individual if interventions and care are to reflect individual perceptions of what is most important. Perceptions of wellness vary amongst individuals to an extent that makes it difficult to predict HRQOL from observations of health or social circumstances. This notion has emerged from research in an idea coined "the disability paradox" (O'Connor 2004). Many individuals living with chronic disease or disability can and do live fulfilling lives in which they perceive themselves as being well against the odds; whilst in some examples the reverse is true. Conversely, stroke studies show that some patients with full physical and functional recovery continue to perceive a reduction in HRQOL two years after stroke (Ahlsio et al. 1984). The impact of disease on an individual cannot therefore be assumed from their physical and disease related signs and symptoms. This presents a strong case for incorporating as an outcome of rehabilitation the perspective of the individual regarding the perceived impact of health on his or her life.

One definition of HRQOL that reflects the idea of health and healthcare from the perspective of the individual was coined by Carr (Carr and Higginson 2001) to distinguish outcomes relevant to health research from life satisfaction research in the general population (Carr et al. 2001, Smith et al. 1999). Carr (2001, pp 1357) suggests that HRQOL is

> "Aspects of an individual's subjective experience that relate both directly and indirectly to health, disease, disability and impairment and to effectiveness of treatment"

The author also suggests that HRQOL is the gap between and individual's expectations of health and their experiences of it, which will vary between individuals, even those with similar health conditions. Because this definition reflects both the perspective of the individual, is broad enough to encompass social, psychological, socioeconomic, demographic, and other cultural factors that may influence an individual's experiences and expectations, as well as incorporating patient satisfaction with treatment, this is the definition that will be accepted and understood for the purposes of this thesis.

Content comparison studies mapping measures of HRQOL used in stroke research against the ICF demonstrated that measures of HRQOL cover patients' perspectives of the full range of ICF domains (Geyh et al.2007, Institute of Medicine 2007). The observation that many domains of HRQOL measures are covered by the ICF indicates that HRQOL focuses more specifically on health issues compared to the scant relationships of some of the QOL models described above to the ICF. It also suggests however that whilst measures may claim to examine HRQOL, all they may in be fact doing is measuring health from the perspective of the individual, rather than measuring the quality of a life lived with a particular condition or disease (Bowling 2004, Brown et al. 2004). Researchers must therefore be clear about the constructs they wish to measure when selecting measures purported to examine HRQOL.

In conclusion, the concept of QOL is broad and is beset by a plethora of definitions and theoretical constructs. Depending on the stance of the observer QOL may encompass objective and subjective indicators, psychological indicators, basic need fulfilment and health. From the perspective of a researcher, it is therefore crucial to be clear about which definition and conceptualisation best matches the research question. However many HRQOL measures in stroke map well to the ICF and this may be a starting point for selection of measures in the field of rehabilitation.
The next section examines what is known about HRQOL in stroke in general and in relation to UL recovery and responses to therapy in particular.

3.2.2 FACTORS INFLUENCING HEALTH RELATED QUALITY OF LIFE IN STROKE

3.2.2.1 Introduction

The main purpose of this chapter is to examine what is known about the impact of stroke related UL rehabilitation on HRQOL. However UL deficits occur within the context of stroke as a whole. After briefly describing how HRQOL has been measured in stroke, an overview of what is known generally about determinants of HRQOL in stroke, including UL dysfunction is presented. This is followed by a review of the impact of responses to UL therapy on HRQOL. The review is not comprehensive or systematic since HRQOL literature in stroke is extensive and in-depth discussion is beyond the scope of the thesis.

3.2.2.2 Measurement of HRQOL in stroke

HRQOL in the stroke literature was initially measured using generic HRQOL measures designed for the general population. As a later development, stroke specific measures designed to capture the issues of importance to individuals with stroke were introduced have been used. Examples of generic HRQOL measures used in stroke include the Nottingham Health Profile (NHP) (Hunt and McEwen 1980), the Sickness Impact Profile (SIP) (Bergner et al 1975) and the SF-36 (Ware and Sherbourne 1992). These measures all examine aspects of body functioning, activity and participation; however the SIP is probably most comprehensively matched to the ICF (Geyh et al. 2007). Whilst key domains of HRQOL examined by these measures appear to apply to everyone, and the scales allow comparison between patients with different diseases, they are less sensitive for investigation of specific effects of particular conditions. Generic measures exclude issues of specific concern to patients with stroke, such as communication and UL functioning. They therefore have limited sensitivity to change in important domains for that population (Ebrahim et al. 1986). Indeed, of six generic measures evaluated for stroke (Buck et al. 2000), only the SIP and the NHP demonstrated reliability, validity, and responsiveness. Limited psychometric robustness means that use of generic measures in stroke and rehabilitation studies should be evaluated carefully.

In response to these limitations, stroke specific measures have now been developed. The Stroke Impact Scale (SIS) is one widely used measure examining eight key areas considered important to life satisfaction by individuals with stroke. The domains included strength, hand function, ADL, mobility, communication, memory and thinking, emotion, and social participation, (Duncan et al. 2003) and maps to the body function, activity and participation domains of the ICF (Geyh 2007). This measure is still undergoing analysis, but appears to exhibit good reliability and validity (Duncan et al. 2003) as well as addressing floor and ceiling effects found with more generic measures (Lai et al. 2003), and as will be apparent, is increasingly used in rehabilitation research. Other stroke specific measures used to examine HRQOL include the Frenchay Activity Index, criticised for its narrow focus on disability (de Haan et al. 1993) the Niemi QOL Scale (Niemi et al. 1988), Ferrans and Powers QOL Index (King 1996) and the Viitanen life satisfaction interview (Viitanen et al. 1988), which have all been criticised for their incomplete development of psychometric qualities and lack of use of patient centred methods in their development (Buck et al. 2000). The stroke specific measures cover a number of domains of the ICF not covered by the generic measures, particularly in relation to mental functioning, however with respect to activities and participation no systematic difference between generic and stroke-specific measures was found in a mapping exercise of measures used in stroke against the ICF (Geyh 2007).

Stroke specific measures are probably more valid in stroke than generic HRQOL measures, particularly where they have been developed in collaboration with patients themselves. The instruments discussed however are underdeveloped, and require more work to establish validity, reliability and responsiveness for a range of stroke populations. All measures use scales to quantify perceived difficulties, rather than providing opportunity for a personalised assessment of the impact of stroke on an individual's life. In that sense such measures are not capable of capturing the very personal "gap between individual's expectations of health and their experiences of it" suggested by Carr as a definition of HRQOL. Most HRQOL measures can therefore be considered to provide perceptions of health status rather than measuring HRQOL. Reflecting this, all of the HRQOL measures cover a wide range of ICF constructs across body functioning, activity and participation, irrespective of whether they are stroke specific or generic (Geyh 2007). The specific ICF component examined by each measure in each domain varies (Geyh 2007) therefore clarity in selection of a measure to meet the intended use is required.

Bearing these caveats in mind, the next section reviews the literature that has examined the predictors of HRQOL in stroke.

3.2.2.3 Factors influencing health related quality of life in stroke

Studies examining factors that influence HRQOL are summarised in Table 14, Appendix 3. These studies demonstrate the diversity of measures used to examine HRQOL in stroke. Most of these were generic measures, with only one (Nichols-Larsen et al. 2005) using a stroke-specific measure, reflecting the early stage of development and use of the stroke specific measures. The tables indicate that the following factors are amongst the most frequently identified determinants of HRQOL in stroke: independence in activities of daily living, depression and gender. Social support, age and having the upper limb affected are also important factors. The following section discusses general predictors of HRQOL, and the relationship between HRQOL and UL dysfunction will be examined thereafter.

DEPRESSION AND ANXIETY

Depression was either significantly associated with or a significant predictor of low HRQOL in eight of the fourteen reviewed studies. Jonsson (2005) demonstrated that lower depression was significantly associated with higher scores on all of the HRQOL domains examined. Robinson-Smith (Robinson-Smith et al. 2000) demonstrated that self-efficacy and depression were closely associated, and significantly related to HRQOL. Ones (2005) found significant differences in the Nottingham Health Profile when comparing patients with and without depression. These studies show that there is a relationship between HRQOL and depression. However other studies examined predictors of HRQOL and in some, depression explained the largest proportion of variance in HRQOL – as much as 32% in the study by Kim et al (1999). Niemi (1988) found that depression and memory explained as much as 50% of the variance in change in HRQOL at four years post-stroke. Ahlsio (1984) confirmed this finding, demonstrating that patients with depression showed greatest deterioration in QOL over two years following onset. All of these studies were conducted at least 6 months after stroke, and suggest that altered emotional status is a consequence of living with stroke that impacts significantly on HRQOL.

Few studies actually examined anxiety, however where it was measured it was also shown to predict HRQOL. Wyller (1998) found that low anxiety was a significant predictor of well-being in a population whose time post-stroke was not defined whilst Alhiso (1984)

demonstrated that anxiety as well as depression predicted poorer HRQOL at two years. These findings suggest that mood disorders are important predictors of HRQOL however caution must be applied in interpreting the predictive strength of these constructs. Some HRQOL measures have been shown to actually measure depression and anxiety anyway (Fruhwald et al. 2001) therefore the strong relationship between depression, anxiety and HRQOL measures may indicate shared constructs that may in fact inflate the explained variance. This demonstrates the difficulties discussed above in relation to the conceptualization of HRQOL and the lack of clear and common theoretical frameworks underpinning it.

MOTOR IMPAIRMENT

Only McEwen (McEwen et al. 2000) examined the impact of overall motor impairment on HRQOL, and demonstrated that in women 14 months post-stroke, impairment measured on the Chedoke McMaster scale explained only 34% of the variance of perceived physical health. The small amount of variance predicted by motor impairment suggests that other factors, for example participation in social, leisure, and vocational activities, or access to these activities which make life worth living, are more important to perceived physical functioning than the stroke related impairment itself.

ACTIVITIES OF DAILY LIVING

Activities of daily living performance was the main activity limitation to be examined in relation to HRQOL. All but two studies (Nichols-Larsen et al. 2005, Wyller et al. 1998) measured independence in ADL or IADL. With the exception of King (1996), who found that ADL independence only predicted 3% of the variance in HRQOL whilst depression and social support predicted the rest of the variance, other studies found ADL to be the strongest predictor, or correlated strongly with better HRQOL following stroke. The population in the study by King demonstrated comparable levels of HRQOL to normal and good ADL independence compared to the other studies and probably explains the difference in findings to other studies. Similarly, Robinson-Smith (2000) demonstrated that self-efficacy relating to self-care ability, or confidence to perform ADL tasks, also predicted better HRQOL. Association between self-care self-efficacy and HRQOL has implications for the way in which health professionals approach training of ADL independence. Loss of independence in basic functions and loss of confidence to perform them may represent a considerable burden for individuals with stroke. Since this has implications for the ability to look after

oneself, and influences requirements for external support and assistance (King 1996); it is unsurprising that ADL independence is strongly associated with HRQOL.

SOCIAL SUPPORT

Five studies demonstrated that perceived social support and marriage are important predictors of HRQOL (King 1996, Robinson-Smith 2000, Kauhanen et al. 2000, Kim et al. 1999, Wyller et al. 1998). Kim (Kim et al. 1999) also reported that quality and not quantity of support is important, with close relationships, such as that with a spouse, being most important for QOL and accounting for 16% of variance. King (1996) also found social support the only variable to predict overall QOL and QOL in each domain of the Ferrans and Powers QOL Index. These findings highlight the need for rehabilitation professionals to be aware of the need to involve family and carers in rehabilitation and adjustment to living with stroke, so that they are supported in their very important role.

OTHER FACTORS

Age and gender were also important predictors of HRQOL. Four studies (Ahlsio et al. 1984, Nichols-Larsen et al. 2005, Jonsson et al. 2005, Kauhanen et al. 2000) demonstrated that HRQOL is reduced with age, however Nicols-Larsen (2005) found disparities in the extent to which age is important to different domains of HRQOL, depending on gender and race. For example, black females and white males demonstrated decreasing social participation with age, whilst black males reported increasing social participation with age, and white females had poor participation irrespective of age. Clearly interactions between factors such as race age and gender and HRQOL are complex and require further research.

In other studies gender and age were important. McEwen (2000) demonstrated that for women's SF-physical health age and general motor impairment explained most of the variance (34%), whilst in men's scores, dexterity was the most important predictor explaining 39% of physical health. Wyller (1998) demonstrated that males rated their QOL as higher than females whilst conversely in another study (Jonsson 2005) females reported higher scores than males on the SF-36 physical, emotional, mental and general health subscales. Niemi (1988) reported greater deterioration in HRQOL at four years in men, particularly for leisure activities. Differences between studies in terms of the constructs examined in the selected measures, sample sizes, physical differences between the populations surveyed and factors such as disability and mood may explain some of the contradictory findings relating to gender. However the impact of gender on HRQOL after

stroke is again complex, and differs according to the constructs examined. The small number of studies examining gender, and the diversity of measures used means that generalisation about the impact of gender on various domains is difficult. Further investigation is required to determine the impact of gender on HRQOL.

In summary, in spite of diverse HRQOL measures and predictive variables, some clear conclusions can be drawn about factors that influence HRQOL. Depression and anxiety are important predictors of HRQOL, with higher levels of anxiety and depression predictive of poorer HRQOL. There is evidence that lower ADL independence is an important predictor of poorer HRQOL. Only one study examining motor impairment (McEwen et al. 2000; 2000) found that it predicted a third of the variance in HRQOL. Unsurprisingly, many studies suggested that better social support is important for better HRQOL. Age may be important, but its significance may vary depending on other characteristics such as race (Nichols-Larsen et al. 2005). The picture is less clear regarding gender, where studies demonstrate conflicting findings. This may indicate gender differences in determinants of HRQOL or may simply reflect differences in how HRQOL and its determinants were measured in individual studies. More work is required to determine the impact of gender on HRQOL.

3.2.3 THE UPPER LIMB AND HEALTH RELATED QUALITY OF LIFE

Several studies demonstrated that UL impairment and activity limitation in addition to ADL independence influenced HRQOL (Table 14, Appendix 3). Upper limb factors are reviewed in the next section. This is followed by a section examining the impact of UL rehabilitation interventions on HRQOL.

3.2.3.1 Upper limb motor impairment and HRQOL

Upper limb motor impairment may be related to HRQOL, however only one study appears to have examined the relationship. Ones (Ones et al 2005) found that upper extremity and hand scores of the Fugl-Myer test significantly correlated with the Nottingham Health Profile Total Score, however the correlation was fairly weak (r=-0.30), suggesting some association between the variables. Clearly further work is required to replicate this finding and to

explore fully how motor impairment and HRQOL are related and to determine the relative importance of UL impairment as a predictor of HRQOL.

3.2.3.2 Upper limb activity limitation and health related quality of life

The three studies examining UL activity limitation suggest that it is an important predictor of lower HRQOL (Table 14, Appendix 3). Wyller (1997) found that UL activity limitation measured on the Sodring Motor Evaluation Scale was a significant predictor of perceived well-being at one year, and with gender, it explained 47% of the variance in well-being measured on the General Health Questionnaire. Upper limb activity was a more important predictor of HRQOL than ADL and IADL in that study, a finding supported by McEwen, (McEwen et al. 2000) who found that for men more than 1 year post-stroke, 34% of the variance of the SF-36 physical health score was predicted by dexterity measured on the box and block test after adjusting for age. Similarly, Nichols-Larson (2005) demonstrated in patients between 3 and 9 months after stroke who were relatively high functioning, that the UL Wolf-Motor function test was significantly associated with physical functioning and communication items of the Stroke Impact Scale, however the proportion of variance explained by each was relatively low at 3.75% and 5.2% respectively, suggesting that UL activity limitation played a very small part in predicting HRQOL. The range in proportions of variance explained by activity limitation across these studies is marked, leading to uncertainty about the importance of UL activity limitation in predicting HRQOL. Reasons for differences in predictive strength of activity limitation are unclear but probably stem from differences in study populations, times and approaches to assessment and from differences in the selected measures and variables included in regression equations in each study. In order to better understand the predictive strength of activity limitation on HRQOL, more studies are required using robust, gold standard measures of each construct. Assessment should be conducted at a time when patients have returned to their own environment and when the impact of stroke on their lives has become apparent.

3.2.3.3 Upper limb rehabilitation and health related quality of life

Given that HRQOL appears to be influenced to some extent by UL impairment and activity limitation, it is logical to ask whether improved UL function as a result of a training intervention, including bilateral training, can in turn influence HRQOL. This section

reviews UL rehabilitation studies involving UL training, which have included HRQOL as an outcome, to investigate whether UL rehabilitation can influence HRQOL. Studies examining bilateral training were also reviewed. Studies are summarised in Table 15, Appendix 3.

GENERAL CHARACTERISTICS OF THE UPPER LIMB REHABILITATION STUDIES

Diversity across studies summarised in Table15, Appendix 3 makes conclusions about the impact of UL rehabilitation effects on HRQOL difficult, since comparisons cannot be easily made. The majority of studies examined patients with moderate to severe UL impairment or activity limitation, although for the constraint therapy studies patients needed to be able to move their wrist and fingers, suggesting less severe impairment (Dettmers 2005, Wu et al. 2007, Wolf et al. 2006), which may make that population more amenable to treatment than more severely affected patients.

All of the studies except one (Kwakkel et al. 1999), were conducted between 14 days and 20 weeks, were conducted with patients more than 3 months following stroke. HRQOL issues may be more relevant in the more chronic stage of stroke when adjustment to living with the condition has occurred. However Kwakkel (1999) only demonstrated an effect on HRQOL approaching significance for a lower limb intervention group, suggesting that an intervention in the more acute phase can have an impact on HRQOL, and that it is relevant to examine HRQOL with this population. Interestingly in that study there was no impact of UL training on HRQOL, which may reflect lower perceived importance of UL compared to lower limb recovery, or might reflect the extent to which UL dysfunction is reflected in the selected HRQOL measure, in that case the Nottingham Health Profile.

The studies examined diverse interventions (Table 3.1), including constraint therapy, bilateral training, Saboflex (an UL exercise system), and robot assisted therapy. These interventions varied in intensity, duration and general characteristics, which may have influenced the impact of each on HRQOL. Only three of the seven studies used a randomised controlled trial (RCT) design (Wu et al. 2007, Wolf et al. 2006, Kwakkel et al. 1999). Although all studies showed some improvement sin UL outcomes, the single group design (Dettmers et al. 2005, Barnes et al. 2006, Finley et al. 2005) and single case studies in the others (Butler et al. 2006) do not control for confounding factors that might influence results, therefore conclusions from those studies regarding the impact of UL rehabilitation on HRQOL should be cautious.

Only one study (Kwakkel et al. 1999) did not use the Stroke Impact Scale. The increasing use of this measure suggests that it is becoming an instrument of choice for HRQOL measurement in rehabilitation and means that some congruence is developing in how stroke HRQOL is measured. Although the Stroke Impact Scale is being badged as a HRQOL measure in many studies, caution must be applied however. Examination of the measure shows that it is fact largely a subjective measure of physical functioning after stroke. Although it does include a section examining the impact of stroke on mood and on participation in life roles, the extent to which it can be said to measure quality of life remains unclear. It is another example of the difficulty and diversity that exists in conceptualising and operationalising HRQOL.

UPPER LIMB IMPAIRMENT AND ACTIVITY LIMITATION OUTCOMES

Like the studies examining HRQOL in general, the impact of impairment outcomes on HRQOL in the context of UL intervention studies is not clear. All of the studies except one (Kwakkel et al.1999) demonstrated significant effects of the various interventions on impairment outcomes - on grip strength (Dettmers et al. 2005, Barnes et al. 2006, Finley et al. 2005) motor impairment measured on the Fugl Meyer test (Wu et al. 2007, Wolf et al. 2006, Finley et al. 2005, Butler et al. 2006) spasticity (Dettmers et al. 2005) and range of movement (Barnes et al. 2006). Four of those studies, including 2 RCTs, demonstrated significant improvements in HRQOL (Dettmers et al. 2005, Wu et al. 2007, Wolf et al. 2006, Butler et al. 2006) with reduced activity limitation and impairment. The other studies also demonstrated improved activity limitation (Kwakkel et al. 1999) or impairment (Barnes et al. 2006, Finley et al. 2005) but demonstrated *no* significant improvements in HRQOL. Furthermore, the study by Wolf (Wolf et al. 2006) demonstrated improvements only in the hand function section of the SIS, suggesting training specificity for subjective activity improvements. In relation to the impact of UL rehabilitation on HRQOL this body of work is limited. It is not possible to tell from these findings whether improvements in activity limitation or impairment most influence HRQOL. The small size of most of these studies and the limitations of the research designs mean that the differential impact of impairment and activity limitation on HRQOL is unclear and requires further investigation.

Two studies showing improved activity limitation also demonstrated improvements in perceived communication and social participation as well as in perceived physical performance (Dettmers et al. 2005, Butler et al. 2006), suggesting that there may be broader

effects of improved UL activity on HRQOL, and that UL recovery may be important to the way in which individuals interact with others, for example through use of gesture. Factors such as the social interactions occurring through participation in the studies may have influenced communication, an area of interest beyond the scope of the present thesis.

Overall, clear conclusions about the relative importance of UL activity limitation and impairment as rehabilitation outcomes in influencing HRQOL cannot be drawn from this small group of studies. It is not clear from these studies whether a relationship exists between improved UL recovery and HRQOL. Only three studies were randomised controlled trial design (Wu et al. 2007, Wolf et al. 2006, Kwakkel et al. 1999). Other study designs and small sample sizes may have led to biased findings because of limited control for factors that may have influenced findings other than the UL interventions. It is unclear therefore whether UL interventions influence HRQOL. There is scope for further investigation of the impact of UL rehabilitation on HRQOL, firstly to investigate the relative roles of impairment and activity limitation in predicting HRQOL, and to determine the impact of UL responses to training on HRQOL in patients at different stages post-stroke.

3.2.3.4 Bilateral training outcomes and health related quality of life

Only one study investigated effects of bilateral training on HRQOL. This was a pre and post treatment design that examined BATRAC training (discussed in Chapter 2, Section 2.2.4) in four subjects with chronic severe stroke and limited UL activity (Barnes et al. 2006) (Table 15, Appendix 3). The study was only available in abstract form therefore in-depth analysis of the results is not possible. There was no effect on HRQOL in spite of improvements in some impairment variables (Barnes et al. 2006). Statistical analysis was performed with data from only four participants therefore conclusions must be cautiously interpreted. Findings suggest however that reduced UL impairment through this intervention may not impact on perceived HRQOL. The study provided no details of other factors such as global severity of stroke, social and emotional factors that may have also influenced HRQOL in this very small sample, therefore clear conclusions cannot be drawn. More work is required to examine the effects of bilateral training on HRQOL and to examine the impact of activity limitation and impairment on HRQOL as outcomes of that training in different populations.

3.2.4 DISCUSSION

There is an ongoing and unresolved debate in the literature about definitions of QOL and HRQOL, and how these concepts are related. The definition of HRQOL used in this thesis(Carr et al. 2001) is appropriate to its overall aim of evaluating effects of a bilateral upper limb training intervention, however many other definitions of HRQOL exist and that are of equal value. Given the range of views around the conceptualisation of HRQOL it is unsurprising that a diversity of measures is used to assess HRQOL. Currently, the available generic measures appear to demonstrate the most robust psychometric properties. Condition specific measures such as the more recent Stroke Impact Scale may be more responsive to change in stroke because of greater validity in that condition. There is evidence that use of the SIS is becoming the most prevalent measure of HRQOL in stroke and work is ongoing regarding the properties of that measure (Duncan et al. 2003). Until the conceptualisation of HRQOL is based on sound theoretical considerations, the diversity in definitions will however persist.

Studies examining predictors of HRQOL (Table 14, Appendix 3) demonstrate how diversity of measures and complexity of some analyses performed on different domains of these measures makes conclusions and generalisations difficult to make. Timing of measurement ranged from one week to 4 years post-stroke, which may have influenced results, since adjustment to living with stroke which inevitably occurs over time may influence perceived HRQOL. Few studies examined HRQOL less than six months after stroke. Generally, it was difficult to make exact judgments about degree of severity of motor and functional deficits of patients in because of the lack of detailed information provided in studies, however most appeared to have been conducted with individuals who had mild to moderate degrees of severity. In spite of this diversity, several common findings emerged:-

There is general agreement that depression is a strong predictor of perceived HRQOL, and two studies identified anxiety as predictors of HRQOL (Ahlsio et al. 1984, Wyller et al. 1998). As discussed in Chapter 2, depression and anxiety are common and potentially serious sequelae of stroke. These probably reflect the psychological and emotional adjustments that individuals need to make to cope with life after stroke. It is unsurprising therefore that these cognitive and emotional factors influence how individuals perceive their life quality. Social support is another important predictor of HRQOL (Table 14, Appendix 3), but appears to be influenced by perceptions of the support, rather than the number of

individuals providing it (Kim et al. 1999). Clearly involvement with key individuals is an important factor in determining social satisfaction, since individuals with stroke may rely on family and carer support for basic ADL functions.

Loss of independence in ADL often has severe implications for the lives of patients, for the support that they might require to look after themselves and therefore for how they perceive their life after stroke. Independence in ADL was therefore a strong predictor of HRQOL in many, although not all, of the reviewed studies, where some of the other factors such as depression were more important (King 1996, Kauhanen et al. 2000). The diverse measures and populations examined may explain the differences in findings however, and the relative importance of factors to HRQOL is an area for further investigation, particularly in the acute post-stroke and early discharge phase when patients are first adjusting to life with stroke. General motor impairment was only examined in one study, but like activity limitation, explained a significant portion of the variance (McEwen et al. 2000)

Age and gender also appear to influence perceived HRQOL, but the relationship is complex and probably inter-related with other demographic characteristics. The picture is further complicated by the diversity of measures used and the domains addressed within each. More work is therefore required to tease out the impact of these factors on HRQOL domains.

Of most relevance to this thesis, UL impairment and activity limitation appear to be associated with reduced HRQOL however this was only examined in three studies (Wyller et al. 1997, Nichols-Larsen et al. 2005, McEwen et al. 2000) (Table 14, Appendix 3) using diverse measures. It is not clear from these studies which domains of UL dysfunction, impairment and activity limitation most impact on HRQOL.

Measurement of HRQOL as an outcome of UL rehabilitation has only been undertaken in a small number of intervention studies. The relationship between improvements in UL impairment, activity limitations and perceived HRQOL has not yet been established. Improved impairment may be reflected less in improved HRQOL than activity limitation, however given the small number of studies involved and the diversity of research designs and interventions; it is very difficult to draw conclusions. Furthermore, given that HRQOL is such a complex, multifaceted concept, and that it is measured even in these few studies using a range of measures, it is unsurprising that extent to which UL rehabilitation outcomes are reflected in HRQOL is unclear. The relationship between UL rehabilitation outcomes

and HRQOL depends on the nature and effectiveness of the intervention, but may also depend on personal and environmental factors pertinent to individual patients, the study design, or comparisons made, and the outcome measures themselves. Clearly, until HRQOL is measured routinely in UL rehabilitation research, the impact of treatment on this important variable will remain uncertain.

Finally, there is very little evidence of the impact of bilateral training on HRQOL. The only study to examine it (Barnes et al. 2006) shows that despite reductions in impairment, the intervention did not influence HRQOL. The study was very small, was not fully reported and was conducted with patients in the chronic post-stroke phase. There is a need therefore to investigate the impact of bilateral training on HRQOL in patients in the more acute stage of rehabilitation, and to investigate the relative impact of impairment and activity limitation on HRQOL in this context.

3.2.5 CONCLUSIONS

In conclusion, it is clear that:

- There is evidence from a number of studies that depression, independence in ADL, social support, age and gender are important determinants of HRQOL in patients with longstanding stroke
- UL impairment and activity limitation are associated with reduced HRQOL in patients with longstanding stroke – although the evidence is limited
- Reduced UL activity limitation and impairment through UL interventions are associated with improvements in HRQOL – although the evidence here is very limited.

It is not clear:

- What the relative importance of UL impairment and activity limitation is in determining HRQOL less than six months following stroke
- What the impact of bilateral UL training is on HRQOL in the acute and sub acute phase following stroke.

3.3 SUMMARY OF FINDINGS FROM LITERATURE REVIEW AND RESEARCH QUESTIONS

This final section of the literature review briefly summarises findings from the review and details the research questions emerging from gaps in the literature which will frame the next part of the thesis.

3.3.1 PHYSICAL OUTCOMES

3.3.1.1 Bilateral training for the contralesional upper limb in stroke

Coming from converging theoretical perspectives and evidence in the fields of motor control science and neuroscience, bilateral training has emerged as a potentially effective intervention for the UL in stroke. Several bilateral training paradigms have been examined in the literature. However studies suffer from methodological limitations and evidence for effectiveness of bilateral training is limited in clinical populations. Whilst some evidence exists for effects of bilateral training paradigms involving assisted technology, and several RCTs show that EMG triggered functional electrical stimulation and certain robotic aids applied bilaterally may be effective in improving upper limb impairment, for bilateral training involving movement function, the evidence is much weaker because of small samples and critical methodological limitations.

The bilateral training paradigm with most relevance to clinical physiotherapy practice is bilateral *task* training. However the evidence of effectiveness of bilateral task training is conflicting and direct comparison to unilateral training has not been undertaken in a properly powered RCT.

Furthermore, most bilateral training studies have been conducted in the chronic stage. Early UL rehabilitation is known to be effective at improving immediate and much later impairment and activity limitation outcomes (Winstein et al. 2004, Feys et al. 2004) therefore it is important to investigate new interventions applied in the acute post-stroke period. It is clear that, to determine whether bilateral task training provides an advantage over conventional unilateral training, it is necessary to conduct a properly powered randomised controlled trial to compare bilateral UL task training with unilateral task training

on UL impairment and activity limitation outcomes with individuals in the acute stage of stroke. This is the primary purpose of this thesis.

Primary research question: Is there a difference in terms of UL impairment, activity limitation, dexterity and independence in activities of daily living between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training?

$H_0$1: There will be no significant differences between acute stroke patients receiving six weeks of bilateral task training compared to those receiving six weeks of unilateral task training in terms of UL impairment, activity limitation, dexterity and independence in activities of daily living at six weeks or at eighteen week follow-up.

3.3.1.2 Factors influencing contralesional upper limb recovery and responses to therapy

Severity of impairment and activity limitation, lesion site, lesion side and hand dominance, proprioception, age and gender may influence recovery and responses to intervention. Little is known however about these factors in relation to bilateral training. Right handed individuals with dominant hemiplegia appear however to demonstrate better responses bilateral training than those with non-dominant hemiplegia (McCombe-Waller and Whitall 2005). This observation requires replication in larger samples and with other bilateral interventions.

Taking a broader perspective of upper limb recovery than responses to a particular intervention, the literature showed that whilst predictive strength of initial impairment has been investigated, little is known about the strength of gross and fine UL activity limitation to predict later activity limitation outcomes.

These findings led to development of two secondary study aims. The first was to examine what demographic and clinical factors influence responses to bilateral training. The second was to determine to what extent activity limitation predicts activity limitation outcomes at least six months after stroke onset and what assessment time is optimal for prediction of later outcome.

Secondary research question 1. Does severity of initial UL activity limitation influence UL training responses to bilateral task training compared to unilateral task training in patients with acute stroke?

$H_0$2 The impact of initial severity of UL activity limitation will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving bilateral task training in terms of changes in UL impairment, activity limitation and dexterity.

Secondary research question 2: Does lesion site influence UL training responses to bilateral task training compared to unilateral task training in patients with acute stroke?

$H_0$3 The impact of lesion site will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of changes in UL impairment, activity limitation and dexterity.

Secondary research question 3: Does side of hemiplegia and having the dominant or non-dominant side affected influence UL training responses to bilateral task training compared to unilateral task training in patients with acute stroke?

$H_0$4 The impact of side of hemiplegia and having the dominant or non-dominant side affected will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of changes in UL impairment, activity limitation and dexterity.

Secondary Research Question 4. Does gender influence UL training responses of bilateral task training compared to unilateral task training in patients with acute stroke?

$H_0$5 The impact of gender will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of changes in UL impairment, activity limitation and dexterity

Secondary research question 5. Does age influence UL training responses to bilateral task training compared to unilateral task training in patients with acute stroke?

$H_0$6 The impact of age will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of changes in UL impairment, activity limitation and dexterity

Secondary research question 6. Does initial proprioceptive sense influence UL training responses to bilateral task training compared to unilateral task training in patients with acute stroke?

$H_0$7 The impact of initial proprioception will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of changes in UL impairment, activity limitation and dexterity

Predicting UL activity limitation research question 1: What baseline participant characteristics and activity limitation variables best predict UL activity limitation at two and six months after stroke onset?

$H_0$8. Participant characteristics and activity limitation scores measured at baseline will not significantly predict activity limitation outcomes at two and six months.

Predicting UL activity limitation research question 2: What two month participant characteristics and activity limitation variables best predict UL activity limitation at six months after stroke onset?

$H_0$9. Participant characteristics and activity limitation scores measured at two months will not significantly predict activity limitation outcomes at six months.

3.3.1.3 Ipsilesional effects of stroke and responses to bilateral training

Ipsilesional deficits detectable on clinical measures of dexterity, gross activity limitation and sensory measures appear to exist. The evidence is however inconsistent regarding severity of these deficits, the nature of deficits in patients with right and left hemisphere damage and recovery patterns. Associations between ipsilesional dysfunction and functional recovery have also been demonstrated but require further investigation in the acute stage and as recovery progresses. Furthermore, bilateral training may benefit ipsilesional performance (McCombe-Waller, and Whitall 2004), but methodological limitations mean that further research is necessary to determine ipsilesional effects of bilateral training. Aims of this

strand of the thesis were: to investigate whether ipsilesional deficits in dexterity, gross activity limitation and sensation can be detected in relation to published norms; to investigate ipsilesional recovery over time; to examine if the deficits differed between patients with right and left UL hemiplegia; to determine if a relationship between ipsilesional dexterity and activity limitation and activities of daily living existed and finally to investigate whether effects of bilateral compared to unilateral training on ipsilesional dexterity and activity limitation.

The first research question was developed just to determine that ipsilesional dysfunction was detectable with participants in the present study, before going on to conduct further analyses. This was an observational question and no null hypothesis was required.

Ipsilesional Research Question 1. On observation, do mean ipsilesional scores on UL activity limitation, dexterity and sensation measures at baseline in individuals with acute stroke differ from expected normal scores on these tests?

Ipsilesional Research Question 2. Do ipsilesional dexterity and UL activity limitation and sensory appreciation differ significantly over time in individuals with acute stroke?

$H_0$10 Ipsilesional UL activity limitation, dexterity and sensation will not differ significantly between initial assessment and six and eighteen week assessments in individuals with acute stroke.

Ipsilesional Research Question 3. Is there a difference in UL ipsilesional motor performance and sensation between patients with acute stroke who have experienced right and left hemispheric damage?

$H_0$11.There will be no significant differences between patients with right and left hemispheric damage in terms of ipsilesional UL activity limitation, dexterity and sensation at initial assessment and six and eighteen week assessments .

Ipsilesional Research Question 4. Are ipsilesional UL activity limitation and dexterity significantly associated with independence in activities of daily living in patients with acute stroke?

$H_0$12 There will be no significant associations between independence in activities of daily living, and ipsilesional UL activity limitation or dexterity measured in patients with acute stroke at initial assessment and six and eighteen week assessments .

Ipsilesional Research Question 5.

Is there a difference in terms of ipsilesional UL activity limitation and dexterity between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training?

$H_0$13: There will be no significant differences between acute stroke patients receiving six weeks of bilateral task training compared to those receiving six weeks of unilateral task training in terms of ipsilesional UL activity limitation and dexterity at six weeks or at eighteen week follow-up.

3.3.2 PSYCHOSOCIAL OUTCOMES

Little is known about the relationship between UL dysfunction and anxiety and depression outcomes or the impact of UL training responses on anxiety and depression outcomes. Upper limb dysfunction is known to predict overall perceived psychological well-being (Wyller et al. 1997) and improved UL recovery may influence anxiety and depression outcomes but this has not been previously investigated.

Similarly, evidence is equivocal regarding whether HRQOL improves as a response to UL training interventions, and little is known about the impact of bilateral training on perceived quality of life. Given that return to a life of quality is an important overall outcome of rehabilitation, it is important to determine whether new interventions such as bilateral training can influence quality of life outcomes for patients.

Finally, although many factors predict HRQOL, the relative strength of UL variables of activity limitation and impairment in determining HRQOL are not clear. This is particularly important when patients have returned home and are learning to live with consequences of stroke on life in their own environment. It is also important for therapists to understand since it will enable them to target interventions appropriately at the domains of dysfunction most likely to influence HRQOL.

The first aim of this thesis strand was to explore whether anxiety and depression and HRQOL outcomes differed between acute stroke patients receiving unilateral and bilateral training. The second aim was to determine the relative importance of UL activity limitation and impairment in predicting HRQOL at a time when patients have returned home from hospital.

Psychosocial research question 1: Is there a difference in terms of anxiety and depression outcomes between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training?

$H_0$14 : There will be no significant differences between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of anxiety and depression at initial assessment and six and eighteen week assessments.

Psychosocial research question 2: Is there a difference in terms of health related quality of life between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training?

$H_0$15 : There will be no significant differences between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of health related quality of life at baseline assessment and six and eighteen week assessments.

.

Psychosocial research question 3: What UL activity limitation, impairment, demographic and clinical variables best predict HRQOL measured six months after stroke onset?

$H_0$16 UL activity limitation, impairment, demographic and clinical variables will not significantly predict HRQOL measured six months after stroke onset.

These research questions will be addressed by data collected from a randomised controlled trial. Study methods will be described next in Chapter 4.

CHAPTER 4

METHODS

4.0 INTRODUCTION

This chapter details the methods of the randomised controlled trial and the statistical analysis to be conducted to answer the aims and research questions listed at the end of Chapter 3. Section 4.2 details the study methodology including the study design, measures, participants and recruitment methods, randomisation and blinding. The intervention is described next with a rationale for each component. This is followed by details of sample size calculations and statistical analyses.

4.1 METHODS

4.1.1 DESIGN

This study was designed to compare a bilateral task training programme with a control group who participated in an identical but unilateral task training programme. The study design was a randomised controlled trial with concealed allocation, blinded assessment using six measures repeated at baseline (T1), post-intervention assessment at 6 weeks (T2) and follow-up assessment at 18 weeks (T3). Participants were recruited from a cohort of stroke patients sequentially admitted to Ninewells Hospital, Dundee, Scotland; a large teaching hospital with acute rehabilitation facilities. Assessment and intervention were conducted there, in associated rehabilitation hospitals, or in participants' homes depending on their rehabilitation status. Tayside Committee on Medical Research Ethics provided ethical approval (Appendix 4).

4.1.2 MEASURES

Two therapists, an occupational therapist and physiotherapist, who were trained to use the measures, blinded to treatment allocation and otherwise uninvolved in the trial collected data using the standardised protocols. Measures were conducted two to four weeks after stroke onset at baseline (T1), following a six week bilateral or unilateral training intervention (T2), and at eighteen weeks (T3), twelve weeks after the end of the intervention. To maintain blinding, participants were instructed not to indicate their group allocation to assessors.

Detailed protocols for each outcome measure and details of equipment are provided in Appendix 5. All the equipment was standardised and fully portable.

Measures were selected to ensure that the ICF domains Body Functioning, Activity and Participation were examined. Measures are summarised in Box 4.1, with a brief summary of the scoring system for each with an indication of how each fits into the ICF framework. Each of the measures is then discussed in detail below.

Box 4.1. Summary of Measures

Measure		Scoring	Test Details	ICF Domains examined by each measure		
				Body Function	Activity	Participation
Primary Outcome Measure	Action Research Arm Test	Maximum = 57 indicating best performance	19 items, hierarchically organised into grasp, grip pinch and gross sub-sections	√	√	
Secondary Outcome Measures	Rivermead Motor Assessment (UL section)	Maximum = 15 indicating best performance	15 items hierarchically organised. Test stops when an item is failed three times	√	√	
	Nine Hole Peg Test	Pegs placed per second	Fastest time to place 9 dowelling pegs in holes		√	
	Modified Barthel Index	Maximum = 100 indicating best performance	10 items of activities of daily living		√	
	Nottingham Health Profile	Weighted scores, maximum = 600 indicating poorer health related quality of life	38 yes/no items arranged in six domains of perceived health	√	√	√
	Hospital Anxiety and Depression Scale	Maximum = 42 indicating greatest anxiety and depression	14 item self-report measure, two subscales of Anxiety and Depression	√		
	The Nottingham Sensory Assessment	Maximum = 84 representing normal sensation	Items arranged into tactile, proprioception and stereognosis sub-domains	√		

4.1.2.1 The primary outcome measure:

The Action Research Arm Test (ARAT) is a validated and reliable measure of UL function that is the most frequently used in stroke UL rehabilitation research (Kwakkel et al. 1999, Lincoln et al. 1999, Parry et al. 1999, Dromerick et al. 2000, van Wijck et al. 2001). It was selected as the primary outcome measure because it examines UL performance at the impairment and activity limitation levels. Impairments included in the test could be categorised as functions associated with the ICF classification of control over and coordination of simple or isolated voluntary movements (ICF category B7600). These were examined in the gross movement section of the test. Other tasks tested by the ARAT would be categorised as executing a simple task with a single major component in the ICF categorisation of activity (ICF category (d2100) (WHO 2001) The psychometric properties of the ARAT have been rigorously tested (Platz et al. 2005a) and because it is widely used in stroke rehabilitation it allows for comparisons with other work.

The test comprises 19 items organised into four subsections: grip, grasp, pinch and gross. Maximum summed score is 57, indicating best performance. It uses ordinal scoring in which 0 indicates that the patient can perform no part of an item and 3 indicates that the patient performs the item normally. Items are organized hierarchically so that a patient scoring maximally or minimally on an item is very likely to score similarly on all items in that subsection and can progress to the next subsection, thus reducing time taken to complete the test. The test was based on the Upper Extremity Function Test (Carroll 1965) which was re-evaluated by Lyle (Lyle 1981). He tested the hierarchy using Guttman scaling, removed redundant items from the subsections to ensure uni-dimensionality, and simplified and reduced time for administration. Reliability (Van der Lee et al. 2001), concurrent validity with other UL tests (Platz et al. 2005a) and sensitivity to change over time have been demonstrated (Hsieh et al. 1998, Hsueh et al 2002). Published guidelines were used to develop protocols for the present study, (Platz et al 2005b). The published protocol involves collection of data for the contralesional and ipsilesional sides.

The blinded raters, a physiotherapist and occupational therapist, were trained to use the test by firstly observing videotaped performances of the test, practice trials with healthy individuals

then with five volunteer patients otherwise uninvolved in the study. This practice was followed by reliability testing for the present study which is reported next.

4.1.2.2 Establishing reliability of the Action Research Arm Test

METHODS

Participants

Participants in the reliability study had been previously filmed for the purposes of a training video, as part of a study by Platz et al. (2005) and were recruited between September 1999 and November 2000 as either inpatients or outpatients from a centre of neurological rehabilitation in Newcastle upon Tyne, UK. The video tapes and standardised scores were made available for the purpose of the reliability study by Queen Margaret University College, Edinburgh. Participants in the videos presented with incomplete central arm paresis: Motricity Index arm score < 100 and >12; tendon reflexes exaggerated due to either stroke, intracerebral haemorrhage or subarachnoid haemorrhage, multiple sclerosis (MS) or traumatic brain injury (TBI). Diagnoses had been established by clinical laboratory or radiographic means as appropriate. Any acute event at the time of recruitment was at least three weeks previously. Stroke patients were recruited who had not more than mild speech comprehension deficits: Hemispheric Stroke Scale score comprehension 2 or 0. Patents with MS were eligible only if ataxia was not a clinically relevant problem; similarly, TBI patients had no more than mild co-ordination deficit of the primarily assessed arm. In general, patients that were recruited should not be unable to perform the Fugl Meyer test (Fugl-Meyer 1979) due to reasons not related to central arm paresis eg Frozen shoulder.

Filming in the original study was conducted using video cameras, which were positioned at standardised distances in front, to the left and to the right of the patient. The patients were filmed performing the ARAT using a protocol that followed guidelines that were subsequently published (Platz et al. 2005) and is provided in Appendix 5.

Procedures

In the current study, the blinded raters, Rater 1, an occupational therapist with 10 years experience working in stroke rehabilitation, and Rater 2, a physiotherapist with eight years working in stroke rehabilitation were familiarised with standardised ARAT equipment, administration procedure and scoring system (Platz et al. 2005). The raters observed the videotapes individually and scored patient performances at T1. Scoring was conducted using the front views apart from with one patient whose scoring was completed using the right view when the videotape in the camera in front of the patient finished prematurely. For intra-rater reliability, the process was repeated two weeks after initial viewing at T2 an interval considered long enough to exclude recall of initial ratings. Score sheets were concealed from raters until completion of the second test. For inter-rater reliability, scores at T2 for Rater 1 and Rater 2 were then compared with data collected in the original study by Rater 3, a research physiotherapist.

Analysis

Data were analysed using SPSS version 9. Single measure intraclass correlation coefficients (ICC) were calculated for test-retest and inter-rater reliability using a two way mixed effect model for total ARAT scores and sub-sections grasp, grip, pinch and gross. Scores for Raters 1 and 2 at T1 and T2 were used to determine intra-rater reliability for each rater. Inter-rater reliability was determined by comparing data collected by Rater 3 in the original study and the T2 scores obtained by Raters 1 and 2.

RESULTS

Videotaped performances involving eight patients were examined. 5 patients presented with ischaemic stroke and 3 with MS. The patients with MS performed the ARAT with both ULs, providing eleven tests, 44 items in total. ARAT scores for each rater for each participant on each occasion are presented in Table 4.1.

Table 4.1. Total ARAT Scores for Test 1 and 2 for Raters 1, 2 and 3 for each participant

Participant	**ARAT Score Test 1**		**ARAT Score Test 2**		**ARAT Score**	**Range**
	Rater 1	Rater 2	Rater 1	Rater 2	Rater 3	
1	0	0	0	0	0	0, 0
2	57	57	57	57	57	57, 57
3	3	3	3	3	3	3, 3
4	37	34	37	32	34	32, 37
5	22	18	21	18	19	18, 22
6	41	56	41	57	52	41, 57
7	3	7	3	3	3	3, 7
8	3	3	3	3	3	3, 3
9	57	57	57	57	57	57, 57
10	16	24	17	20	19	16, 24
11	4	4	2	4	3	2, 4

ARAT deotes Action Research Arm Test

Single measure ICC's for total ARAT and sub-section scores for intra-rater reliability are presented in Table 4.2, with 95% confidence intervals. Intraclass Correlation Coefficients for both raters were higher than 0.99 for total scores and higher than 0.95 for sub-scores, indicating very high test-retest reliability (Kirkwood and Sterne, 2003).

ICC's for inter-rater reliability are presented in 4. 3. With the exception of the gross movement sub-section, all of the values were above 0.95, indicating very high agreement (Kirkwood and Sterne, 2003).

Table 4.2. Single Measure ICCs (95% Confidence Interval) for intra-rater reliability for Rater 1 and Rater 2

ICC Value (95% Confidence Interval)									
Total ARAT Score		**Grasp**		**Grip**		**Pinch**		**Gross**	
Rater 1	**Rater 2**	**Rater 1**	**Rater 2**	**Rater 1**	**Rater 2**	**Rater 1**	**Rater 2**	**Rater 1**	**Rater 2**
0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.99 (0.99-1.00)	0.99 (0.99-0.99)	1.00	1.00	0.98 (0.95-0.99)	1.00	0.95 (0.84 - 0.98)	0.97 (0.92-0.99)

ICC denotes Intraclass Correlation Coefficient; ARAT denotes Action Research Arm Test

Table 4.3. Single Measure ICCs (95% Confidence Interval) for inter-rater reliability for Raters 1, 2 and 3.

ICC Value (95% Confidence Interval)				
Total ARAT Score	**Grasp**	**Grip**	**Pinch**	**Gross**
0.98 (0.94-0.99)	0.98 (0.95-0.99)	0.96 (0.91-0.99)	0.95 (0.88-0.98)	0.94 (0.86-0.98)

ICC denotes Intraclass Correlation Coefficient; ARAT denotes Action Research Arm Test

DISCUSSION

The intra-rater reliability of the ARAT for Raters 1 and 2 was very high overall and indicates that raters 1 and 2 scored the ARAT consistently over the two occasions. Similarly, agreement

between scores of the three raters was high, and with the exception of the gross movement sub-section was greater than 0.95 for total and all sub-section scores. Using the convention suggested by Youdas et al (1991), values of between 0.91 and 1.0 can be considered to indicate high reliability. All of the scores fell within this range, indicating high reliability.

The high intra-rater reliability for the total ARAT score for blinded raters compared well with that of other studies (Hseih et al 1998, Van der Lee 2001). The slightly lower agreement on the gross function test for both raters may be attributed to difficulty visualising movements on video and in judging when these were complete with cameras placed in front of the participant. In retrospect, the right and left views should also have been viewed to ensure better scoring reliability. The use of videotape to score performances guaranteed stable performances that were unaffected by factors such as natural recovery or effects of therapy, however even with cameras placed at different points, use of videotaping may have diminished scoring accuracy because of poor lighting and small field of view.

The two week interval between scoring sessions may have been too short to exclude recall of scoring and may have contributed to high agreement in the intra-rater study. Van der Lee (2001) suggests that 4-6 weeks is an adequate interval between tests, however in line with this study, others have considered that 2 weeks is an adequate (Baer et al. 2003). Score variability between participants was high. This automatically enhances the ICC (Armitage and Berry 1994), another factor that may explain the high levels of overall agreement.

Inter-rater agreement was lowest for gross and pinch sections. Lower agreement for the gross movement section may be attributed again to poor visualisation. Similarly the front view video had stopped during performance of the pinch section for one patient and performances were rated by the raters using a right view. Change of angle may have influenced rater scoring leading to lower agreement. Although lower than for other sections, the level of inter-rater agreement was nonetheless high and compares favourably with other studies (Lyle 1981, Hseih et al 1998, Van der Lee 2001). The Intraclass Correlation Coefficient for the total score was 0.98, and is similar to the 0.99 found by Van der Lee (2001) and 0.99 found by Hseih (1998). It should be noted that scores calculated by Hseih and colleagues differed since they used total scores for both arms together, providing a possible total of 114, instead of 57 in this study, therefore direct comparison is difficult.

The study had several limitations. Firstly the sample was small, whereas a larger sample may have provided a more precise estimate of the ICC. In their reliability study, Baer et al (2003) suggest that for generalisable results, the number of participants should be greater than 20 with two raters. Thus present findings for the ARAT from 11 participants should not be generalised beyond the present study, but they do meet the purpose of the present study which was to provide evidence for the RCT that the ARAT was scored consistently by individual raters to be involved in the present study, and that scores between the raters were in high agreement.

The studies were conducted post-hoc; tapes were used because they were available and presented a range of appropriate patients, however the use of this method may have influenced results. The instructions to move to the next sub-test when maximum or minimum scores are achieved were designed to shorten the test (Lyle, 1981). In the videotaped performances the test was conducted in this manner by Rater 3. The other raters were therefore provided with information that would have influenced their scoring for patients with maximum or minimum scores on sub-tests since each patient demonstrated maximum or minimum scoring on one or more subsections. This may have increased rater agreement, and results probably reflect higher agreement for both inter and intra-rater reliability than if all items had been scored or if raters had each conducted testing with patients.

Patients in the videos had longstanding stroke and multiple sclerosis, quite different conditions to acute stroke, the condition to be examined in the bilateral training RCT. Therefore the levels of reliability demonstrated may not apply to another population whose performances are not videotaped. This should be considered when analysing findings of the RCT.

Although the use of videotaped performances demonstrated some limitations, in conclusion this small study provided important assurances that intra and inter-rater reliability of the blinded raters on the bilateral training RCT was high and it demonstrated that the raters had been trained to use the ARAT in a reliable way. In line with other studies it also demonstrated that the ARAT is a highly reliable tool for the measurement of UL disability resulting from neurological diseases.

4.1.2.3 Secondary Outcome Measures

1. To ensure that the ICF constructs of UL functioning were adequately covered by the selected measures the **Rivermead Motor Assessment UL Section** (RMA) was selected as a more impairment orientated measure of UL performance than the ARAT. Although examining a few tasks that could be considered as activities, the majority of tasks involved the ICF definition of impairment. The test examined functions defined in the ICF as associated with control over and coordination of simple or isolated voluntary movements, or.functions associated with coordination of simple and complex voluntary movements whilst performing movements in an orderly combination (ICF categories b7600 and b7601).. Between the ARAT and the RMA, impairment and activity limitation of the UL were thus fairly comprehensively examined. This measure is also widely used in UL rehabilitation research (Lincoln et al. 1999). The test comprises a scale of 15 hierarchically organized items. Scores range from 0-15. A score of 1 is allocated if the patient can perform an activity, 0 if he/she cannot. If the patient cannot perform an item after three consecutive attempts, the hierarchical organization of the items assumes that he/ she is unlikely to be able to perform the remaining items and the test is stopped. Successfully completed item scores are summed, creating an UL score out of 15 with higher scores representing better performance. The scale was developed based on assumed recovery patterns, and item order was determined using Guttman Scaling. Reliability, concurrent validity (Lincoln and Leadbitter 1979, Collin and Wade 1990) and scalability in patients with acute stroke (Adams et al. 1997) have been demonstrated. The protocol is designed for testing only of the contralesional side.

2. To discriminate performance at upper ranges of ability, manual dexterity was measured using the **Nine Hole Peg Test** (9HPT), in which patients were required to place nine pegs of 9 mm diameter, 32 mm length into holes on a pegboard (Heller et al. 1987). This was related to the ICF category of activity; specifically to carrying out complex and coordinated actions related to a single task (ICF category d2100) (WHO 2001). Peg placement was timed using an electronic timer that was started by the independent rater when the participant's hand left the table and stopped by the rater when the last peg was placed. A cut-off at 50 seconds was used, when the number of pegs placed was recorded and the number of pegs placed per second was calculated. Three trials were attempted and the mean

score of the three was calculated and used. This simple, rapid test is sensitive to change at upper ranges of ability, demonstrates test-retest and inter-rater reliability (Grice et al. 2003) and has concurrent validity with other UL measures (Parker et al 1986, Heller et al. 1987). Published norms for elderly adults are available (Heller et al. 1987). Test data was collected for the ipsilesional and contralesional sides.

3. Independence in activities of daily living was measured using the **Modified Barthel Index** (MBI) (Shah et al. 1989). This scale represents a participant's ability to perform 10 items of activities of daily living independently and relates to the mobility and self-care categories of activity within the ICF. In this way another important aspect of the activities domain of functioning was covered in the battery of tests. According to published scoring instructions (Shah et al. 1989) assessment is conducted by asking the participant, friends, relatives or nurses about their independence in performing each item, however direct observation is also allowed. Performance is rated on a five point scale, and scores for each category of item are weighted in terms of the overall score. The maximum score is 100, indicating best performance. A modified version of the original Barthel Index, the test was designed to increase sensitivity to change by increasing item responses to differentiate quality and quantity of assistance required (Shah et al. 1989). The scale was selected because of its increased sensitivity to change compared to the original Barthel Index. Widely used in stroke research trials (Chua and, Kong 1996) the measure demonstrates good inter and intra-rater reliability and validity (Fricke and Unsworth 1997).

4. **The Nottingham Health Profile** (NHP) is a self-report scale (Hunt and McEwen 1980) that was used to measure perceived health related quality of life. Agreement to use the scale was obtained from the European Group for Quality of Life and Health measurement (Appendix 6). As advised in the user's guide, only Part 1 was used (The European Group for Quality of Life and Health Measurement, 1992). This section comprised 38 yes/no items that participants were asked to complete themselves and measured six domains of perceived health: energy level, pain, emotional reactions, sleep, social isolation, physical activities. Weighted item scores were used since these reflect the relative seriousness of statements in each section (McKenna et al. 1981). The weighted scores provide a possible total score of 100 for each domain. Lower scores indicate better quality of life. The test was selected because at the time of study design it demonstrated robust psychometric properties for use in

stroke compared to other measures (Buck et al. 2000). The scale was developed using interviews from 700 people to ascertain typical experiences of illness (Hunt and McEwen 1980). Concurrent validity for use in stroke has been demonstrated (Ebrahim et al. 1986) and the scale is widely used in stroke outcome studies (Rudd et al. 1997, Marigold et al. 2005).

The scale covers a number of categories across the ICF, but from the perspective of the patient. Body functions covered include energy, sleep, self and time, emotional functions, pain and exercise tolerance. Activities covered in the scale are undertaking a simple task, changing and maintaining body position, hand and arm use, walking moving around and moving around in different locations, dressing, preparing a meal, doing housework, caring for household objects. Participation examined in the scale includes the categories of complex interpersonal relationships. The scale thus provides a comprehensive assessment of a number of ICF categories of impairment, activity limitation and participation restrictions.

In terms of models of QOL, this measure examines the health related model of QOL, focusing mainly on the impact of physical effects of stroke on perceived health domains. In contrast to some of the more recently developed stroke specific scales, the scale is less comprehensive in terms of the ICF domains. It does not cover ICF body function constructs such as orientation, attention, memory and thought that are more specific to impairments experienced in stroke, nor does it specifically cover UL functioning, all categories which are examined in scales such as the Stroke Impact Scale (Duncan et al. 2003). At the time of study design however, the Stroke Impact Scale had not been developed and the NHP represented the HRQOL scale with the best psychometric properties and that covered a broad range of ICF domains including participation.

5. The fourteen item self-report scale the **Hospital Anxiety and Depression Scale** (HADS) measured anxiety and depression (Zigmond and Snaith 1983). The scale measures impairment in the ICF category of emotional functions and thus ensured that the selected measurement battery provided a comprehensive approach to assessment of the affects of the intervention. Total score ranges between 0 and 42 with two subscales for anxiety and depression each ranging from 0-21. Higher scores indicated greater depression and/or anxiety. The scale was developed as a short assessment and screening test for anxiety and

depression disorders in non-psychiatric settings (Zigmond and Snaith 1983). Reliability and concurrent validity have been demonstrated, as well as bi-dimensionality for anxiety and depression and specificity and sensitivity for case detection (Bjelland et al. 2002, Aben et al. 2002). Internal consistency for use with diverse populations including stroke has been demonstrated (Johnston et al. 2000) and the scale is widely used in stroke outcomes research (Green et al. 2004, Ryan et al. 2006).

6. The revised **Nottingham Sensory Assessment** (NSA) was used to measure somatosensory impairment of the UL (Lincoln et al. 1998), defined as sensory functions in the body functioning category of the ICF. The test adds another important ICF category of impairment to the test battery given that sensory impairment is known to influence UL recovery (Schmidt and Wrisberg 2004) and bilateral co-ordination (Jackson et al. 2000). The test examines the domains of light touch, pressure, pinprick, temperature, tactile localisation, bilateral simultaneous touch, kinaesthesia, stereognosis and two-point discrimination and the areas tested were shoulder, elbow, wrist and hand. For the tactile items and stereognosis, scores range from 0 representing absent sensation to 2 representing normal touch. For kinaesthesia, scores range from 0 representing absent appreciation of movement to 3 representing accurate joint position sense. To assess UL sensation, the shoulder, elbow wrist and hand were tested. The UL score maximum score was 84, indicating normal sensation. The scale was originally developed by Lincoln et al (Lincoln et al. 1991) to provide a standardised method for clinical sensory assessment and was modified at a later date to improve inter-rater reliability (Lincoln et al. 1998). Inter-reliability in patients receiving rehabilitation appears good for light touch, pressure, proprioception (Lincoln et al. 1998) and stereognosis (Gaubert and Mockett 2000) whereas for other domains reliability is more limited (Lincoln et al. 1998). In spite of limited reliability in some domains, the test was selected for use in the present study because it was a standardized clinical measure for which reliability coefficients were known. Scoring guidelines involve collection of data for the ipsilesional and contralesional sides.

7. The battery of measures was selected to ensure that the major ICF constructs of impairment, activity limitation and participation restriction were examined. Box 4.1 demonstrates that the selected measures in the present study do examine all of the major constructs to a degree. It was also important to seek the perspective of the individual with stroke on the impact of

stroke across those domains and it is clear from the literature that the NHP does this with reasonable validity and reliability (Buck et al. 2000)

Where participants had communicative and physical limitations leading to difficulties in completing measures involving questionnaires, the raters read the questionnaires to patients and where necessary completed the forms.

4.1.3 PROCEDURES

4.1.3.1 Recruitment

The acute rehabilitation stage was the period of interest, therefore to ensure that patients could still be considered acute but were medically stable with persistent UL impairment, screening and study inclusion occurred between 2 and 4 weeks following stroke onset.

The recruitment protocol is provided in Appendix 7 and the procedure is summarised in Figure 4. 1 below.

A consecutive cohort of patients admitted to Ninewells Hospital, Dundee with a provisional diagnosis of stroke, transient ischaemic attack, cerebrovascular accident, CVA or left or right sided weakness was screened for inclusion. Stroke team physiotherapists identified all patients admitted through the medical receiving wards within two days of admission and made that information available to the research team within one week of the patient being admitted. Confirmation of the diagnosis of stroke was made from CT scanning results. Where CT scanning conducted within the first two days of onset was negative because of an isodense infarct but patients presented with sudden and persistent UL weakness, the diagnosis of stroke was confirmed by the consultant stroke physician prior to screening.

Between two and four weeks, initial screening for all patients still in hospital was conducted by the research team comprising the author, a physiotherapist and the lead researcher, or the research physiotherapist employed to deliver the intervention. These were different therapists to those acting as blinded raters. Screening was conducted in collaboration with stroke team physiotherapists using information collected routinely by them. Patients were assessed for ability to participate in usual once daily 30-minute physiotherapy sessions on 5 weekdays per week, and for residual UL impairment defined as <6 on each of the Motor Assessment Scale (MAS) UL domains(Carr et al. 1985). The MAS is a valid and reliable assessment of motor function (Malouin et al. 1994) used routinely by physiotherapists in Ninewells Hospital stroke unit and in which the research physiotherapists were trained (Appendix 8). Participants fulfilling these initial criteria at two weeks were provided with an information sheet (Appendix 9). After

48 hours and after checking that they had read and understood the information, patients were invited to participate in full screening for participation in the study.

Between two and four weeks following stroke onset, patients meeting initial criteria and agreeing to further assessment were assessed to determine whether they met other study inclusion criteria (below). Those meeting all study criteria were asked to sign the Tayside Ethics Committee consent form (Appendix 10) to consent to participate in the study. Patients who had been discharged at this point or transferred to rehabilitation and who demonstrated residual UL impairment as assessed on MAS scores by the stroke team physiotherapist at discharge from Ninewells Hospital were followed up and also screened for inclusion.

Assessment for inclusion was conducted by the lead researcher or by the research physiotherapist. Each had 17 years experience as a physiotherapist and was trained in the use of the screening tools.

Patients not meeting initial criteria or full criteria for inclusion at two weeks because of illness, medical testing, poor sitting balance, communication problems or other reasons underwent initial screening again at three and four weeks to ensure that all eligible patients were included within the timescale.

Reasons for non-inclusion were collected but individual patient identification details were not attached to this information because these patients had not provided consent for their data to be used.

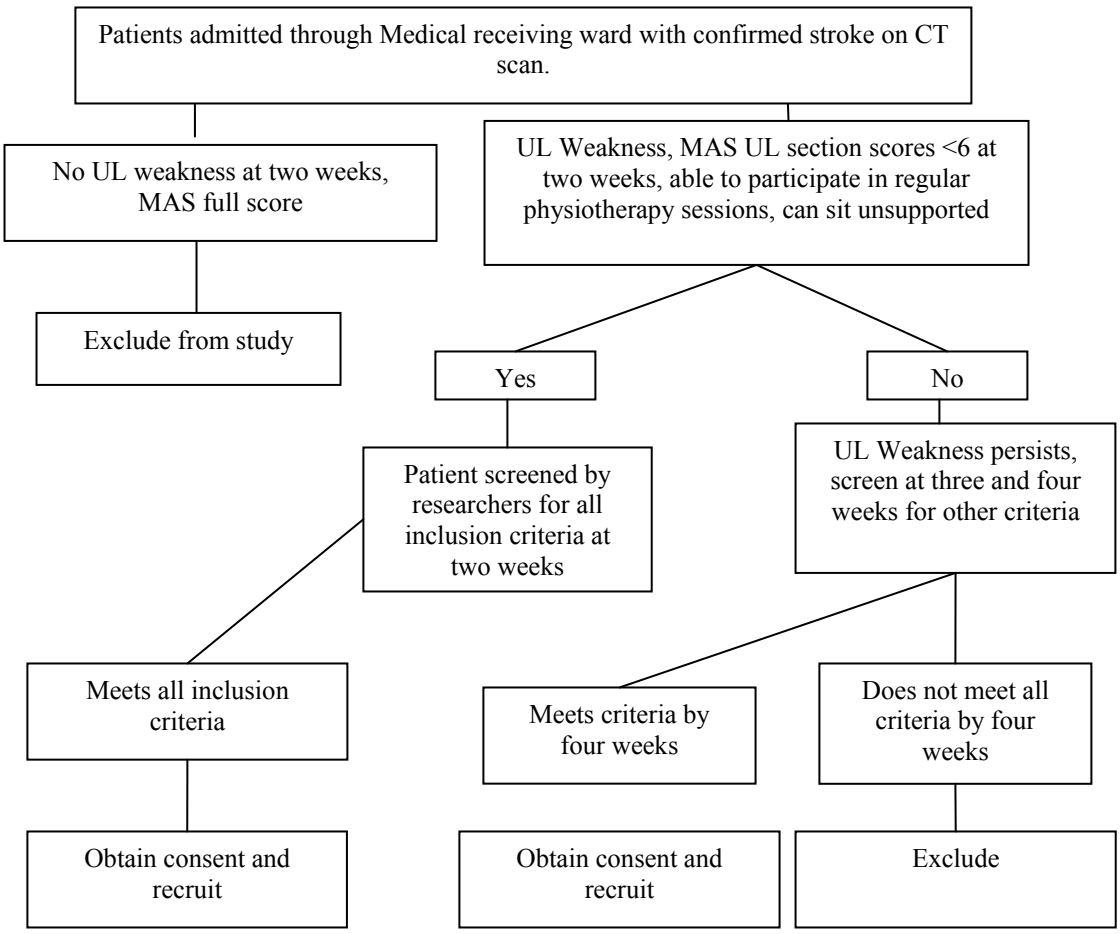


Figure 4.1 Summary of recruitment procedure

4.1.3.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria are summarised in Box 4.2 and are explained in more detail below.

Box4.2. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. Acute unilateral stroke confirmed by CT scan. 2. Persistent UL motor impairment, defined by scores of < 6 on any of the UL sections of the Motor Assessment Scale 3. Ability to participate in 30-minute physiotherapy sessions 4. Preserved cognitive function, indicated by scores of 0 or 1 on consciousness, communication and neglect items of the National Institute of Health Stroke Scale 5. Ability to sit unsupported for 1 minute	1. Previous stroke resulting in residual disability 2. Inability to provide informed consent due poor comprehension or communication 3. Unwillingness to provide informed consent 4. Premorbid UL impairment or hemiplegic shoulder pain

INCLUSION CRITERIA

1. Clinical diagnosis of acute unilateral stroke confirmed by CT scan. Where the scan was isodense because it had been taken too early for an infarction to show up, diagnosis was confirmed in collaboration with the consultant stroke physician.
2. Persistent UL motor impairment, defined by scores of < 6 on each of the UL sections of the Motor Assessment Scale.
3. Ability to participate in usual once daily 30-minute physiotherapy sessions on 5 weekdays per week. This criterion was necessary to ensure that patients were likely to be able to tolerate 20 minutes of additional experimental intervention.
4. Ability to sit unsupported for 1 minute. This criterion was included to ensure that participants had sufficient balance to perform the required UL activities at a table.

EXCLUSION CRITERIA

1. Severe neglect, aphasia or cognitive impairment that would limit the ability to provide informed consent evidenced by scores > 1 on the consciousness, communication and

neglect items of the National Institutes of Health Stroke Scale (NIHSS) (Brott et al. 1989) (Appendix 8). The lead researcher and the research physiotherapist were trained and tested by the consultant stroke physician in use of the NIH Stoke scale using the NIHSS training video. Where uncertainties about cognitive impairment existed, the speech and language therapist was also consulted.

2. Previous stroke resulting in residual UL disability. Although previous stroke was not an exclusion criterion, it was important to ensure that the patient could be categorised as having an acute stroke and that the UL deficit was new. The existence of previous stroke was evidenced in medical records and the existence of residual disability was established through review of medical and physiotherapy records and consultation with patients and carers.
3. Unwillingness to provide informed consent. Where patients met inclusion criteria but refused to provide consent to participate.
4. Other pre-morbid arm impairment or hemiplegic shoulder pain, again established through medical record check and consultation with patients and carers. This exclusion criterion was set to exclude participants who might not be able to undertake the training because of pre-existing UL problems, and to avoid confounding the results due to pre-existing UL problems.

Baseline assessments were conducted on patients meeting inclusion criteria and who had provided consent to participate. Participants were allocated an identification number which was then used in the randomisation process (detailed below) and for all paperwork. Screening data for patients not included in the trial or refusing consent was destroyed.

The stages of the study are illustrated in Figure 4.2 (Below).

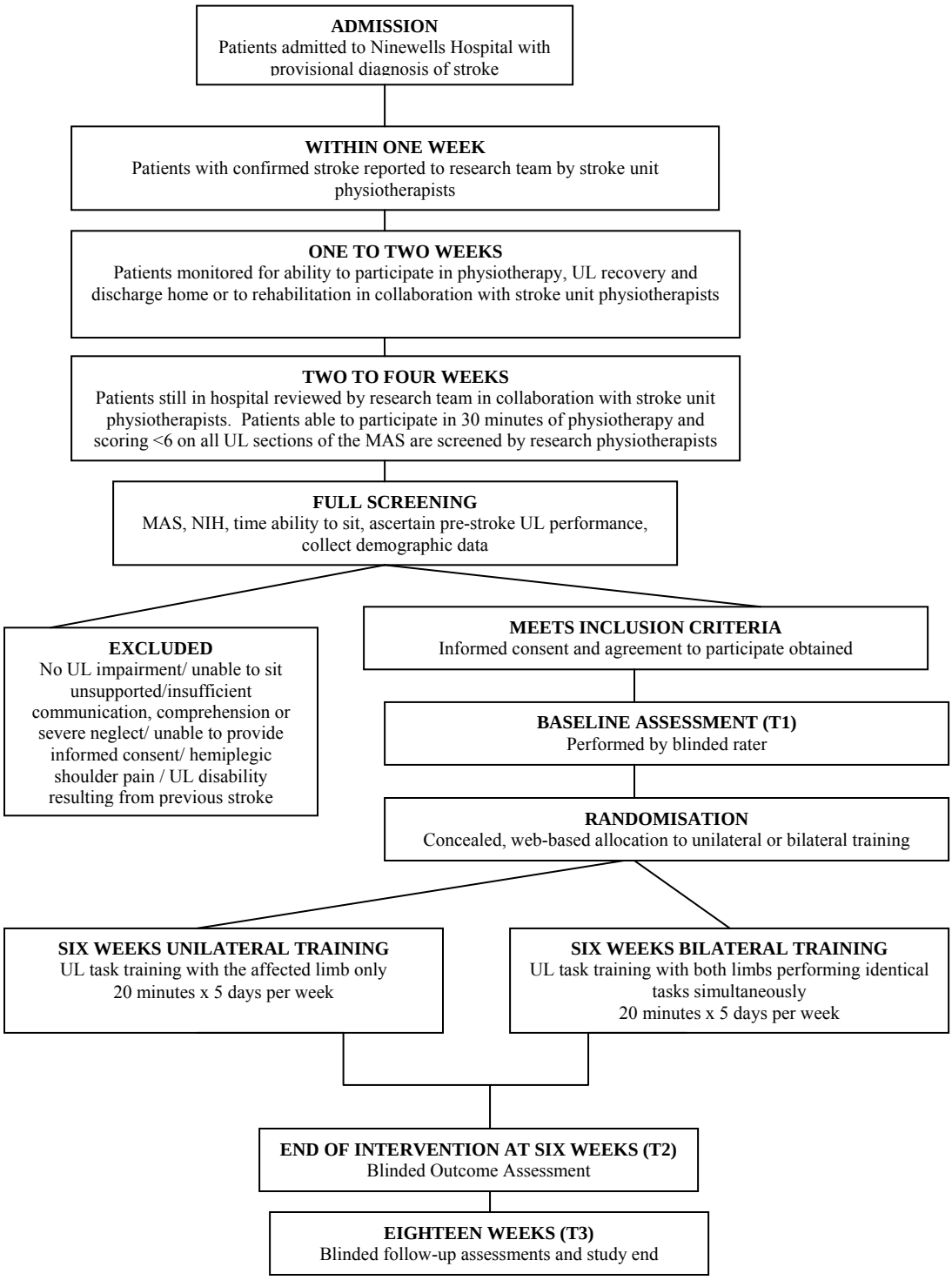


Figure 4.2 Study Procedures

4.1.4 RANDOMISATION AND BLINDING

4.1.4.1 Randomisation

Participants were randomly assigned to receive bilateral or unilateral training using a concealed web-based computerized random-number generator, designed by the study statistician. Patients were randomised after baseline assessment, two to four weeks after stroke onset and following provision of written informed consent and baseline assessment. A study identification number for the patient was entered into the computerised system by the lead researcher (JM). Stratification factors detailed below were also then entered and the system indicated the group allocation which was then intimated to the research physiotherapist. The randomisation protocol is detailed in Appendix 7.

Stratifying factors were:

1. Side of hemiplegia. The characteristics of right and left hemisphere damage differ, which may influence post-stroke presentation and recovery (Abdullaev and Posner 2005, Harris and Eng 2006). Side of stroke was therefore considered to be an important stratifying factor to ensure equivalent randomised groups for comparison.

2. Stroke classification determined by the Oxford Community Stroke Project Classification (Bamford et al. 1991). Stroke subgroups determined by clinical signs are known to recover differently (Bamford et al. 1991), therefore participants were stratified according to whether they had lacunar stroke or not to ensure even distribution of those patients who generally make better recovery and those less likely to do so. Patients were classified by therapists in consultation with the stroke consultant who was an advisor for the study and who determined classification using CT scan and the Oxford Community Stroke Project Classification.

3. Baseline UL activity limitation assessed by ARAT score (Lyle 1981). Initial severity of UL motor and functional deficit is known to influence outcome (Sunderland et al. 1994), therefore to ensure equivalence in terms of severity participants were also stratified for severity on the ARAT. Stratification was applied based on ARAT scores of five or less

or six or more which discriminated those with little or no motor control from those who demonstrated some control.

4.1.4.2 Blinding

The two therapists (an occupational therapist and physiotherapist) trained to administer the measures, were blinded to treatment allocation and were otherwise uninvolved in the trial. They had no access to study documentation other than the information directly relevant to the assessments they were undertaking. Participants were instructed by the raters not to indicate their group allocation to the raters. The raters were asked to inform the lead researcher immediately if blinding had not been preserved. The raters were also asked at monthly intervals by the lead researcher whether blinding had been preserved in all cases.

4.1.5 TASK TRAINING INTERVENTION

Training tasks were based on tasks previously used in bilateral training single case studies reported in the literature review (Mudie and Matyas 1996, Mudie and Matyas 2000, Lewis and Byblow 2004). These tasks were the core tasks on which the intervention was based. Equipment and the core tasks is described in section 4.2.6.3. Core and modified protocols involving modified versions of the tasks were developed to account for different levels of UL dysfunction at baseline assessment. The tasks were developed and piloted to provide a progressive programme of task difficulty by incorporating variations in reaching distances, accuracy, dexterity, and strength requirements. The intervention was also based on known principles of motor learning and these are discussed in section 4.2.6.4. Next, details of the intervention procedures are provided in section 4.2.6.5.

4.1.5.1 Bilateral and unilateral groups

Participants in each training group underwent training of identical duration, intensity and content, with the exception that participants allocated to bilateral training practised identical tasks with each arm simultaneously, whilst the unilateral group practised the same training tasks with the affected arm only.

4.1.5.2 Equipment

Patients sat on a chair (seat height 45cm) with armrests, at a table (76cm high, with a tabletop of 100 cm x 60 cm). The table was designed with two detachable, adjustable height shelves which were fixed 47cm from front of table (Figure 4.3). The table and shelves were marked at various points to provide targets for task completion. The marks varied in distance from the front of the table or shelf and in width with distance progressively increasing in 10 cm increments.

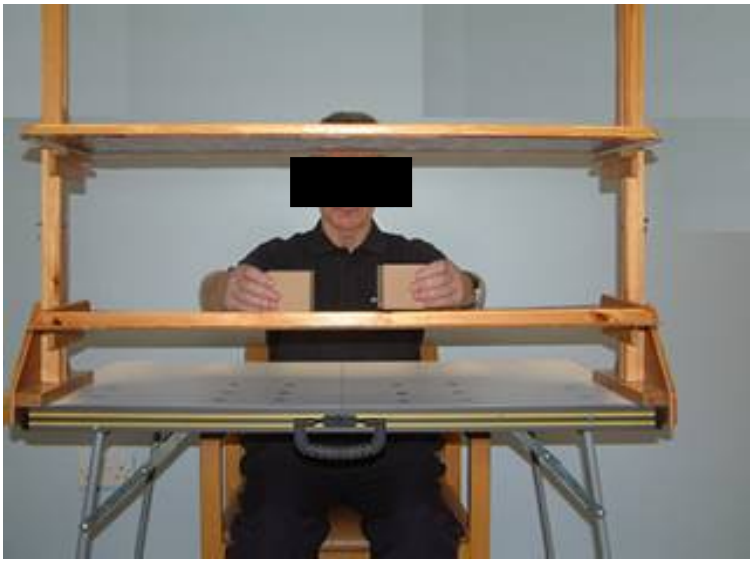


Figure 4.3.Table and Shelf Apparatus

Additional equipment comprised 2 mobile vertical target boards, each 17.5 cm^2, and fixed to stand 30cm in height, two drinking glasses (7.5 cm high, 7.5 cm diameter at widest part), round dowelling pegs 2cm diameter x 4 cm long, $7cm^3$ wooden cube and everyday objects of varying shapes and sizes.

4.1.5.3 Core and modified training tasks

The training programme was based on four core tasks developed and used in other bilateral training studies that represented tasks of functional relevance found difficult by individuals with stroke (Carr and Shepherd 1998). The pointing task (Task 1) was included since pointing is an important UL function used in many daily tasks such as pressing buttons to programme a microwave oven or ringing a doorbell and as a key component of non-verbal communication (Goldin-Meadow 2007). It involves proximal and distal control, for which task constraints could be progressed using targets of varying size. The three other tasks (tasks 2-4) had been used previously in bilateral training studies (Mudie and Matyas 1996, Mudie and Matyas 2000, Lewis and Byblow 2004) and involved pointing, reaching, grasping, object manipulation and transportation sequences to a degree of accuracy typical of many functional tasks. The core tasks are described in Box 4.3

Box 4.3 Core intervention tasks

Core Intervention Tasks	
1	Point to targets raised 30cm from the table and positioned at midline, 40cm to the right and 40cm to the left of midline.
2	Move a doweling peg 2cm diameter x 4cm height from tabletop to attach to underside of a shelf placed at eye level and at 10cm to right or left of midline
3	Move a 7.5cm^3 block from the table onto a shelf at shoulder height and 10cm to right or left of midline. Height was adjusted for each participant and was noted and replicated at each session.
4	Grasp an empty glass, take to the mouth, and return to starting position.

Participants allocated to the bilateral group were instructed to move both arms simultaneously and to achieve the task goal with both arms at the same time whilst the unilateral group focused only on the affected arm. This approach was detailed in previous literature (Mudie and Matyas 1996, Mudie and Matyas 2000) discussed in Chapter 1, Section 2.2.3.

Participants were assigned to a core or modified protocol depending on whether they could successfully complete the four core tasks on assessment at the first training session. This assessment was conducted by research physiotherapists according to set criteria for successful task completion (Appendix 11). Progressive, standardized graded variations of both protocols addressed specific motor or functional goals, and incorporated a range of everyday objects of differing shapes and sizes.

The core protocol comprised the core tasks and variations of the same task with changes in distance, weight and shape. In some cases, the progressions involved the same general movement was retained e.g. reach, but the task was changed, for example in task 1 from pointing to a target board to making dots with a pen or picking up keys to hang on a hook on the target

board (Box 4.4). The progression aimed to challenge participants, maintain their interest and enable them to develop strategies to perform more functionally orientated tasks (Appendix 11). The progressions for each task are described in Box 4.4. Participants were also invited to choose the activities they preferred to practise at some stages within the protocol.

Box 4.4 Progressions of core tasks

Core Intervention Tasks		Core Progressions
1	Point to targets raised 30cm from the table and positioned at midline, 40cm to the right and 40cm to the left of midline.	• Widen targets on tabletop • Reduce target size • Point to progressively smaller targets • Make dots with pen on target board • Make dots in progressively smaller targets placed wider apart • Pick up keys, hang on hook • Pin drawing pin onto board • Progressive range of small objects to target at board
2	Pick up a doweling peg 2cm diameter x 4cm height from tabletop and attach to underside of a shelf placed at eye level and at 10cm to right or left of midline	• Widen target attachment point • Attach and detach peg and return to table • Perform same with smaller peg • Hang cups on hooks underneath shelf • Variations in cup size and weight • Hang keys on hooks • Stick Velcro underneath shelf • Fasten clothes pegs to string line underneath shelf at various widths • Lift weighted cylinders to touch underside of shelf • Progressive range of other undershelf tasks such as screwing a nut onto a bolt
3	Move a 7.5cm^3 block from the table onto a shelf at shoulder height and 10cm to right or left of midline. Height was adjusted for each participant and was noted and replicated at each session.	• Progressively increase target width on shelf • Reduce size of object • Altered shape of object – increasing requirement for dexterity and accuracy
4	Grasp an empty glass, take to the mouth, and return to starting position.	Progress to • cup with handle • cup filled with water • polystyrene cup • theraputty • jelly bean • fork • load fork with simulated food • load spoon with beans/water

The modified protocol based on the four core tasks was developed for participants meeting study inclusion criteria, but who because of more severe initial UL deficits were unable to actively participate in core activities. Since the motor learning literature supports the view that active rather than passive activity is important for learning (Ada et al 1990, Turton, 1998, Dobkin, 1998, Carr and Shepherd 1998), these patients practised related but modified activities that were achievable and that progressively increased in difficulty towards the core tasks. Generally, a task involved components of movement of the core task, for example forearm supination and grasp release in preparation for picking up a glass to take to the mouth (Task 4, Box 4.5) This protocol therefore initially involved tabletop activities incorporating components of the core tasks, including reaching, forearm pro and supination, wrist extension and grasp and progressively increased in difficulty to modified versions of the core tasks for which key components were made easier to achieve. Assistance from the therapist was provided when necessary but was withdrawn as soon as the participant became active. The modified protocol is detailed with the core protocol in Appendix 11. The main tasks and task progressions are summarised in Box 4.5. Development and piloting of the core and modified protocols and the practice schedule is described in the next section.

Box 4.5. Progressions of modified tasks

	Modified Version of Core Task	Modified Progressions
1	Reach to touch	• Slide to touch marks on tabletop with assistance • Increase distance and width • Lift hand off table to touch marks on tabletop • Increase distance and width • Lift hand to touch/point to target board at increasing height
2	Supination, grasp and reach to touch	• Simple forearm supination • Supination whilst grasping dowelling • Grasp dowelling and target it into putty on table whilst maintaining midline supination • Supinate to touch underside of shelf • Grasp wide cylinder and attach to underside of shelf • Grasp narrower cylinder and attach to underside of shelf • Use pinch grip to target wide dowelling on underside of shelf • For all progressions gradually increase distance and width
3	Grasp to lift object	• Slide to reach target on table • Lift hands to place on beanbag on table • Place cylinder on table • Place cylinder on beanbag on table • Grasp and move large cylinder across tabletop • Grasp and move large cylinder onto low shelf • Grasp and move glass onto low shelf • For all progressions gradual increase in distance and width
4	Object to mouth	• Grasp small cylinder placed in hand and supinate • Maintain supination and flex elbow to take cylinder towards mouth • Maintain midline supination, extend wrist and open hand to attempt to grasp glass • Take stack of plastic tumblers toward mouth • Gradual reduction in stack to move one tumbler accurately to mouth

4.1.5.4 Piloting the experimental intervention

The purpose of this pilot study was to determine how the principles of motor learning could be applied to inform the content and organization of practice and feedback in a task orientated intervention for patients with a wide range of impairments that could be applied bilaterally *and* unilaterally. The intervention was complex, involving the implementation of various theories of motor learning and incorporating a number of components. Phase 1 of the Medical Research Council (MRC) Framework for Complex Interventions (Campbell et al. 2000) suggests that a phased approach to development of complex interventions should be applied. In an MRC Framework Phase 1 series of pilot studies, the intervention was therefore examined for patient acceptability, and modelling was conducted to determine the distinct components and to examine how they interacted and related to each other before the Phase 11 trial that comprised the main RCT. The report of the pilot study is provided next.

Specific Aims of Pilot Study

To develop variations and part-task options of the identified activities to maximise active patient participation regardless of degree of impairment within the core and modified protocols

- To determine if assumptions about order of difficulty of tasks were correct
- To examine how acceptable the experimental activities were to patients and determine if they were sufficiently interesting and challenging for patients to want to undertake a 6-week trial.
- To determine optimum organization of practice and feedback and to examine the acceptability of blocked and random practice

METHODS

Task Selection

To develop the intervention tasks and practice schedules it was firstly important to identify appropriate tasks. Four experimental training tasks were identified because they had been previously used in other bilateral training studies (Mudie and Matyas 2000, Mudie and Matyas 1996) and represented motor activities found difficult by stroke patients (Carr and Shepherd 1998). The pointing task (Task 1) was included since pointing is an important UL function used in many daily tasks such as pressing buttons to programme a microwave oven or ringing a doorbell and as a key component of non-verbal communication (Goldin-Meadow 2007).

The core tasks were:

1. Reach and point to 3 targets raised 30cm from the table and positioned in front, 50cm to the right and 50cm to the left of midline.
2. Move a doweling peg 2cm diameter x 4 cm height from tabletop to touch underside of a shelf placed at eye level.
3. Move a 7.5 cm block from table onto a shelf at shoulder height.
4. Grasp a cup, take to the mouth and return to starting position.

An intervention protocol was designed on the basis of these tasks to provide active training for participants with a range of severity of upper limb deficits whilst retaining the motor characteristics of the core tasks. It was predicted that many patients meeting study inclusion criteria, but with severe initial impairment would be unable to actively participate in these activities. These patients were included to enhance the external validity of the study. It was clear however, that they would benefit from related but modified versions of the core tasks to make them actively achievable and that progressively increased in difficulty towards the core tasks. Since the motor learning literature supports the view that active rather than passive activity is important for learning (Turton 1998, Ada 1990, Dobkin 1998, Carr and Shepherd 1999), a modified protocol was developed based around the four original tasks to address this issue.

At the other end of the continuum, patients with less severe impairment who were able to perform the four core tasks at initial assessment were likely to find repetitive practice of easily achievable tasks monotonous. A programme of related but progressively more difficult tasks was therefore developed to challenge them, maintain their interest and enable them to develop strategies to perform more functionally orientated tasks. This core protocol would also involve varied practice to provide training of individual tasks across a range of movement parameters.

The core and modified tasks that were piloted are described next:

Core Protocol and Modified Protocols

Task 1: **Reach to touch targets at 30cm high.**

For the core task, target boards were constructed so that interchangeable laminated targets could be stuck with velcro onto the boards. The laminated targets contained progressively smaller circles that the patient was to touch. Further progression of this task came through succession to more functional tasks such as sticking drawing pins into "blu tac" on the board and hanging keys onto hooks attached to the boards with velcro. The modified protocol involved reaching to touch small targets on the tabletop.

Task 2: **Move a doweling peg 2cm diameter x 4 cm height from tabletop to touch underside of a shelf placed at eye level**

Doweling pegs were to be picked up and attached to the underside of the shelf with Velcro and placed at target points at increasing widths from midline. This task was progressed to incorporate functional tasks such as hanging cups onto hooks under the shelf and attaching pegs onto a string attached to the hooks. The modified protocol involved supination, then supination to midline followed by reach to grasp various cylindrical objects starting with a universal container then dowelling 2cm in diameter. The next progression was to lift the cylindrical objects to place them horizontally then upright on the table and then to place them upright at different locations on the table before targeting them at the underside of the shelf.

Task 3**: Move a 7cm block from table onto a shelf at shoulder height**

A 7.5 cm block was to be placed on a shelf at eye level. This task was made more challenging by progressing to a variety of everyday objects of differing shapes and sizes such as cotton wool balls, golf tees, and paperclips. It was made less difficult for the modified protocol by reaching to touch objects on the tabletop, then reaching and grasping, then reaching grasping and moving the object on the table-top before progressing to placing the block onto the shelf.

Task 4**: Grasp a glass, take to the mouth and return to starting position**

The progression here was to progress from the glass through a variety activities to use of cutlery and spooning beans to the mouth, an activity requiring finely co-ordinated motor control. The modified protocol, involved supination to midline, grasp and release of cylinders on the tabletop, hand to mouth and finally cup to mouth.

Both protocols were designed to incorporate some or all of the principles of motor learning discussed in the introduction namely:

- Goal achievement
- Whole task training and part-task training (modified protocol)
- Varied practice, when the learner practices the same task in a variety of ways in a session
- Blocked practice involving repeated rehearsal of a single task during a training session and random practice where tasks are randomly interspersed during practice
- Feedback scheduling where knowledge of results and performance is provided
- Guided practice where therapists provided physical assistance during the initial stages of task recognition to familiarise patients with features of the task

Design

This was a series of pilot trials to develop core and modified standardised training protocols of progressive difficulty for the four training tasks. For each protocol, task progressions were tested on patient volunteers who were asked to rank the progressions in order of difficulty and to provide feedback relating to the scheduling of practice and feedback.

Participants

Physiotherapists in two rehabilitation hospitals were asked to identify current in-patients with a diagnosis of stroke without severe communication difficulties and with residual upper limb impairment leading to activity limitation. These patients were approached by the research physiotherapists, who explained the procedure and invited them to participate. Once written consent had been obtained the patients participated in between one and three test sessions over a four-week pilot phase.

PROTOCOL TESTING

Piloting the hierarchy of difficulty of part and whole task training

Patients were asked to perform each of the tasks bilaterally, using each hand independently but simultaneously; and unilaterally, with the affected arm only, and to try as many of the progressions as they could manage. Patients were asked to comment on the hierarchy of task difficulty and the practice scheduling, as well as their enjoyment of the activities. Patients started on the modified version of each task if unable to perform the original tasks and on the standard progression for each task if they could perform the original task.

Patients were invited to perform each task progression in an order of difficulty initially determined by the lead researcher. Patients were asked to consider each task for degree of difficulty, and to compare it to each of the previous tasks. The research therapists also observed participant performance and judged performance and the degree of difficulty through observation. By moving through all of the tasks in this way the perceived difficulty of each task permutation was determined through therapist observation and patient perception.

Practice Scheduling: Blocked or Random

All of the patients participated in block practice of the various tasks, in which they practiced each task in sequential blocks of 10 repetitions. Given that it is clear that block practice may not be optimal scheduling for task acquisition (, random sequencing was also piloted. Patients were asked to compare block practice with random.

Feedback Scheduling

Feedback on both on knowledge of results, that is, number of accurate trials, and on knowledge of performance, that is the quality of movement during the task was provided. Feedback also influences motor learning therefore patients were asked to compare feedback after both 5 and 10 trials and to indicate their preferred interval for feedback (Schmidt 1988).

Goals

Each task and task progression had a specific motor goal. This might be touching a target or placing an object. The goals were determined as part of the task protocol development by the lead researcher and were not patient generated goals, however participants in the pilot study were asked to comment on how valuable they perceived the goals to be.

RESULTS

Participants

A convenience sample of 11 patients was invited to participate. All participants had a history of stroke and ranged in time since onset from 2 weeks to 3 months. Ages ranged from 62 years to 84 years. Four participants demonstrated left hemiplegia and seven demonstrated right hemiplegia. Six participants would not have met inclusion criteria for the main study for various reasons, including time since stroke, history of rheumatiod arthritis, insufficient sitting balance, neglect and impaired communication. All of the participants were however willing and

sufficiently able to participate and provide important feedback. Eight participants were involved in one session only another participated in two sessions whilst a final participant was involved in three sessions.

Part task training and varied practice

Task 1: **Reach to touch targets at 30cm high.**

The core task of Task 1, reaching to touch the targets at midline and 50cm wide was piloted with all of the participants, sequenced in massed blocks of 10 trials. Participants found this task particularly difficult and tiring to perform in massed blocked sequence since they were working at arm's length during the task. The proposed hierarchy of difficulty of the modified task was tested with 8 participants. This involved reaching to markers on the tabletop. Testing demonstrated that the hierarchy followed a sequence of increasing difficulty.

Task2: **Move a doweling peg 2cm diameter x 4 cm height from tabletop to touch underside of a shelf placed at eye level**

Ten participants piloted this task. For the core progression four participants reported that this task was challenging, but found it less difficult to perform in blocks than Task 1. The hierarchy was changed for the modified protocol since two participants of the three tested found a universal container difficult to grasp as the first progression, therefore an item including only supination without grasp was added as the first activity.

Task 3: **Move a 7.5 cm block from table onto a shelf at shoulder height**

The hierarchy of difficulty for the core progression was tested with 5 participants. Since participants needed to be able to attempt to grasp and move most of the objects to establish the ranking of difficulty, all of the participants selected for this item had good upper limb function. Participants were asked to move each of the objects in turn, and then to rank them successively in order of difficulty.

Participants were in broad agreement that the hierarchy should be changed. The objects found more difficult to grasp than anticipated were the polystyrene cup and the china cup in a grasp hold, both of these were moved down the order of difficulty. The cotton wool was considered much easier to grasp than anticipated and was moved up, and four out of the five participants agreed that ball bearings were the most difficult objects to pick up.

The modified progression of tasks as presented it in the protocol (Appendix 11) was considered by all participants to be an accurate ranking of difficulty.

Task 4: **Grasp a glass, take to the mouth and return to starting position**

Again the main finding was that the four participants assessing the core protocol found the polystyrene cup more difficult to grasp than the other cups or the cup full of water. The order of hierarchy was changed accordingly. Otherwise the hierarchy for core and modified protocols appeared sound.

Blocked Practice

The initial plan was for blocked practice in blocks of 10 trials followed by rest of 5 seconds before the next block of 10, up to a maximum of three blocks of 10 trials of the same task. In general participants reported that block repetition was monotonous, and motivation to complete 30 massed trials waned. Some participants were unable to complete 3 consecutive blocks of 10 repetitions of all of the activities because of fatigue.

As a result of this feedback and observations that performance deteriorated during block practice, the opportunity for participants to practice tasks in repetitive blocks was preserved within the protocol, but the interval between rest periods was reduced to five. Five repetitions were scheduled followed by rest of approximately five seconds then another five repetitions of the same task then rest, followed randomly by another task to be practised in the same way. In this way block practice occurred, but blocks of each task were randomly interspersed after ten trials to maintain interest and prevent fatigue.

In this way during the early phase of task acquisition, tasks were practised in blocks of five but the blocks of each task were distributed throughout the session. Block practice was conducted to a maximum of 30 trials in one session until it was clear, through accurate performance on five consecutive trials, that the patient recognised the demands of the task and could perform it before moving on to single trials, randomly scheduled. This schedule was found more acceptable and less tiring by the five participants with whom it was tried.

Random Practice

Random number sequences were generated on Microsoft Excel (Appendix 12). Single trial random practice was also piloted. When single trials randomly interspersed were piloted with

two participants, fatigue was not reported and participants reported that randomization of practice trials was stimulating and motivating. Thus the final scheduling was organised to incorporate block trials of five trials of a task, five seconds rest, five trials of the block then randomly change to another task. Once any task is performed so that five trials in a row were successfully completed, move to single randomly interspersed trials of that task. Once 75% of single random trials are accurate, progress to the next task and start again with blocks of five.

Feedback Scheduling

The two feedback schedules of 5 and 10 trials were tried with two participants. Both preferred feedback after 5 blocked or randomly sequenced trials. They reported that this provided them with enough information to work to improve their performance whilst feedback after 10 trials was considered too much of an interval. Since an interval of 5 trials has been shown in the literature as optimum for retention of complex activities (Schmidt 1988), this was considered an appropriate interval for feedback on the study tasks.

Active and Guided Practice

Participants reported that they found the active practice challenging and stimulating, and that it was different from their usual therapy which often involved guided practice. Guided practice was only provided to two participants who had the most severe impairment during tabletop activities. Assistance was minimal and was withdrawn when the patients became more active providing the therapists with an opportunity to judge how to assist, provide encouragement and to judge when to withdraw assistance.

Goals

Participants reported that they found the goals challenging and interesting and that attempts to achieve them made the sessions interesting. They reported that the target of 75% accuracy was realistic and that setting it presented a motivational challenge.

Summary

The original practice programme followed a reasonable hierarchy of difficulty with recovering stroke participants. Following piloting the hierarchy required some modification from the first version, but on the whole it was sound. The range of activities was adequate to enable participants to participate irrespective of severity of impairment. The tasks were interesting for participants to perform, however the massed practice scheduling in which participants performed

repetitive blocks of the same activity was less acceptable than block practice of different tasks interspersed or random scheduling. Principles from motor learning literature regarding scheduling of feedback were followed and it was found that the optimally preferred interval was feedback after 5 trials.

DISCUSSION

During piloting, tasks from the original proposal were developed to incorporate activities that would enable participants with differing severity of impairment to participate actively in achieving clearly defined goals, albeit set by the protocol.

The originally proposed protocols provided task variations of increasing difficulty for each task. Piloting demonstrated that in the main, the hierarchy of difficulty was sound, but was altered accordingly where found to be incorrect. Since all of the tasks were piloted with at least 8 participants, it is possible to be fairly confident of the amended order of difficulty. Additionally, participants found the tasks and motor goals interesting and stimulating and were therefore likely to complete the 6 week intervention schedule.

The hierarchy was based on verbal feedback from participants and informal observations from therapists. More formal evaluation of the hierarchy could have been undertaken, for example using Guttmann Scaling however this was beyond the scope of the study.

Observations relating to practice scheduling reflect findings in the motor learning literature. Participants found block practice excessively tiring and monotonous. It is clear from the literature that blocked practice is beneficial during the acquisition phase of learning a new task, but is detrimental to learning and retention of the task (Shea et al 1990). Contextual interference, that is, performing a task in an unpredictable situation, created by random practice, appears to enhance learning through forcing subjects to reconstruct movements for each attempt, a fact supported by evidence that random practice enhanced learning in stroke (Hanlon et al 1996). The participants reflected this, reporting that distributed block practice and random practice were more interesting and stimulating than block repetition, although because of the timescale and resources available for the pilot, it was not possible to specifically test the effects on learning of practice scheduling.

Evidence indicates that summary feedback on performance enhances learning, and it has been suggested that feedback after five trials leads to optimum learning of a complex motor task (Schmidt 1988). Participants in this pilot found feedback on performance and accuracy useful and preferred the shorter interval of 5 trials. This schedule was incorporated into the protocol.

One limitation of this pilot study was that participants were not identical to the intended study population, and some were only available on one occasion making it difficult to determine the acceptability of longer term participation in the intervention. Secondly, although patient feedback was carefully documented, the information was gathered relatively informally without a specific interview schedule or questionnaire. This may have led to useful information being missed. Again however, more formal evaluation was beyond the scope of the present study.

CONCLUSION

The protocol was based on results from piloting activities with participants and on evidence of learning from the movement science literature. The practice schedule was more acceptable to participants than the originally proposed blocked practice; activities enabled participants of all ranges of impairment to actively participate in the intervention. Participants in the pilot study indicated that the amended protocol was sufficiently interesting and challenging for them to want to complete the 6 week intervention.

Having developed and piloted the tasks, it was then important to determine how practice would be structured. For this, eight principles of motor learning were applied to maximize effects of training on motor skill learning. Firstly, one model of skill acquisition is the stages of motor learning model in which skill acquisition is thought to occur in three stages (Fitts and Posner 1967). The cognitive stage is the initial stage of learning when the individual is concerned with understanding the task. This stage requires a high degree of cognitive effort such as attention. Here, performance is variable since the individual is trying out various strategies for performance. The second stage is the associative stage during which refinement of the task occurs, variability is less and the focus is less on trying strategies than on refining one particular pattern. The final stage is the autonomous stage in which the skills performed automatically and the degree of attention required is low. Although there has been less research on the autonomous stage of learning than the other stages, this is now an accepted model of processes

of skill acquisition (Schmidt 2004) and will be used to explain some of the decisions made in developing the present intervention.

Another consideration before describing how the motor learning principles were incorporated in the present study is to distinguish between performance and learning. Performance in this context can be seen as a motor behaviour resulting from a complex interaction between many variables (Shumway –Cooke and Woolacott 1995). Changes in performance resulting from practice may occur, however they can only be viewed as learning when they are still present when tested at a later time, often referred to as retention or transfer testing. If an intervention designed to improve UL recovery does not demonstrate learning through assessment at a retention test, for example at a follow-up period after the end of the intervention, it is likely that learning has not occurred. In this study, two follow-up assessments were therefore scheduled – one at the end of the intervention, and one at a follow-up three months later. The next section describes how principles of motor learning were applied to the intervention.

4.1.5.5 Discussion of motor learning principles applied to the training protocols

There is good evidence from stroke rehabilitation (Van Peppen et al. 2004) and other fields of study, including sports, of the benefits of task-specific training and principles motor learning to motor skill acquisition (Schmidt 2004). A small number of studies have examined application of motor learning principles to stroke and brain injury and support their use (Gauggel et al. 2002, Gauggel et al. 2001) therefore a range of principles to enhance skill acquisition were applied to the modified and core protocols.

TASK-RELATED TRAINING

The principle of specificity of learning is an established idea which proposes that the most effective practice for motor learning is that which best reflects the target skill (Schmidt and Wrisberg 2004). In stroke rehabilitation, evidence from recent high quality randomized controlled trials and systematic reviews support this principle. They suggest that interventions involving repetitive training of functional tasks or training of parameters such as strength and endurance in a functional way are more effective in terms of activity outcomes than the more traditional impairment focused training, or exercises with no specific functional focus (Van

Peppen et al. 2004, Barreca et al. 2006). Functional task-related training in which the participant is active, contrasts with traditional neurorehabilitation approaches where the therapist performs movement and the patient is more passive, and may explain the greater effectiveness of task-related training compared to traditional UL rehabilitation (Butefisch et al. 1995, Dean and Shepherd 1997). Indeed, functional neuroimaging studies support this, demonstrating that functional task training induces activity-dependent lasting cortical reorganisation (Liepert et al. 2001) even with low intensity practice such as that in the present study (Classen et al. 1998), suggesting that in order to improve function, training must be active and focus on the target skill. Functional and functionally-related task specific activities therefore formed the basis of the training intervention for the present study.

WHOLE AND PART- TASK TRAINING

Although practice of a functional task in its entirety is the most desirable practice mode for motor learning (Schmidt and Wrisberg 2004), allowance must be made for patients who are unable to perform the whole task because of the severity of their motor deficits. It was appropriate therefore to create a modified protocol which - although reflecting motor components of the core tasks - enabled participants to practice at a level appropriate to their ability. Thus the complexity of the selected four core tasks was reduced through development of part-task training. Simplification of the whole tasks was the first strategy used in creation of the modified protocol. The difficulty of a whole task was reduced, for example through use of larger objects that were easy to grasp to facilitate reach and grasp, and moving an object to a target point on the table before lifting it onto a shelf (Schmidt and Wrisberg 2004). Part-task training also involved segmentation, a process of practicing components of the target skill separately before adding other components (Schmidt and Wrisberg 2004), for example by practising supination to midline then adding wrist extension to prepare for grasp/release, until the whole task is achieved. This strategy is known to facilitate learning, provided the components are natural sub-units of the whole task (Winstein 1991). Whole task training was used in the core protocol. Simplification was the next step to modifying tasks and was used to develop modifications where all of the main component parts of the core task could be performed. Segmentation was used to develop the simplest progressions in the modified protocol for patients who were severely impaired and could only perform components of each task.

VARIED PRACTICE

Varied practice occurs when the same task is practised in a variety of ways in a session, and is intended to develop the same skills in a number of contexts, for example drinking liquid from a glass or from a polystyrene cup. The vessels may be full, half full or nearly empty and the liquid may be cold or hot. In these examples the basic movement patterns is the same, however task conditions are variable. In this way, the learner builds a profile of skill parameters for variations of the task (Schmidt 2004, Shumway-Cooke and Woolacott 1995). Task progressions in both protocols therefore involved varied practice in which the patient practiced the same type of task but under variable conditions. Evidence shows that variable practice positively influences carryover of learning to novel tasks (Shumway-Cooke and Woolacott 1995) and is appropriate for training skills for carryover to functional situations encountered by patients. Tasks were made progressively more difficult or different by increasing or decreasing the size or weight of the object to be moved, by placement of an object onto a shelf of varying height, and by increasing the distance to be reached. All of the core progressions involved tasks that could be related to an everyday functional activity.

BLOCKED AND RANDOM PRACTICE

Blocked practice involves repeated rehearsal of tasks in blocks during which the same task is repeated many times during a training session, whereas random practice involves practice of a number of tasks in random order (Schmidt 2004). There is evidence that blocked practice may be beneficial during task acquisition, that is, during the cognitive stage of learning where task parameters are unfamiliar and performance requires a high degree of attention (Shea et al 1990). Blocked practice also improves performance within a practice session, however it appears detrimental to long-term retention of training effect compared to random practice, particularly during the associative stage of learning when familiarity with task parameters has been achieved and the focus is on refining the pattern of movements (Shea et al 1990, Shumway-Cooke and Woollacott et al 1995, Schmidt, 2004).

Random practice leads to poorer performance during practice, but has been shown to provide better retention of learning at follow-up testing (Schmidt and Wrisberg 2004). These effects apply in stroke rehabilitation where one study demonstrated superior effects on retention tasks of random compared to block practice during training of UL tasks (Hanlon 1996). There are at least two possible explanations for the benefits of random practice. One theory is that random

practice may make the learner distinguish the tasks from each other more clearly, leading to better and more durable learning of task requirements and patterns of the separate tasks compared to block practice where within each block, the tasks are all are the same (Shea et al 1990). Another explanation is that in random practice the individual shifts from one task to another and in doing so they forget what they did in the previous tasks. The random scheduling requires the learner to then repeatedly use retrieval processes to come up with solutions and plans to address the distinct motor challenges, not required in block practice when all trials within each block are the same. In this way random practice may to lead to more effective learning (Shea et al 1990, Shumway-Cooke and Woollacott 1995, Schmidt and Wrisberg 2004).

Because of the benefits of each to different stages of learning, both block and random scheduling were incorporated into the protocol. Participants initially undertook block practice comprising 10 repeated trials during the cognitive phase of learning. Once they had moved to the associative stage of learning, evidenced by five successive trials, participants progressed to random practice scheduling determined by a computer generated randomisation table (Appendix 12), in which the four tasks were randomly interspersed.

FEEDBACK SCHEDULING

Knowledge of results about movement outcome through augmented feedback is known to be an important learning variable that facilitates self-evaluation of performance. Defined as augmented verbalised post-response information about the outcome in terms of the goal, feedback is an important factor in augmenting motor skill acquisition (Schmidt and Wrisberg 2004, Winstein 1991). Research shows that summary or average feedback on the success of the trials and goal achievement, after several no-feedback trials, is superior in terms of learning and skill retention compared to feedback after every trial (Schmidt and Wrisberg 2004, Winstein 1991, Winstein et al. 1994). The effect is thought to occur because delayed feedback provides opportunity for self-evaluation of performance and minimises dependence on feedback from the therapist (Schmidt 1991).

Similarly, knowledge of performance, also known as kinematic feedback, provides information about performance quality. However this type of feedback may also foster dependency that can be detrimental to learning if provided too frequently (Winstein et al. 1994) making the learner dependent on external information. Hence this type of feedback should be provided in summary

to enable the learner to develop his own judgement about performance (Schmidt and Wrisberg 2004). The literature is unclear as to the optimum schedule for feedback**.** Intervals of between 5 and 20 trials have been reported (Winstein, 1991), with feedback after 5 trials considered optimal for learning of complex tasks. Delayed feedback on knowledge of results and knowledge of performance was therefore provided in both protocols of the present study. Frequency of feedback after 5 trials was determined as optimal in the pilot study, above.

GUIDED PRACTICE

Guided practice where therapists provided physical assistance is also known to be detrimental to learning compared to independent active practice (Shumway-Cooke and Woollacott 1995) (Schmidt and Wrisberg 2004). To accommodate the activity limitations of more severely affected participants, guided practice was used in the present protocol during the initial stages of task recognition, equating to the cognitive stage of learning, to familiarise patients with features of the task. Therapists withdrew manual guidance as soon as the patient became active to enable them to move onto the associative stage of learning. Only patients with severe paresis, who were unable to perform any task component, received ongoing guided practice during attempts to achieve goals. Goals for these participants, within the modified protocol, involved simple wrist and hand movement and reaching to points marked on the tabletop.

GOAL SETTING

Goal setting is known to enhance motivation and skill acquisition in patients with acquired brain damage, particularly where the goals present a challenge and even where they are assigned by the therapist rather than self-selected (Gauggel et al. 2002, Gauggel et al. 2001). The protocols were therefore developed so that each task progression had a simple but specific motor goal, for example reaching a target point or placing an object in a particular place, which participants were asked to perform as accurately as possible. Goals should be challenging, but also attainable (Schmidt and Wrisberg 2004) therefore participants were encouraged to improve their accuracy to a target of 75% accuracy, after which progression to the next task occurred. This degree of accuracy was selected since it provided a realistic challenge, and high degree of expected success, whereas an expected 100% accuracy might lead to lack of success and cause loss of motivation. The goals were set in the protocol to ensure that they were standardised for all participants, however there was also an opportunity within the protocol for individual choice

where participants could choose tasks that they wanted to practice using objects that they felt were most relevant to their needs.

The ways in which motor learning principles were applied in the study are summarised in Box 4.6 (below).

Box 4.6. Summary of motor learning principles applied in the study

Motor Learning Principle	Application
Part and whole task training	• Whole tasks practised where possible • Simplified versions of whole tasks where whole task not achieved e.g. use of easy to grasp objects • Segments of tasks practiced in isolation where whole or simplified tasks could not be performed
Varied practice	• Variations in distance, weight, strength, accuracy requirements for each task and task progression
Blocked and random practice	• Blocked practice until 5 consecutive repetitions possible, then random practice
Feedback scheduling	• Delayed summary feedback on knowledge of results (e.g. three trials of 5 were accurate) and knowledge of performance (e.g. Try opening your fingers wider when trying to grasp the glass) • Feedback after 5 trials
Guided Practice	• Guided practice only where task could not be performed. Withdrawn as soon as participant became active
Goal Setting	• Each task and modified task has specific motor goal involving targeting or placing. Participant goal setting also offered

4.1.5.6 Intervention Procedures

Two senior stroke rehabilitation physiotherapists, the lead researcher and the research physiotherapist who was trained by the lead researcher in the intervention, shared the conduct of the intervention. The lead researcher provided the intervention to participants whilst they were in the teaching hospital, and the research physiotherapists provided intervention when participants transferred to rehabilitation hospitals or home. Hospital sessions occurred away from normal therapy areas so that regular therapists were unaware of group allocation. The intervention started the day after baseline assessment occurred. Training lasted 20 minutes per session, five weekdays per week over six weeks, in addition to usual therapy. Participants performed as many trials as possible in each session to a maximum of 30 trials of each of the four training tasks, a total of 120 trials per session. Duration and intensity of training was selected to reflect other bilateral task training studies (Mudie and Matyas 1996, Mudie and Matyas 2000).

Reflecting the pragmatic nature of the study, participants discharged home before the end of the intervention period continued training at home twice per week through supervised visits of 30 minutes duration from the research therapists, in line with usual discharge and follow-up procedures. The same standardised protocols and equipment were used.

4.2 POWER CALCULATION

Change in UL activity limitation was selected as the primary outcome measure since activity limitation was the main clinical variable of interest. Van der Lee (Van der Lee et al. 2001) suggested that a difference of 10% of maximum Action Research Arm Test score may represent a minimal clinically significant difference. This is approximately 6 units. Powell (Powell et al. 1999) showed changes in standard deviation of the ARAT of 12.7 and 9.0 in study groups. Assuming an average standard deviation of 11 units suggests that sample sizes of 53 in each group will have 79% power to detect a difference in means of 6 units at 5% significance level using the formula for sample size calculation for comparison of two means (Kirkwood and Sterne 2003).

As stipulated in the CONSORT statement for reporting of randomised controlled trials, (Moher et al. 2001), the primary outcome measure, the main clinical variable of interest, was selected for power calculation rather than the secondary outcomes. Selection of one important clinical variable as the primary outcome avoids problems of interpretation associated with multiplicity in interpreting findings (Moher et al. 2001), and avoids the large samples required to avoid type II errors where multiple primary outcomes are considered. The other measures were considered as secondary and more exploratory and were therefore of less importance in determining sample size. It should be noted however, that with these measures, type II errors may occur because the study was not specifically powered to detect significant differences on them.

4.3 STATISTICAL ANALYSIS

4.3.1 DATA SCREENING

All data were analysed using SPSS version 11.5 (Norusis 1993). Data were double entered and checked for accuracy by the author and the research physiotherapist. The descriptive function of SPSS also allowed the accuracy of the database to be examined. All variables were checked to ensure that they fell into the minimum and maximum range for each variable and means and standard deviations were observed to ensure that they were plausible (Tabachnick and Fidell 2001).

4.3.1.1 Skewness and kurtosis

Data distribution was examined by checking for approximation to normal distribution by using skewness and kurtosis statistics. Z scores for skewness for each outcome and change variable were calculated by comparing the skewness value to 0, which represents the skewness of the normally distributed population, and by dividing this by the standard error of skewness to give a z score. The critical value of z skewness was set at 3.30, with $p = 0.0005$ (Tabachnick and Fidell 2001). Skewness or kurtosis scores >3.30 were transformed to approximate normality using square root or logarithmic transformation as appropriate.

4.3.1.2 Screening for outliers

Data were screened for univariate outliers using standardised scores with a critical value for z scores set at <3.30; $p<0.001$(Tabachnick and Fidell 2001). Because outliers are extreme values, their inclusion or exclusion may have a considerable effect on results of statistical analysis (Altman 1991). One way to assess the impact of univariate outliers is to conduct analysis with and without outliers. If there is little difference, then the effect of the outliers can safely be ignored (Altman 1991). Where outliers do make a difference to results, steps need to be made to address their impact. Firstly, the outliers need to be identified and reasons for the extreme scores determined. Cases should be examined to determine if they are in fact from the same population as the rest of the sample and to determine if the value has been entered in error. Where inclusion

of outliers does lead to significant differences, responses of the outlying cases to the intervention should be examined since this may yield important information about how particular cases respond (Tabachnick 2001). Next, where warranted, their impact should be reduced. One such approach is to transform the data to change the shape of the distribution to obtain a more normal distribution. In this situation, the outliers fall in to the tail of the distribution, but their overall impact is reduced (Tabachnick 2001). A second approach is to change the deviant values so they remain deviant but not as deviant as before. This could be done is by assigning a value that is one unit larger than the next most extreme score (Tabachnick and Fidell 2001). This approach conserves the deviancy, but ensures that the impact of very extreme cases is reduced, however it does mean imputation of new values which may influence findings. Finally, if none of these approaches is effective, analysis should be conducted using rank methods, which are a distribution free approach to analysis (Altman 1991), however these methods are not as powerful as parametric tests and may limit the strength of the analysis. To assess effects of univariate outliers in the present study, analysis was therefore run with and without outliers to identify differences in results at the $p<0.05$ level.

It is more difficult to change scores in multivariate analysis to reduce the impact of outliers since the problem is with combinations of scores on two or more variables and the case is discrepant because of the combination of scores (Tabachnick and Fidell 2001). Even after data transformation, some cases often remain far away from others and in this case they it is recommended that they are deleted since if they remain they may distort the data in any direction (Tabachnick and Fidell 2001). Multivariate outliers within regression analysis were examined using a $p<0.001$ criterion for Mahalanobis distance and standardised residuals >3.0. Where multivariate outliers were found after data transformation, they were removed from the equation and the process repeated without them to assess their effects on regression. Multivariate data were also examined for linearity and homoscedasticity of the residuals using scatterplots of predicted standardized residual scores plotted against standardized residual scores.

4.3.1.3 Missing data

Data were also screened for missing data. Two databases were prepared, one for complete case analysis, and one for intention to treat analysis. For intention to treat, estimation of missing data

was calculated using the SPSS Expectation Maximisation function, provided there was less than 20% of missing data (Tabachnick and Fidell 2001). To create the estimated data, all available existing data for that variable was entered into the equation as predictor variables along with age and gender. Expectation maximisation is a less robust approach to estimating the data than multiple imputation, since it does not account for the variability and uncertainty about missing variables that multiple imputation can (Fielding et al. 2006). Software and expertise for multiple imputation approaches was not available and expectation maximisation was considered the best available approach given available resources. Thus was also considered superior to a simpler approach such as mean substitution, which underestimates the variance (Fielding et al. 2006). The same analyses were conducted on each database. In Chapter 5, presented data is complete case analysis. Intention to treat analysis is reported in the main text only when differences in findings in significance at the $p<0.05$ level exist, otherwise it is found in Appendix 13.

4.3.2 BASELINE EQUIVALENCE

Bilateral and unilateral group characteristics and T1 data were examined for baseline equivalence using t-tests or non-parametric equivalents. To determine if baseline characteristics influenced non-completion of the intervention, comparison was also made at T1 of those participants who completed the intervention and those who did not using t-tests or non-parametric equivalents.

4.3.3 PHYSICAL OUTCOMES

4.3.3.1 Effects of bilateral task training compared to unilateral training for the contralesional side

To examine effects of bilateral training on contralesional UL impairment, activity limitation, and dexterity and ADL independence, repeated measures ANOVAs for between group differences were conducted using data at T1, T2 and T3 after checking that data met assumptions for that test. Where significant main and interaction effects were found, post-hoc Bonferroni pairwise comparisons were conducted as appropriate to determine the location of the effects.

4.3.3.2 Exploration of factors that may influence UL responses to bilateral and unilateral training

Exploration of the influence of baseline severity of UL activity limitation and dexterity, stroke classification, side of hemiplegia and hand dominance, sex, age and proprioception on responses to bilateral compared to unilateral training were examined using factorial ANOVAS for change scores on the UL outcomes of the ARAT, the 9HPT and the RMA. Change scores represented short-term change (T1 to T2) and overall change (T1 to T3) and were created by subtraction of T1 scores from T2 and T3 scores. For all of the ANOVAS, Levene's homogeneity of variance tests where $p<0.05$ was the criterion to identify violations of equality of variance, and randomisation procedures ensured that groups were independent. Factorial ANOVAS using change scores were selected for this analysis in preference to repeated measures ANOVAS because of the complexity of interpreting repeated measures ANOVAS examining within and between group factors *and* the selected factors of interest.

To determine the effects of the range of factors listed above on training responses, sub-groups were created for each factor. To examine the effects of initial severity of activity limitation on outcomes, ARAT and 9HPT T1 scores were examined to provide clinical indicators of severity of activity limitation. Main and interaction effects of ARAT Level sub-groups, and treatment group allocation were examined using 2*3 factorial ANOVA, with change between baseline and 6 weeks, and baseline and 18 weeks on ARAT, RMA and 9HPT scores as dependent variables. Proprioception scores on the Nottingham Sensory Assessment were dichotomised into variables with deficit/no proprioceptive deficit as values. This approach had been used in other studies of examining proprioceptive deficit (Rand et al. 1999) and was considered a clear and clinically useful approach to defining the groups.

To examine effects of age, participants were also dichotomised according to age based on a median split. Proprioception and age were entered as independent variables into separate 2*2 factorial ANOVAS with change in ARAT, RMA and 9HPT between baseline and six weeks and baseline and 18 weeks as dependent variables.

To examine effects of stroke classification, side and hand dominance and gender, these binary variables were entered into two 4*2 and a 2*2 factorial ANOVA respectively as independent variables with change in ARAT, RMA and 9HPT between baseline and six weeks and baseline and 18 weeks as dependent variables.

It was decided in advance to conduct these sub-analyses on factors that might influence training responses irrespective of whether significant differences between the BT and UT groups were found. These analyses were exploratory and although sub-groups were small and the analyses likely to be underpowered, it was considered appropriate to conduct them as they may yield new knowledge that would inform future research. Findings were therefore be interpreted as exploratory and not as definitive results.

4.3.3.3 Exploring predictors of UL activity limitation

To examine which factors, including initial activity limitation, best predicted UL activity limitation at both T2 and T3, the ARAT at those assessment points was selected as the dependent variable for multiple regression.

Potential predictors of T2 ARAT were first identified. These were identified by correlating participant characteristics (sex, age, side of hemiplegia, handedness, dominant side affected, stroke type, days to initial assessment, training group, Motor Assessment Scale at baseline) and all outcome measure scores at T1 with the ARAT at T2. Correlations used were: Spearman's Rho for non-parametric data, Pearson's r for parametric data and point biserial correlation for correlations between dichotomous and continuous variables. The same process was then repeated using the same characteristics and T1 scores on the outcome measures, but this time with T3 ARAT as the dependent variable. Having established which characteristics and T1 variables demonstrated significant correlation with the dependent variable at T2 and T3 ($p<0.05$), these were entered into two regression equations, one with the T2 ARAT as the dependent variable, and one with the T3 ARAT as the dependent variable, to explore which participant characteristics and T1 variables best predicted T2 and T3 ARAT scores. Next, participant characteristics and T2 variables demonstrating significant correlation with the T3

ARAT were entered into a third regression equation to determine which T2 variables best predicted the T3 ARAT scores.

For each regression equation, independent variables were checked for multicollinearity. Variables demonstrating correlations of >0.70 with other independent variables were removed from the equation. Regression assumptions were checked using scatterplots of predicted standardized residual scores plotted against standardized residual scores. The Oxfordshire Community Stroke Project Classification (OCSP) discrete variables were converted into a set of dummy variables numbering one fewer than the number of discrete categories. Values for each category were either 1 or 0 (Tabachnick and Fidell 2001). All variables were entered simultaneously into the regression equations, followed by dummy variables for the OCSPC as a separate block (Tabachnick and Fidell 2001). Finally, to assess the effect of removal of baseline ARAT as a predictor, and to account for the lack of independence of the ARAT scores as independent variables, the regression analyses were repeated without the inclusion of the ARAT.

4.3.3.4 Examining ipsilesional dysfunction and comparing effects of bilateral to unilateral training on the ipsilesional side

Ipsilesional data for the whole sample was also examined for data quality and missing data. To explore within-group differences in ipsilesional performance at T1, T2 and T3, repeated measures ANOVA with "time" as a factor was used for normally distributed data. For data not meeting the parametric assumptions of ANOVA, Friedman's test for related samples was used to compare scores at T1, T2 and T3. T-tests and their non-parametric equivalents were used to compare effects of right and left hemisphere damage on ipsilesional dexterity, activity limitation and sensation. Next, to explore the correlation between ipsilesional motor performance and ADL independence at T1, T2 and T3, Spearman's rho was calculated for non-parametric data, and Pearson's r was calculated for parametric data. Finally, effects of bilateral training on ipsilesional dexterity and activity limitation were examined. Mixed ANOVA was the selected approach to compare effects of bilateral and unilateral training at T1, T2 and T3. Where data was skewed, differences in mean short-term change between T1 and T2 and in overall change between T1 and T3 using were examined using appropriate tests. Change scores were created by subtraction of T1 scores from T2 and T3 scores.

4.3.4 PSYCHOSOCIAL OUTCOMES

4.3.4.1 Effects of bilateral task training compared to unilateral training on anxiety, depression and health related quality of life

In line with the investigation of effects of bilateral training on contralesional UL outcomes, for anxiety, depression and health related quality of life, repeated measures ANOVAs for between-group differences were conducted using data at T1, T2 and T3 after checking that data met assumptions for that test. Where significant main and interaction effects were found, post-hoc Bonferroni pairwise comparisons were conducted as appropriate to determine the location of the effects.

4.3.4.2 Examining predictors of health related quality of life at eighteen weeks (T3)

To examine the relative importance of different UL constructs in predicting health related quality of life (HRQOL), Nottingham Health Profile total scores and each sub-domain at 18 weeks were selected as dependent variables. NHP scores at 18 weeks were selected as the dependent variable since at this point most participants were discharged to home or residential or long-term care from the more artificial environment of hospital. Examination of predictors of HRQOL was therefore appropriate at this point for patients who had adjusted or were in the process of adjusting to life at home after stroke, rather than at the two earlier assessment points when most patients remained in hospital. Potential independent variables comprised sex, age, side of hemiplegia, handedness, dominant side affected, stroke type, days to initial assessment, training group, and Motor Assessment Scale at baseline and depression, anxiety, ADL independence (MBI) and UL impairment (RMA) and activity limitation (ARAT, 9HPT) measures at 18 weeks. Relationships between the independent variables and the dependent variables - total NHP score and the sub-sections energy levels, pain, emotional reactions, social isolation, sleep, physical activities - were examined using Spearman's rho for non-parametric data, Pearson's r for parametric data and point biserial correlation for correlations between dichotomous and continuous variables. Variables demonstrating significant correlation ($p<0.05$) with the independent variable were entered into the regression equation. Independent variables

were next checked for multi collinearity and variables demonstrating correlations of >0.70 with other variables removed from the equation. Regression assumptions were checked using scatterplots of predicted standardized residual scores plotted against standardized residual scores. All variables were entered simultaneously into the regression equations.

For all analyses, significance levels were set at $p \leq 0.05$.

These analyses involve a large battery of tests which may lead to significant findings occurring due to chance where no real effects exist (Type I error). To minimise the risk of spurious findings, ANOVAS and regression analysis have been selected where appropriate, however the number of tests means that spurious findings are possible. Bonferroni corrections which adjust p-values for multiple comparisons is one method of dealing with potentially spurious effects, however this approach is controversial since the calculation of p-values based on the number of tests is now thought to be somewhat arbitrary and is likely to increase the chances of creating type II errors, where significant results might be missed (Feise 2002). An alternative and more accepted approach is to present what was done and to explain why it was done whilst discussing the possible interpretations of each result. This is what the present section and Chapters 5 and 6 will endeavour to do.

The results of the analyses are presented in Chapter 5. Here, the same structure is followed. Findings from data screening and baseline analysis for group equivalence are presented, followed by results of analysis examining physical outcomes and psychosocial outcomes.

CHAPTER 5

RESULTS

5.0 INTRODUCTION

This chapter presents the study findings. The main focus of this randomised controlled trial was to compare upper limb (UL) bilateral task training (BT) to unilateral task training (UT) in patients with acute stroke. The primary findings of interest relate to the effects of BT on physical outcomes of the contralesional upper limb (UL) and independence in activities of daily living (ADL). Data were collected at baseline (T1), at six weeks (T2) at the end of BT or UT, and twelve weeks later at 18 week follow-up (T3). The primary outcome measure for the UL was the Action Research Arm Test. Secondary measures of UL dysfunction were impairment measured on the Rivermead Motor Assessment (RMA) and dexterity measured on the Nine Hole Peg Test (9HPT). Independence in activities of daily living was measured using the Modified Barthel Index. Findings for the primary research question are presented in section 5.5.

Having compared BT with UT in terms of their effectiveness for UL physical outcomes, a secondary analysis explored the impact of a range of clinical and demographic factors on responses to training of the contralesional UL, again comparing BT with UT. The factors comprised initial severity of UL activity limitation, stroke classification, side of stroke and hand dominance, age, gender and proprioception. The training responses were operationalised as short-term change scores between T1 and T2 and as overall change, between T1 and T3. These findings are presented in section 5.6.

The next area of secondary analysis relating to the physical outcomes of the contralesional UL in the acute stage after stroke relates to the prediction of UL activity limitation, irrespective of the intervention. Here, for the whole sample, an analysis was conducted to determine significant predictors of UL activity limitation at the T2 and T3 assessment points. In this way it was possible to examine the strength of predictors over time and to determine the optimum point for prediction of activity limitation outcomes. These findings are presented in section 5.7.
A final secondary analysis relating to physical outcomes returns to the effects of bilateral training, but this time to examine whether BT influences *ipsilesional* UL outcomes compared to

the UT group who received no specific ipsilesional training. Prior to this, however, it was necessary to establish the extent of clinically detectable ipsilesional dysfunction. Findings relating to the clinical nature of ipsilesional dysfunction and to the effects of BT compared to UT are presented in section 5.8.

So far, the analysis focused on physical outcomes of impairment and activity limitation. Progressing from physical UL outcomes, the final two sections present findings regarding psychosocial outcomes of anxiety and depression and health related quality of life (HRQOL). In Section 5.9 the effects of BT compared to UT on anxiety and depression and health related quality of life (HRQOL) are presented, whilst section 5.10 explores the role of UL dysfunction in predicting HRQOL for the cohort as a whole at T3.

Before presenting findings from these primary and secondary analyses, details of participants' progress through the trial, including dropouts and reasons for dropping out at each stage is shown in section 5.1. This is followed in section 5.2 by details of the data screening processes and findings. Here data quality was examined for skewness and kurtosis, and outliers. Next, missing data were examined, with actions taken. Section 5.3 presents a comparison of participants who completed the intervention with those who did not. Section 5.4 details a baseline comparison between the BT and UT groups at T1 in terms of characteristics and baseline scores.

5.1 PROGRESS OF PARTICIPANTS THROUGH THE TRIAL

In this section, the participant details are presented, followed by a chart indicating their flow through the study and reasons for attrition. Between October 2002 and June 2005, 1239 patients were screened for inclusion. One hundred and six patients (61 male, 45 female) met inclusion criteria and agreed to participate. Ninety-seven participants (91.5%) completed the intervention and testing at T2 (Figure 5.1). Five participants from the BT group and four from the UT group dropped out before T2. Eighty-five participants (80%) completed follow-up at T3 with five in the BT group and seven in the UT group lost to follow-up. Reasons for loss to follow-up are provided in Figure 5.1.

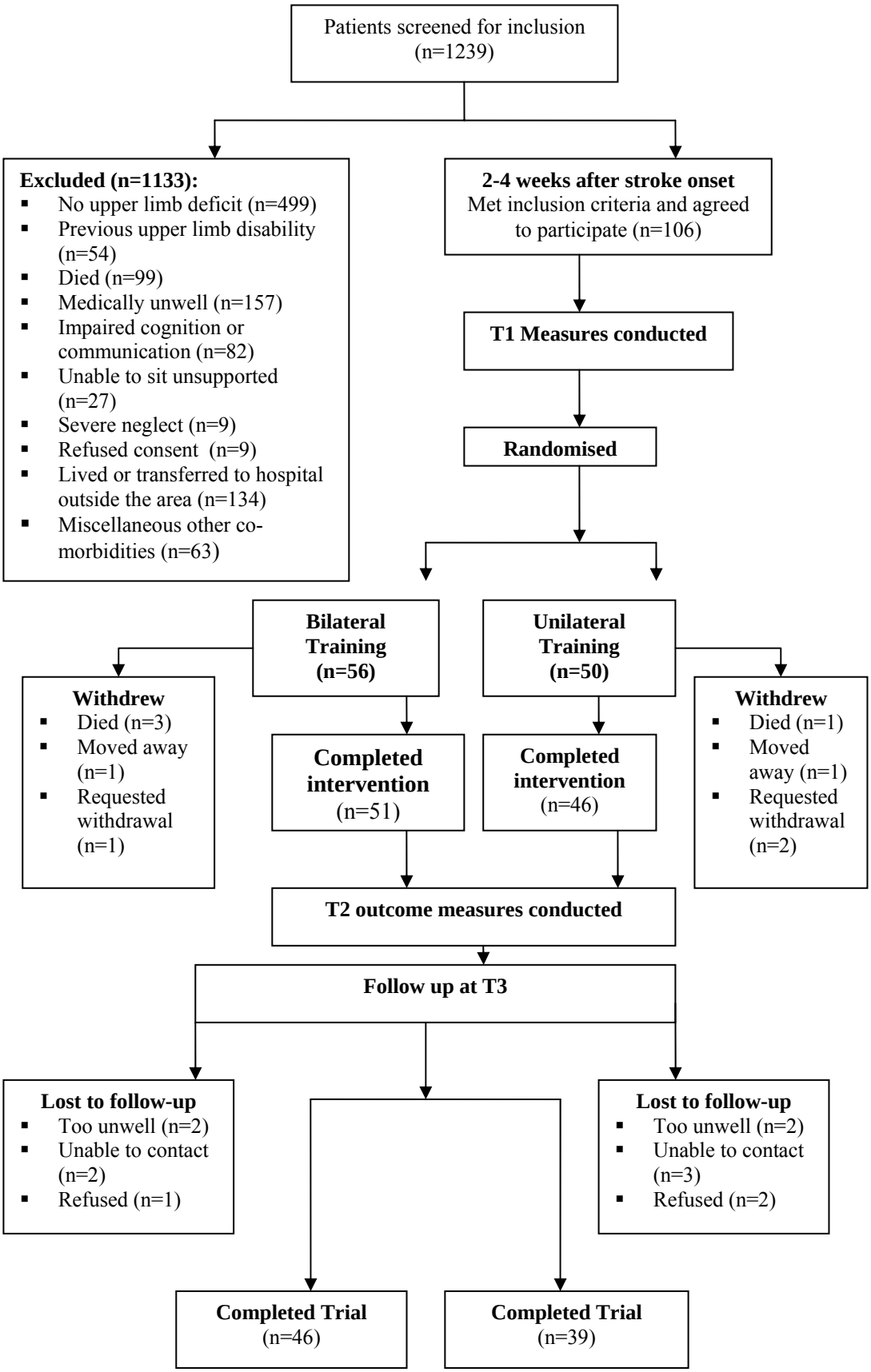


Figure 5.1 Flowchart of participant recruitment and attrition

5.2 DATA SCREENING

Data were inspected for quality in terms of skewness and kurtosis, and skewness z scores and their critical values were calculated. Data were also screened for univariate outliers and missing data.

5.2.1 DATA QUALITY

All data were entered into SPSS by the study author and double-checked for accuracy by the research physiotherapist. Outcome and change data were checked for approximation to normal distribution using SPSS Frequencies. Skewness and kurtosis scores for outcome and change scores are presented in Tables 1 and 2 in Appendix 13, Data Appendix.

The mean modified Barthel Index (MBI) and Nottingham Health Profile (NHP) scores at T2 and T3 and all mean Nine Hole Peg Test (9HPT) and Nottingham Sensory Assessment (NSA) outcome scores all showed skewness, with z scores > 3.30, p>0.0005 (Table 1, Appendix 13, Data Appendix). Negative skewness occurred on the MBI because by T2 and T3, a large proportion of participants demonstrated high scores, indicating good independence in daily living, whilst positive skewness occurred on the NHP because a large proportion of participants scored low indicating good quality of life. Nine Hole Peg Test scores were positively skewed because many participants (T1: n=78, T2: n=40, T3: n=28) were unable to place any pegs, and NSA scores were negatively skewed because a large proportion of patients demonstrated high scores on the test at each assessment.

The MBI at T2 and T3 was reflected and transformed to approximate normality using square root (T2 transformed data: S = 0.73: z^s= 3.19; K = -0.31; z^k=-0.63; T3 transformed data: S= 0.71; z^s = 3.15; K=0.82 z^k =1.58). The NHP total score at T2 and T3 was transformed using square root (T2 transformed data S = -0.07, z^s = -0.30; K = -0.58; z^k=-1.18; T3 transformed data S = 0.21; z^s = 0.79; K = -0.33; z^k=-0.63), which resulted in z scores of $\leq$3.30. Similarly, all subsections of the NHP responded to square-root transformation, leading to z skewness$\leq$3.30, p$\leq$0.0005. The NSA responded to logarithmic transformation (T1 transformed data S = -0.29: z^s = 2.94; K = -0.29; z^k=-0.63; T2 transformed data S = 0.41: z^s = 0.35; K = -0.41; z^k=-0.89; T3 transformed data S = 0.60; z^s = -0.38; K = 0.60; z^k=1.28).

The NSA total score, tactile and proprioception T2 scores were also severely negatively skewed. All sensory variables responded to reflection and logarithmic transformation to provide skewness <1.00 with z scores < 3.30 the critical value, and p< 0.0005.

The 9HPT was positively skewed before transformation but responded to inverse and square root transformation (T1 transformed data S = 0.78 z^s = 3.25; K = -1.15; z^k=2.14; T2 transformed data S = 0.48: z^s = 1.96; K = -1.05; z^k=-2.25; T3 transformed data S = 0.18; z^s = 0.69; K = -1.30; z^k=2.5). A dichotomised variable of "pegs/no pegs" was used in multiple regression analysis.

Change scores were normally distributed for all measures (z >3.30, p>0.0005) except change on the 9HPT T1 to T2 and T1 to T3 (Table 2, Appendix 13, Data Appendix). This responded to square root transformation (T1-T2 transformed data S= 0.56: z^s = 2.24; K=-0.97; z^k=0.49; T1-T3 transformed data skewness = 0.24; z skewness = 0.92; K=-1.32; z^k= -2.28) so for univariate analysis parametric testing was used on the transformed data. Although data from all measures except the Nine Hole Peg Test pegs/second was ordinal, the sample size was large enough for data to be treated as continuous (Kirkwood and Sterne, 2003). The NSA was not used as an outcome measure therefore change scores are not reported.

5.2.2 OUTLIERS

All analysis was performed with and without outliers. Results were unchanged in terms of significance ($p \leq 0.05$) therefore the reported results include the outliers. Table 1, (Appendix 13, Data Appendix), provides frequencies of univariate outliers with z scores > 3.29 (p<0.001) (Tabachnick and Fidell 2001).

5.2.3 MISSING DATA

Data were also screened for missing values (Table 3, Appendix 13, Data Appendix). There was less than 20% of missing data for all variables, which occurred because patients withdrew from the study for a number of reasons (Figure 5.1), except for the NSA. The NSA demonstrated more than 20% of missing data for the total score at each measurement point because patients were unable to complete the test, but examination of each sub-section revealed that less than 20% of data were missing at T1 and T2, whereas T3 tactile, stereognosis and proprioception had 26.4%, 22.6% and 24.5% of data missing respectively. Two databases were prepared, one for complete case analysis which included only complete cases and another for intention to treat analysis (ITT). For ITT data were imputed using the Estimated Maximisation function in SPSS, provided there was less than 20% of data missing (Tabachnick and Fidell 2001).

Complete case analysis is presented in the main body of the thesis and, ITT analysis is presented in Appendix 14, ITT Data Appendix. Where differences in results between complete case analysis and the ITT analysis were found in terms of significance at the $p \leq 0.05$ level, both sets of results are presented. Because the amount of missing data in the NSA total score at T1, T2 and T3 and proprioception and stereognosis sub-sections at T3 exceeded 20%, which was too much for imputation methods, those variables were only used in sub-analyses (Tabachnick and Fidell 2001).

5.3 COMPARISON OF COMPLETERS AND NON-COMPLETERS

To determine whether there were differences between the 97 participants who completed the intervention, and the nine who did not, a comparison of characteristics and T1 scores was made. Independent samples t-tests, Chi square tests and Mann Whitney U tests were used as appropriate. No significant differences at T1 in terms of characteristics or T1 scores on any of the outcome measures existed between participants completing the intervention and those who did not ($p>0.05$) (Table 4a,b, Appendix 13, Data Appendix).

5.4 GROUP EQUIVALENCE AT BASELINE (T1)

To check that the randomisation was successful, baseline comparison of BT and UT groups was conducted in terms of participant characteristics and T1 scores (Table 5.1a-c) (below). T-tests were used on normally distributed data (Table 5.1a), Mann-Whitney U-tests were used on data that was not normally distributed (Table 5.1b), and Chi Square tests were conducted on categorical data (Table 5.1c). To provide a clear picture of the study population, the findings of the T1 group comparisons are presented below with a general description of the population characteristics. To determine whether participants who were discharged home before the end of the intervention and those who were not differed significantly, a comparison at baseline was conducted using T-tests or Mann Whitney U tests as appropriate and Chi Squared tests for categorical data.

Table 5.1(a): Equivalence of BT and UT Groups at T1: T-tests

	BT Group (n=56)		**UT Group (n=50)**		**T-Test**			
Measure	*Mean (SD)*	*Median (Range)*	*Mean (SD)*	*Median (Range)*	*df*	*t*	*p*	*95% Confidence Interval*
Age	67.9 (13.1)	70.0 (36.0,94.0)	67.8 (9.9)	68.5 (47.0,87.0)	104	-0.07	0.94	-4.69 to 4.36
Days to start of intervention	22.6 (5.6)	23.0 (12,36)	23.2 (5.7)	23 (12,38)	104	0.54	0.59	-1.46 to 0.47
UL Activity: ARAT *(min =0, max=57)*	13.4 (15.3)	4.0 (0.0,45.0)	18.5 (17.2)	15.5 (0.0,56.0)	104	1.62	0.11	-1.15 to 11.37
Impairment: RMA *(min = 0, max =15)*	3.4 (3.4)	3.0 (0.0,10.0)	4.3 (3.1)	4.0 (0.0,10.0)	104	1.44	0.15	-0.28 to 2.21
ADL Independence: MBI*(min = 0, max = 100)*	58.5 (25.3)	59 (12,98)	65.5 (23.5)	72 (12,98)	104	1.52	0.13	-2.22 to 16.66
9HPT *(Pegs/sec)*	0.02 (0.07)	0.0 (0.0,0.42)	0.04 (0.08)	0.0 (0.0,0.30)	95.7	1.17	0.25	-0.01 to 0.04
Anxiety: HADS: (*min = 0, max = 21)*	6.6 (4.8)	6.0 (0.0,19.0)	5.9 (3.3)	6.0 (0.0,12.0)	103	-0.79	0.43	-2.21 to 0.94
Depression: HADS: *(min = 0, max = 21)*	6.2 (3.2)	6.0 (0.0,13.0)	6.6 (3.7)	6.0 (0.0,14.0)	103	0.59	0.55	-0.93 to 1.72
Quality of Life: NHP *(max = 0, min =600)*	180.0 (121.0)	160.2 (0.0,460.6)	174.0 (118.0)	166.2 (9.8,433.2)	104	-0.26	0.79	-52.43 to 40.12
Number of Intervention sessions	20.5 (6.0)	22.0 (6.0,30.0)	18.0 (6.1)	18.5 (5.0,28.0)	104	-2.07	0.04*	-4.95 to -0.23
Number of training trials	1066.1 (412.8)	1049 (245,2193)	1172.7 (711.0)	1014 (373,2196)	104	0.96	0.34	-114.53 to 327.63
Days to hospital discharge	91.9 (56.4)	80.0 (3.0,259.0)	65.6 (60.3)	47.0 (9.0,284.0)	92	-2.17	0.03*	-50.3 to -2.19

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NHP denotes Nottingham Health Profile; HADS denotes Hospital Anxietyand Depression Scale *indicates $p \leq 0.05$

Table 5.1(b): Equivalence of BT and UT Groups at T1:

Mann-Whitney U Tests

T1 Measure	BT Group (n=56)	UT Group (n=50)	Mann Whitney U Test	
	Median (Range)	Median (Range)	*U*	*p*
MAS *(Max=18)*	2.0 (0.0,14.0)	5.5 (0.0, 12.0)	1317.5	0.15
NSA *(Max=84)*	71.3 (0.0, 79.0)	65.2 (8.0, 80.0)	1193.0	0.19

MAS denotes Motor Assessment Scale; NSA denotes Nottingham Sensory Assessment

Table 5.1 (c). Equivalence of BT and UT Groups at T1: Pearson's Chi Square Tests

	BT Group (n=56)	UT Group (n=50	*df*	χ^2	*p*
Gender *(Male/Female)*	34/22	27/23	1	0.49	0.48
Side of Deficit *(Left/Right)*	27/29	27/23	1	0.35	0.55
Handedness *(Left/ Right)*	3/53	6/44	1	1.50	0.30
Dominant Hand affected *(Yes/No)*	27/29	25/25	1	0.03	0.85
Stroke Type *(Ischaemic/Haemorrhagic)*	49/7	43/7	1	0.05	0.82
Oxfordshire Community Stroke Project TACS/PACS/LACS/POCS	3/31/21/1	2/29/17/2	3	0.64	0.89
Modified/Standard Training protocol	39/17	28/22	1	2.11	0.15

TACS denotes total anterior circulation stroke; PACS denotes partial anterior circulation stroke; LACS denotes lacunar stroke; POCS denotes posterior circulation stroke

5.4.1 DESCRIPTION OF POPULATION AND T1 COMPARISONS BETWEEN GROUPS

This was an elderly population with a mean age (sd) of 67.9 (±13.1) years in the BT group and 67.8 (±9.9) in the UT group. Participants were well enough to start the intervention at 22.6 ±5.6 days (BT group) and 23.2 (±5.7) days (UT group) after stroke onset; a difference that was not significant (p=0.59) (Table 5.1a). Both groups had more male (BT group n=34, UT group n=27) than female participants (BT group n=22, UT group n=23). Whilst the ratio of right to left sided stroke was fairly even in both groups, the BT group had more participants with right UL hemiplegia (n=29) than left (n=27), whilst the UT group had more participants with left hemiplegia (n=27) than right (n=23) (Table 5.1c). None of these differences were statistically significant (p>0.05). As expected, right handedness dominated in both groups, but the proportion of participants with right and left hand dominance in each group was not statistically different between the groups (p=0.30) (Table 5.1c). The majority of participants had ischaemic stroke with only seven in each group presenting with haemorrhage, and this proportion did not differ significantly between the groups (p=0.82). Most participants (BT group n=52, UT group n=46) presented with either partial anterior circulation stroke or lacunar stroke, and the proportion of participants with each stroke classification did not differ significantly between groups (p=0.89) (Table 5.1c).

Nineteen participants (34%) in the BT group scored 0 on the ARAT at T1, compared to 10 (20%) in the UT group, indicating no UL function or movement. The majority of participants in each group (BT group 65%, UT group 80%) however demonstrated some UL movement evidenced by scores greater than 0 on the ARAT. For the 9HPT, 42 participants (75%) in the BT group at T1 were unable to place any pegs, compared to 36 (72%) in the UT group, indicating very poor dexterity. Thus whilst most patients had some UL control or movement at T1, only a small proportion in each group had sufficiently good fine dexterity to place any pegs in the 9HPT. Both groups also demonstrated sensory deficits with all participants scoring <84, the maximum score for UL sensation on the NSA. For all measures, scores were lower for the BT group, although there was no statistical difference between the groups (p>0.05) (Tables 5.1 a, b).

In terms of ADL independence, the BT group demonstrated a lower score on the MBI than the UT group, but the difference was not statistically significant (p=0.15) (Table 5.1a). The BT group demonstrated a mean score of 58.5±25.3, indicating severe dependence (Shah et al. 1989) with 28 (50%) participants scoring <60. In the UT group, 18 (36%) of participants

scored less than 60 on the MBI and the mean score was 65.5 ±23.5, a score of >60, indicating moderate dependence. The mean HADS depression and anxiety scores were <8 in both groups, this score being the accepted threshold for sensitivity and specificity of the measure for detecting anxiety and depression (Bjelland and Dahl et al. 2002). For anxiety 24 (42%) of participants in the BT group and 17 (34%) of participants in the UT group demonstrated scores of 8 or more, indicating possible anxiety. For depression, 20 (35%) of the BT group and 18 (36%) of the UT group demonstrated scores of 8 or more, indicating the possible presence of depression. Both groups demonstrated mean scores of >170 on the weighted NHP, higher scores indicating greater impact of stroke on perceived health (max=600).

Two significant differences between the groups existed for days to hospital discharge which was significantly longer for the BT group (p=0.03) and for number of intervention sessions which was also significantly greater in that group (p=0.04) (Table 5.1a). These differences occurred because 19 out of 56 participants in the BT group (34%) compared to 27 out of 50 (54%) in the UT group went home during the intervention period and in this pragmatic study, patients at home received training only twice per week. It is important to note, however, that the mean number of practice trials of each task undertaken by each participant across the sessions was 1093 (± 711) for the UT group and 1066 (± 413) for the BT group which was not significantly different between the groups (p = 0.34) (Table 5.1a, above). It is possible therefore to be fairly confident that the dose of therapy was similar for participants in each group.

5.4.2 T1 COMPARISONS BETWEEN PATIENTS WHO WERE DISCHARGED HOME DURING THE INTERVENTION AND THOSE WHO WERE NOT

To further explore the characteristics of participants who were discharged home during the intervention and those who were not, differences between training groups in T1 characteristics of those participants were compared. There were no significant differences at T1 in terms of any characteristics or outcome measures between participants in the BT group and those in the UT group who were discharged during the intervention period (p>0.05) (Tables 5 a, b, Appendix 13, Data Appendix) suggesting that baseline differences between groups did not influence hospital discharge.

5.4.3 T1 COMPARISONS BETWEEN PATIENTS WHO WERE ALLOCATED TO THE CORE AND MODIFIED PROTOCOLS AT BASELINE

At T1, 39 patients of 56 (69%) in the BT group and 28 of 50 (56%) in the UT group were allocated to the modified task protocol, as opposed to the core protocol described in Chapter 4, a difference that was not significant (p=0.15) (Table 5.1c). During the study, 12 patients in the BT group and 13 in the UT group progressed to one or more of the core tasks so that by the end of the study, of the participants who completed the intervention, 27 out of 51 (52%) in the BT group and 15 out of 46 (33%) in the UT group had undertaken only the modified task protocol, again a difference that was not significantly different ($\chi^2 = 3.66$; df = 1; p=0.06). The mean number of training sessions before progression to the core protocol occurred was 15.1 (±6.0) in the BT group and 14.1 (±5.4) in the UT group, a difference that was not significant (t = -0.42; df = 25; p=0.68).

5.4.4 USUAL THERAPY

Usual UL therapy involved approximately 10 minutes each of occupational and physiotherapy per weekday. This typically involved practising unilateral stretching and a range of functional tasks selected by the therapists. Review of usual therapy records indicated that BT was used by regular occupational therapists in one case over four sessions with one patient who was in the BT training group, and involved bringing a cup to the mouth using both hands.

5.4.5 SUMMARY

Data screening indicated that four measures, the Modified Barthel Index (MBI), the Nottingham Health Profile (NHP), the Nine Hole Peg Test (9HPT) and the Nottingham Sensory Assessment (NSA) demonstrated abnormally distributed data. For all of the measures, the data responded to transformation. Univariate outliers were found on four measures, the Modified Barthel Index, the Nine Hole Peg Test, Hospital Anxiety and Depression Scale (HADS) depression and the Nottingham Sensory Assessment as well as on the change scores of the Action Research Arm Test (ARAT), and the Nine Hole Peg Test. Analysis was conducted with and without these outliers and no differences were found in terms of significance at the $p \leq 0.05$ level, therefore reported results include outliers.

For most measures, missing data occurred because patients dropped out of the study however the Nottingham Sensory Assessment demonstrated a greater proportion of missing data because patients were unable to complete the test. Where less than 20% of data were missing, complete case analysis and intention to treat analysis was conducted. For the Nottingham Sensory Assessment sub-analysis using complete cases only was conducted since the amount of missing data were too great for data imputation.

There were no significant baseline (T1) differences between participants who completed the intervention and those who did not. The only significant baseline difference between the unilateral training (UT) and bilateral training (BT) groups was that hospital stay was significantly longer for the BT group, which also received significantly more intervention sessions than the UT group. However the number of UL training trials did not differ significantly indicating that therapy dose was equivalent across the groups. There were no significant baseline differences between the BT and UT in characteristics of participants who went home before the end of intervention.

The groups did not differ significantly in terms of the number of participants allocated to the core and modified protocols at baseline, however more participants in the unilateral training group progressed to the core protocol during the intervention than did in the bilateral training group. This was not a significant difference, but it did approach significance.

The next section reports findings from analysis of data addressing the primary research question. Here the effects of bilateral and unilateral training on upper limb outcomes and activities of daily living are presented.

5.5 PHYSICAL OUTCOMES: COMPARISON OF EFFECTS OF BILATERAL AND UNILATERAL TRAINING ON UPPER LIMB OUTCOMES AND INDEPENDENCE IN ACTIVITIES OF DAILY LIVING

In this section, the primary research question is addressed. Here, effects of BT compared to UT were examined for the three UL measures, the ARAT, the RMA and the 9HPT along with the effects of the training on independence in activities of daily living measured on the MBI.

5.5.1 PRIMARY RESEARCH QUESTION AND HYPOTHESIS

The research question addressed in this section is:
"Is there a difference in terms of UL impairment (RMA), activity limitation (ARAT), dexterity (9HPT) and independence in activities of daily living (MBI) between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training?"

$H_0$1. There will be no significant difference between acute stroke patients receiving six weeks of bilateral task training compared to those receiving six weeks of unilateral task training in terms of UL impairment (RMA), activity limitation (ARAT), dexterity (9HPT) and independence in activities of daily living (MBI) at T2 (six weeks) or T3 (eighteen weeks).

For this analysis, 3*2 mixed ANOVAs were conducted to examine effects of BT compared to UT on the total ARAT and ARAT sub-sections Grasp, Grip, Pinch (square root transformation), 9HPT (square root transformation), RMA and MBI (reflected square root transformation) at T1, T2 and T3. Scores at T1, T2 and T3 were entered as the within-subject variable Time, with training group as the between-group factor Group. With transformations (Section 5.2.1) all variables demonstrated approximately normal distribution. For all variables at each time point, Levine's test of equality of error variances indicated homogeneity of variance across the groups ($p>0.05$), an assumption underlying ANOVA use. For all variables, Mauchly's sphericity test ($p<0.001$) indicated that sphericity could not be assumed; therefore the Greenhouse-Geisser Epsilon estimate was used. (Brace

et al. 2003). Post-hoc Bonferroni pairwise comparisons were used as appropriate to examine significant effects where these existed.

5.5.1.1 Findings for UL activity limitation

For total ARAT score, ($F_{1.41}$ =1.52, p=0.23), and sub-sections Grasp ($F_{1.65}$ =0.37, p=0.65), Grip ($F_{1.47}$ =1.55, p=0.22) and Gross ($F_{1.75}$ =0.43, p=0.62) the between group interaction between Time and Group was not significant indicating that there was no significant difference between BT and UT Groups on the ARAT or these subsections at any assessment point (Table 5.2).

There were significant main within-group effects of Time for total ARAT score ($F_{1.41}$ =108.45, p<0.001), and sub-sections Grasp ($F_{1.65}$ =58.82, p<0.001), Grip ($F_{1.47}$ =85.05, p p<0.001) and Gross ($F_{1.75}$ =40.05, p p<0.001) indicating that there was an effect of Time that influenced scores on these measures that was not related to training group (Table 5.2).

The significant within group main effects of Time, which applied to the whole sample, were of secondary interest since the primary research question related to between-group differences for BT and UT, however because the effects may be of general interest to stroke recovery, they were explored using unplanned post hoc Bonferroni pairwise comparisons. The comparisons for the significant within group main effects of Time indicated that T2 (p<0.001) and T3 scores (p<0.001) were significantly higher than T1 scores for Total ARAT, Grasp, Grip and Gross scores (Tables 6-9 Appendix 13, Data Appendix). T3 scores were not significantly higher than T2 scores (p>0.05), indicating that significant improvement for the entire study sample occurred between T1 and T2 but not after T2 (Tables 6-9 Appendix 13, Data Appendix).

The main effect of Time is illustrated in Figure 5.2 for total ARAT score, which shows how scores for the whole group differed over time.

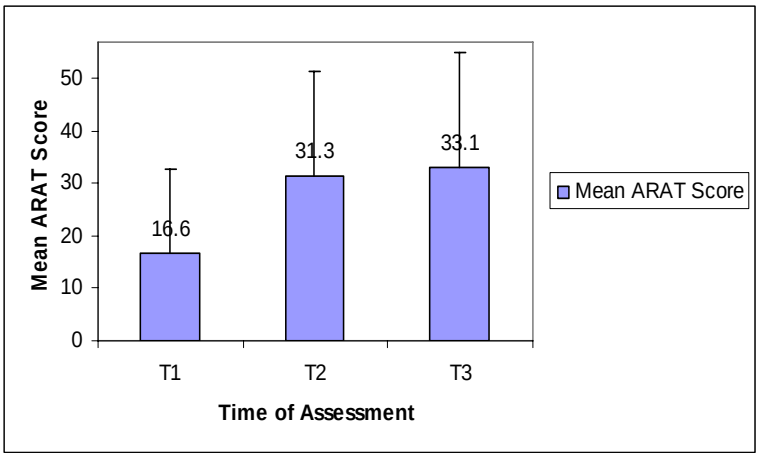


Figure 5.2. Main effect of time (sd) on total ARAT score

For ARAT Pinch the between-group interaction between Time and Group was significant ($F_{1.62}$ =3.50, p=0.04) indicating a significant difference between the BT and UT groups over time (Table 5.2). For pinch at T3, the profile plot Figure 5.3 showed that the UT Group demonstrated a higher mean score (11.1±7.4) than the BT Group (7.8±7.6). An independent samples t-test confirmed that there was a significant difference between Groups on the ARAT Pinch Section at T3 (t=2.35, df = 103, p=0.02).

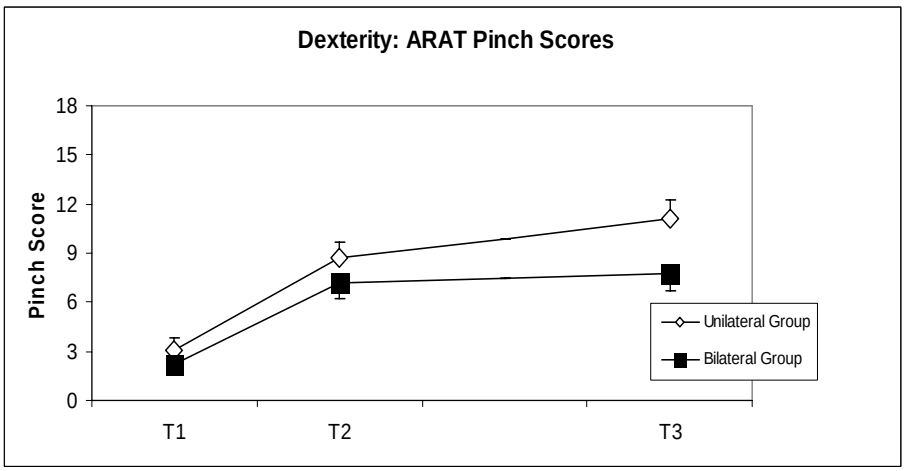


Figure 5.3. Dexterity: Mean ARAT Pinch Scores (sd) at T1, T2 and T3.

For Pinch, the main within group of Time was significant ($F_{1.62}$ =76.78 p<0.001) (Table 5.2).

For Pinch, post-hoc Bonferroni pairwise comparisons for the main within group effect of Time indicated that irrespective of training group, the ARAT Pinch scores at T2 and T3 were

significantly higher than scores at T1 ($p<0.001$) (Table 10 Appendix 13, Data Appendix). The ARAT Pinch score at T3 was significantly higher than the score at T2 ($p<0.01$). These findings indicate a significant improvement in ARAT Pinch at each consecutive assessment for the whole sample, irrespective of training group. The main effects for Pinch are illustrated in Figure 5.4.

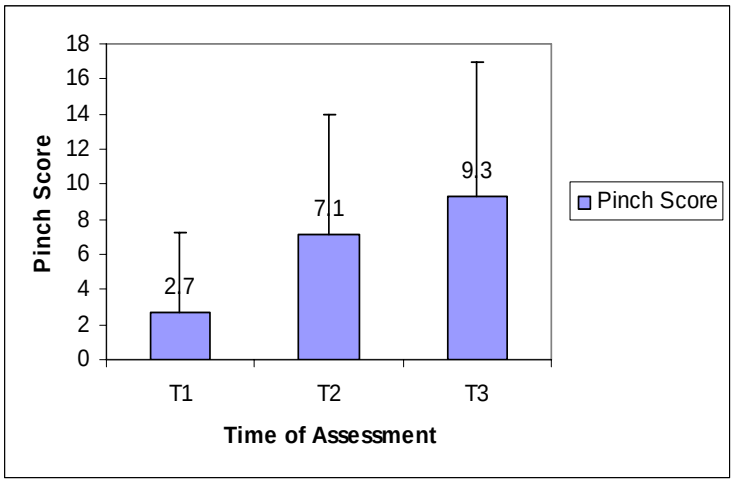


Figure 5.4. Main effect of time (sd) on ARAT Pinch score

Table 5.2. Repeated measures ANOVA for effects of BT and UT: ARAT Total and ARAT Sub-sections and 9HPT

Measure	Time	BT Group Mean Scores (sd) N=45	UT Group Mean Scores (sd) N=39	Source of variance		df	F	p
ARAT	T1	13.4 (15.3)	18.5 (17.2)	Within Subject	Time	1.41	108.45	<0.001*
	T2	27.9 (19.5)	34.3 (19.8)		Time x Group	1.41	1.52	0.23
	T3	29.0 (21.9)	37.6 (21.2)	Between Subject	Group	1	2.54	0.12
Grasp	T1	5.7(6.3)	7.1(6.3)	Within Subject	Time	1.65	58.82	<0.001*
	T2	9.9(7.1)	11.7(7.0)		Time x Group	1.65	0.37	0.65
	T3	9.9(7.5)	11.0(7.3)	Between Subject	Group	1	1.72	0.19
Grip	T1	3.0(3.5)	4.3(3.9)	Within Subject	Time	1.47	85.05	<0.001*
	T2	6.0(4.4)	7.7(4.4)		Time x Group	1.47	1.55	0.22
	T3	5.8(4.8)	8.2(4.6)	Between Subject	Group	1	4.17	0.06
Pinch	T1	2.6(4.3)	2.8(4.8)	Within Subject	Time	1.62	76.78	<0.001*
	T2	7.2(6.9)	8.6(6.9)		Time x Group	1.62	3.50	0.04*
	T3	7.8(7.6)	11.1(7.4)	Between Subject	Group	1	1.78	0.18
Gross	T1	3.8(3.2)	4.7(3.1)	Within Subject	Time	1.75	40.05	<0.001*
	T2	5.5(3.5)	6.4(3.1)		Time x Group	1.75	0.43	0.62
	T3	5.7(3.5)	6.2(3.4)	Between Subject	Group	1	1.24	0.27
9HPT	T1	0.02 (0.01)	0.04 (0.07)	Within Subject	Time	1.64	65.60	<0.001*
	T2	0.10 (0.04)	0.14 (0.15)		Time x Group	1.64	4.10	0.03*
	T3	0.12 (0.04)	0.19 (0.16)	Between Subject	Group	1	2.94	0.09†

*denotes $p \leq 0.05$; † denotes a difference in terms of significance between Complete Case Analysis and Intention to Treat Analysis

5.5.1.2 Findings for UL dexterity: 9HPT

For the 9HPT there was a significant between-group interaction effect between Time and Group ($F_{1.64}$ =4.10, p=0.03) suggesting a significant difference in scores between the BT and UT Groups over time (Table 5.2).

The profile plot (Figure 5.5) indicated that at T3, the UT Group placed more pegs/second (0.19±0.16) than the BT Group (0.12±0.04). An independent samples t-test confirmed that the UT Group demonstrated a significantly higher score than the BT Group on the 9HPT at T3 (t=2.54, df = 103, p=0.01).

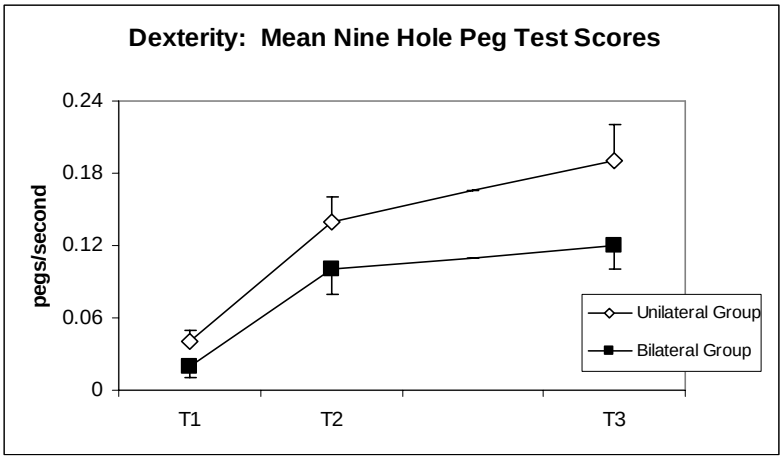


Figure 5.5. Dexterity: Mean Nine Hole Peg Test scores (sd) at T1, T2 and T3

There was a significant main within-group effect of Time ($F_{1.64}$ =65.60 p<0.001) suggesting that the scores for the entire sample also differed significantly between assessments, irrespective of training group (Table 5.2). This effect is illustrated in Figure 5.6.

For 9HPT scores, post-hoc Bonferroni pairwaise comparisons for the main effect of time indicated that irrespective of training groups, scores at T2 and T3 were significantly higher than at T1 (p<0.001)(Table 11, Appendix 13, Data Appendix). There was also a significant difference between scores at T2 and T3 indicating that there was a significant improvement after T2.

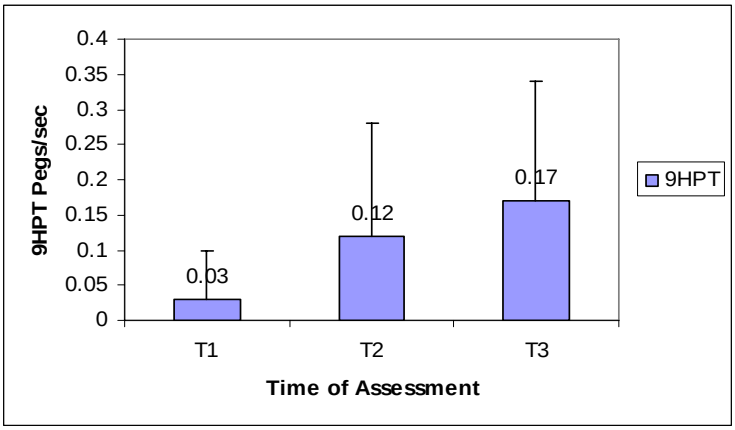


Figure 5.6. Main effect of time (sd) on 9HPT pegs/sec

5.5.1.3 Findings for UL impairment: RMA

For the RMA the between-group interaction effect between Time and Group was not significant ($F_{1.74}$=1.00, p=0.36) suggesting that the BT and UT Groups did not differ significantly at any assessment (Table 5.3, below).

There was again a significant main within group effect of Time ($F_{1.75}$ =50.14, p<0.001), suggesting that scores for the entire sample, irrespective of training group differed significantly between assessments. Unplanned post-hoc Bonferroni pairwise comparisons for the main within group effect of Time on the RMA indicated that T2 and T3 scores were significantly higher than T1 scores (p<0.001) (Table 12 Appendix 13, Data Appendix). There was no significant difference between T2 and T3 scores (p=0.67) (Table 12 Appendix 13, Data Appendix) again indicating that significant change for the entire study sample occurred between T1 and T2 but not after T2, the end of the intervention.

This effect is illustrated in Figure 5.6.

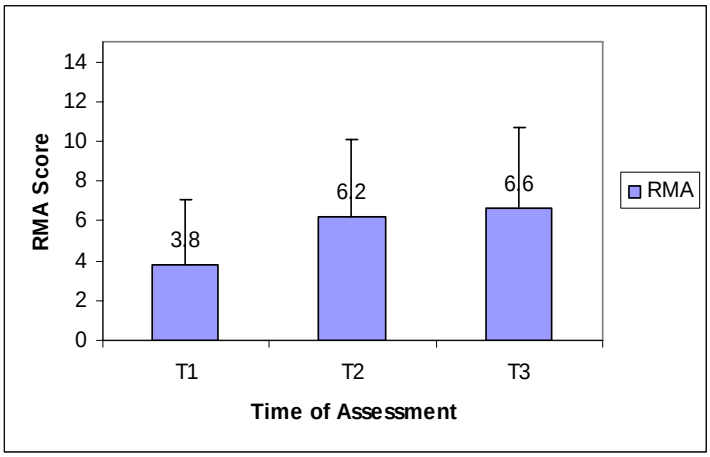


Figure 5.7. Main effect of time (sd) on RMA Score

5.5.1.4 Findings for independence in activities of daily living: MBI

For the MBI the between group interaction effect between Time and Group was not significant ($F_{1.48}$ =1.84, p=0.17) suggesting that the BT and UT Groups did not differ significantly at any assessment (Table 5.3). The main within group effect of Time was significant ($F_{1.48}$ =93.74, p<0.001), suggesting that the scores for the entire sample differed significantly between assessments irrespective of training group.

Post-hoc Bonferroni pairwise comparisons for Time indicated that for the MBI, T2 and T3 scores were significantly higher than T1 scores (p<0.001) (Table 13 Appendix 13, Data Appendix). There was no significant difference between T3 and T2 scores (p=1.00) indicating that significant change for the entire study sample occurred between T1 and T2 but not after T2, the end of the intervention.

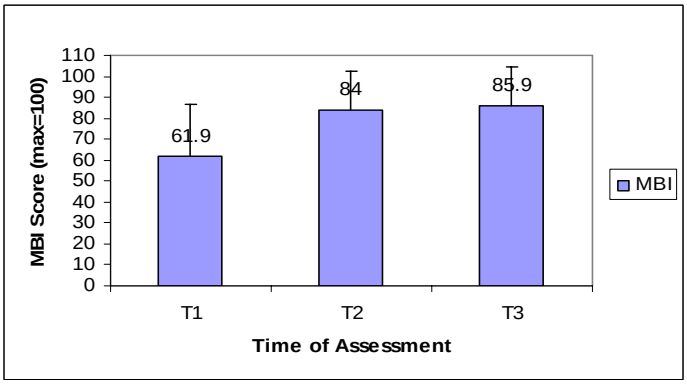


Figure 5.8. Main effect of time (sd) on MBI Score

Table 5.3. Repeated measures ANOVA for effects of BT and UT: RMA and MBI

Measure	Time	BT Group N=45	UT Group N=39	Source of variance		df	F	p
RMA	T1	3.4 (3.3)	4.3 (3.1)	Within Subject	Time	1.74	0.14	<0.001*
	T2	5.5(3.5)	7.1(3.8)		Time x Group	1.74	1.00	0.36
	T3	6.0(4.1)	7.3 (4.0)					
				Between Subject	Group	1	2.73	0.10
MBI	T1	58.5(25.3)	65.7(23.5)	Within Subject	Time	1.48	3.74	<0.001*
	T2	83.0(16.2)	85.1(19.2)		Time x Group	1.48	1.84	0.17
	T3	86.0(16.9)	86.3(18.4)					
				Between Subject	Group	1	0.99	0.32

RMA demotes Rivermead Motor Assessment (upper limb section); MBI denotes Modified Barthel Index)

*denotes $p \leq 0.05$

5.5.2 SUMMARY OF FINDINGS

Significant between group interaction effects were found between Action Research Arm Test (ARAT) Pinch and Nine Hole Peg Test (9HPT) scores at eighteen weeks (T3), indicating that the unilateral training group demonstrated significantly higher scores than the bilateral training group. There were no significant interaction effects between Group and Time for any of the other measures indicating that there were no other differences between the training groups over time.

For all measures there was a significant within group main effect of Time with six and eighteen week scores significantly higher than baseline scores, indicating improvement in the entire study population. Only the Action Research Arm Test Pinch section and the Nine Hole Peg Test demonstrated significant improvement between six and eighteen week scores, suggesting that for these measures, change continued to occur after the end of the intervention.

Although bilateral training was not more effective than unilateral training, certain participant sub-groups may have responded differently to the training. The next section goes on to explore whether training responses in the bilateral and unilateral groups were influenced differentially by factors including severity of baseline activity limitation, lesion site, side of hemiplegia and hand dominance, gender, age, and proprioception. These were factors identified in the literature that may potentially influence upper limb recovery.

5.6. PHYSICAL OUTCOMES: AN EXPLORATION OF FACTORS THAT MAY INFLUENCE UL RESPONSES TO BILATERAL AND UNILATERAL TRAINING.

In this section, an exploration of effects of several factors identified in the literature as likely to influence responses to BT was conducted. These were severity of baseline (T1) activity limitation, lesion site, side of hemiplegia and hand dominance, gender, age, and proprioception. Analysis was conducted using between subject factorial ANOVAS with short term change scores between T1 and six weeks (T2) and overall change between T1 and eighteen weeks (T3) representing training responses. Change scores were created by subtracting the T1 scores from T2 and T3 scores. Change scores were entered into each ANOVA as the dependent variable with training Group and the factors of interest as fixed factors. Details of how sub-groups were created is provided in the statistical methods section 4.2.8 in Chapter 4, but a brief reminder is also provided before each finding along with the research question being addressed.

5.6.1 EFFECTS OF SEVERITY OF INITIAL UL ACTIVITY LIMITATION ON RESPONSES TO BILATERAL AND UNILATERAL TRAINING

This section explores effects of initial severity measured on the ARAT and the 9HPT on training responses between T1 and T2 and T1 and T3.

5.6.1.1 Secondary research question 1

The question addressed in this section is: "Does severity of initial UL activity limitation influence UL training responses to six weeks of BT compared to UT in patients with acute stroke?"

$H_0 2$ The impact of initial severity of UL activity limitation defined by T1 ARAT and 9HPT scores will not be significantly different between acute stroke patients receiving six weeks bilateral task training compared to those receiving unilateral task training in terms of changes

in impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3

5.6.1.2 Findings for effects of severity of initial activity limitation

To examine effects of initial severity of activity limitation on outcomes, three severity sub-groups were identified by examination of ARAT and 9HPT T1 scores, which provided clear clinical indicators of severity of activity limitation. Participants in ARAT Level 1 scored 0 - 3 on the ARAT (n=38), had little or no UL movement and no manual dexterity, evidenced by an inability to place any pegs in the 9HPT. Participants in ARAT Level 2, scored between 4 and 28 on the ARAT (n=42), demonstrated some UL motor control, but no fine manual dexterity, evidenced by inability to place any pegs. Participants in ARAT Level 3, scoring between 29 and 56 on the ARAT (n=26) and could - with only 4 exceptions - place some or all pegs, indicating good manual dexterity. Proportions of patients in each severity ARAT Level for ARAT with Nine Hole Peg Test T1 sores are illustrated in Figure 5.9.

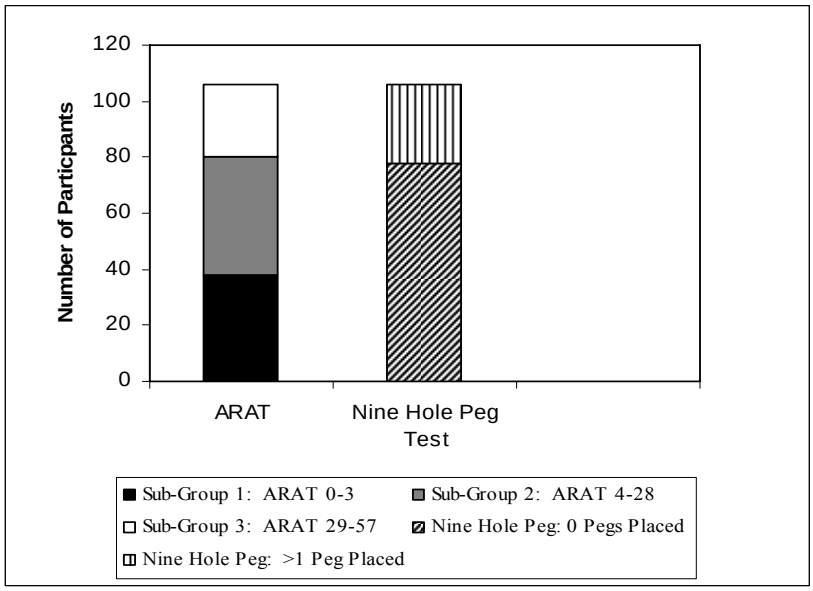


Figure 5.9: Proportion of participants in severity sub-groups determined by ARAT and Nine Hole Peg Test scores at T1

Data met assumptions for ANOVA: data were normally distributed and where it was not, data transformations were used (section 5.2.1); Levine's test for equality of variance indicated that for each group the data did not differ significantly ($p>0.05$); and data could be treated as ratio because the sample size was >40 (Kirkwood and Sterne 2003). Main and

interaction effects of ARAT Level, and Group were examined using two way 3*2 between subject factorial ANOVAs with change between T1 and T3, and T1 and T3 on ARAT, RMA and 9HPT (square root transformation) scores as dependent variables. ARAT Level and treatment Group allocation were fixed factors.

FINDINGS FOR CHANGE T1 to T2

There were no significant interaction effects between change scores from T1 to T2 and Group for the ARAT ($F_{2,89}$=0.13, p=0.87) for the RMA ($F_{2,89}$=1.30, p=0.28) or for the 9HPT ($F_{2,89}$=0.84, p=0.43) (Table 5.4a. below). This suggests that initial severity did not influence change scores differentially for the BT compared to the UT group. Of note however, the bilateral group in the most severe sub-group, ARAT Level 1, demonstrated higher change scores than the unilateral group on the ARAT and the RMA but the difference was not significant (Table 5.4a. below)

There were however three significant main effects where change varied on the ARAT according to T1 severity ($F_{2,89}$= 7.94, p<0.01), the RMA ($F_{2,89}$=4.12, p=0.02) and the 9HPT ($F_{2,89}$=18.1, p<0.01) (Table 5.4a). This was not related to training group.

Although not a primary research question, it was considered appropriate to explore these main effects since they may be relevant to UL rehabilitation in general. Unplanned multiple pairwise comparisons using Bonferroni tests indicated that for change in the ARAT and RMA between T1 and T2, patients in ARAT Level 2, the moderately affected group, demonstrated significantly greater change compared to ARAT Level 1, the severe group (ARAT p<0.01, 95% CI =-17.2 to -3.3; RMA p<0.01, 95% CI =-19.1 to -2.5) (Tables 14 and 15, Appendix 13, Data Appendix). There were no other significant post-hoc differences between the sub-groups for change between T1 and T2 on the ARAT or the RMA (Tables 14, Appendix 13, Data Appendix). The main effects of severity on change in ARAT and RMA are shown in Figures 5.10 and 5.11 respectively.

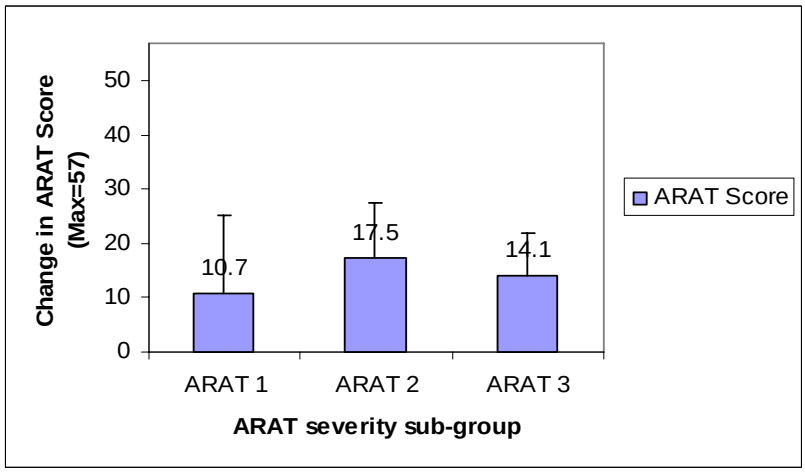


Figure 5.10. Main effects of severity sub-grouping (sd) on change in ARAT T1-T2

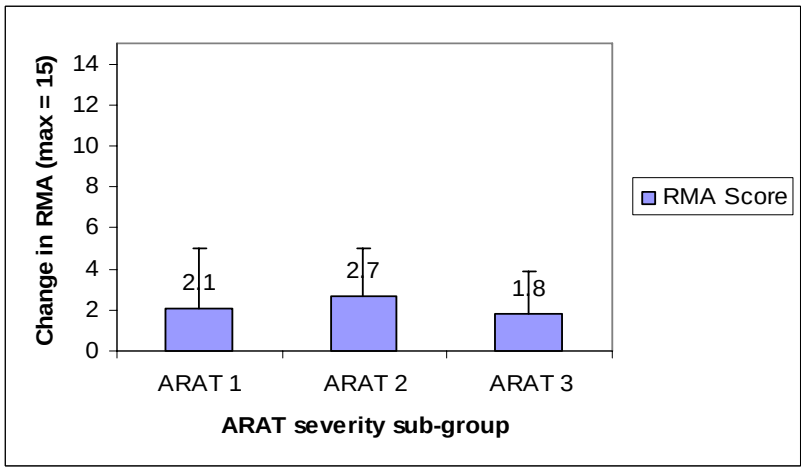


Figure 5.11. Main effects of severity sub-grouping (sd) on change in RMA T1-T2

For the 9HPT, all three sub groups were significantly different from each other, with least change in ARAT Level 1, the severe group, and most change in the least severely affected participants, ARAT Level 3 ($p \leq 0.05$) (Table 16, Appendix 13, Data Appendix), Figure 5.12.

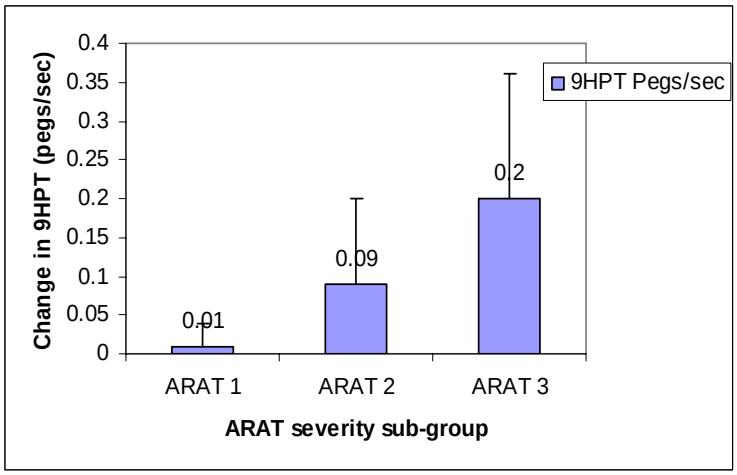


Figure 5.12. Main effects of severity sub-grouping (sd) on change in 9HPT T1-T2

FINDINGS FOR CHANGE T1 to T3

There were no significant interaction effects between ARAT Level change scores and training group from T1 to T3 for the ARAT ($F_{2,78}$= 0.74, p=0.48) for the RMA ($F_{2,78}$= 0.47, p=0.63) or for the 9HPT ($F_{2,78}$=2.48, p=0.12) (Table 5.4b) again suggesting that initial severity did not influence change scores in the BT compared to the UT groups.

Three significant main effects unrelated to group allocation existed, where T1 severity on the ARAT predicted recovery over this period on the ARAT ($F_{2,78}$= 5.41, p=0.01) the RMA ($F_{2,78}$=3.27, p=0.04) and the 9HPT ($F_{2,78}$=17.9, p<0.001) (Table 5.4b).

Again, these were of secondary interest to the main research question but were explored because of their relevance to rehabilitation in general. Unplanned multiple pairwise comparisons for the ARAT using Bonferroni tests showed that patients in ARAT Level 2, the moderately affected group demonstrated significantly more change than those in ARAT Level 1 (ARAT p=0.01, 95% CI=-18.8 to -2.7) (Table 17 Appendix 13, Data Appendix), indicating that most improvement occurred in the moderately affected group. The same comparison was not significant for the RMA (p=1.00) (Table 18 Appendix 13, Data Appendix). There were no other significant post-hoc comparisons for change T1-T3 on those measures (Tables 17 and 18 Appendix 13, Data Appendix).

Change for each sub-group T1-T3 on the ARAT is illustrated in Figure 5.13.

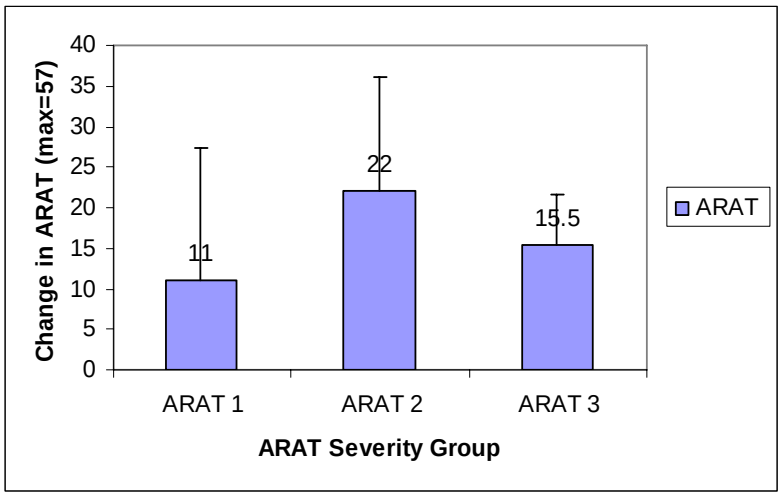


Figure 5.13. Main effects of severity sub-grouping (sd) on change in ARAT score T1-T3

Again for the 9HPT, all three sub groups were significantly different from each other, with least change in ARAT Level 1 and most in ARAT Level 3 ($p \leq 0.05$) (Table 19 Appendix 13, Data Appendix) as illustrated in Figure 5.14.

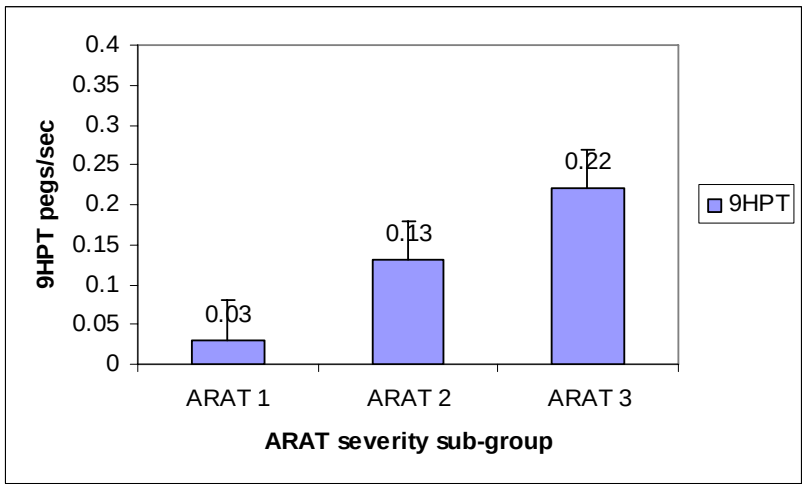


Figure 5.14. Main effects of severity sub-grouping (sd) on change in 9HPT score T1-T3

Table 5. 4 (a). Factorial ANOVA examining effects of initial severity on change scores for ARAT, RMA and 9HPT T1 to T2

		BT Group			**UT Group**			**Factorial ANOVA**			
Measure	***ARAT Level***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T2	**ARAT Level 1 (0-3)**	23	11.7	15.3	**12**	8.4	12.0	Main Effects: Group	1, 89	0.04	0.85
	ARAT Level 2 (4-28)	17	20.1	11.2	**22**	20.4	13.1	ARAT Level	2, 89	7.94	0.00*
	ARAT Level 3 (29-57)	11	13.5	8.3	**12**	13.4	8.3	Group x ARAT Level	2, 89	0.13	0.87
RMA T1-T2	**ARAT Level 1 (0-3)**	23	3.0	2.8	**12**	1.7	3.0	Main Effects: Group	1, 89	2.48	0.12
	ARAT Level 2 (4-28)	17	1.9	1.8	**22**	3.6	2.6	ARAT Level	2, 89	4.12	0.02*
	ARAT Level 3 (29-57)	11	1.4	1.9	**12**	2.6	2.4	Group x ARAT Level	2, 89	1.30	0.28
9HPT T1-T2	**ARAT Level 1 (0-3)**	23	0.01	0.04	**12**	0.01	0.01	Main Effects: Group	1,89	0.10	0.75
	ARAT Level 2 (4-28)	17	0.08	0.12	**22**	0.11	0.12	ARAT Level	2,89	18.1	0.00*
	ARAT Level 3 (29-57)	11	0.19	0.19	**12**	0.17	0.11	Group x ARAT Level	2,89	0.84	0.43

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; *denotes significant result $p \leq 0.05$

Table 5. 4 (b). Factorial ANOVA examining effects of initial severity on change scores for ARAT, RMA and 9HPT T1 to T3

		BT Group			**UT Group**			**Factorial ANOVA**			
Measure	***ARAT Level***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T3	**ARAT Level 1 (0-3)**	**20**	11.0	17.2	**10**	10.9	15.1	Main Effects: Group	1, 78	0.68	0.41
	ARAT Level 2 (4-28)	**15**	17.8	13.7	**18**	24.9	13.4	ARAT Level	2, 78	5.41	0.01*
	ARAT Level 3 (29-57)	**11**	15.7	5.5	**11**	15.3	7.0	Group x ARAT Level	2, 78	0.74	0.48
RMA T1-T3	**ARAT Level 1 (0-3)**	**20**	2.3	3.9	**10**	2.5	3.9	Main Effects: Group	1, 78	0.38	0.54
	ARAT Level 2 (4-28)	**15**	2.1	2.6	**18**	3.4	2.8	ARAT Level	2, 78	3.27	0.04*
	ARAT Level 3 (29-57)	**11**	2.6	1.6	**11**	2.3	2.4	Group x ARAT Level	2, 78	0.47	0.63
9HPT T1-T3	**ARAT Level1 (0-3)**	**20**	0.02	0.06	**10**	0.04	0.06	Main Effects: Group	1, 78	2.48	0.12
	ARAT Level2 (4-28)	**15**	0.09	0.13	**18**	0.15	0.15	ARAT Level	2, 78	17.9	0.00*
	ARAT Level3 (29-57)	**11**	0.21	0.12	**11**	0.24	0.15	Group x ARAT Level	2, 78	0.48	0.62

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test;
*denotes significant result $p \leq 0.05$

5.6.2 EFFECTS OF LESION SITE ON RESPONSES TO BILATERAL AND UNILATERAL TRAINING

In this section it was planned to explore the effects of lesion site operationalised by the Oxfordshire Community Stroke Project Classification on training responses between T1 and T2 and T1 and T3.

5.6.2.1 Secondary research question 2

The question addressed in this section is:
"Does lesion site influence UL training responses to BT compared to UT in patients with acute stroke?"

$H_0$3. The impact of lesion site operationalised by the Oxfordshire Community Stroke Project Classification will not be significantly different between acute stroke patients receiving six weeks of bilateral task training compared to those receiving unilateral task training in terms of change in UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.

5.6.2.2 Findings for effects of lesion site

Preliminary analysis showed that Levine's test of homogeneity of variance was significant, indicating that there was heteroscedacity of variance. This analysis was therefore not conducted because assumptions for ANOVA were not met.

5.6.3 EFFECTS OF SIDE OF HEMIPLEGIA AND HAND DOMINANCE ON RESPONSES TO BILATERAL AND UNILATERAL TRAINING

In this section effects of side of hemiplegia and having the dominant or non-dominant side affected by stroke were explored. The effects of these factors on responses to BT compared to UT were examined. Effects were measured for the ARAT, the RMA and the 9HPT on training responses between T1 and T2 and T1 and T3.

5.6.3.1 Secondary research question 3

The question addressed in this section is:
"Does side of hemiplegia and having the dominant or non-dominant side affected influence UL training responses to six weeks of BT compared to UT in patients with acute stroke?"

$H_0$4. The impact of side of hemiplegia and having the dominant or non-dominant side affected will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of change in UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.

5.6.3.2 Findings for effects of side of hemiplegia and hand dominance

To test the impact of side of hemiplegia and having the dominant or non dominant hand affected on outcomes of BT compared to UT, three-way 2*2*2 factorial ANOVAs were conducted with change in ARAT, 9HPT and RMA between T1 and T2 and T1 and T3 as dependent variables and training group, side of hemiplegia and dominant or non-dominant side affected as two level fixed factors. Levine's test for equality of variance indicated that population variances were equal across the cells ($p>0.05$).

FINDINGS FOR CHANGE T1 to T2 and T1 to T3
There was no significant interaction effect between dominance, side affected and training group for any of the measures for change between T1 and T2 or T1 and T3 ($p>0.05$) (Tables 5.5 a, b) indicating that there was no significant difference in change scores between BT and UT groups for participants according to hand dominance and side of stroke affected.

There was a significant interaction effect between side of hemiplegia and hand dominance on change on the RMA between T1 and T3 ($F_{1,84} = 4.06$; p= 0.04) (Table 5.5b). Unplanned multiple pairwise comparisons using Bonferroni tests demonstrated that participants with right non-dominant hemiplegia, (left handed patients whose right hand was hemiplegic) deteriorated significantly between T1 and T3 (mean change = -0.75 $\pm$ 3.0, n=4) compared to patients with right dominant hemiplegia (right handed patients whose right hand was affected) (mean change = 3.2 $\pm$ 3.1, n=38) (p=0.05, 95% confidence interval = -8.06 to 0.08) (Table 20, Appendix 13, Data Appendix). Patients with left dominant hemiplegia, (left handed patients with left hemiplegia) demonstrated approximately the same magnitude of change (change = 2.2 $\pm$ 2.6, n=4) as those with left non-dominant hemiplegia (right handed patients with left hemiplegia) (mean change = 2.3 $\pm$ 2.9, n=39). Figure 5.5 illustrates the effect. The unplanned multiple pairwise comparisons revealed no further significant differences between the sub-groups (Table 20 Appendix 13, Data Appendix). There were no other main or interaction effects between training group, hand dominance or side between T1 and T2 and T1 and T3. Results are presented in Tables 5.5 (a, b).

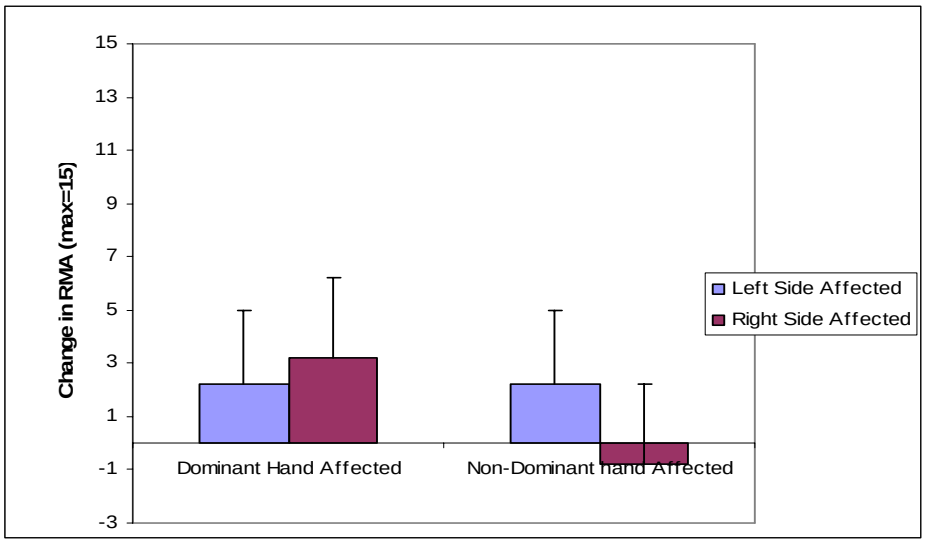


Figure 5.15. Effect of side of hemiplegia and hand dominance on change in the RMA between T1 and T3.

Table 5.5 (a). Factorial ANOVA examining effects of side of hemiplegia and hand dominance on change in ARAT, RMA and 9HPT, T1 to T2:

Measure				n	Mean	SD	*Source of Variance.*		*df*	*F*	*p*
ARAT T1-T2	UT Group	Right Side Affected	non-dominant	2	9.5	7.8	**Main Effects :**	Group	1	0.77	0.38
			dominant	20	17.3	14.8		Side	1	0.05	0.82
		Left Side Affected	non-dominant	21	14.1	10.9		Dominance	1	0.24	0.63
			dominant	3	15.7	13.6	**Interaction Effects:**	Group x Side	1	0.27	0.61
	BT Group	Right Side Affected	non-dominant	2	25.5	0.70		Group x dominance	1	0.17	0.68
			dominant	24	15.8	14.4		Side x dominance	1	0.45	0.50
		Left Side Affected	non-dominant	23	11.5	12.2		Group x side x dominance	1	1.64	0.20
			dominant	1	22.0	-					
RMA T1-T2	UT Group	Right Side Affected	non-dominant	2	1.5	2.1	**Main Effects :**	Group	1	0.00	0.98
			dominant	20	2.6	2.5		Side	1	0.52	0.47
		Left Side Affected	non-dominant	21	3.2	3.0		Dominance	1	0.36	0.55
			dominant	3	2.7	2.9	**Interaction Effects:**	Group x Side	1	0.03	0.86
	BT Group	Right Side Affected	non-dominant	2	2.5	0.71		Group x dominance	1	0.11	0.74
			dominant	24	2.0	2.5		Side x dominance	1	0.09	0.76
		Left Side Affected	non-dominant	23	1.6	2.2		Group x side x dominance	1	1.27	0.26
			dominant	1	4.0	-					
9HPT T1-T2	UT Group	Right Side Affected	non-dominant	2	0.04	0.03	**Main Effects :**	Group	1	0.04	0.85
			dominant	20	0.13	0.14		Side	1	0.73	0.79
		Left Side Affected	non-dominant	21	0.08	0.10		Dominance	1	1.46	0.23
			dominant	3	0.07	0.06	**Interaction Effects**:	Group x Side	1	0.22	0.64
	BT Group	Right Side Affected	non-dominant	2	0.04	0.06		Group x dominance	1	0.15	0.70
			dominant	24	0.10	0.17		Side x dominance	1	0.08	0.78
		Left Side Affected	non-dominant	23	0.06	0.10		Group x side x dominance	1	0.41	0.53
			dominant	1	0.16	-					

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; *denotes significant result $p \leq 0.05$

Table 5.5 (b). Factorial ANOVA examining effects of side of hemiplegia and hand dominance on change in ARAT, RMA and 9HPT T1 to T3

Measure				n	Mean Change	SD	*Source of Variance.*		*df*	*F*	*p*
ARAT T1-T3	UT Group	Right Side Affected	non-dominant	2	13.0	12.7	**Main Effects :**	Group	1	0.04	0.84
			dominant	1	18.8	14.0		Side	1	0.95	0.33
		Left Side Affected	non-dominant	17	19.3	14.2		Dominance	1	1.16	0.28
			dominant	3	17.3	15.3	**Interaction Effects:**	Group x Side	1	0.30	0.58
	BT Group	Right Side Affected	non-dominant	2	13.0	22.6		Group x dominance	1	0.55	0.46
			dominant	21	14.8	12.7		Side x dominance	1	0.16	0.68
		Left Side Affected	non-dominant	22	13.2	15.3		Group x side x dominance	1	1.19	0.28
			dominant	1	32.0	-					
RMA T1-T3	UT Group	Right Side Affected	non-dominant	2	1.0	1.4	**Main Effects :**	Group	1	2.29	0.13
			dominant	17	3.3	3.1		Side	1	0.30	0.59
		Left Side Affected	non-dominant	17	2.6	3.1		Dominance	1	1.81	0.18
			dominant	3	3.0	2.6	**Interaction Effects:**	Group x Side	1	0.00	0.99
	BT Group	Right Side Affected	non-dominant	2	-2.5	3.5		Group x dominance	1	0.04	0.83
			dominant	21	3.2	3.1		Side x dominance	1	4.05	0.04*
		Left Side Affected	non-dominant	22	2.0	2.7		Group x side x dominance	1	1.49	0.23
			dominant	1	0.0	-					
9HPT T1-T3	UT Group	Right Side Affected	non-dominant	2	0.11	0.07	**Main Effects :**	Group	1	0.62	0.44
			dominant	17	0.16	0.19		Side	1	0.54	0.47
		Left Side Affected	non-dominant	17	0.14	0.13		Dominance	1	0.44	0.51
			dominant	3	0.15	0.15	**Interaction Effects:**	Group x Side	1	0.25	0.62
	BT Group	Right Side Affected	non-dominant	2	0.04	0.06		Group x dominance	1	0.04	0.84
			dominant	21	0.08	0.12		Side x dominance	1	0.12	0.90
		Left Side Affected	non-dominant	22	0.10	0.14		Group x side x dominance	1	0.09	0.76
			dominant	1	0.16	-					

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test;

*denotes significant result, $p \leq 0.05$

5.6.4 EFFECTS OF GENDER ON RESPONSES TO BILATERAL AND UNILATERAL TRAINING

In this section effects of gender on responses to BT compared to UT were explored. Effects were measured for the ARAT, the RMA and the 9HPT on training responses between T1 and T2 and T1 and T3.

5.6.4.1 Secondary Research Question 4

The question addressed in this section is:
"Does gender influence UL training responses to six weeks of BT compared to UT in patients with acute stroke?"

$H_0$5 The impact of gender will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of change in UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.

5.6.4.2 Findings for effects of gender

To test the impact of side of gender on outcomes of BT, two way between subject 2*2 factorial ANOVAs were conducted with change in ARAT, 9HPT and RMA between T1 and T2 and T1 and T3 as dependent variables and training group, and gender as two level fixed factors. Levine's test for equality of variance was not significant for any of the tests, indicating that the assumption of homogeneity was met.

There was no significant interaction between gender and training group for any of the variables for change between T1 and T2 and T1 and T3 (Table 5.6 a, b), suggesting that there was no effect of gender on recovery for the UT or BT training groups. There was, however, a significant within subject main effect of gender on change in ARAT between T1 and T3 ($F_{1,84} = 4.44$; p=0.04) (Table 5.6 b), where male patients achieved significantly greater overall recovery on the ARAT (18.6 $\pm$ 13.3) compared to female patients (13.1$\pm$ 14.5). The effect is illustrated in Figure 5.14.

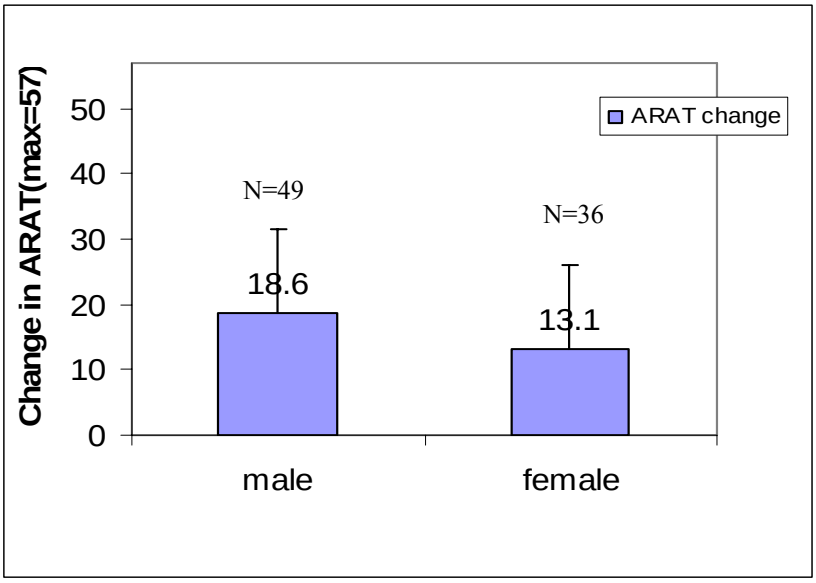


Figure 5.16.Change in ARAT score (sd) for male and female patients between T1 and T3 weeks

There were no other significant main or interaction effects for group or gender in change between T1 and T2 and T1 and T3. Results are shown in Tables 5.6 (a, b) below.

Table 5.6 (a). Factorial ANOVA examining effects of gender on change in ARAT, RMA and 9HPT, T1 to T2

		BT Group			**UT Group**			**Factorial ANOVA**			
Measure	***Gender***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
	Male	31	13.8	11.8	23	17.5	11.7	Main Effects: Group	1, 96	0.12	0.73
ARAT	**Female**	19	15.2	15.6	23	13.3	13.4	Gender	1, 96	0.28	0.60
T1-T3								Group x Gender	1, 96	1.04	0.31
	Male	31	2.0	2.2	23	3.1	2.7	Main Effects: Group	1, 96	3.63	0.06
RMA	**Female**	19	1.7	2.4	23	2.6	2.7	Gender	1, 96	0.58	0.45
T1-T2								Group x Gender	1, 96	0.10	0.75
9HPT	**Male**	31	0.09	0.15	23	0.12	0.12	Main Effects: Group	1, 96	0.62	0.43
T1-T2	**Female**	19	0.06	0.11	23	0.08	0.11	Gender	1, 96	1.59	0.21
								Group x Gender	1, 96	0.01	0.91

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test;

*denotes significant result, $p \leq 0.05$

Table 5.6 (b). Factorial ANOVA examining effects of gender on change in ARAT, RMA and 9HPT, T1 to T3

		BT Group			**UT Group**			**Factorial ANOVA**			
Measure	***Gender***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T3	**Male**	29	14.9	12.0	20	24.0	13.5	Main Effects: Group	1, 85	2.09	0.15
	Female	17	13.4	17.5	19	12.9	11.6	Gender	1, 85	4.44	0.04*
								Group x Gender	1, 85	2.50	0.12
RMA T1-T3	**Male**	29	2.6	2.8	20	3.3	3.0	Main Effects: Group	1, 85	0.84	0.36
	Female	17	1.9	3.5	19	2.4	3.0	Gender	1, 85	1.41	0.24
								Group x Gender	1, 85	0.04	0.85
9HPT T1-T3	**Male**	29	0.09	0.12	20	0.18	0.14	Main Effects: Group	1, 85	3.78	0.06
	Female	17	0.09	0.14	19	0.11	0.15	Gender	1, 85	1.94	0.17
								Group x Gender	1, 85	1.62	0.21

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test;

*denotes significant result, $p \leq 0.05$

5.6.5. EFFECTS OF AGE ON RESPONSES TO BILATERAL AND UNILATERAL TRAINING

In this section effects of age on responses to BT compared to UT were explored. Effects were measured for the ARAT, the RMA and the 9HPT on training responses between T1 and T2 and T1 and T3. The median age of the sample was 69 (range 36- 94) years. Two age sub-groups were determined using a median split which resulted in one group with participants aged 36 to 69 years (n=50), and another with participants aged 70 to 94 years (n=46).

5.6.5.1 Secondary research question 5

The question addressed in this section is:
"Does age influence UL training responses to six weeks of BT compared to UT in patients with acute stroke?"

$H_0$6. The impact of age will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of change in UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.

5.6.5.2 Findings for effects of age

To test the impact of age on outcomes of BT compared to UT, two way 2*2 between subject factorial ANOVAs were conducted with change in ARAT, 9HPT and RMA between T1 and T2 and T1 and T3 as dependent variables and training group, and age as two level fixed factors. Levine's test for equality of variance was not significant for any of the tests, indicating that the assumption of homogeneity was met.

There was no significant interaction effect between Group and Age on change between T1 and T2 and between T1 and T3 on the ARAT, RMA or 9HPT ($p>0.05$) (Table 5.7 a, b), indicating that age did not significantly influence responses to BT or UT.

There was a significant main effect of Group on change in 9HPT (using the square root transformation) between T1 and T2 ($F_{1,84} = 8.44$; $p=0.005$) (Table 5.7b), where the UT group achieved greater overall recovery on the 9HPT (mean change = 0.15±0.15) compared to the BT training group (mean change = 0.09± 0.13). This supports the significant interaction effect between time and group in section 5.5.1.2.

There was also a significant main effect of age on change in 9HPT (square root transformation) between T1 and T3 ($F_{1,83} = 4.31$; $p = 0.04$). Here participants who were 69 years or less (n=43) demonstrated poorer recovery (mean change = 0.09 ± 0.12) than those who were 70 or more (n=42), (mean change = 0.15 ± 0.15).

There were no other significant main or interaction effects for Group or Age in change between T1 and T2 and T1 and T3. Results are shown in Tables 5.7 (a, b) below.

Table 5.7 (a). Factorial ANOVA examining effects of age on change in ARAT, RMA and 9HPT, T1 to T2

		BT Group			**UT Group**			**Factorial ANOVA**			
Measure	***Age (years)***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T2	**≤ 69**	24	14.4	13.2	26	16.9	13.2	Main Effects: Group	1, 96	0.11	0.75
	> 69	26	14.2	13.4	20	13.5	11.8	Age	1, 96	0.47	0.50
								Group x Age	1, 96	0.36	0.55
RMA T1-T2	**≤ 69**	24	1.7	2.3	26	2.7	2.6	Main Effects: Group	1, 96	3.69	0.06
	> 69	26	2.0	2.3	20	3.0	2.9	Age	1, 96	0.23	0.63
								Group x Age	1, 96	0.02	0.89
9HPT T1-T2	**≤ 69**	24	0.05	0.10	26	0.09	0.11	Main Effects: Group	1, 96	0.54	0.47
	> 69	26	0.11	0.16	20	0.10	0.12	Age	1, 96	2.01	0.16
								Group x Age	1, 96	1.14	0.29

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test;

*denotes significant result, $p \leq 0.05$

Table 5.7 (b). Factorial ANOVA examining effects of age on change in ARAT, RMA and 9HPT, T1 to T3

		BT Group			**UT Group**			**Factorial ANOVA**			
Measure	***Age***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T3	**≤ 69**	21	12.3	11.9	22	19.8	14.8	Main Effects: Group	1, 85	1.93	0.17
	> 69	25	16.0	15.8	17	17.1	12.3	Age	1, 85	0.03	0.86
								Group x Age	1, 85	1.08	0.30
RMA T1-T3	**≤ 69**	21	2.5	3.6	22	2.7	2.8	Main Effects: Group	1, 85	0.66	0.42
	> 69	25	2.2	2.6	17	3.0	3.3	Age	1, 85	0.00	0.97
								Group x Age	1, 85	0.19	0.66
9HPT T1-T3	**≤ 69**	21	0.03	0.06	22	0.14	0.15	Main Effects: Group	1, 85	8.45	0.01*
	> 69	25	0.14	0.15	17	0.16	0.16	Age	1, 85	4.31	0.04*
								Group x Age	1, 85	2.77	0.10

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test;

*denotes significant result, $p \leq 0.05$

5.6.6 EFFECTS OF PROPRIOCEPTION ON UPPER LIMB RESPONSES TO BILATERAL COMPARED TO UNILATERAL TRAINING

In this section effects of proprioception on responses to BT compared to UT were explored. Effects were examined for the ARAT, the RMA and the 9HPT on training responses between T1 and T2 and T1 and T3. To explore whether T1 proprioception significantly influenced training outcomes, participants were categorised into two sub-groups according to whether they had intact proprioception at baseline (proprioception score = 12; n=24) or impaired proprioception (proprioception score <12; n=72).

5.6.6.1 Secondary research question 6

The research question addressed in this section was:

"Does initial proprioception influence UL training responses to bilateral task training compared to unilateral task training in patients with acute stroke?"

$H_0$7 The impact of initial proprioception will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of changes UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.

5.6.6.2 Findings for effects of proprioception

Descriptive data for proprioception scores at T1 has not previously been presented. Mean and median scores for proprioception for the BT and UT groups at T1 are presented in Table 5.8.

Table 5.8. Mean, standard deviation, median, range of Nottingham Sensory Assessment proprioception scores at T1 for UT and BT groups

Proprioception score (min = 0, max = 12)	**BT Group (N=56)**	**UT Group (N=50)**
Mean (SD) Median (Range)	8.3 (3.7) 9.0 (0,12)	8.0 (3.9) 9.0 (0,12)

To test the impact of proprioceptive sense on change in UL outcomes in response to BT compared to UT training, two way between subjects 2*2 factorial ANOVAs were conducted with change in ARAT, 9HPT and RMA between T1 and T2 and T1 and T3 as dependent variables and training group and proprioception group as dichotomous factors. Levine's test for equality of variance was not significant for any of the tests, indicating that the assumption of homogeneity was met.

There were no significant main or interaction effects of T1 proprioception on change in any of the UL outcome measures between T1 and T2 and T1 and T3 (Table 5.9a, b) or any main effects of Group ($p>0.05$) (Table 5.9a, b). These findings suggest that proprioception did not significantly influence BT compared to UT, and had no overall effect on responses.

Table 5.9 (a) Factorial ANOVA examining effects of proprioception (as per NSA) on change in ARAT, RMA and 9HPT, T1 to T2

		UT Group			**BT Group**			**Factorial ANOVA**			
Measure	***Proprioception Sub-group***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T2	**Impaired Proprioception**	33	16.3	13.1	39	13.2	12.6	Main Effects: Group	1	0.13	0.72
	Intact Proprioception	13	13.0	11.4	11	18.4	15.3	Proprioception .Level	1	0.08	0.77
								Group x Level	1	1.95	0.16
RMA T1-T2	**Impaired Proprioception**	33	3.1	2.6	39	1.9	2.2	Main Effects: Group	1	1.95	0.17
	Intact Proprioception	13	2.3	3.0	11	1.8	2.6	Proprioception .Level	1	0.59	0.49
								Group x Level	1	0.35	0.56
9HPT T1-T2	**Impaired Proprioception**	33	0.10	0.12	39	0.08	0.14	Main Effects: Group	1	0.09	0.77
	Intact Proprioception	13	0.09	0.11	11	0.10	0.12	Proprioception .Level	1	0.01	0.91
								Group x Level	1	0.33	0.57

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test;
Impaired Proprioception was defined as a score of 12 on the NSA proprioception section;
intact proprioception was defined as a score of <12 on the NSA proprioception section

Table 5.9 (b). Change scores for UT and BT groups for proprioception levels on ARAT, RMA and 9HPT, T1-T3

		UT Group			BT Group			Factorial ANOVA			
Measure	***Proprioception Sub-group***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT								Effects: Group	1	0.15	0.22
T1-T3	**Impaired Proprioception**	27	19.1	14.1	35	11.9	11.9	Proprioception Level	1	1.54	0.70
	Intact Proprioception	12	17.4	13.0	11	22.0	18.2	Group x Level	1	3.09	0.08
RMA								Effects: Group	1	0.11	0.74
T1-T3	**Impaired Proprioception**	27	2.9	2.7	35	2.1	2.9	Proprioception Level	1	0.36	0.55
	Intact Proprioception	12	2.7	3.7	11	3.1	3.4	Group x Level	1	0.62	0.43
9HPT								Effects: Group	1	2.11	0.11
T1-T3	**Impaired Proprioception**	27	0.14	0.13	35	0.07	0.11	Proprioception Level	1	2.60	0.15
	Intact Proprioception	12	0.18	0.19	11	0.14	0.15	Group x Level	1	0.20	0.66

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test;
Impaired Proprioception was defined as a score of 12 on the NSA proprioception section;
intact proprioception was defined as a score of <12 on the NSA proprioception section

5.6.7 SUMMARY OF FINDINGS

In this section, effects of various factors identified from the stroke literature and presented in Chapter 2, were explored for their impact on upper limb responses to bilateral training (BT) compared to unilateral training (UT).

Initial severity of activity limitation did not significantly influence responses to bilateral training compared to unilateral training. A secondary finding was that baseline (T1) severity of upper limb activity limitation significantly influenced change in some Action Research Arm Test (ARAT) sub-groups, but this was not related to training group. Further exploration of this finding suggested that for activity limitation and motor impairment (RMA) there was a significant difference between the most severe (ARAT level 1) and moderately severe (ARAT Level 2) sub-groups in change during treatment (baseline to six weeks) and in overall change on the Action Research Arm Test (baseline to eighteen weeks) with the most severely affected participants recovering least. For dexterity, all severity sub-groups differed from each other significantly, in terms of change over both time periods. Here the most severely affected sub-group improved least whilst the least severely affected sub-group improved most.

There was no interaction effect between hand dominance or side and treatment group, suggesting that these factors did not differentially influence responses to bilateral training compared to unilateral training. The only significant effect of hand dominance and side of lesion was an interaction effect that reached significance. This suggested that left-handed patients with right sided hemiplegia demonstrated recovery that was significantly poorer than that of right handed patients with right sided hemiplegia in terms of overall change in impairment between baseline and six weeks.

There was no interaction effect between gender and treatment group suggesting that gender did not influence responses to BT compared to UT. However, men demonstrated significantly more recovery than women in terms of overall recovery of activity limitation measured on the Action Research Arm Test – but this was irrespective of treatment group.

Age did not significantly influence training responses for bilateral training compared to unilateral training. There was a secondary finding of a significant main effect of age

suggesting that younger participants improved less between baseline and eighteen weeks on the Nine Hole Peg Test.

There was no significant interaction between proprioception and training group suggesting that proprioception did not significantly influence responses to bilateral training compared to unilateral training.

Progressing from the effects of bilateral training on the contralesional upper limb, the next section examines predictors of contralesional upper limb activity limitation for the sample as a whole.

5.7 PHYSICAL OUTCOMES: AN EXPLORATION OF PREDICTORS OF UPPER LIMB ACTIVITY LIMITATION

The literature review (Chapter 2) suggested that several factors and patient characteristics might influence UL recovery. These included initial impairment and activity limitation, side of hemiplegia, whether the dominant or non-dominant side is affected, sensory impairment, gender, lesion site and age, and these were examined with respect to their impact on training responses in Section 5.7. The literature also suggested that the predictive strength of these variables may vary over time. This final section relating to the physical outcomes therefore examines the relative strength of T1 and T2 variables and participant characteristics to predict T2 and T3 ARAT scores for the whole sample. First, to meet regression assumptions, participant characteristics, including training group, and T1 and T2 scores on all measures were tested for significant correlation with the dependent variables, T2 and T3 ARAT scores to identify potential predictors. Data were screened for multivariate outliers and to ensure that assumptions for regression were met. Variables that were significantly correlated with the dependent variables were then entered into multiple linear regression equations. Finally, because the ARAT scores at T1 and T2 were not independent of the ARAT as a dependent variable, the equations were also run without the ARAT as a dependent variable to determine predictors when the ARAT was not included. Findings are presented below.

5.7.1 DATA SCREENING FOR MULTIPLE LINEAR REGRESSION

5.7.1.1 Descriptive Data

Details of patient characteristics of the whole sample at T1 had not been previously presented so these are shown in Table 21, Appendix 13, Data Appendix. T1, T2 and T3 outcome scores for the whole sample are shown in Table 1, Appendix 13, Data Appendix. The mean T1 ARAT score was 15.8 (±16.3), the mean T2 ARAT score was 30.9 (± 18.6) and increased to 32.9 (± 18.6) at T3 (Figure 5.15).

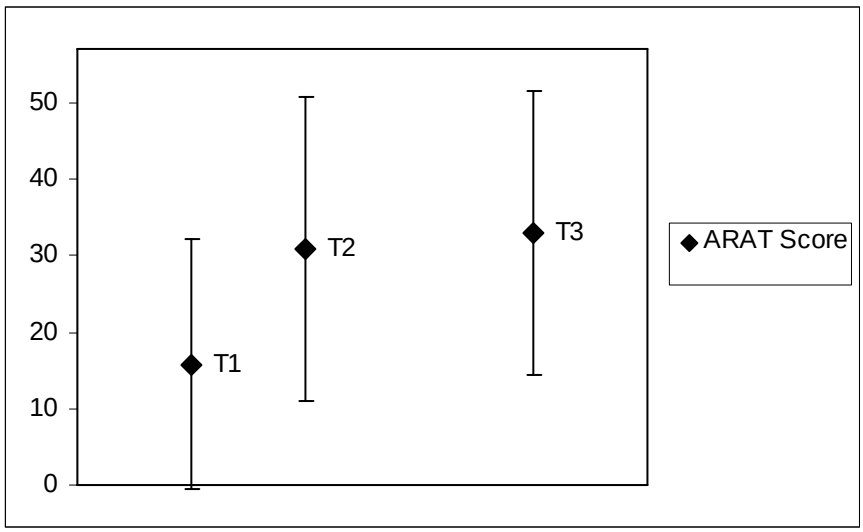


Figure 5.17 Mean ARAT Scores (SD) at T1, T2 and T3 for the entire study sample.

5.7.1.2 Correlations between patient characteristics, T1 and T2 outcome measures and T2 and T3 ARAT scores

To determine which variables should be entered into the regression equations as independent variables, correlations were conducted between potential predictors and the dependent variables, the T2 and T3 ARAT scores. Spearman's rho was used for non-parametric data, and Pearson's correlation was used for parametric and point biserial correlations. T1 outcome scores and patient characteristics were tested for correlation with T2 ARAT and T3 scores, and T2 outcome scores and patient characteristics were tested for correlation with T3 ARAT score (Table 5.10).

The results showed that T1 ARAT RMA, 9HPT and MBI scores were positively and significantly correlated with T2 and T3 ARAT scores (Table 5.10). Presence of The Oxfordshire Community Stroke Project classification TACS was significantly and negatively correlated with T2 and T3 ARAT scores, indicating that presence of a total anterior circulation stroke was associated with poorer outcome. Days from stroke onset to initial assessment, and T1 Depression and Anxiety, measured on the HADS demonstrated weaker but significant negative correlations with T2 and T3 ARAT scores.

T2 ARAT, RMA, 9HPT and MBI scores were also significantly and positively associated with T3 ARAT scores (Table 5.10). T2 tactile sensation, proprioception and total sensory scores, measured on the NSA, were also weakly but significantly associated with T3 ARAT

score, whilst T2 Depression and Anxiety were not significant correlates of T3 ARAT score (Table 5.10). Treatment group (BT or UT) was not a significant correlate of T2 ARAT at (r=0.16; p=0.07) or T3 ARAT (r=0.17; p=0.08) and was therefore not included in the regression models as an independent variable.

Table 5.10 Correlation coefficients between mean values of independent variables measured at T1 and T2 and ARAT outcome scores at T2 and T3

Potential Independent Variables	**T2 ARAT** *Correlation Coefficient*	**T3 ARAT** *Correlation Coefficient*
Participant Characteristics	*N=97*	*N=85*
Oxford Community Stroke Classification		
TACS	r=-0.34*	r=-0.34*
LACS	r= 0.23*	r= 0.24*
PACS	r=-0.10	r=-0.13
POCS	r= 0.07	r= 0.11
Age	r= 0.09	r= 0.17
Gender	r= 0.07	r= 0.15
Side affected	r=-0.09	r=-0.01
Handedness	r=-0.02	r=-0.04
Dominant side affected	r= 0.05	r= 0.01
Ischaemic/haemorrhagic stroke	r=-0.04	r=-0.16
Days from stroke onset to initial assessment	r=-0.35**	r=-0.37**
T1 Outcome Scores		
UL Activity: ARAT T1		
UL impairment: RMA T1	r= 0.76**	r= 0.70**
Dexterity: Nine Hole Peg Test T1	r= 0.60**	r= 0.57**
ADL: MBI T1	r= 0.56**	r= 0.56**
Anxiety T1	r=-0.26*	r= -0.32**
Depression T1	r=-0.26**	r= -0.32**
NSA Overall sensation T1	r=-0.03	r= 0.03
NSA Tactile sensation T1	r=-0.01	r= 0.02
NSA Proprioception T1	r= 0.06	r= -0.16
Training Group	r= 0.16	r= 0.17
T2 Outcome Scores		
UL activity: ARAT T2 score		r= 0.94**
UL impairment: RMA T2		r= 0.85**
Dexterity: Nine Hole Peg Test T2		r= 0.79**
ADL: MBI T2		r= 0.56**
HADS Anxiety T2		r= -0.19
HADS Depression T2		r= -0.19
NSA Overall sensation, T2		r= -0.27*
NSA Tactile Sensation T2		r= -0.23*
NSA Proprioception, NSA T2		r= -0.29**

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; HADS denotes Hospital Anxiety and Depression Scale, NSA denotes Nottingham Sensory Assessment. *Correlation is significant at the $p \leq 0.05$ level;
** Correlation is significant at the 0.01 level

5.7.2 EXPLORING T1 PREDICTORS OF UL ACTIVITY LIMITATION AT T2 and T3

In this section, significant T1 correlates of ARAT T2 and T3 scores were entered into two regression equations to determine the predictors of the ARAT at each of these assessments.

5.7.2.1 Predicting UL activity limitation: Research question 1

The research question addressed in this section is:
"What participant characteristics and T1 activity limitation outcome variables best predict UL activity limitation scores at T2 and T3?"

$H_0$8 Participant characteristics and T1 activity limitation outcome scores will not significantly predict UL activity limitation measured on the ARAT at T2 and T3.

5.7.2.2 Findings for T1 predictors of upper limb activity limitation at T2 and T3

DATA SCREENING
To determine the T1 models that best predicted ARAT scores at T2 and T3, multiple linear regression equations were performed. T2 and T3 ARAT scores were dependent variables respectively, and their significant T1 correlates (Table 5.10) were independent variables. These were ARAT T1 scores, 9HPT T1scores, MBI T1 scores, Anxiety and Depression at T1, days to initial assessment and Oxfordshire Community Stroke Project Classification.

The 9HPT was dichotomised into pegs/no pegs for the purpose of the regression equations (Section 5.2.1). All variables were entered simultaneously into the multiple linear regression equations in a block, followed by the Oxfordshire Community Stroke Project Classification indicator variables TACS, POCS, LACS, PACS which, as four discrete variables, were entered as dichotomous dummy variables in a second block (Tabachnick and Fidell 2001).

MULTIVARIATE OUTLIERS, LINEARITY AND HOMOSCEDASTICITY
Only cases with complete data at T2 (n=97) and T3 (n=85) were included in the regression equations. No multivariate outliers were found with standardised residuals greater than 3.0 or with the $p<0.001$ criterion for Mahalanobis distance ($df = 9$; $X^2 < 23.0$) (Tabachnick and

Fidell 2001). Linearity and homoscedasticity of the multivariate residuals was examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001).

COLLINEARITY

The RMA T1 score demonstrated collinearity of 0.89 with the ARAT at T1 (Table 22, Appendix 13, Data Appendix). Since this correlation had p >0.70, the RMA was removed from the analysis (Tabachnick and Fidell 2001). The OCSPC item PACS demonstrated collinearity with the LACS item and PACS was dropped from the block as the T1 indicator variable in the dummy variable group. Collinearity tolerance statistics <0.01 for all variables indicated that there were no further problems with multicollinearity (Brace et al. 2003).

T1 PREDICTORS OF T2 ACTIVITY LIMITATION

A significant regression equation model emerged that explained 68% of the variance in T2 ARAT scores (adjusted $R^2 = 0.675$; $F_{6, 89} = 22.94$; $p<0.001$) (Table 23, Appendix 13, Data Appendix). Beta values indicate that ARAT T1 score was significantly predictive of ARAT T2 score (ß=0.64; p<0.001) followed by MBI T1 score (ß=0.18, p=0.03). Fewer days from stroke onset to initial assessment was also significantly predictive of T2 ARAT score (ß= -0.15, p=0.02), and presence of a total anterior circulation stroke was also significantly predictive of ARAT T2 score (ß=-0.13; p=0.04). Addition of the OCSPS as a group did not add significantly to the model (R^2 change = 0.02; $F_{3, 86} = 1.50$; p=0.22) (Table 23, Appendix 13, Data Appendix).

T1 PREDICTORS OF T2 ACTIVITY LIMITATION WITH T1 ARAT REMOVED AS AN INDEPENDENT VARIABLE

To assess the effects of the independent variables on T2 ARAT without the ARAT T1 score, whose inclusion may lead to biased estimates because of autocorrelation with the dependent variable, the regression was run again as before but excluding the ARAT T1 score.

A significant linear regression model emerged that explained 54% of the variance in T2 ARAT scores (Adjusted $R^2 = 0.544$; $F_{8,87} = 15.17$; $p<0.001$). Beta values indicated that higher MBI T1 score (ß=0.38; p<0.001) and ability to place pegs (ß=0.38; p<0.001) were the strongest predictors of higher T2 ARAT scores (Table 24; Appendix 13, Data Appendix). Fewer days from stroke onset to initial assessment was also a significant predictor of better

ARAT score (ß=-0.23; p<0.01), whilst presence of a total anterior circulation stroke was predictive of poorer ARAT T2 score (ß=-0.16; p=0.04) (Table 24; Appendix 13, Data Appendix). Addition of the OCSPS as a group did not add significantly to the model (R^2 change = 0.03; F Change $_{3, 87}$ = 1.87; p=0.14).

T1 PREDICTORS OF T3 ACTIVITY LIMITATION

For T3 ARAT scores, a significant linear regression model emerged that explained 64% of the variance (Adjusted R_2 = 0.635; F $_{9, 87}$ = 17.06; p<0.001). Beta scores show that higher ARAT (ß=0.53; p<0.001) and MBI scores (ß=0.21; p=0.04) at T1 were the strongest significant predictors of higher ARAT scores at T3 at the p≤0.05 level (Table 25, Appendix 13, Data Appendix). Fewer days to T1 assessment (ß=-0.16; p=0.04) was also a significant predictor. Addition of the OCSPS as a group did not add significantly to the model (R^2 change = 0.01; F Change $_{3, 87}$ = 0.91; p=0.44).

T1 PREDICTORS OF T3 ACTIVITY LIMITATION WITH T1 ARAT REMOVED AS AN INDEPENDENT VARIABLE

Excluding the ARAT as an independent variable led to the emergence of a significant model that explained 55% of the variance in T3 ARAT scores (Adjusted R^2 = 0.546; F $_{8, 75}$ = 20.96; p=0.00). Beta scores show that ability to place pegs at T1 was the strongest significant predictor of higher T3 ARAT scores at the p≤0.05 level when T1 ARAT scores were excluded (ß=0.39; p<0.001) followed by T1 MBI scores (ß=0.37; p<0.001) and fewer days to initial assessment (ß=-0.23; p<0.001) (Table 26, Appendix 13, Data Appendix). Addition of the OCSPS as a group did not add significantly to the model (R^2 change = 0.01; F Change $_{3, 75}$ = 0.94; p=0.43).

5.7.3 EXPLORING T2 PREDICTORS OF UL ACTIVITY LIMITATION AT T3

In this section, significant T2 correlates of ARAT T3 scores were entered into two regression equations to determine the predictors of the ARAT at T3.

5.7.3.1 Predicting upper limb activity limitation: Research question 2

The research question addressed in this section is:
"What participant characteristics and T2 activity limitation outcome variables best predict ARAT scores at T3?"

$H_0$9.Participant characteristics and T2 activity limitation outcome scores will not significantly predict UL activity limitation measured on the ARAT at T3.

5.7.3.2 Findings for T2 predictors of T3 ARAT scores

DATA SCREENING

To determine which T2 variables predicted T3 ARAT scores, multiple linear regression was conducted using the T3 ARAT as the dependent variable, and significant T2 correlates as independent variables (Table 5.10). The variables entered into the regression model in the first block were: UL activity: ARAT T2 score; ADL: MBI T2, Dexterity: Nine Hole Peg Test T2; proprioception score T2, NSA tactile sensory score T2. This was followed by the Oxfordshire Community Stroke Project Classification indicator variables entered as a second block. Only cases with complete data were entered into the model (n=85). Transformed data were used in the analysis (Section 5.3.1).

MULTIVARIATE OUTLIERS, LINEARITY AND HOMOSCEDASTICITY

Four multivariate outliers were found, with standardized residuals of greater than 3.0. These cases, 48 and 59, 26 and 40 were removed from the database (Tabachnick and Fidell 2001)and the analysis was run without them. In the subsequent run of regression no further outliers were found with standardised residuals greater than 3.0 or using the $p<0.001$ criterion for Mahalanobis distance ($df = 8$, $X^2 < 26.1$). Linearity and homoscedasticity of the residuals was examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001).

COLLINEARITY

The RMA demonstrated collinearity with the 9HPT ($r = 0.73$) and with the ARAT at T3 ($r=0.89$), and was therefore removed from the model (Table 27, Appendix 13, Data Appendix). The NSA total score demonstrated high collinearity with its subsections tactile

sensation, proprioception and stereognosis (r > 0.7) (Table 27, Appendix 13, Data Appendix) and was removed from the model.

T2 PREDICTORS OF T3 ACTIVITY LIMITATION

A significant model emerged that explained 93% of variance in the ARAT at T3: (adjusted $R^2 = 0.93$: $F_{8, 73} = 126.46$; $p<0.0001$). ARAT score at T2 was the only significant predictor of ARAT scores at T3 at the $p \leq 0.05$ level (ß=0.86; $p<0.001$). Significant and non-significant variables are shown in Table 28 (Appendix 13, Data Appendix). Addition of the OCSPC did not add significantly to the model (R^2 change =0.003; F $change_{3,73}$ =1.24; p=0.30).

T2 PREDICTORS OF T3 ACTIVITY LIMITATION WITH T2 ARAT REMOVED AS AN INDEPENDENT VARIABLE

To assess the effects of the independent variables on T3 ARAT score without the ARAT T2 score, the regression was run again as before but excluding the ARAT T2 score.

The model explained 72% of the variance of the ARAT at T3: (Adjusted $R^2 = 0.72$; $F_{7,74}$ = 31.18; ;p=0.00). Beta values show that ability to place pegs was the strongest significant predictor of ARAT scores at T3 at the $p \leq 0.05$ level (ß=0.65; $p<0.001$) followed by the T2 MBI score (ß=0.27; $p<0.001$) (Table 29, Appendix 13, Data Appendix). Addition of the OCSPC did not add significantly to the model (R^2 change =0.01; F $change_{3,74}$ =1.36; p=0.26).

5.7.4 SUMMARY OF FINDINGS

Using baseline (T1) measures and patient characteristics as independent variables, a model emerged that predicted 68% of the variance in six week (T2) Action Research Arm Test (ARAT) scores. The model shows that Action Research Arm Test score at baseline was the strongest significant predictor, followed by T1 Modified Barthel Index (MBI) score and finally days from stroke onset to initial assessment, where fewer days to assessment predicted better Action Research Arm Test score. Presence of a total anterior circulation stroke was predictive of poorer Action Research Arm Test score, but was a weaker predictor than the other variables. With removal of the Action Research Arm Test six week score from the equation as an independent variable, the model explained 54% of the variance.

Better Modified Barthel Index scores followed by ability to place pegs in the Nine Hole Peg Test (9HPT) at six weeks, then days to initial assessment emerged as the strongest predictors of six week Action Research Arm Test scores. Again presence of a total anterior circulation stroke was predictive of poorer ARAT score, but was the weakest predictor of all the variables.

A significant model emerged that predicted 64% of the variance in eighteen week ARAT scores from baseline measures and patient characteristics. In this model, unsurprisingly, baseline Action Research Arm Test score was the strongest predictor, followed by Modified Barthel Index scores and days from stroke onset to initial assessment. Presence of a total anterior circulation stroke was no longer a significant predictor of Action Research Arm Test scores at eighteen weeks. With removal of the baseline Action Research Arm Test score from the equation as an independent variable, 55% of variance was explained, with the Nine Hole Peg Test ability to place pegs, Modified Barthel Index baseline score and days to initial assessment emerging respectively as the strongest and significant predictors.

Action Research Arm Test score was the only predictor from the six week variables that significantly predicted eighteen week Action Research Arm Test score and accounted for 93% of the variance. Removal from the equation of the Action Research Arm Test six week score as an independent variable led to the emergence of a model that predicted 72% of variance at eighteen weeks. Here, the Nine Hole Peg Test ability to place pegs, and Modified Barthel Index six week score were significant predictors, with ability to place pegs emerging as the strongest predictor.

In summary, the most important baseline post-stroke predictors of upper limb activity at six weeks and eighteen weeks are baseline Action Research Arm Test and Modified Barthel Index scores. The Action Research Arm Test at six weeks is the single strongest predictor of eighteen weeks scores. Presence of a total anterior circulation stroke and days to initial assessment are important predictors of early recovery at six weeks but are no longer important by eighteen weeks. When the Action Research Arm Test is not included in the model, the Nine Hole Peg Test becomes a predictive factor of Action Research Arm Test score at six and eighteen weeks.

Having examined the contralesional effects of bilateral training on UL outcomes and the factors that predict contralesional UL activity limitation, the next physical outcomes section examines the effects of stroke and bilateral training on ipsilesional upper limb performance.

5.8 PHYSICAL OUTCOMES: AN EXPLORATION OF IPSILESIONAL DYSFUNCTION AFTER STROKE AND THE EFFECTS OF BILATERAL TRAINING ON DEXTERITY AND ACTIVITY LIMITATION.

In this section, the primary question of interest is the effect of BT compared to UT on UL motor performance measured on the ARAT and the 9HPT. Since ipsilesional dysfunction is more subtle than dysfunction of the contralesional limb, it was necessary firstly to establish the extent of clinically detectable ipsilesional dysfunction. To do that, data were firstly inspected to determine descriptively whether the mean scores for the whole sample were different from published normal values for those measures. This was followed by an exploration of change in the scores over time. Next, scores for individuals with left and right hemiplegia were analysed for statistical differences, and an evaluation of the association between ipsilesional data and ADL independence measured by the MBI for the whole sample was conducted. Finally having explored the nature of ipsilesional dysfunction, using the randomised BT and UT groups, an examination of the effects of BT training compared to UT on ipsilesional motor performance measured by the ARAT and the 9HPT was conducted.

Prior to conducting the above analysis, the data were inspected for quality and missing data and this is presented first in section 5.8.1.

5.8.1 IPILESIONAL DATA SCREENING

5.8.1.1 Data quality

Data were checked for approximation to normal distribution using SPSS FREQUENCIES (Table 30, Appendix 13, Data Appendix). Z scores for skewness for each variable were calculated by comparing the skewness value to 0, which represents the skewness of the normally distributed population, and by dividing this by the standard error of skewness to give a z score (Tabachnick and Fidell 2001). The critical value of Z was set at 3.30, with p = 0.0005.

All data except the 9HPT pegs per second demonstrated severe skewness (Table 30, Appendix 13, Data Appendix) and did not respond to transformation. Non-parametric tests were therefore used with the skewed variables.

5.8.1.2 Missing Data

For the ARAT and the 9HPT, data were missing only due to the withdrawal of patients from the study (Table 31 Appendix 13, Data Appendix). For these variables, complete case analysis and analysis with data imputed using SPSS Estimated Maximisation function was conducted. Findings from the analysis with imputed data are presented in Appendix 14, ITT Data Appendix. Where findings differ from complete case analysis in terms of significance at the $p \leq 0.05$ level, results from both analyses are presented. For the Nottingham Sensory Assessment, in addition to data missing because of patient withdrawal, data were also missing because patients were unable to complete the test, leading to missing data of between 20 and 70% for proprioception and total tactile scores (Table 31, Appendix 13, Data Appendix). Examination of the tactile sub-scores indicated that inability to complete tactile localisation was the main reason for the large volume of missing data of the total score. Since the amount of data missing for proprioception and tactile localisation was too great either to ignore, or to replace (Tabachnick and Fidell 2001), these variables were not tested. Missing data exceeded 20% for some assessments of stereognosis and each of the tactile sub-sections, but was not as excessive as for proprioception and tactile localisation. Sub-analysis of complete cases only was conducted on these variables.

Finally, since according to published instructions (Lincoln et al. 1998), pressure and pinprick were not tested where light touch was intact, these variables were not included in the analysis. Also since bilateral simultaneous touch was measuring a global perceptive function and not an exclusively ipsilesional function, it was not examined for the ipsilesional analysis. Thus of the ipsilesional NSA subsections, light touch, temperature, two-point discrimination and stereognosis were the only ipsilesional sensory functions examined**.**

5.8.2 IPSILESIONAL PERFORMANCE AT T1, T2 AND T3 AND AN EXPLORATION OF CHANGE OVER TIME

In this section the ipsilesional scores on the ARAT and the 9HPT and the sensory scores measured by the Nottingham Sensory Assessment (NSA) were firstly compared descriptively to published norms, to determine whether ipsilesional dysfunction could be detected by the selected clinical measures. This was undertaken because no normal population was available within the context and timescale of the thesis for comparison. Furthermore this evaluation provided a basis for proceeding to analyse how the scores changed over time. This was followed by an analysis of how the scores did change over time.

5.8.2.1 Ipsilesional Research Question 1

On observation, do mean ipsilesional scores on UL activity limitation, dexterity and sensation measures at T1 in individuals with acute stroke differ from expected normal scores on these tests?

5.8.2.2 Findings for descriptive comparison to published normal values

ACTION RESEARCH ARM TEST

At T1, seven patients of 106 (7%) scored less than 57 on the Action Research Arm Test, with scores ranging from 42 to 56 for those patients, leading to a mean score of 56.7±1.8. By T2, three of those patients had improved and demonstrated scores of 57 on the ARAT and one had dropped out because of illness. The three remaining patients with submaximal scores (3% of the 97 patients remaining in the study) demonstrated scores ranging from 48 to 56 leading to a mean score for the sample of 56.9±0.1. At T3, two of those patients demonstrated a submaximal ARAT score of 56, one had withdrawn, and a third patient who had previously scored 57, now demonstrated a score of 56, leading to a mean ARAT score of 57.0±0.2 These patients represented 3.5% of the remaining 85 patients. Figure 5.16 demonstrates the proportion of patients scoring maximally and sub-maximally at each point.

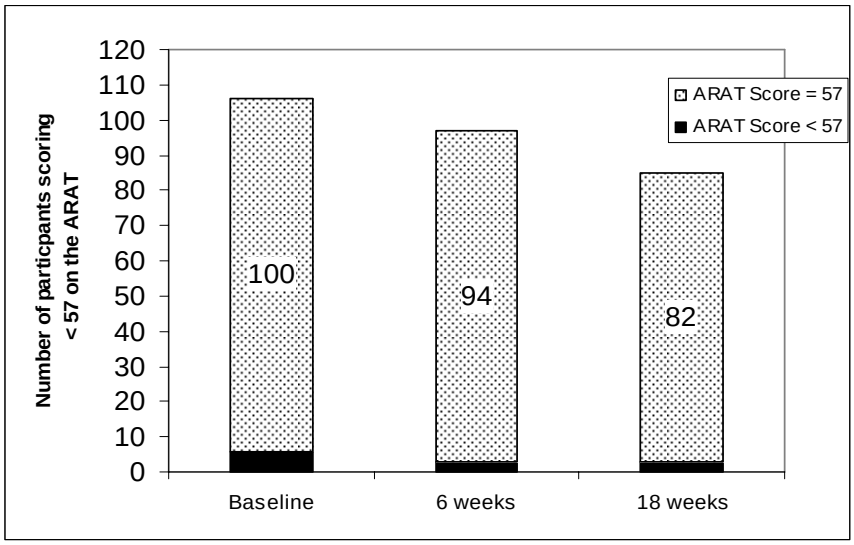


Figure 5.18 Ipsilesional ARAT Scores: Number of patients scoring maximally and submaximally at baseline (T1), 6 weeks (T2) and 18 weeks (T3).

More participants scored sub-maximally on the Grip and Pinch sections, particularly at T1 and T2, with five participants scoring less than fully on the pinch section at T1 (Table 5.11). The lowest score for Grasp was 15 (max =18) at T2; for Grip was 9 at T1 and 11 at T2 and T3 (max =12); for Pinch this was 6 at T1, 14 at T2 and 17 at T3 (max=18) and for Gross 8 at T1 and T2 (max = 9) (Table 5. 11).

Table 5.11. Number of participants scoring submaximally with the ipsilesional UL on the ARAT and range of scores at T1, T2 and T3.

	Participants scoring less than maximally					
ARAT Section	**T1** ***n***	**Range of Scores**	**T2** ***n***	**Range of Scores**	**T3** ***n***	**Range of Scores**
Grasp (max=18)	0	-	1	15, 18	0	-
Grip (max=12)	2	9, 12	2	11,12	1	11, 12
Pinch (max=18)	5	6, 18	2	14, 18	1	17, 18
Gross (max = 9)	1	8, 9	1	8, 9	0	-

NINE HOLE PEG TEST

The mean time to complete the 9HPT with the ipsilesional side at T1 was 20.4 ± 7.9 seconds, with a mean of 0.48 ± 0.15 pegs placed per second. The mean time for completion was longer than the 18 seconds described in the literature as normal for elderly individuals with a mean age of 72.0± 9.9) years (Heller et al. 1987) a population broadly similar in age to the present study population (age 67.9± 11.7 years). At T2, mean time for completion had reduced to 18.4 ± 7.3 seconds (0.53 ± 0.15 pegs/sec), and at T3 was 17.9 ± 5.6 seconds (0.55 ± 0.15 pegs/sec). Change in the time taken to complete the 9HPT between T1, T3 and T3 and change in the pegs placed per second is demonstrated in Figures 5.19 and 5.20.

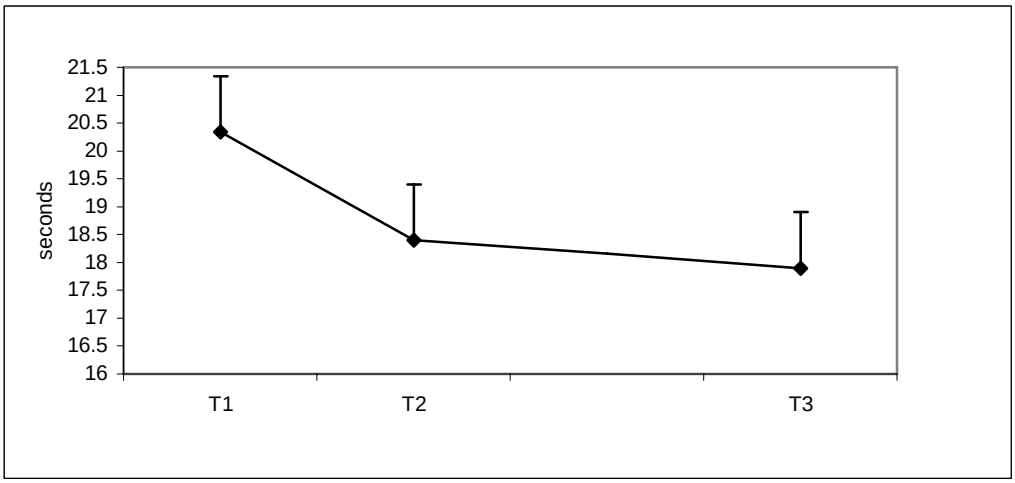


Figure 5.19 Ipsilesional 9HPT mean time (s) to completion at T1, T2, T3

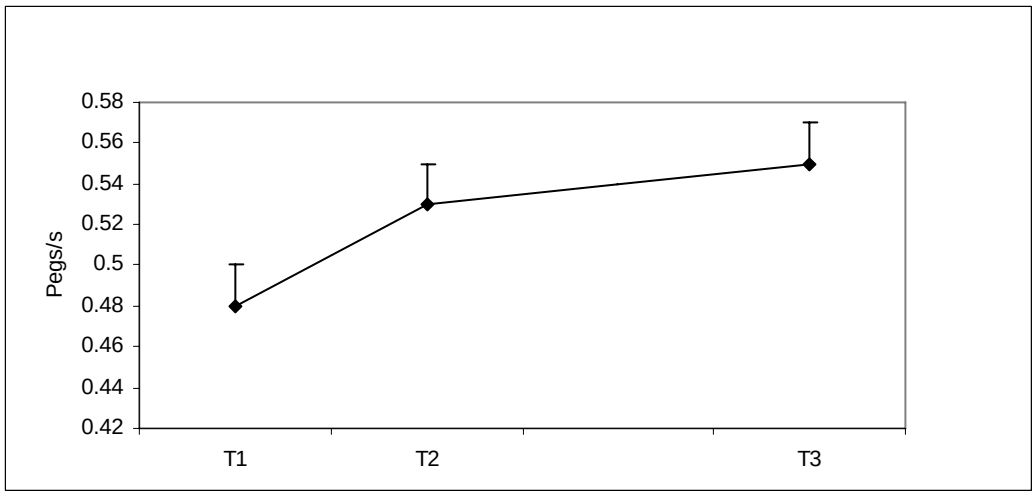


Figure 5.20 Ipsilesional 9HPT mean number of pegs/second (sd) at T1, T2 and T3

NOTTINGHAM SENSORY ASSESSMENT

Mean scores on the NSA at each assessment point are presented in Table 5.12 (below) with the percentage of patients at each point who did not score maximally. All subsections demonstrated a proportion of patients who did not score maximally and at T1 this ranged from 3% for Light Touch to 90.1% for Stereognosis, suggesting the existence of ipsilesional sensory deficits. At T3 all patients scored maximally on Light Touch, but for the other subsections the proportion of patients demonstrating impairment ranged from 1.2% for pressure to 81% for stereognosis, suggesting that some patients continued to demonstrate impaired ipsilesional sensation at T3.

5.8.2.3 Ipsilesional Research Question 2

The research question addressed in this section is:

"Do ipsilesional dexterity, activity limitation and sensory appreciation differ significantly over time in individuals with acute stroke?"

$H_0$10 Ipsilesional UL activity limitation, dexterity and sensation scores measured on the ARAT, the 9HPT and the NSA will not differ significantly between T1, T2 and T3 in individuals with acute stroke.

5.8.2.4 Findings for differences in ipsilesional scores over time

ACTION RESEARCH ARM TEST

The ARAT data were severely positively skewed at all measurement points because most participants scored maximally on the test. Since the data remained skewed after square root and logarithmic transformations, parametric testing was not appropriate and the non-parametric equivalent to repeated measures ANOVA, the Friedman Test was selected and ARAT scores at T1, T2 and T3 were entered as test variables. The test indicated that the scores did not differ significantly between each measurement point ($X^2 = 3.6$; df = 2; p=0.17) (Table 5.12, below), suggesting that although descriptively the proportion of participants scoring sub-maximally reduced over time, the improvement did not translate to significant improvements in scores.

NINE HOLE PEG TEST

With the 9HPT, to maintain continuity with the main BT study, peg placed per second was the main variable of interest for analysis. Data were normally distributed (Table 30 Appendix 13, Data Appendix). Scores for pegs per seconds at T1, T3 and T3 were entered into a repeated measures ANOVA as the within subject factor "time". Mauchly's test of sphericity indicated that sphericity could not be assumed (p=0.03) therefore Greenhouse-Geisser Epsilon was used. There was a significant effect of Time ($F_{2, 1.85} = 7.95$; $p = 0.001$) Table 5.13). Post-hoc Bonferroni adjusted pairwise comparisons indicated a significant mean difference between T1 and T2 (p<0.0.01), and T1 and T3 scores (p<0.01) whilst the mean difference between T2 and T3 scores was not significant (p=1.000), suggesting that most improvement occurred during the six weeks between T1 and T2.

NOTTINGHAM SENSORY ASSESSMENT

For the NSA sub-sections, scores at each assessment point were compared using Friedman's test for repeated measures (Table 5.12). This test was selected because the ipsilesional data for the NSA was severely skewed and did not respond to transformation, and a non-parametric equivalent to the repeated measures ANOVA was appropriate. The test indicated that the rankings differed significantly over time only for stereognosis. Post-hoc Wilcoxon paired tests were conducted, again because the data were skewed and a non-parametric approach was appropriate, to examine which pair of measures differed significantly. Results demonstrated that T2 Stereognosis scores were significantly higher than T1 scores ($z = -2.04$; $p=0.04$) as were T3 scores ($z = -2.88$; $p <0.01$) however there was no significant difference between T2 and T3 Stereognosis scores ($z = -1.44$, $p=0.15$) suggesting no further change after T2. There were no other significant differences in sensation between assessments, however for Light Touch the difference approached significance (p=0.06) (Table 5.12). These results indicate that the ipsilesional sensory domain of stereognosis improved significantly over time, particularly between T1 and T2, but that ipsilesional scores on the other sensory domains did not change significantly over time.

Table 5.12. Ipsilesional NSA Touch, Temperature and Stereognosis: mean (sd), range, percentage of patients scoring submaximally and results of Friedman's test comparing scores at T1, T2 and T3

NSA Sub-Section	Possible score	n	Time	Mean (sd)	Range	% of participants scoring less than maximally	Friedman's Test X^2	df	p
Light Touch	Min=0	100	T1	7.9 (0.5)	(4.0, 8.0)	3.0%			
	Max=8	93	T2	8.0 (0.0)	(8.0, 8.0)	0.0%	6.0	2	0.06
		82	T3	8.0 (0.0)	(8.0, 8.0)	0.0%			
Temperature	Min=0	96	T1	7.7 (1.1)	(0.0, 8.0)	9.4%			
	Max=8	93	T2	7.8 (0.0)	(0.0, 8.0)	6.5%	4.6	2	0.10
		81	T3	7.9 (0.0)	(7.0, 8.0)	1.2%			
Two Point Discrimination	Min=0	88	T1	2.6 (1.1)	(0.0, 4.0)	73.9%			
	Max=4	90	T2	2.7 (0.1)	(1.0, 4.0)	72.2%	0.5	2	0.76
		77	T3	2.7 (0.9)	(1.0, 4.0)	71.6%			
Stereognosis	Min=0	91	T1	17.5 (2.2)	(8.0, 20.0)	90.1%			
	Max=20	91	T2	18.2 (1.2)	(15.0, 20.0)	82.4%	9.3	2	0.01*
		79	T3	18.1 (1.0)	(15.0, 20.0)	81.0%			

NSA denotes Nottingham Sensory Assessment; * denotes a significant difference at the $p \leq 0.05$ level

Table 5.13. Ipsilesional ARAT and 9HPT: mean (sd), range, percentage of patients scoring submaximally and results of Friedman's test and repeated measures ANOVA comparing scores at T1, T2 and T3

Measure	**Possible score**	**n**	**Time**	**Mean (sd)**	**Range**	**% of patients scoring less than - maximally**	**Friedman's Test** X^2	**df**	**p**
ARAT	Min=0 Max=57	106 97 85	T1 T2 T3	56.7(1.7) 56.9(0.3) 57.0(0.2)	(42,57) (48,57) (56,57)	5.7% 2.8% 4.7%	3.6	2	0.17
							Repeated Measures ANOVA *F*	*df*	*p*
9HPT	Peg/sec	106 97 85	T1 T2 T3	0.51(0.13) 0.54(0.14) 0.55(0.16)	(0.02,0.78) (0.10,0.94) (0.25,0.96)	-	7.95	2, 1.85	<0.001*

ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test
* denotes a significant difference at the $p \leq 0.05$ level

5.8.3. EXPLORING EFFECTS OF SIDE OF HEMIPLEGIA ON IPSILESIONAL ACTIVITY LIMITATION, DEXTERITY AND SENSATION

To further explore the nature of ipsilesional dysfunction, an exploration of differences in ipsilesional activity limitation, dexterity and sensation between participants with right and left hemispheric damage was conducted. The findings are presented in this section

5.8.3.1 Ipsilesional Research Question 3

This section addresses the question:
"Is there a difference in ipsilesional motor performance and sensation between patients with acute stroke who have experienced right and left hemispheric damage?"

$H_0$11 There will be no significant differences between patients with right and left hemispheric damage in terms of ipsilesional activity limitation measured on the ARAT; dexterity measured on the 9HPT and sensation measured on the NSA scores at T1, T2 and T3.

5.8.3.2 Descriptive data

Of the sample of 106 patients, 54 demonstrated left sided hemiplegia, and 52 demonstrated right sided hemiplegia. Scores for the ARAT, 9HPT and NSA for patients with left and right hemispheric damage at T1, T2 and T3 are shown in Table 5.14.

5.8.3.3 Findings for differences between patients with right and left sided hemiplegia

To explore whether the effects of side of hemiplegia influenced scores on each measure at T1, T2 and T3, Kruskall Wallis tests were selected to compare NSA and ARAT outcome scores for patients with right and left hemiplegia at each time point on all measures. This test was used because of the highly skewed nature of the data on these tests. T-tests were used to compare mean scores on the on the normally distributed 9HPT.

No significant differences were found for any of the measures between patients with right and left hemiplegia at T1, T2 or T3 (Table 5.14).

Table 5.14. Ipsilesional ARAT, 9HPT and NSA: Mean scores (SD), range and comparisons between patients with right and left sided hemispheric damage

Measure	Time	Hemiplegic side: Right			Hemiplegic side: Left			Kruskall Wallis Tests		
		n	Mean (sd)	Range	n	Mean (sd)	Range	X^2	df	p
ARAT	T1	54	56.8 (1.1)	51, 57	52	56.6 (2.2)	42, 57	0.00	1	0.98
	T2	49	56.9 (0.5)	54, 57	46	56.8 (1.3)	48, 57	0.38	1	0.54
	T3	44	56.9 (2.1)	56,57	42	56.9 (0.2)	56,57	0.39	1	0.53
NSA										
Light Touch	T1	54	7.9 (0.7)	4.0, 8.0	46	7.9 (0.4)	5.0, 8.0	0.53	1	0.47
	T2	46	8.0 (0.0)	8.0, 8.0	47	8.0 (0.0)	8.0, 8.0	0.00	1	1.00
	T3	42	8.0 (0.0)	8.0, 8.0	39	8.0 (0.0)	8.0, 8.0	0.00	1	1.00
Two Point Discrimination	T1	47	2.6 (1.0)	0.0, 4.0	41	2.7 (1.2)	0.0, 4.0	0.86	1	0.35
	T2	47	2.8 (1.0)	1.0, 4.0	43	2.6 (1.0)	1.0, 4.0	0.86	1	0.35
	T3	41	2.6 (1.0)	1.0, 4.0	36	2.7 (0.9)	1.0, 4.0	0.01	1	0.94
Temperature	T1	51	7.7 (1.3)	0.0, 8.0	45	7.8 (0.7)	0.0, 8.0	0.03	1	0.86
	T2	47	7.6 (1.3)	0.0, 8.0	46	8.0 (0.0)	0.0, 8.0	1.05	1	0.30
	T3	42	8.0 (0.0)	7.0, 8.0	39	8.0 (0.0)	7.0, 8.0	0.93	1	0.34
Stereognosis	T1	50	17.7 (2.1)	8.0, 20.0	41	17.2 (2.5)	9.0, 20.0	0.99	1	0.32
	T2	47	18.0 (1.0)	15.0, 20.0	44	18.4 (1.4)	15.0, 20.0	3.04	1	0.08
	T3	41	18.4 (0.8)	17.0, 20.0	38	18.5 (1.2)	15.0, 20.0	0.32	1	0.57
								Independent Samples t test		
								t	*df*	*p(95% CI)*
9HPT (pegs/sec)	T1	54	0.48 (0.13)	0.14, 0.75	52	0.50 (0.14)	0.08, 0.78	0.58	102	0.56 (-0.04 to 0.07)
	T2	47	0.52 (0.15)	0.16, 0.94	50	0.55 (0.14)	0.10, 0.79	0.97	96	0.33 (-0.03 to 0.09)
	T3	43	0.53 (0.15)	0.25, 0.96	42	0.57 (0.16)	0.26, 0.83	1.12	82	0.27 (-0.03 to 0.11)

NSA denotes Nottingham Sensory Assessment; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test

5.8.4 EXPLORING THE ASSOCIATION BETWEEN IPSILESIONAL UL ACTIVITY LIMITATION AND DEXTERITY AND INDEPENDENCE IN ACTIVITIES OF DAILY LIVING.

In the final examination of the nature of ipsilesional dysfunction before presenting findings relating to the effects of BT on this dysfunction, an exploration of the relationship between ipsilesional dysfunction and more general performance of activities was conducted. Here, associations between the Modified Barthel Index, the measure of independence in activities of daily living and ipsilesional UL activity limitation measured on the ARAT and dexterity measured on the 9HPT are reported.

5.8.4.1 Ipsilesional Research Question 4

This section addresses the research question:
"Are ipsilesional activity limitation and dexterity significantly associated with independence in activities of daily living in patients with acute stroke?"

$H_0$12. There will be no significant associations between independence in activities of daily living, measured on the MBI and ipsilesional UL activity limitation measured on the ARAT or dexterity measured on the 9HPT at T1, T2 and T3.

5.8.4.2 Findings for association between ipsilesional upper limb activity limitation and dexterity and independence in activities of daily living.

MBI scores for the sample are presented in Table 1 (Appendix 13, Data Appendix). Associations between the MBI (square root transformation) and ipsilesional ARAT and 9HPT scores at T1, T2 and T3 were examined using Spearman's rho for the ARAT, which was not normally distributed and Pearson's r for the 9HPT pegs/second, which was normally distributed (Table 1, Appendix 13, Data Appendix).

There was a significant but mild correlation (Polgar and Thomas 1991) between the 9HPT and the MBI at T1 ($r = 0.25$, $p=0.01$), at T2 ($r = 0.30$, $p<0.001$), and at T3 ($r = 0.39$, $p=0.00$) (Table 5.15).

There was no significant association between the ARAT and the MBI at any measurement point (Table 5.15).

These findings suggest that there was a mild but significant relationship between ipsilesional dexterity and ADL independence at T1, T2 and T3.

Table 5.15. . Associations between the ARAT and 9HPT at T1, T3, T3: Correlation coefficients and p values

		ARAT T1	**9HPT T1 (pegs/sec)**	**ARAT T2**	**9HPT T2 (pegs/sec)**	**ARAT T3**	**9HPT T3 (pegs/sec)**
MBI T1 (n=106)	Correlation coefficient *p*	-0.07 0.51	0.25 0.01*				
MBI T2 (n=97)	Correlation coefficient *p*			-0.06 0.58	0.30 <0.001*		
MBI T3 (n=85)	Correlation coefficient *p*					-0.01 0.93	0.39 <0.00*

MBI denotes Modified Barthel Index; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test * denotes significance at $p \leq 0.05$

5.8.5. EFFECTS OF BILATERAL TRAINING ON IPSILESIONAL ACTIVITY LIMITATION AND DEXTERITY

This final section exploring ipsilesional dysfunction reports findings from a comparison of the effects of BT compared to UT on change in ipsilesional activity limitation and dexterity. The BT group trained with both arms, whilst the UT group trained the stroke affected arm only and thus had no additional training for the ipsilesional side. The UT group therefore acts as an ipsilesional control group for comparison with the BT group.

5.8.5.1 Ipsilesional Research Question 5

This section addresses the research question:
"Is there a difference in terms of ipsilesional UL activity limitation and dexterity between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training?"

$H_0$13: There will be no significant differences between acute stroke patients receiving six weeks of bilateral task training compared to those receiving six weeks of unilateral task training in terms of ipsilesional UL activity limitation measured on the ARAT and dexterity measured on the 9HPT at T2 and T3.

Change was selected as a relevant clinical variable and short-term change was examined between T1 and T2 and overall change between T1 and T3. ARAT change scores were severely positively skewed therefore group scores were compared using the non-parametric Kruskall Wallis test, whilst 9HPT scores which were normally distributed were compared using t-tests.

5.8.5.2 Findings

IPSILESIONAL ACTIVITY LIMITATION
ARAT scores were not significantly different for the BT and UT groups at T1 (X^2=1.02, df =1, p=0.31) (Table 5.16).

Change in ARAT score between T1 and T2 was not significantly different for the BT and UT groups (X^2=0.24, df =1, p=0.62) (Table 5.16).

Change in ARAT score between T1 and T3 was not significantly different for the BT and UT groups (X^2=1.91, df =1, p = 0.17) (Table 5.16).

To explore whether within-group change could be explained mainly by greater improvement in motor skills of the non-dominant compared to the dominant ipsilesional UL, raw data were examined. ARAT data were highly negatively skewed therefore median (range) was reported. For the BT group, median change in ARAT between T1 and T2 was 0.0 (-1.0 to 0.0) for participants in whom the dominant hand was ipsilesional, and 0.0 (0.0, 2.0) for participants in whom the non-dominant hand was ipsilesional. Between T1 and T3, median change scores in the BT group did not differ from those at T1 to T2. For the UT group, median change in ARAT between T1 and T2 was 0.0 (0.0 to 5.0) for participants in whom the ipsilesional limb was dominant, and 0.0 (0.0 to 5.0) for participants in whom the non-dominant side was ipsilesional. Again, between T1 and T3, median change scores did not differ in either from those at T1 to T2. Inspection of the raw data therefore suggested that recovery could not mainly be explained by greater recovery of the non-dominant UL.

Table 5.16. Ipsilesional effects of BT and UT on change in activity limitation: Mean, median, standard deviation, between group comparison for the ARAT

	Bilateral Training (n=51) Mean(Median)	**SD**	**Unilateral Training (n=46) Mean(Median)**	**SD**	**X^2**	**df**	**p**
ARAT Score T1	56.9 (57.0)	0.5	56.8 (57.0)	0.1	1.02	1	0.31
ARAT Score T2	56.9 (57.0)	0.5	56.9 (57.0)	0.2			
ARAT Score T3	57.0 (57.0)	0.2	57.0 (57.0)	0.2			
ARAT ChangeT1-T2	0.0 (0.0)	0.0	0.2 (0.0)	0.8	0.24	1	0.62
ARAT ChangeT1-T3	0.0 (0.0)	0.3	0.2 (0.0)	0.8	1.91	1	0.17

ARAT denotes Action Research Arm Test

IPSILESIONAL NINE HOLE PEG TEST SCORES

There was no significant difference in ipsilesional scores between the BT and UT groups at T1 (T=-0.09, df = 104, p=0.93) (Table 5.17).

Change in 9HPT score between T1 and T2 approached significance in favour of the BT group (t=-0.81, df = 96, p=0.07) (Table 5.17). In the ITT analysis, conducted with estimated

data to account for effects of missing data, the difference did however reach significance (t =-2.08, df = 104, p=0.04) (Table 24, Appendix 14, ITT Data Appendix). The effect is illustrated in Figure 5.21.

Skill acquisition in the non-dominant ipsilesional UL through practice of tasks not normally performed with that limb may again explain overall ipsilesional improvement on the 9HPT. As an initial exploration of this possibility, raw data for change in dexterity in the dominant and non-dominant ipsilesional limbs in each group was examined more closely. For the BT group, mean change (sd) in pegs per second between T1 and T2 in patients in whom the non-dominant hand was ipsilesional was 0.05 (±0.09). For participants in whom the dominant hand was ipsilesional, median change was 0.04 (±0.08) pegs per second. Between T1 and T3 mean change (sd) in pegs per second in patients in whom the non-dominant hand was ipsilesional was 0.05 (±0.13). For participants in whom the dominant hand was ipsilesional, median change was 0.07 (±0.11) pegs per second.

For the UT group mean change (sd) in dexterity between T1 and T2 in participants in whom the non-dominant hand was ipsilesional was 0.02 (± 0.09) pegs per second. For participants in whom the dominant hand was ipsilesional, mean change was 0.03 (±0.08) pegs per second. Between T1 and T3 mean change (sd) in pegs per second in patients in whom the non-dominant hand was ipsilesional was 0.05 (±0.13). For participants in whom the dominant hand was ipsilesional, median change was 0.02 (±0.09) pegs per second. As there was little observed difference in dominant and non-dominant ipsilesional performance in either group, there was therefore no indication that further statistical testing was required. It appears that changes in ipsilesional dexterity cannot be explained mainly by skill acquisition in patients for whom the non-dominant UL is ipsilesional.

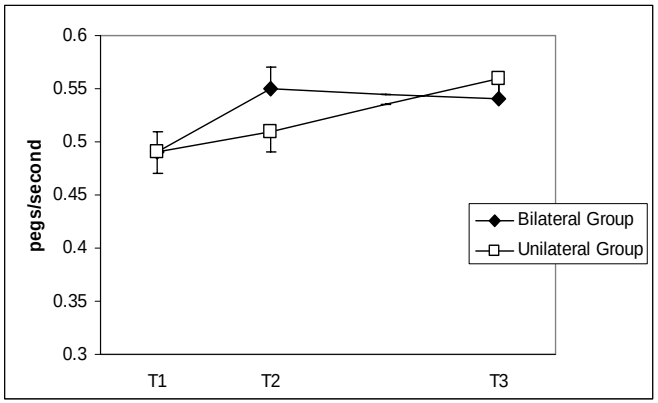


Figure 5.21 Ipsilesional 9HPT: 9HPT at T1, T2 and T3 (sd)

Table 5.17 Ipsilesional effects of BT and UT on change in dexterity: Mean, median, standard deviation, between group comparison for the 9HPT pegs/sec

	BT Group (n=51) Mean(Median)	SD	UT Group (n=46) Mean(Median)	SD	t	df	P (95% confidence interval for difference in means)
9HPT Pegs/sec T1	0.48 (0.52)	0.14	0.49 (0.53)	0.15	-0.09	104	0.93 (-0.06 to 0.05)
9HPT Pegs/sec T2	0.55 (0.56)	0.15	0.51 (0.54)	0.13	-1.38	96	
9HPT Pegs/sec T3	0.54 (0.53)	0.16	0.56 (0.57)	0.14	0.65	82	
ChangeT1-T2	0.05 (0.08)	0.09	0.02 (0.02)	0.09	-1.81	96	0.07† (-0.07 to 0.00)
ChangeT1-T3	0.04 (0.04)	0.11	0.05 (0.04)	0.12	0.64	82	0.53 (-0.03 to 0.07)

† indicates difference in significance in terms of $p<0.05$ with compared to Intention to Treat Analysis

5.8.6 SUMMARY OF FINDINGS FOR IPSILESIONAL DATA

There was evidence of ipsilesional deficits in some participants on the Action Research Arm Test, the Nine Hole Peg Test (9HPT) and the Nottingham Sensory Assessment (NSA). The number of patients scoring sub-maximally on the Action Research Arm Test had reduced from six to three by eighteen weeks (T3), and the mean Action Research Arm Test score had improved, although not significantly. Six week (T2) and eighteen week scores were significantly improved from baseline on the Nine Hole Peg Test but eighteen week scores did not differ significantly from six week scores, suggesting that most improvement occurred during the first six week period of the study. Similarly, stereognosis scores were significantly higher at six weeks and eighteen weeks compared to baseline. For stereognosis, again eighteen week scores did not differ significantly from six weeks, suggesting greatest improvement in the first six weeks. Other Nottingham Sensory Assessment sections did not show significant improvements over time.

Interestingly, Nine Hole Peg Test scores were modestly but significantly correlated with activities of daily living scores at each measurement point, but there was no significant relationship at any assessment point between ipsilesional Action Research Arm Test and Modified Barthel Index (MBI) scores.

Finally, there was no significant effect of bilateral training on change in ipsilesional upper limb activity limitation over the intervention period (baseline to six weeks) or in overall change (six to eighteen weeks). In terms of change in dexterity, the change between baseline and six weeks approached significance in favour of the bilateral group and for the intention to treat analysis this did in fact reach significance. Overall, between baseline and eighteen weeks however there was no significant difference in change in dexterity between the groups, suggesting that initial recovery may have been faster for the bilateral group but that advantage was lost by follow-up.

Having examined physical outcomes for the contralesional and ipsilesional upper limbs, the next two sections report results of the examination of psychosocial outcomes. Starting with effects of bilateral compared to unilateral training on these outcomes in Section 5.9, the final section (5.10) examines upper limb variables as predictors of health related quality of life.

5.9 PSYCHOSOCIAL OUTCOMES: EFFECTS OF BT COMPARED TO UT ON ANXIETY, DEPRESSION AND HEALTH RELATED QUALITY OF LIFE

This section presents an exploration of the influence of bilateral training (BT) compared to unilateral training (UT) on the psychosocial outcomes firstly of perceived anxiety and depression and secondly of health related quality of life (HRQOL).

5.9.1 ANXIETY AND DEPRESSION

Effects of BT compared to UT on anxiety and depression measured on the Hospital Anxiety and Depression Scale were examined first.

5.9.1.1 Psychosocial outcomes: Research question 1

The research question addressed in this section is:
"Is there a difference in terms of anxiety and depression between acute stroke patients receiving BT compared to those receiving UT?"

$H_0$14 There will be no significant differences between acute stroke patients receiving six weeks of BT compared to those receiving six weeks of UT in terms of Anxiety and Depression Scores measured on the Hospital Anxiety and Depression Scale at T2 and T3.

5.9.1.2 Findings for effects of BT compared to UT on anxiety and depression

Anxiety and depression scores at T1, T2 and T3 for each group are shown in Table 5.18. 3*2 repeated measures ANOVAs were conducted to examine effects of BT and UT on the HADS at T2 and T3. Scores for Anxiety and Depression at T1, T2 and T3 were entered as the within subject variable Time, BT and UT groups were the between subject factor Group. Data for Anxiety and Depression was normally distributed, and at each time point, Levine's test of equality of error variances indicated homogeneity of variance across the groups, an assumption underlying ANOVA use ($p>0.05$). Mauchly's sphericity test ($p>0.00$) indicated that sphericity could be assumed for Anxiety and Depression.

For Depression, the interaction between Time and Group was not significant (F_2 = 0.51, p=0.60) indicating that the BT and UT groups did not differ significantly on that outcome at any assessment point (Table 5.18). The main within group effect of Time was significant (F_2 =6.45, p<0.001), indicating that scores varied significantly over time. To explore the pattern of recovery of depression further, unplanned Bonferroni pairwise comparisons showed that T3 scores were significantly lower than T1 scores (p<0.01) (Table 32, Appendix 13, Data Appendix) indicating that Depression had reduced significantly from baseline by the follow-up assessment. There were no other significant post-hoc findings.

For Anxiety, the interaction between Time and Group was not significant (F_2 =2.07, p=0.13) indicating that the BT and UT groups did not differ significantly at any assessment point (Table 5.18). The main within group effect of Time was not significant although it approached significance (F_2 =2.54, p=0.08), suggesting that Anxiety did not change significantly over the assessments. The Intention to Treat Analysis was conducted to address effects of missing data by using estimated values for missing values. For this analysis it indicated a significant effect of Time however (F_1 = 5.29, p=0.01) (Table 25, Appendix 14, ITT Data Appendix). To explore recovery of Anxiety further, unplanned Bonferroni post-hoc pairwise comparisons of the ITT analysis showed that T3 scores were significantly lower than T1 scores (p=0.01, 95% CI for difference = 0.21 to 1.97) indicating that Anxiety reduced significantly across the study period. There were no other significant post-hoc findings for the ITT analysis.

Table 5.18. Repeated measures ANOVA for effect of bilateral training compared to unilateral training on the Hospital Anxiety and Depression Scale

Measure	Time	Bilateral Group N=45	Unilateral Group N=39	Source of variance		df	F	p
HADS Depression	T1	6.3(3.1)	6.1(3.6)	Within Subject	Time	2	6.45	<0.001
	T2	5.8(3.3)	5.6(3.6)		Time x Group	2	0.51	0.60
	T3	5.4(3.8)	4.6(3.2)					
				Between Subject	Group	1	0.39	0.53
HADS Anxiety	T1	6.6(4.4)	5.1(2.9)	Within Subject	Time	2	2.54	0.08†
	T2	5.2(4.4)	5.2(3.6)		Time x Group	2	2.07	0.13
	T3	5.6(4.5)	4.6(3.6)					
				Between Subject	Group	1	1.10	0.30

*denotes $p \leq 0.05$ † denotes a difference in terms of significance between Complete Case Analysis and Intention to Treat Analysis

5.9.1.3 Summary of findings

There was no effect of BT compared to UT on Depression or Anxiety, suggesting that BT did not significantly influence Anxiety or Depression scores. Depression scores for the entire study population improved significantly over the duration of the study, however the significant improvement occurred between the end of the intervention and follow-up. Anxiety scores also did not differ significantly across the study, suggesting no significant within group change; however there was a significant effect of time with the intention to treat analysis, suggesting that Anxiety did improve significantly at eighteen weeks compared to baseline, but this was not related to training group. The ITT analysis has greater power to detect significant effects and should probably be given more weight in interpreting this finding.

5.9.2. HEALTH RELATED QUALITY OF LIFE

This section examines the effects of BT compared to UT on the psychosocial outcome of Health Related Quality Of Life.

5.9.2.1 Psychosocial research question 2

The research question addressed in this section is:
"Is there a difference in terms of health related quality of life between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training?"

$H_0$15 There will be no significant differences between acute stroke patients receiving six weeks of BT compared to those receiving six weeks of UT in terms of Health Related Quality of Life measured on the Nottingham Health Profile (NHP) at T2 and T3.

5.9.2.2 Findings for effects of BT compared to UT on HRQOL

In line with analyses for the other measures, 3*2 repeated measures ANOVA analyses were conducted to examine effects of BT and UT on the total NHP scores and its sub-sections at T2 and T3. Scores at T1, T2 and T3 were entered as the within group variable Time, with training group as the between group factor Group. The data for the total NHP, and for all subsections was skewed or kurtotic leading to z skewness scores >3.30 (Table 33, Appendix 13, Data Appendix) so for each, square root transformations were used leading to z scores <3.30 for all variables. For all variables at each time point, Levine's test of equality of error variances indicated homogeneity of variance across the groups, an assumption underlying ANOVA use ($p>0.05$). Mauchly's sphericity test ($p=<0.001$) indicated that sphericity could not be assumed for items Sleep and Physical Activity therefore the Greenhouse-Geisser Epsilon estimate was used for these variables. For other variables, sphericity was assumed.

For the total NHP score, the interaction effect between Time and Group was not significant ($F_2 =0.72$, $p=0.49$), suggesting that NHP total score did not differ between the BT and UT groups over time. The main effect of Time was significant indicating a within group improvement over time ($F_2 =23.5$, $p<0.001$) (Table 5.19).

For Emotional Reactions (F_2 =0.19, p=0.83), Energy Levels (F_2 =0.56, p=0.57), Sleep ($F_{1.76}$ =0.73, p=0.47), Social Isolation (F_2 =2.16, p=0.12), Pain (F_2 =1.95, p=0.15), Physical Activities ($F_{1.83}$ =0.17, p=0.82), the interaction effect between Time and Group was not significant (Table 5.19) indicating that the bilateral and unilateral groups did not differ significantly on these outcomes at any assessment point.

There were several significant main effects of Time for Emotional Reactions (F_2 =5.99, p<0.001), Energy Levels (F_2 =10.88, p<0.001), Sleep (F_2 =13.54, p<0.001), Social Isolation(F_2 =8.58, p<0.001) and Physical Activities ($F_{1.83}$ = 28.80, p<0.001), indicating significant improvements in scores over time irrespective of training group. For Pain there was no significant effect of time (F_2 =0.35, p=0.71), indicating that scores did not differ significantly over the assessments.

Examining the main effects of Time, Bonferroni post-hoc pairwise comparisons showed that for NHP total score and its items Emotional Reactions, Energy Levels, Sleep, Social Isolation, and Physical Activities subsections, T2 scores and T3 scores were significantly lower than T1 scores (p<0.001), indicating improved perceived HRQOL in both groups (Tables 34-39, Appendix 13, Data Appendix). T3 scores were not significantly lower than T2 scores (p=1.00), indicating that total HRQOL and HRQOL in each of the domains improved significantly during the six weeks intervention, but did not improve significantly thereafter compared to T2. For Pain, scores at T1, T2 and T3 did not differ significantly from each other (p>0.05), demonstrating similar scores at all assessments. Pain scores for the whole sample were low, with mean scores of 13.8±21.8 at T1; 11.6±17.8 at T2; 10.6 ±16.6 at T3. The maximum possible score for Pain was 100.

Table 5.19. Repeated measures ANOVA for between and within group differences: NHP total score and sub-sections at T1, T2 and T3

Measure	Time	BT Group N=45	UT Group N=39	Source of variance		df	F	p
NHP Total	T1	180.4(121.3)	174.3 (118.1)	Within Subject	Time	2	23.5	<0.001*
	T2	126.1(105.9)	103.9 (89.2)		Time x Group	2	0.72	0.49
	T3	122.6(110.3)	91.9 (91.8)					
				Between Subject	Group	1	0.94	0.33
Emotional Reactions	T1	23.1(25.3)	19.6(21.9)	Within Subject	Time	2	5.99	<0.001*
	T2	14.8(23.6)	11.7(16.9)		Time x Group	2	0.19	0.83
	T3	14.2(25.5)	10.1(19.5)					
				Between Subject	Group	1	1.46	0.23
Energy Levels	T1	42.5(36.6)	39.9 (33.9)	Within Subject	Time	2	10.88	<0.001*
	T2	30.8(35.7)	22.9(28.2)		Time x Group	2	0.56	0.57
	T3	28.3(34.1)	19.8 (27.1)					
				Between Subject	Group	1	0.74	0.39
Sleep	T1	33.8(35.1)	36.2 (32.1)	Within Subject	Time	1.76	13.54	<0.001*
	T2	20.3(27.3)	23.5 (26.0)		Time x Group	1.76	0.73	0.47
	T3	20.4(28.8)	14.8(21.0)					
				Between Subject	Group	1	0.08	0.78
Social Isolation	T1	20.5(23.7)	18.9(22.5)	Within Subject	Time	2	8.58	<0.001*
	T2	11.7(19.8)	8.6(14.9)		Time x Group	2	2.16	0.12
	T3	16.7(20.9)	7.7(15.8)					
				Between Subject	Group	1	2.26	0.14
Pain	T1	12.2(19.5)	15.6 (24.3)	Within Subject	Time	2	0.35	0.71
	T2	14.6(20.9)	8.2 (13.2)		Time x Group	2	1.95	0.15
	T3	10.2(17.5)	10.9 (15.6)					
				Between Subject	Group	1	0.02	0.89
Physical Activity	T1	51.7(24.2)	44.7(25.7)	Within Subject	Time	1.83	28.80	<0.001*
	T2	33.8(24.4)	28.8(24.4)		Time x Group	1.83	0.17	0.82
	T3	33.3(20.7)	27.6(23.4)					
				Between Subject	Group	1	1.65	0.20

*denotes significance at $p \leq 0.05$

5.9.2.3 Summary

Bilateral training did not significantly influence Health Related Quality of Life more than unilateral training at any of the assessment points.

The findings indicate that Nottingham Health Profile total score and its items Emotional Reactions, Energy Levels, Sleep, Social Isolation, and Physical Activities at six weeks were significantly lower for the whole sample than at baseline, indicating improvement in these domains for both groups during the training period. Six and eighteen week scores did not differ significantly, indicating that there was no further significant improvement after six weeks. Pain did not change significantly over the study period, but scores were low at all assessments.

The final section explores the relative importance of upper limb variables in predicting health related quality of life at eighteen weeks.

5.10. PSYCHOSOCIAL OUTCOMES: EXPLORING UPPER LIMB VARIABLES AS PREDICTORS OF POST STROKE HEALTH RELATED QUALITY OF LIFE.

In this section, an exploration was conducted to determine relative predictive strength of UL variables in predicting HRQOL at T3, which occurred 20 to 22 weeks following stroke onset. T3 HRQOL was selected as the dependent variable of interest since at this time the majority of participants had returned home and could assess the impact of stroke on their lives in the context of their own environment. Patient characteristics and T3 outcome measures including the RMA, ARAT and 9HPT were the potential independent variables.

5.10.1 PSYCHOSOCIAL RESEARCH QUESTION 3: PREDICTING HRQOL AT EIGHTEEN WEEKS (T3)

What UL activity limitation, impairment, demographic and clinical variables best predict HRQOL measured on the NHP at T3, between 20 and 22 weeks following stroke onset?

$H_0$16 UL activity limitation, impairment, demographic and clinical variables will not significantly predict HRQOL measured on the Nottingham Health Profile at T3.

5.10.1.1 Descriptive data for patients remaining in the study at T3

Descriptive variables and outcome scores for patients remaining in the study at T3 are shown in Table 40 (Appendix 13, Data Appendix) with skewness and z skewness scores for the NHP sub-sections which have not been previously reported.

5.10.1.2 Correlations between patient characteristics, psychological and physical outcomes and Nottingham Health Profile total and sub-section scores at T3

Correlations between potential independent variables and NHP total score at T3, and its sub-domains energy levels, pain, emotional reactions, sleep, social isolation and physical activities were firstly examined according to the method described by Tabachnick and Fidell (2001). Pearson's, Spearman's and point biserial correlations were conducted as appropriate (Table 5.20). Training group was not a significant correlate of the NHP total score or any of the sub-sections, and was not included as an independent variable in any of the regression equations (Table 5.20).

Lower total NHP scores, indicating better HRQOL at T3, was significantly associated with being female, with having the dominant hand affected, with better UL activity limitation scores, with higher UL impairment scores, more independence in ADL, and lower levels of anxiety and depression (Table 5.20).

Table 5.20 Patient characteristics and outcome scores at T3: Correlations with T3 NHP total and sub-scores

Potential Independent Variables	NHP Total Score	Energy Levels	Pain	Emotional Reactions	Sleep	Social Isolation	Physical Activities
Training group	0.15	0.14	-0.02	0.09	0.11	0.08	0.15
Age(years)	011	-0.02	-0.03	0.94	0.11	0.11	0.24*
Gender	-0.20*	-0.18	-0.00	-0.05	-0.06	-0.21	-0.38**
Side of Hemiplegia	0.12	0.11	0.08	0.22*	0.08	0.25*	0.02
Dominant hand affected by stroke	-0.26*	-0.19	-0.13	-0.28*	-0.12	-0.37**	-0.13
OCSPC							
TACS	-0.10	-0.07	-0.13	-0.08	-0.10	0.09	-0.04
PACS	0.08	0.05	0.01	0.03	-0.04	0.03	0.08
POCS	0.08	-0.12	-0.01	-0.08	-0.11	-0.10	-0.13
LACS	-0.20	0.01	0.07	0.03	-0.03	0.04	-0.02
Days to hospital discharge	0.15	0.03	-0.08	-0.01	0.09	-0.10	0.25*
ARAT	-0.25*	-0.18	0.06	0.08	-0.11	-0.19	-0.39**
9HPT	-0.08	-0.03	0.18	0.18	-0.06	0.03	-0.19
RMA	-0.30**	-0.21	-0.14	0.02	-0.20	-0.19	-0.47**
MBI	-0.46**	-0.24*	-0.19	-0.07	-0.25*	-0.22*	-0.70**
Anxiety	0.53**	0.46**	0.35**	0.66**	0.35**	0.49**	-0.35**
Depression	0.52**	0.43**	0.22*	0.58**	0.34**	0.50**	-0.40**
NSA Total	-0.14	-0.23	-0.01	-0.18	0.02	-0.12	-0.00
Proprioception	-0.20	-0.09	-0.07	-0.10	-0.02	-0.17*	-0.25*
Stereognosis	-0.09	0.01	0.02	0.01	0.13	-0.16	0.02
Tactile Sensation	-0.11	-0.19	0.07	-0.15	0.10	-0.18	-0.03

*denotes significance at the $p \leq 0.05$ level **denotes significance at the $p \leq 0.01$ level

5.10.1 3 Findings for predictors of HRQOL

PREDICTORS OF T3 NHP TOTAL SCORE

The significant correlates of NHP total score were entered into a linear regression equation. NHP total score was the dependent variable and the significant correlates were independent variables. Because of skewness identified in the MBI and NHP T3 scores (Section 5.1.3), square root transformations were used.

The ARAT and the RMA demonstrated collinearity (r=0.88) therefore the ARAT, which demonstrated a lower correlation with the NHP than the RMA (Table 5.20) was removed from the equation. Mahalanobis distances indicated three multivariate outliers with p>0.001 (df=8; X^2 >26.13). These outliers, cases 25, 4 and 11 were removed from the analysis and no further outliers were found. The regression analysis was repeated. Linearity and homoscedasticity of the residuals were examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001).

A significant model emerged that explained 49% of the variance in total NHP score (adjusted R^2 = 0.493; $F_{6, 74}$ = 13.97; p<0.05). Beta values indicate that Anxiety was the strongest significant predictor of overall HRQOL at T3 (ß=0.38 p<0.001), followed by Depression (ß=0.27 p=0.01) (Table 5.21). There were no other significant predictors of T3 HRQOL. However in the intention to treat analysis, the RMA emerged as an additional significant predictor of HRQOL (Table 27, Appendix 14, ITT Data Appendix).

Table 5.21. Predictors of Total NHP Score at T3: beta, significance and adjusted R^2

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.38	3.47	<0.001*	0.20 to 0.73	0.493
Depression	0.27	2.56	0.01*	0.09 to 0.70	
MBI	-0.09	-0.90	0.37	-1.84 to 0.70	
RMA	-0.15	-1.57	0.12†	-0.40 to 0.05	
Hand dominance	-0.14	-1.71	0.09	-3.09 to 0.24	
Gender	0.04	-0.42	0.67	-2.15 to 1.39	

MBI denotes Modified Barthel Index; RMA denotes Rivermead Motor Assessment Scale (UL Section).
*denotes significance at the p≤0.05 level, † denotes a difference in significance at p≤0.05 in the intention to treat

PREDICTORS OF T3 NHP SUB-SECTION ENERGY LEVEL

Of the potential variables, independence in ADL, and lower levels of anxiety and depression significantly associated with Energy Level scores (Table 5.20).

These significant correlates were entered into a regression equation with Energy Level as the dependent variable and the significant correlates as independent variables. Square root transformation of Energy Levels was used (skewness=0.42, z skewness = 1.35, $p<0.0005$).

Mahalanobis distances indicated no multivariate outliers $p<0.001$ ($df = 3$; $X^2 < 16.27$). Linearity and homoscedasticity of the residuals was examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001). The model accounted for 30% of the variance in Energy Levels at T3. The model was significant (adjusted $R^2 = 0.302$; $F_{2,78} = 12.56$; $p<0.0001$). Anxiety (ß=0.37; $p<0.001$) and Depression (ß=0.25; $p<0.001$) were significant predictors of Energy Levels at T3, with Anxiety as the strongest predictor (Table 5.22).

Table 5.22. Predictors of NHP Energy at T3: beta, significance and adjusted R^2

Predictor Variable	**Beta**	**t**	**p**	**95% Confidence Interval for ß**	**Adjusted R^2**
Anxiety	0.37	2.93	<0.001*	0.11 to 0.56	0.302
Depression	0.25	1.98	0.05*	0.00 to 0.52	
MBI	-0.03	-0.29	0.37	-1.05 to 0.78	

MBI denotes Modified Barthel Index; *denotes significance at the $p \leq 0.05$ level.

PREDICTORS OF T3 NHP SUB-SECTION ENERGY LEVELS

Lower Pain Scores, indicating lower pain levels at T3, were significantly associated only with lower Anxiety and Depression scores (Table 5.20). These correlates were entered into a regression equation with a logarithmic transformation of pain as the dependent variable (skewness =0.378; z skewness = 1.42, $p<0.0005$) and Anxiety and Depression as independent variables.

Mahalanobis distances indicated no multivariate outliers $p<0.001$ ($df=2$; $X^2 < 13.82$). Linearity and homoscedasticity of the residuals was examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001). The model that best explained Pain at T3 accounted for only 12% of the variance in pain. The model was

significant (adjusted R^2 = 0.126; $F_{2, 78}$= 6.28; p=0.003). Significant and non-significant variables, beta values and adjusted R^2 are shown in Table 5.23. Anxiety was the only significant predictor of pain.

Table 5.23. Predictors of NHP Pain at T3: beta, significance and adjusted R^2

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.34	2.44	0.02*	0.01 to 0.10	0.117
Depression	0.05	0.37	0.71	-0.04 to 0.06	

MBI denotes Modifies Barthel Index; *denotes significance at the $p \leq 0.05$ level.

PREDICTORS OF T3 NHP SUB-SECTION EMOTIONAL REACTIONS

Lower Emotional Reaction scores, at T3 were significantly associated with having a right sided hemiplegia, having the dominant side affected, and having lower levels of anxiety and depression (Table 5.20).

These significant correlates were entered into a regression equation with emotional reactions as the dependent variable and the significant correlates as independent variables.

Mahalanobis distances indicated no multivariate outliers $p<0.001$ (df = 4; X^2 <18.47). Linearity and homoscedasticity of the residuals was examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001). Because of skewness of the emotional reactions variable, a logarithmic transformation was used, which demonstrated normality (Skewness = -0.58, z skewness = 2.25, $p<0.0005$).

The model was significant (adjusted R^2 = 0.498; $F_{4,76}$= 20.86; p=0.00) and explained 50% of the variance in Emotional Reactions. Significant and non-significant variables, beta values and adjusted R^2 at each step are shown in Table 5.24. Anxiety was the only significant predictor of Emotional Reactions.

Table 5.24. Predictors of NHP Emotional Reactions at T3: beta, significance and adjusted R^2

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.50	4.72	0.00*	0.05 to 0.12	0.498
Depression	0.17	1.57	0.12	-0.01 to 0.08	
Hand dominance	-0.23	-1.67	0.10	-0.69 to 0.06	
Side of stroke	0.08	0.61	0.54	-0.26 to 0.49	

MBI denotes Modifies Barthel Index; *denotes significance at the $p \leq 0.05$ level

PREDICTORS OF T3 NHP SUB-SECTION SLEEP

Better sleep at T3, indicated by lower NHP Sleep score, was significantly associated with better ADL independence, and having lower levels of Anxiety and Depression (Table 5.25). These significant correlates were entered into a regression equation with Sleep as the dependent variable and the significant correlates as independent variables.

Mahalanobis distances indicated no multivariate outliers $p<0.001$ ($df=4$; $X^2 <18.47$). Linearity and homoscedasticity of the residuals was examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001). Because of skewness of the sleep variable, a logarithmic transformation was used, which demonstrated normality (Skewness = -0.14, z skewness = 0.52, $p<0.0005$).

The model was significant (adjusted $R^2 = 0.19$; $F_{3,80}= 7.38$; $p<0.001$) and explained 19% of the variance in Sleep at T3. Anxiety was a significant predictor of Sleep ($p=0.02$). Depression and the MBI were not significant predictors of sleep ($p>0.05$). Beta values and adjusted R^2 for all variables are shown in Table 5.25.

Table 5.25. Predictors of NHP Sleep at T3: beta, significance and adjusted R^2 at each step

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.26	2.37	0.02*	-0.90 to -0.08	0.193
Depression	0.19	1.40	0.16	0.87 to 3.02	
MBI	0.15	1.10	0.27	-0.50 to 2.88	

MBI denotes Modified Barthel Index; *denotes significance at the $p \leq 0.05$ level

PREDICTORS OF T3 NHP SUB-SECTION SOCIAL ISOLATION

Lower Social Isolation score at T3 indicating less social isolation was significantly associated with having the dominant hand affected, with having the right hemiplegia, with better independence in ADL, and with lower levels of Anxiety and Depression (Table 5.20). The significant variables were entered into a regression equation with Social Isolation as the dependent variable and the significant correlates as independent variables.

Mahalanobis distances indicated no multivariate outliers $p<0.001$ ($df = 5$; $X^2 < 20.51$). Linearity and homoscedasticity of the residuals was examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001). Because of skewness of the Social Isolation variable, a logarithmic transformation was used, which demonstrated normality (Skewness = -0.59, z skewness = 2.24, $p<0.0005$).

The model was significant (adjusted $R^2 = 0.23$; $F_{5,75} = 5.64$; $p<0.0001$), and accounted for 23% of the variance in Social Isolation at T3 (Table 5.26). Anxiety approached significance as a predictor of T3 social isolation ($p=0.06$) and in the Intention to Treat Analysis did reach significance ($p<0.001$) (Table 32, Appendix 14, ITT analysis). The other variables in the model were not significantly predictive (Table 5.26). Beta values and adjusted R^2 for all variables are shown in Table 5.26.

Table 5.26 Predictors of NHP Social Isolation at T3: beta, significance and adjusted R^2 at each step

Predictor Variable	**Beta**	**t**	**p**	**95% Confidence Interval for B**	**Adjusted R^2**
Anxiety	0.25	1.88	0.06†	-0.00 to 0.09	0.225
Depression	0.23	1.70	0.09	-0.01 to 0.10	
MBI	0.02	0.20	0.85	-0.17 to 0.21	
Side of stroke	-0.02	-0.14	0.89	-0.52 to 0.45	
Dominant side affected	-0.26	-1.51	0.13	-0.86 to 0.12	

MBI denotes Modified Barthel Index; *denotes significance at the $p \leq 0.05$ level,
† denotes a difference in significance at $p \leq 0.05$ in the intention to treat analysis

PREDICTORS OF T3 NHP SUB-SECTION PHYSICAL ACTIVITIES

Better physical activity scores at T3 were significantly associated with being male, with lower age, with better UL activity limitation and impairment scores and independence in ADL, with better proprioception, fewer days to hospital discharge and with lower levels of anxiety and depression (Table 5.20). The significant variables were entered as a group into a regression equation with Physical Activities as the dependent variable and the significant correlates as independent variables.

Again, the RMA was used as the UL variable because of collinearity with the ARAT ($r = 0.88$). Mahalanobis distances indicated no multivariate outliers $p<0.001$ ($df=7$; $X^2 <24.32$). Linearity and homoscedasticity of the residuals was examined using scatterplots of predicted standardized residual scores plotted against standardized residual scores which indicated that assumptions for regression were met (Tabachnick and Fidell 2001).

The model explaining the variance in Physical Activities at T3 accounted for 36% of the variance in the variable. The model was significant (adjusted $R^2= 0.36$; $F_{8,71} = 7.88$; $p<0.0001$). UL motor impairment and ADL independence were the only significant predictors of Physical Activity, with better scores on those measures predictive of better physical activity scores. Beta values and adjusted R^2 are shown in Table 5.27.

Table 5.27. Predictors of NHP Physical Activities at T3: beta, significance and adjusted R^2

Predictor Variable	**Beta**	**t**	**p**	**95% Confidence Interval for B**	**Adjusted R^2**
Age	0.14	1.59	0.12†	-0.14 to 0.62	0.36
Gender	-0.21	-1.70	0.09	-14.97 to 2.25	
Days to hospital discharge	-0.22	-1.70	0.09	-0.15 to 0.02	
RMA	-0.33	-3.24	0.00*	-2.79 to 0.45	
MBI	-0.26	-2.16	0.00*	-15.56 to -1.57	
Anxiety	0.22	1.74	0.09	-0.40 to 2.29	
Depression	0.07	0.55	0.58	-0.96 to 2.07	
Proprioception	0.10	0.09	0.93	-1.02 to 2.25	

MBI denotes Modifies Barthel Index; *denotes significance at the $p\leq0.05$ level.
† denotes a difference in significance at $p\leq0.05$ in the intention to treat analysis

5.10.1.4 Summary of Predictors of HRQOL at T3

Using T3 scores and patient characteristics as independent variables, a model emerged that predicted 49% of the variance in total NHP score at T3. Here, lower Anxiety and Depression scores were the significant predictors of lower NHP scores indicating that less perceived anxiety and depression predicted better quality of life. Intention to treat analysis indicated that UL impairment was a significant predictor of total NHP score.

For the Energy sub-section of the NHP the regression model explained 30% of the variance. Anxiety and Depression were the only significant predictors of Energy Level, demonstrating that less perceived anxiety and depression predicted higher perceived degrees of energy.

Anxiety predicted 12% of the variance in Pain scores at T3, 50% of the variance in Emotional Reaction scores, 19% of the variance in Sleep scores and 23% of variance in Social Isolation and was the only significant predictor of all of these sub-domains of the NHP.

Finally, the regression model for Physical Activity explained 36% of the variance, with better UL impairment and ADL independence scores as significant predictors of perceived Physical Activity levels. UL impairment was the strongest predictor of this domain.

5.11 SUMMARY OF THESIS FINDINGS

This section provides an overview of the main study findings. In Box 5.1 (below), each research question is reported, with main findings. The null hypotheses are also presented with an indication of whether the null hypothesis can be rejected.

The primary focus for this thesis was a randomised controlled trial to examine the effects of a bilateral compared to a unilateral upper limb task training programme on contralesional upper limb outcomes and activities of daily living in patients with acute stroke. The main finding was that bilateral training was no better than unilateral training for upper limb impairment and activity limitation, or for independence in activities in daily living. For dexterity at the follow-up assessment at eighteen weeks, the unilateral group in fact demonstrated a significantly better outcome than the bilateral group.

In a secondary exploration of the physical effects of this training, a range of factors that might influence training responses, operationalised by change scores, were examined. These were severity of baseline activity limitation, lesion site, side of hemiplegia and hand dominance, gender, age, and proprioception. None of these factors significantly influenced training responses of the bilateral compared to the unilateral group. There were main effects of severity, side of stroke, gender and age however, indicating that these factors did in fact influence within group recovery. This was irrespective of training group however and applied to the whole sample.

Clinically it is important for therapists and patients to be able to predict upper limb recovery In the final analysis of the physical effects of stroke on contralesional upper limb outcomes, predictors of upper limb activity limitation at different times were explored. To determine the factors that predicted overall upper limb activity limitation, this time for the whole sample, significant predictors of six and eighteen week activity limitation were examined. The most important predictors of upper limb activity limitation at six weeks, explaining 68% of the variance, were baseline scores for UL activity limitation and independence in activities of daily living. Days to initial assessment and having a total anterior circulation stroke were also significant predictors, but were weaker predictors than the other factors. When upper limb activity limitation was removed from the equations, dexterity became the most important predictor.

For eighteen week activity limitation scores, the most important baseline predictors explaining 64% of variance were UL activity limitation and independence in activities of daily living. The only significant six week predictor of eighteen week upper limb activity limitation scores was the six week activity limitation score on the same measure. This explained 93% of variance in the dependent variable. When it was removed from the predictive equation, dexterity and independence in activities of daily living became the only significant predictors, explaining 72% of the variance in eighteen week activity limitation.

Performance data were also collected for activity limitation, dexterity and sensation on the ipsilesional side. Another secondary focus for the study was to determine the effects of bilateral training compared to unilateral training on ipsilesional dysfunction. Firstly, the extent and nature of ipsilesional dysfunction was explored. Observational analysis indicated that there was a mean deficit in activity limitation, dexterity and sensation in relation to published normative values, indicating that the selected clinical measures could detect ipsilesional upper limb dysfunction. Analysis showed that dexterity and stereognosis improved significantly over time with most recovery between the baseline and six week assessments. The other measures did not show significant improvement but the initial dysfunction was mild on those measures with only a few participants demonstrating deficits. There was no difference between participants with right and left sided hemisphere damage on any of the measures. Examining the association between ipsilesional dysfunction and independence daily living, there was a significant but mild association between dexterity and the Modified Barthel Index. Finally, bilateral training appears to have significantly influenced ipsilesional dexterity with a small but significant difference on the intention to treat analysis between unilateral and bilateral groups at six weeks. The difference, which approached significance in the complete case analysis had disappeared at eighteen weeks.

The next focus for the secondary analysis of the study data examined the broader effects of bilateral training by examining its impact on the psychosocial variables of anxiety, depression and health related quality of life. Analysis indicated that there was no impact of bilateral training compared to unilateral training on anxiety, depression or health related quality of life.

Finally, the role of upper limb outcome in predicting health related quality of life was explored. The analysis was conducted with the eighteen week data collected after most patients had returned to living in their own environments with the consequences of stroke.

The main predictors of health related quality of life at eighteen weeks were anxiety and depression although with the intention to treat analysis, upper limb impairment was also a significant predictor. The thesis findings are summarised in Box 5.1.

The next chapter discusses the meaning and implications of these findings. There, findings are interpreted in the context of other literature, study limitations and implications for clinical practice and future research. The primary research findings relating to the effects of bilateral compared to unilateral training is presented first, followed by secondary findings in order of their importance in terms of implications for clinical practice and future research.

BOX 5.1 Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	**Findings**	**/Reject Null Hypothesis?**
PRIMARY RESEARCH QUESTION.	Is there a difference in terms of UL impairment (RMA), activity limitation (ARAT), dexterity (9HPT) and independence in activities of daily living (MBI) between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training? **$H_0$1.** There will be no significant difference between acute stroke patients receiving six weeks of bilateral task training compared to those receiving six weeks of unilateral task training in terms of UL impairment (RMA), activity limitation (ARAT), dexterity (9HPT) and independence in activities of daily living (MBI) at T2 (six weeks) or T3 (eighteen weeks).	BT was not more effective for any outcomes compared to UT. For dexterity at eighteen week follow-up, the UT group performed significantly better than the BT group. A secondary finding that emerged from the analysis and pertaining to the entire study sample, was that with the exception of dexterity, which improved significantly for the whole sample at each assessment, most recovery occurred between baseline and six weeks	No
Secondary Research Question 1	Does severity of initial UL activity limitation influence UL training responses to six weeks of BT compared to UT in patients with acute stroke? **$H_0$2** The impact of initial severity of UL activity limitation defined by T1 ARAT and 9HPT scores will not be significantly different between acute stroke patients receiving six weeks bilateral task training compared to those receiving unilateral task training in terms of changes in impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3	Severity of initial UL activity limitation did not significantly influence UL training responses of BT compared to UT. A secondary finding emerging from the analysis was that for the whole sample, the severity sub-groups demonstrated significantly different magnitudes of recovery on each UL measure.	No

BOX 5.1(Cont). Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	Findings	Reject Null Hypothesis?
Secondary Research Question 2	Does lesion site influence UL training responses to BT compared to UT in patients with acute stroke? **$H_0$3.** The impact of lesion site operationalised by the Oxfordshire Community Stroke Project Classification will not be significantly different between acute stroke patients receiving six weeks of bilateral task training compared to those receiving unilateral task training in terms of change in UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.	It was not possible to address this question because the assumptions for ANOVA were not met	n/a
Secondary Research Question 3	Does side of hemiplegia and having the dominant or non-dominant side affected influence UL training responses to six weeks of BT compared to UT in patients with acute stroke? **$H_0$4**. The impact of side of hemiplegia and having the dominant or non-dominant side affected will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of change in UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.	Hand dominance and side of stroke did not significantly influence UL training responses for BT compared to UT. A secondary finding was that left handed participants with right hemiplegia demonstrated significantly poorer overall UL impairment than other participants.	No

BOX 5.1 (Cont) Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	Findings	Reject Null Hypothesis?
Secondary Research Question 4	Does gender influence UL training responses to six weeks of BT compared to UT in patients with acute stroke? **$H_0$5** The impact of gender will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of change in UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.	Gender did not significantly influence UL training responses for BT compared to UT. A secondary finding for the whole sample was that for UL activity limitation, women's overall recovery was poorer than men's.	No
Secondary Research Question 5	Does age influence UL training responses to six weeks of BT compared to UT in patients with acute stroke? **$H_0$6.** The impact of age will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of change in UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.	Age did not significantly influence UL training responses for BT compared to UT. A secondary finding was that for the whole sample, younger participants demonstrated poorer overall recovery of dexterity.	No

BOX 5.1 (Cont) Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	Findings	Reject Null Hypothesis?
Secondary research question 6	Does initial proprioception influence UL training responses to bilateral task training compared to unilateral task training in patients with acute stroke? **$H_0$7** The impact of initial proprioception will not be significantly different between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training in terms of changes UL impairment measured on the RMA; activity limitation measured on the ARAT; and dexterity measured on the 9HPT between T1 and T2, and T1 and T3.	Proprioception did not significantly influence UL training responses for BT compared to UT.	No

BOX 5.1 (Cont) Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	Findings	Reject Null Hypothesis?
Predicting UL Activity Limitation: Research Question 1:	What participant characteristics and T1 activity limitation outcome variables best predict UL activity limitation scores at T2 and T3? **$H_0$8** Participant characteristics and T1 activity limitation outcome scores will not significantly predict UL activity limitation measured on the ARAT at T2 and T3. .	For UL activity limitation at six weeks measured on the ARAT, baseline ARAT and MBI scores were significant predictors with days to initial assessment and presence of a total anterior circulation stroke. For UL activity limitation at eighteen weeks measured on the ARAT, baseline ARAT and MBI scores were significant predictors with days to initial assessment.	Yes
Predicting UL Activity Limitation: Research Question 2:	What participant characteristics and T2 activity limitation outcome variables best predict ARAT scores at T3? **$H_0$9**.Participant characteristics and T2 activity limitation outcome scores will not significantly predict UL activity limitation measured on the ARAT at T3.	Upper limb activity limitation at six weeks was the only significant predictor of UL activity limitation at eighteen weeks When UL activity limitation was removed from the equation, dexterity and independence in activities of daily living significantly predicted activity limitation at eighteen weeks	Yes

BOX 5.1 Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	**Findings**	**Reject Null Hypothesis?**
Ipsilesional Research Question 1	On observation, do mean ipsilesional scores on UL activity limitation, dexterity and sensation measures at baseline in individuals with acute stroke differ from expected normal scores on these tests?	Mean scores were all lower than expected norms, indicating that ipsilesional dysfunction could be detected by these clinical measures	N/A
Ipsilesional Research Question 2	Do ipsilesional dexterity, activity limitation and sensory appreciation differ significantly over time in individuals with acute stroke? **$H_0$10** Ipsilesional UL activity limitation, dexterity and sensation scores measured on the ARAT, the 9HPT and the NSA will not differ significantly between at T1, T2 and T3 in individuals with acute stroke.	Dexterity and stereognosis improved significantly between baseline and six weeks but neither improved significantly after that. Activity limitation and the other sensory domains did not differ significantly over the three assessments.	Yes, for dexterity and stereognosis
Ipsilesional Research Question 3	Is there a difference in ipsilesional motor performance and sensation between patients with acute stroke who have experienced right and left hemispheric damage? **$H_0$11** There will be no significant differences between patients with right and left hemispheric damage in terms of ipsilesional activity limitation measured on the ARAT; dexterity measured on the 9HPT and sensation measured on the NSA scores at T1, T2 and T3.	There were no significant differences between participants with right and left hemisphere damage.	No

BOX 5.1 (Cont) Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	**Findings**	**Reject Null Hypothesis?**
Ipsilesional Research Question 4	Are ipsilesional activity limitation and dexterity significantly associated with independence in activities of daily living in patients with acute stroke? **$H_0$12**. There will be no significant associations between independence in activities of daily living, measured on the MBI and ipsilesional UL activity limitation measured on the ARAT or dexterity measured on the 9HPT at T1, T2 and T3.	Ipsilesional dexterity but not UL activity limitation was significantly but modestly associated with independence in activities of daily living at each assessment.	Yes, for dexterity
Ipsilesional Research Question 5	Is there a difference in terms of ipsilesional UL activity limitation and dexterity between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training? **$H_0$13**: There will be no significant differences between acute stroke patients receiving six weeks of bilateral task training compared to those receiving six weeks of unilateral task training in terms of ipsilesional UL activity limitation measured on the ARAT and dexterity measured on the 9HPT at T2 and T3.	For dexterity, the difference between groups approached significance in favour of the bilateral training group at six weeks. The difference was significant for the intention to treat analysis. The effect had disappeared by eighteen weeks. There were no significant differences for activity limitation.	Yes for dexterity at six weeks

BOX 5.1 (Cont) Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	Findings	Reject Null Hypothesis?
Psychosocial research question 1	Is there a difference in terms of anxiety and depression between acute stroke patients receiving BT compared to those receiving UT? **$H_0$14.** There will be no significant differences between acute stroke patients receiving six weeks of BT compared to those receiving six weeks of UT in terms of Anxiety and Depression Scores measured on the Hospital Anxiety and Depression Scale at T2 and T3.	There was no significant effect of BT compared to UT on Depression or Anxiety. A secondary finding was that depression improved significantly overall, whilst anxiety did not change significantly. However intention to treat analysis suggested that anxiety did improve significantly between baseline and six weeks.	No
Psychosocial research question 2*:*	Is there a difference in terms of health related quality of life between acute stroke patients receiving bilateral task training compared to those receiving unilateral task training? **$H_0$15** There will be no significant differences between acute stroke patients receiving six weeks of BT compared to those receiving six weeks of UT in terms of Health Related Quality of Life measured on the Nottingham Health Profile (NHP) at T2 and T3.	BT did not significantly influence HRQOL more than UT at any of the assessment points. HRQOL was measured using the total NHP score and each of its subsections Secondary findings showed that NHP total score and its items Emotional Reactions, Energy Levels, Sleep, Social Isolation, and Physical Activities improved significantly between baseline and six weeks for the whole sample but did not improve further by eighteen weeks. Pain did not change significantly.	No

BOX 5.1 (Cont) Summary of research questions, null hypotheses and main study findings

	Research Question and Null Hypothesis	Findings	Reject Null Hypothesis?
Research question 3: predicting HRQOL	What UL activity limitation, impairment, demographic and clinical variables best predict HRQOL measured on the NHP at T3, between 20 and 22 weeks following stroke onset? **$H_0$16** UL activity limitation, impairment, demographic and clinical variables will not significantly predict HRQOL measured on the Nottingham Health Profile at T3.	Anxiety and Depression scores were the significant predictors of total NHP score at eighteen weeks although intention to treat analysis indicated that UL impairment was also a significant predictor. These variables were also the only significant predictors of energy levels. Anxiety was the only significant predictor of Pain, Emotional Reactions, Sleep and Social Isolation. UL impairment and ADL independence scores significantly predicted Physical Activities	Yes

CHAPTER 6

DISCUSSION AND INTERPRETATION OF FINDINGS

6.0 INTRODUCTION

In this chapter, main aims of the thesis and study findings are presented and interpreted in relation to previous work, and theoretical and methodological considerations are discussed. Study limitations, implications for clinical practice and ideas for future research are also considered.

The primary aim of this thesis was to investigate effects of bilateral UL task training in patients with acute stroke on a range of physical and psychosocial outcomes. A secondary aim was to explore some broader questions relating to physical and psychosocial aspects of UL recovery after stroke. To address these aims, the thesis was organised into two themes: physical outcomes and psychosocial outcomes.

The first and main theme, discussed in section 6.1, was concerned with physical outcomes. Under this theme, physical effects of bilateral compared to unilateral training on contralesional UL outcomes and independence in activities of daily living were examined, followed by exploration of five clinical factors likely to influence bilateral and unilateral training responses. Physical effects of bilateral compared to unilateral training on ipsilesional UL outcomes were then explored before the theme broadened to explore - for the whole sample - clinical and demographic predictors of contralesional UL activity limitation over time.

The second and secondary theme, discussed in section 6.2, was concerned with psychosocial outcomes related to the impact of bilateral training on anxiety, depression and health related quality of life (HRQOL). The theme then broadened to finally examine whether contralesional UL dysfunction predicted health related quality of life at six months after

stroke. A randomised controlled trial (RCT) was conducted to address research aims relating to both themes.

Within the physical theme, the primary study aim was to investigate effects of six weeks bilateral compared to unilateral task training on UL impairment (Rivermead Motor Assessment), activity limitation (Action Research Arm Test), dexterity (Nine Hole Peg Test) and activities of daily living (Modified Barthel Index) in participants with acute stroke. Outcome assessment was conducted at three time points: Baseline, two to four weeks after stroke onset (T1); end of six week intervention (T2); and follow-up at twelve weeks post intervention (T3). Findings are summarised and discussed in section 6.1.1.

A second aim within this theme was to explore the impact of clinical and demographic factors, namely initial severity of UL activity limitation, side of stroke and hand dominance, age, gender and proprioception on UL responses to bilateral compared to unilateral training. Findings are summarised and discussed in sections 6.1.2 to 6.1.6.

A third aim was to explore the impact of bilateral task training compared to unilateral training on ipsilesional dexterity and activity limitation. Findings are summarised and discussed in section 6.1.7.

The final aim within the physical outcomes theme was to explore, for the whole sample, having accounted for effects of training, predictors of short and longer term recovery of UL activity limitation. Findings are summarised and discussed in section 6.1.8.

Within the psychosocial theme, the first study aim was to examine effects of bilateral compared to unilateral training on anxiety and depression measured on the Hospital Anxiety and Depression Scale and on HRQOL measured on the Nottingham Health Profile. Findings are summarised and discussed in section 6.2.2. The final study aim was to explore the relative importance of UL dysfunction in predicting HRQOL at eighteen weeks. Findings are summarised and discussed in section 6.2.3.

General study limitations are discussed in section 6.3, followed by a summary and conclusions in section 6.4.

6.1. PHYSICAL OUTCOMES: EFFECTS OF BILATERAL TRAINING AND DETERMINANTS OF TRAINING RESPONSES AND RECOVERY

6.1.1 CONTRALESIONAL UPPER LIMB OUTCOMES AND INDEPENDENCE IN ACTIVITIES OF DAILY LIVING

This was, to the author's knowledge, the largest randomised controlled trial to compare effects of bilateral UL task training to unilateral task training in acute stroke. The study was designed to address methodological limitations of previous studies examining this intervention and to investigate its effects in an acute stroke population which had not been examined at the time of study design.

6.1.1.1 Findings

Primary study findings showed no significant differences in upper limb (UL) impairment, activity limitation, dexterity or independence in activities of daily living (ADL) between bilateral and unilateral groups at six weeks. At eighteen weeks however, unilateral training was more effective than bilateral training for dexterity measured on the Nine Hole Peg Test and on the Pinch section of the Action Research Arm Test. There were no other differences between groups in impairment, activity limitation or independence in ADL at eighteen weeks. Findings demonstrate that bilateral task training was no more effective than unilateral training for UL impairment and activity limitation, but for long-term recovery of dexterity, unilateral task training was more effective.

6.1.1.2 Previous literature and interpretation of findings

The finding that bilateral training demonstrated no advantage over unilateral training is contrary to previous studies in which participants with chronic stroke exhibited improved UL performance with bilateral task training compared to unilateral training (Mudie and Matyas 1996, Mudie and Matyas 2000). This may be due to the methodological limitations of these studies. Those were single case series designs and study inclusion criteria were unclear,

compared to the present RCT design where both strict inclusion criteria and a unilateral control comparison were applied, there were no control comparisons in those studies, which may have positively influenced findings. Secondly, outcomes in the single case studies comprised sensitive kinematic parameters including movement speed, deceleration and movement angles. Those parameters were not detectable by measures in the present, pragmatic clinical study and may explain differences in outcome.

Findings from this study are congruent with another investigation involving 41 participants between 10 days and 2 months post-stroke (Desrosiers et al. 2005). That study also found no advantage of bilateral task training on several activity and impairment outcomes when comparing bilateral training with mainly unilateral conventional therapy. Both studies included complex functional tasks that progressively increased in difficulty and attentional demands, which may have influenced outcomes compared to other bilateral task training studies where task difficulty remained constant (Mudie and Matyas 1996, Mudie and Matyas 2000, Lewis and Byblow 2004). However Desrosiers (Desrosiers et al. 2005) mixed bilateral, unilateral and asymmetric bilateral movement limiting conclusions that can specifically be drawn regarding effectiveness of bilateral task training.

Present study findings contradict several bilateral training studies utilising simple movement function as training tasks (Whitall et al. 2000, Cauraugh and Kim 2002, Luft et al. 2004, Stinear and Byblow 2004b, Stinear et al. 2008). Each study demonstrated improved movement parameters, impairment or activity limitation. Differences in outcomes compared to the present study suggest that bilateral task training may be less effective than more simple bilateral movement functions. Differences may again relate to difficulties participants in the present study demonstrated maintaining interlimb coupling. Another factor may be the difference in timing post-stroke. The present study was conducted in the acute period, commencing two to four weeks post-stroke whilst other studies were conducted in the chronic phase. These and other reasons for differences in outcomes are discussed in detail in the next section.

TASK COMPLEXITY AND INTERLIMB COUPLING

The free movement tasks and task progressions in the present study were selected because evidence suggests task training in stroke rehabilitation is effective (Van Peppen et al. 2004). Tasks were also selected for ecological validity in relation to function. Principles of motor learning suggest that training specificity needs to be considered to optimise learning. Thus,

to improve specific functional task performance, functional tasks should be trained (Schmidt and Wrisberg 2004). The complex multi-joint functional tasks in this study were progressively changed, as participants improved performances on each task, to challenge performance and enable participants to develop functionally relevant skills.

Anecdotally, participants in the bilateral group reported difficulty attending to both limbs during practice, suggesting that attentional demands and task complexity may indeed have influenced outcomes. Some activities required participants to perform tasks involving two targets separated horizontally by at least 20cm, at arms length. Evidence suggests that stroke patients find tasks requiring divided attention difficult (McDowd et al. 2003), and aimed hemiplegic arm movements require greater attentional resources than aimed movements in healthy subjects (Platz et al. 2001). Visualising and processing information from the non-affected limb, whilst simultaneously performing new, progressively changing, relatively complex precise motor goals with both arms may have provided a dual task challenge greater than in other bilateral training studies. In turn, this may have affected motor learning.

The requirement to constantly address new challenges may have meant that participants remained in the cognitive and associative stages of learning identified by Fitts and Posner (1967) and discussed in Chapter 4. In these stages considerable attention is still required during performance as the learner refines task performance. The progressively and frequently increasing task difficulty may have meant that participants did not have the opportunity to move into the autonomous stage of learning where a low degree of attention is required for performance. Added to this was another attentional demand - the requirement to perform tasks bilaterally. Together the high attentional demands of increasing task complexity and performance of tasks bilaterally may have led to reduced interlimb coupling which in turn may have adversely influenced the effectiveness of bilateral training.

Furthermore, although participants were instructed to move both ULs simultaneously, no external control of coupling was provided. Several studies demonstrating benefits of bilateral training involved simple, non-progressive bilateral movements which entrained the ULs tightly during movement. These studies used electrical stimulation (Cauraugh and Kim 2002), auditory cueing (Whitall et al. 2000, Luft et al. 2004) or rhythmic wrist movements facilitated by the unaffected arm (Cauraugh and Kim 2002, Stinear and Byblow 2004b, Stinear et al. 2008) In line with dynamic systems theory (Chapter 1, Section 2.1.2.1), the rhythmic, repetitive movements in those studies may have created conditions that generated

strong coupling with in-phase or anti-phase movements, through self-organising characteristics of the motor system. In the present study, tasks were discrete, involved multiple degrees of freedom and were not rhythmically controlled. Theoretically, interlimb coupling may have been tighter and more stable if externally forced, rhythmic co-ordinated patterns of movement were used involving only a few degrees of freedom and cueing of movement timing. The simplicity and forced timing of such activities may have reduced the attentional demands of the tasks making motor learning more effective. Thus potential advantages generated by characteristics of tasks to create tight interlimb coupling may have been missed in the present study because of the discrete, complex nature of selected tasks.

Failure to maintain tight interlimb coupling during movement as an explanation for findings is also congruent with the theoretical neural crosstalk model (Cardoso de Oliveira 2002). That model assumes that each hemisphere generates separate motor plans. Interactions between limbs occur through crosstalk between signals from both limbs. Effectively, "leaking" information to the opposite limb medicated via the ipsilateral corticospinal tract is thought to explain interlimb co-ordination. (Chapter 1 section 1.2.2.4) Congruent with this model, in stroke, shared motor commands theoretically free ipsilesional corticospinal excitatory impulses from interhemispheric inhibition. Summation of ipsilateral motor impulses with impulses from the damaged hemisphere may facilitate improved motor control leading to enhanced hemiparetic limb performance (Mudie and Matyas 2000) (Chapter 1 section 1.2.2.5). In the present study, motor commands for tasks were identical because of instructions and shared motor goals for each limb. However lack of external coupling probably limited tightness of interlimb coupling during task execution. Coupling was probably insufficient to invoke interhemispheric crosstalk and "leaking" of ipsilesional control to the hemiparetic limb. The discrete, complex tasks may have been insufficient to create the bilateral advantage seen with rhythmic, simple tasks in other studies (Whitall et al. 2000, Luft et al. 2004, Stinear and Byblow 2004b, Stinear et al. 2008).

DUAL TASK CHALLENGE

Some selected tasks are not normally performed bilaterally; for example simultaneous use of two forks. Individuals had to simultaneously learn new tasks and co-ordinate both ULs, whilst some tasks were not normally performed with the non-dominant arm. In retrospect, more time may have been necessary for the bilateral group to achieve these dual tasks. Equally, tasks more normally performed bilaterally could have been included, such as opening a drawer, using a rolling pin, carrying a box. However tasks were required that

could also be performed unilaterally, which excluded these more normal bilateral tasks. The greater dual task demands for the bilateral group may have nonetheless detrimentally influenced their outcomes.

SCHEDULING OF BILATERAL PRACTICE

The present study assumed, based on previous research (Mudie and Matyas 1996, Mudie and Matyas 2000, Whitall et al. 2000, Lewis and Byblow 2004, Luft et al. 2004), that training effects would transfer from bilateral practice to unilateral performance. Another trial of 32 individuals with chronic stroke testing active-passive training of simple wrist movements randomised participants to bilateral practice *prior* to unilateral practice or to unilateral practice only. Significant improvements with bilateral training in motor performance were found after training (Stinear et al. 2008) with greater primary motor cortex excitability and increased intracortical inhibition measured using transcranial magnetic stimulation (TMS). The authors suggested that bilateral training *before* unilateral training primed the motor system for activity by providing symmetrical afferent input and altering the balance of interhemispheric inhibition and excitability of the primary motor cortex. This study raises questions regarding how and when bilateral training should be used in relation to unilateral training. Effects of bilateral training in the present study may have been missed because bilateral practice was not followed by unilateral training to consolidate and capitalise on priming effects of bilateral training for unilateral skill acquisition.

TIMING OF BILATERAL TRAINING AFTER STROKE

Outcomes may also have also been influenced by timing in terms of time post-stroke. There was no benefit of bilateral over unilateral training in the present study which commenced between two and four weeks post-stroke. Previous studies demonstrating positive effects of bilateral training were conducted mainly in the chronic phase (Whitall et al. 2000, Cauraugh and Kim 2002, Summers et al. 2007, Stinear et al. 2008, Luft et al. 2004), suggesting a possible difference in responses depending on chronicity. Stroke appears to alter normal transcallosal inhibition resulting in increased intact hemisphere excitability during hemiparetic arm movement that may be inhibitory in nature thus suppressing output from the damaged hemisphere (Liepert et al. 2000). Depending on lesion site and size, this over-activation appears transient and more normal contralateral activation patterns eventually resume (Feydy et al. 2002). Identical motor commands generated in each hemisphere during bilateral movement may modulate transcallosal inhibition. In turn this may balance stroke related interhemispheric over-activity to facilitate damaged hemisphere output and normally

inhibited ipsilateral output from the undamaged hemisphere thus augmenting paretic UL control (Stinear and Byblow 2004b, Cauraugh and Summers 2005, Stinear et al. 2008). Disrupted normal transcallosal inhibition soon after stroke may render bilateral training less effective than in chronic stages when interhemispheric interactions have resumed a more normal balance. Effects of bilateral training may therefore be dependent on time after stroke.

DEXTERITY

The unilateral group demonstrated significantly better dexterity outcomes on the Nine Hole Peg Test and the Action Research Arm Test Pinch sections at eighteen weeks (Chapter 5 Section 5.6.1), suggesting accelerated dexterity gains over the bilateral group in the post-treatment phase. For the unilateral group, the mean change in dexterity from baseline to eighteen weeks was 0.15 (±0.15) pegs per second representing a 375% change from the baseline score of 0.04 (±0.08) pegs per second. For the bilateral group, the change was 0.09 (±0.12) pegs per second, representing a change of 300% from the baseline score of 0.02 (±0.07) pegs per second. The difference in percentage change between the groups was greater than 10%, which probably represents a clinically significant difference (Van der Lee et al. 2001). The mean difference in pinch score between groups was 3.4 (standard error 1.6) which was more than, 10% of total Pinch score (max=12), the difference considered clinically significant on the ARAT (Van der Lee et al. 2001) and represents the difference between being able to pick up and place a ball bearing or marble and not. Percentage change for Pinch was 292% from baseline for the unilateral group and 200% for the bilateral group, again representing a difference in change between groups that was probably clinically significant.

Given that training specificity may be critical to training effect (Winstein et al. 2004), bilateral practice of dexterity, where ULs perform identical movement may be somewhat artificial and probably insufficiently related to everyday life dexterity requirements to provide a training effect. Tasks involving fine finger control are most commonly performed unilaterally or with hands performing bimanually different but co-ordinated tasks, for example when tying shoelaces or typing. Mismatch between practice mode and performance requirements for everyday dexterity tasks may have led to lower transfer of training effects to recovery of long-term dexterity in the bilateral training group.

Furthermore, anatomically, distal UL muscles involved in dexterity demonstrate predominantly contralateral corticospinal control whilst contributions of ipsilateral and bilateral control mechanisms to distal performance are limited (Tanji et al. 1988). Ipsilateral pathways from the undamaged hemisphere thought to become accessible for hemiparetic UL motor control during bilateral training (Stinear and Byblow 2004) are unlikely to be involved in dexterity, which may explain poorer bilateral group dexterity.

ADL INDEPENDENCE

Independence in ADL did not differ between groups during the study, despite greater unilateral group dexterity. The MBI is probably too insensitive to detect dexterity changes and participants may also have compensated with the unaffected UL to achieve independence in ADL, a recognised phenomenon (Platz et al. 2005).

6.1.1.3 Study Limitations and directions for new research

There were several study limitations. These are discussed first along with ways in which they can be addressed in future studies, starting with the characteristics of the study population, features of the intervention, outcome measures and finally the research paradigm underpinning the study. Directions for new research are also discussed.

STUDY LIMITATIONS

Population

The population of this pragmatic clinical study was heterogeneous with a wide range of severity of initial UL dysfunction, which may have influenced findings. A more homogeneous sample could have been recruited, however this was intended to be a pragmatic clinical trial, therefore heterogeneity reflecting the range of severities found in clinical practice was in that context a strength of the study. Comparison of bilateral to unilateral training in more homologous study populations defined either by severity of dysfunction or by lesion site and size should be conducted using adequately powered sample sizes to determine whether there is an advantage for different well-defined stroke populations.

Severity at baseline

Initial severity of activity limitation may have been a confounding factor. In spite of stratification in randomisation for severity of UL dysfunction, the bilateral group demonstrated lower baseline scores on all physical measures. Although not statistically different, the mean difference in total ARAT scores between the groups was 5.1 units (standard error 3.2) which approached the clinically significant figure of 5.7 units (Van der Lee et al. 2001), and may have influenced results (Van der Lee et al. 2001). Poorer initial scores were reflected in significantly greater length of hospital stay and more intervention sessions for the bilateral training group. Despite more intervention sessions, but not more training trials, the bilateral training group did not recover more. Therefore, bilateral training was either not more effective than unilateral training for UL recovery or effects were confounded by the clinical difference in severity between the groups. The ARAT was used as a stratification factor for randomisation. It may not have been sensitive enough to detect differences in severity for participants who were most severely affected, leading to an imbalance in terms of clinical severity between the groups. Future studies should include more sensitive measures as stratification factors in the randomisation process. Grip strength and finger tapping speed might be more sensitive markers of severity of impairment for stratification of participants at the bottom and top ends of the severity spectrum than the ARAT used in the present study.

Stratification factors

The Oxfordshire Community Stroke Project was a stratification factor. This was determined using a clinical examination conducted by the therapists with the consultant stroke physician based on the NIH Stroke Scale and CT scan reports. The NIH scale was conducted two to four weeks after stroke onset by which time many clinical signs had improved or disappeared. The categorisation may not therefore have been accurate and may have contributed to the clinical difference between the groups at baseline. Future studies should include a more accurate assessment of stroke classification using radiological analysis with CT or MRI scans.

Control intervention

The main purpose of this trial was to compare effectiveness of unilateral to bilateral training. To address this question, a two-group comparison was made in which both groups received identical training of the same dose frequency, intensity and duration unilaterally. This was a logical design to answer that research question. Because no control group receiving usual

therapy only was used however it is unclear whether either unilateral or bilateral delivery of the intervention had additional benefits over usual therapy. There were several pragmatic reasons for not including a usual therapy only control group.

Firstly, based on the clinical experience of the author in that clinical setting, usual therapy varied in duration and frequency between patients, and comprised activities ranging from task practice to movement training or passive movement. Bobath therapy predominated, but motor learning approaches were also used by some therapists. Most therapy was unilateral, however some bilaterally different functional activities such as dressing and cooking were practiced. This diversity made usual therapy difficult to quantify clearly, which could have confounded findings in a three group design. Detailed description of usual therapy would also have been required, necessitating additional paperwork for therapists that would have been unlikely to have been completed adequately, given the volume of their usual paperwork and service delivery requirements and workload. As part of planning, the author considered proposing that the research therapists only could treat patients' upper limbs as part of the study, in order to provide standardized unilateral, bilateral or usual therapy. However this option was rejected since it was not appropriate ethically to interfere with usual care delivery.

Secondly, patient recruitment and retention to a usual treatment only control group may have been difficult since one of the appeals to patients of participating in this trial was that they would receive additional physiotherapy.

Given all of these considerations, the author decided that the best option was to randomise patients to unilateral and bilateral groups, and assume that variation in dose and nature of usual therapy was randomly distributed between the groups. In fact, therapy records were checked to obtain some idea of what occurred, however it was impossible to determine the accuracy of these records with great certainty therefore the confounding impact of regular therapy on study outcomes cannot be totally discounted. Steps should clearly be taken in future studies to better control and quantify usual therapy.

There was no differential effect of bilateral over unilateral training however there was a small benefit for overall dexterity of unilateral training. An appropriate future development may therefore be in fact to compare the unilateral intervention programme with usual therapy

in a randomised controlled trial since the intervention programme itself may represent a useful clinical tool in its own right when applied unilaterally.

Modified and core protocols

Participants were allocated to modified or core tasks depending on initial performance. Each protocol involved standardized progressive tasks with either unilateral or bilateral practice. In the modified protocol, when participants could not achieve a task, physical assistance was provided by the therapist until the task could be performed independently. This added a degree of clinical judgment to the carefully standardised program that may have influenced results. No significant differences between groups in the proportion of participants allocated to the core and modified protocols existed, nor was there a difference in the number of sessions taken to progress to the core protocol. Nonetheless, more participants in the bilateral group received modified training throughout, probably reflecting the baseline clinical characteristics of that group. The less standardised nature of the modified protocol may have affected outcomes in that group in spite of the greater number of treatment sessions undertaken. Ways in which assistance can be more standardised possibly using assistive technology such as robotic devices that have previously been used bilaterally (Lum et al. 2004, Hesse et al. 2005) should be explored in future.

Dose

Although the training dose was similar to other bilateral training studies (Whitall et al. 2000, Mudie and Matyas 1996), compared to other UL interventions involving constraint induced movement therapy (Taub et al. 2006, Wolf et al. 2007), therapy dose in this study was low. Dose may have influenced outcomes particularly given the dual task challenges the bilateral group faced. Before rejecting bilateral task training as a useful intervention, optimum training dose should be determined. Comparison should be made between combinations of low and high doses of bilateral versus unilateral training and between long blocks of practice and regular shorter blocks of practice distributed throughout the day.

Additionally, whilst participants practiced with the research therapists for 20 minutes per day, there was no practice protocol for participants to follow in between sessions. The reason for this was that participants were already receiving regular therapy and instructions to practice from their own therapists. It was thought that to provide additional requirements for practice related to the study therapy would have been too much for participants to manage. Lack of structured practice between sessions may have limited the effectiveness of

the intervention however. The effectiveness of self-directed practice in addition to therapy led intervention is another area for future research, and the role of carers in supporting therapy practice should also be examined. Self-directed practice paradigms would also facilitate investigation of optimum practice strategies, for example by comparison between massed practice as occurred in this study, and the distributed practice of other studies (Whitall et al. 2000).

Measurement

Measurements were conducted at two end-points using functional measures selected for clinical relevance, but were relatively crude. Other studies, using kinematic analysis, have demonstrated immediate improvements in quality and timing of UL movement during bilateral conditions in chronic stroke (Cunningham et al. 2002) and in some cases during subsequent unilateral performance (Mudie and Matyas 1996, Mudie and Matyas 2000, Cauraugh and Kim 2002). Immediate and subtle effects of bilateral training on movement parameters may have therefore been missed in this study. Future studies should therefore include both clinical and kinematic measures to determine macro and micro effects of bilateral training interventions.

Furthermore the established UL tests used in the study all examined unilateral function, and the effect of bilateral training on bimanual UL functioning or co-ordination, which may be an important outcome of bilateral training, was not examined and to the author's knowledge has not been addressed in previous studies. Future studies should therefore measure effects of bilateral training interventions on activities involving interlimb co-ordination and bilateral functioning.

Motor impairment was the only outcome measure of impairment in the present study. Impairments such as muscle tone and muscle strength should have been included to provide a more complete picture of effects of training. Spasticity is a potential problem that may influence recovery even in participants only one month after stroke onset (Pandyan et al. 2002, Bhakta 2000). It is of particular relevance in participants with more severe deficits and little or no functional use of the UL (Bhakta 2000) and may have explained why the bilateral group, which demonstrated poorer initial activity limitation, and poorer dexterity outcomes than the unilateral group. Other bilateral training studies have shown an effect on muscle strength (Whitall et al. 2000), another outcome that was not included in the present study and should be included in future studies. Effects on a more complete measure of

motor impairment should also be examined, such as the Fugl Meyer test since this would provide a more even comparison with many other bilateral training studies (Whitall et al. 2000, Luft et al. 2004, Waller and Whitall 2004, Stinear and Byblow 2004, Stinear et al. 2008).

Design

The randomized controlled trial design was selected as the most robust design to test the effectiveness of the intervention, and the measures were selected with the aim of evaluating the constructs with tools that were known to be valid and reliable in stroke. It was not possible to assess the participants' experiences of participating in the trial however, or to obtain their opinions about the intervention and the ease of participating, their enjoyment and perceived benefits from their own perspective. Future studies should include a qualitative evaluation of the experiences and opinions of the participants in addition to the quantitative measurement of outcomes. This would provide important information about the acceptability of the intervention and included tasks.

DIRECTIONS FOR NEW RESEARCH

This section discusses options for future research that have emerged from the findings of the randomised controlled trial and from identification of its limitations.

Comparison to usual therapy

The findings suggested that bilateral training as delivered in the present study was no more effective than unilateral training for an acute stroke population. As discussed above, participants in the acute and chronic stages of stroke may respond differently to bilateral interventions because of the cortical reorganisation and altered interhemispheric interactions that occur during the acute post-stroke period. Before rejecting the bilateral training intervention therefore, comparison should be made in an RCT between unilateral and bilateral training and a no or usual therapy control group in the chronic phase.

Functionally relevant tasks

Systematic reviews of physiotherapy in stroke suggest that functional task training is beneficial for UL recovery (Van Peppen et al. 2004). Although in the present study there was no advantage of training these tasks bilaterally, functionally relevant tasks should not be rejected immediately as an appropriate and ecologically valid bilateral intervention activity. Future research should first examine attentional demands of different functionally orientated

UL tasks to determine which task characteristics make bilateral performance difficult. This could be conducted using kinematic analysis of movement or through videotaping of performance focusing on visual attention, eye movements and UL symmetry during bilateral tasks. Furthermore, neuroimaging studies using functional MRI should be conducted to identify the neural networks involved in tasks of differing complexity and attention. In this way it will be possible to better understand how training characteristics of bilateral tasks influence motor learning and to determine those that are most appropriate for use in bilateral task training interventions.

Furthermore, to determine optimal bilateral training characteristics future research should then *compare* differential effects of functional and ecologically valid tasks appropriate for bilateral training to simpler movement function training. Comparisons should be conducted bilaterally and impairment and activity outcomes examined. In this way it will be possible to determine optimum bilateral characteristics on both impairment and activity outcomes.

Interlimb Coupling

Similarly, ways should be explored to optimise interlimb coupling during bilateral task training. Auditory cueing, which has been used with simple movements (Luft et al. 2004) and approaches to visual cueing, should be examined for effectiveness in maintaining interlimb coupling during free, discrete tasks such as those included in the present study, and optimal approaches for timing established.

Furthermore, and particularly for participants with more severe UL dysfunction where activity limitation is severe, robotic devices used in some of the bilateral training studies examined in the literature review (Chapter 2, Section 2.2.5) should be examined for utility and feasibility. These might be useful for training of more complex tasks than the simple movements often trained with these devices (Hesse et al. 2005). Robotic devices may provide control of interlimb coupling whilst facilitating practice of simple movement function and specific goal orientated functionally related tasks. Such an approach would enable comparison between unilateral and bilateral training and evaluation of optimal patterns of timing for each within a training programme. It could also allow for comparison of effectiveness between bilateral movement function training with tight interlimb coupling *and* more complex activities involved in task training. In this way motor control and rehabilitation intervention paradigms might inform each other in new ways.

Additionally, use of robotic devices programmed to repeat bilateral movements or tasks would address the issue in the present study of the loss of standardisation when therapists were assisting participants to perform activities. Comparison between effectiveness of rhythmic, repetitive activities such as those used in some studies (Whitall et al. 2000, Luft et al. 2004) and discrete tasks such as those used in the present study on impairment *and* activity outcomes could then be examined whilst interlimb coupling was tightly maintained by the devices. These can programmed to exactly mirror movements of the less affected ipsilesional UL (Burgar et al. 2000). Although potentially expensive, this may provide an effective approach towards evaluation of bilateral training of functionally useful tasks in which interlimb coupling can be assured.

Training tasks

Dexterity improved significantly after unilateral training in the present study, whilst other outcomes did not, raising the question of what intervention mode should be optimally employed to improve different outcomes. Bilateral task training should possibly be targeted only at tasks that are usually performed bilaterally symmetrically, such as lifting, carrying, catching, folding, pushing, whereas the present study suggests that fine dexterity tasks that are always unilaterally performed should be probably be trained unilaterally. Similarly, specific training should target tasks that are performed using both ULs differently such as typing or tying laces. More research is therefore required to investigate the optimal training modes for specific tasks and to investigate how and when bilateral and unilateral training should optimally be employed. Comparison of bilateral and unilateral training for specific tasks should therefore be conducted.

Scheduling of bilateral training

Furthermore, whilst the present study showed that there was no advantage of bilateral versus unilateral task training, another study has shown using simple wrist movements that bilateral training *before* unilateral training may be effective in improving outcomes and the inter and intra hemispheric balance of neuronal excitability (Stinear et al. 2008). Therefore before rejecting bilateral task training as an effective intervention, different combinations of sequencing of bilateral and unilateral task training should be compared, in which bilateral training of tasks is practised before unilateral practice. This should be compared in an RCT to bilateral alone and unilateral practice alone to determine the best combinations of practice mode.

Neurophysiological assessments

It was not possible to identify neurophysiological explanations for why there was no advantage of bilateral training. Several bilateral training studies of movement function have demonstrated effects of training using TMS (Stinear and Byblow 2004, Stinear et al. 2008) or functional MRI (Luft et al. 2004). Future studies of bilateral task training should also include TMS or fMRI assessment in parallel with physical outcomes since this may identify the neurophysiological mechanisms including cortical activation patterns and explain responses or lack of responses to bilateral training. Studies should also compare cortical activation patterns during bilateral task training in the early post-stroke period and compare them to what happens in the more chronic phase. In this way it will be possible to determine which participants may respond best to bilateral task training and the optimal timing for commencement of bilateral training.

6.1.1.4 Implications for clinical practice and rehabilitation research

This study provides evidence from a properly powered RCT to suggest that there is no advantage of a progressive programme of bilateral task training over the same programme delivered unilaterally for UL outcomes and ADL in participants with acute stroke undertaking rehabilitation. Findings are clinically important since authors of previous studies involving small single case series (Mudie and Matyas 1996, Mudie and Matyas 2000) have visited the UK to conduct courses for physiotherapists and occupational therapists promoting bilateral task practice as a therapeutic approach (Mudie 2000b). Given that the present study tested effectiveness of similar tasks using robust research design and found that no advantage of bilateral over unilateral training, this raises serious questions about strength of evidence used to inform clinical practice. Current findings show that therapists should be cautious about adopting interventions until robust evidence from well conducted trials is available to support their application in defined patient populations. Observations highlight the need to educate clinicians about interpreting research findings and about what constitutes adequate evidence for clinical practice. It also indicates the danger in adopting clinical practices based on small studies with highly selected populations.

Within the context of the body of work relating to bilateral training in stroke, this study suggests that task training of complex functionally orientated tasks may not be the most appropriate approach to bilateral training. This is probably because of high attentional demands of performing and learning new complex tasks whilst bilaterally synchronising movement of both ULs. Studies using simple rhythmic repetitive movements where

interlimb coupling was tight concur with predictions of motor control models in suggesting that for bilateral training to be effective tight interlimb coupling is required that anecdotally was not achieved with the tasks in the present study.

The intervention in the present study was based on evidence from stroke rehabilitation literature that task specificity for function was important to achieve improvements in UL function. The lack of an advantage over unilateral training with the present bilateral paradigm suggests that interlimb coupling of the training rather than *task specificity* for function may be most important in influencing UL outcomes through bilateral training. Thus the study adds to the body of evidence on bilateral training suggesting that simple movements repeated rhythmically appear to be more effective than training complex, functional tasks for which undivided attention may be required. Future research should involve collaboration between researchers with an interest in motor control science and in stroke rehabilitation. Ways in which theoretical and intervention approaches can be shared should be explored to inform development of optimal bilateral training strategies for UL recovery in stroke.

In summary, placing this study into the context of other literature highlights several questions about bilateral training that need to be explored more fully if it is to be adopted as an effective intervention in stroke UL rehabilitation:

- *What* tasks should be trained bilaterally? Should they be complex, functionally orientated, or simple, movements with little direct functional relevance?

- *Who* should undertake bilateral training? Patients who demonstrate some dexterity appear to benefit most from unilateral not bilateral training. Do those with greater severity benefit more from bilateral training if the movements are simple and both limbs can be strongly coupled?

- *How* should bilateral training be delivered? The optimum strategy for maintaining interlimb coupling should be determined. Questions should be asked about whether synchrony should be maintained by auditory cueing with free movement or whether devices are required, either mechanical or robotic, to maintain coupling. Sequencing should also be addressed – is purely bilateral training optimal, or should it be sequenced before or after unilateral training? Is there an advantage of phasing bilateral in-phase movement with bilateral anti-phase movement?

- *How much and how often* should bilateral training be delivered?

- *When* should bilateral training best be delivered? The present study suggests that the acute phase may not be the optimal timing for introduction of bilateral training, so what timing is optimal?

- *What* should be measured? Movement parameters, motor impairment or activity limitation?

- *How* do different bilateral training strategies work at a neurophysiological level?

In short, the present study highlights the fact that bilateral training is a complex intervention and it may not be possible to give an overall judgement on its merit as an effective intervention for stroke until much more research has been conducted.

The next section discusses the exploration of five clinical and demographic factors on contralesional responses to bilateral training.

6.1.2 EFFECTS OF CLINICAL AND DEMOGRAPHIC FACTORS

In order to appropriately target UL interventions it is important for therapists to understand what factors are likely to influence responses to specific interventions. Continuing the examination of contralesional effects of bilateral task training, this section discusses the analysis of factors highlighted in the literature as likely to influence training responses of bilateral compared to unilateral training. Literature presented in Chapter 2, Section 2.3 demonstrated that the most plausible factors that might influence bilateral compared to unilateral training responses were severity of initial activity limitation, side of stroke and hand dominance, age, gender and proprioception. It was planned also to examine site of lesion operationalised by the Oxfordshire Community Stroke Project Classification, however this was not done due to uneven numbers of participants in some of the sub-groups leading to violation of assumptions for ANOVA.

6.1.2.1 Findings

Findings showed that none of the factors mentioned above significantly influenced bilateral or unilateral training, suggesting that training responses in neither group was affected by these variables. Other than the small overall advantage for the unilateral group in dexterity at eighteen weeks, there were no significant differences between groups which may also explain why there were no effects of any of the factors on bilateral or unilateral outcomes. Three findings stand out as warranting detailed discussion: severity of initial activity limitation, side of stroke and hand dominance, which were relevant to previous bilateral training literature. These are discussed in turn to place present findings into the context of previous literature and to identify future directions for research in each area.

Finally, although gender did not influence training responses, there was a main effect of gender relating to UL recovery in the *sample as a whole*, which is briefly discussed in section 6.2.2.2:

6.1.3. SEVERITY OF INITIAL ACTIVITY LIMITATION

Three severity sub-groups were defined by motor and functional status at baseline on two commonly used clinically outcome measures, the Nine Hole Peg Test and the Action Research Arm Test (See Chapter 5, Section 5.6.1.2 for details of how groups were defined). Effects of severity of initial activity limitation on bilateral and unilateral training responses were not significant for any of the UL measures. Of note, however, was the observation that participants in the "severe" group receiving bilateral training demonstrated highest change scores in motor impairment and activity limitation between baseline and six weeks, compared to other severity subgroups (Table 5.4a, Chapter 5). This suggests that participants with most severe initial activity limitation *might* respond better to bilateral training however the finding was not significant and must be considered very cautiously, but does deserve brief discussion.

Of secondary interest, post hoc examination of a significant main effect of severity on recovery of all of the UL variables showed that *for the whole sample*, recovery within each of the sub-groups differed significantly.

6.1.3.1 Previous literature and interpretation of findings

The finding that the most severe sub-group demonstrated greatest change with bilateral training compared to unilateral training is worthy of brief consideration. Although not significant, the finding is in line with another small study that showed a small and again non-significant effect of bilateral compared to unilateral training on shoulder activation EMG patterns in patients with severe hemiparesis (Mudie and Matyas 2001). Comparisons must be cautious because that intervention comprised one session of training only compared to the present six week intervention. Nonetheless, with the present study, findings suggest that there *may* be effects of bilateral training for the most severely affected participants but since in both studies differences were small and neither reached significance, interpretation must be cautious. Higher scores for the bilateral group in the present study were possibly due to chance since the pattern was not sustained for overall change between baseline and eighteen weeks.

Theoretically, bilaterally projecting descending motor pathways, such as the medullary rubrospinal tract, are thought to be mediators of proximal muscle activity activated by

brainstem descending systems, and can be controlled by either or both hemispheres (Mudie and Matyas 2000, Tanji et al. 1988). Proximal movements appropriate to the abilities of participants with severe hemiplegia comprised the simplest tasks in the modified protocol in the current study. Because of these proximal central control mechanisms, proximal movements may have responded better to bilateral training than unilateral training. That concept is supported also by the observation that dexterity recovered best in the unilateral group, supporting the idea of unilateral contralateral control of distal musculature. Clearly more research with properly powered studies and more homologous study populations is required to determine effects of bilateral UL training in severely affected patients.

In line with other literature (Wade et al. 1983, Loewen and Anderson 1990, Nakayama et al. 1994, Katrak et al. 1998, Feys et al. 2000a, Kwakkel et al. 2003, Kwakkel and Kollen 2007), a secondary post-hoc finding from this analysis showed that the sub-groups differed significantly in terms of recovery on the UL measures irrespective of training group, and is worthy of brief consideration here. Improvement in activity limitation (Action Research Arm Test) and impairment (Rivermead Motor Assessment) was greatest in the moderate group compared to the other two sub-groups between baseline and six weeks and baseline and eighteen weeks (Chapter 5, Section 5.7.1.2). The mild group demonstrated higher change scores than the severe group but the difference was not significant. For dexterity (Nine Hole Peg Test) the mild group demonstrated most improvement followed by the moderate group with least change in the severe group. All three groups differed significantly in terms of dexterity.

Exact neurophysiological mechanisms underpinning clinical presentation in the present study were not identified because neuro-radiological advice was not available. It is probable that patients with severe initial UL impairment demonstrated large lesions, with little sparing of cortico-motoneurones and less preservation of the corticospinal tract (Turton 1998) than in the two other sub-groups. A ceiling effect of the activity limitation and impairment measures probably explains why the least severe group did not demonstrate greater recovery on those measures than the moderate group. In contrast, for dexterity, the three groups were significantly different, with least recovery in the severe group and most in the mild group. This suggests, unsurprisingly, that the ceiling effect that appeared to exist for activity limitation and impairment did not exist for the more sensitive, timed Nine Hole Peg Test. This finding confirms other work showing that the Nine Hole Peg Test is more sensitive to change for patients with least impairment than the other measures (Sunderland et al. 1989,

Heller 1987, Wade et al. 1987). The findings clearly indicate that patients with differing degrees of severity recover differently.

6.1.3.2 Study limitations and directions for future research

The study was originally powered to examine effects of training for bilateral and unilateral training groups. The creation of severity sub-groups probably reduced study power, particularly since 21 participants had dropped out by eighteen weeks. Significant effects may have consequently been missed. Findings suggest that effects of bilateral compared to unilateral training in the most severely affected participants warrants further study with properly powered randomised controlled trials and a more homogeneous sample.

Sub-groups defined using the Nine Hole Peg Test and Action Research Arm Test represent a useful development in defining UL severity. There is a need to further validate these sub-groups against other measures of UL severity and to determine their usefulness in clinical practice for describing UL recovery patterns of participants with UL deficits and in research for defining severity groups for comparison.

6.1.4 SIDE OF STROKE AND HAND DOMINANCE

6.1.4.1 Findings

There was no effect of side or hand dominance on bilateral compared to unilateral training responses, suggesting that these factors are not important in determining training responses to bilateral training. The finding is discussed below in relation to a previous bilateral training study.

A secondary finding was that for the whole sample, left handed participants with right hemiplegia demonstrated significantly less change between baseline and eighteen weeks in UL motor impairment. Implications of that finding are briefly discussed.

6.1.4.2 Previous literature and interpretation of findings

Hand dominance and side of stroke did not influence bilateral training outcomes, in contrast to McCombe et al. (McCombe et al. 2005), who found significantly greater change in UL motor impairment and activity limitation in right handed participants with dominant right sided hemiplegia, compared to non-dominant left hemiplegia. That group of 22 participants received BATRAC bilateral training (see Chapter 2, Section 2.2.4). All participants in that study participated in bilateral training with no comparison to a control group. Therefore it is unclear whether the effect relates exclusively to their bilateral paradigm or whether it applies across interventions. Also, as no comparison to *left* handed participants with dominant and non-dominant hemiplegia was made by McCombe et al. (2005), it is not clear whether side of hemiplegia *or* hand dominance was most important in determining training responses. The current findings demonstrated that neither was important, however the number of participants in each sub-group was small and probably influenced findings.

A secondary, serendipitous finding from this analysis warrants brief discussion. Although hand dominance and side did not influence bilateral training outcomes there was a significant interaction effect between side and dominance that was unrelated to training group. Post-hoc examination showed that participants with left handedness and right hemiplegia recovered significantly less in terms of overall motor impairment than the other sub-groups (Chapter 5, Section 5.7.3.2). Findings are partly congruent with another study in which 93 community dwelling participants demonstrated less impairment of the dominant hand (Harris and Eng 2006), but the effect was not specific to left handed individuals. Differences in study populations and time since stroke mean that comparison to the present study is difficult; however together the studies do suggest that hand dominance is a factor that might influence recovery. This raises the question of why in the present study the effect occurred only with left handed and not right handed participants

The most likely explanation for the present findings however emerges from the data. Only four participants were left-handed with right hemiplegia, of whom two demonstrated no overall change, one demonstrated a small improvement of two points on the Rivermead Motor Assessment and one participant demonstrated deterioration with overall change of -7 on the Rivermead Motor Assessment. The number of left handed participants with right hemiplegia was very small, the result is not reflected in scores for the other measures *and* the p value was only just significant at p=0.04, hence the interaction effect probably simply reflects the large deterioration experienced by one patient. The finding should therefore be

regarded very cautiously indeed, but does seem to suggest that there may be some effect of side and dominance on recovery of impairment for participants with right hemiplegia who are left handed that warrants further investigation in other studies.

6.1.4.3 Study limitations and directions for future research

There were several study limitations. These are discussed first along with ways in which they can be addressed in future studies. Findings from the present study also point to directions for new research and these are also discussed.

As stated above, the study was originally powered to examine the effects of bilateral training on bilateral and unilateral training groups. The creation of sub-groups based on these factors probably reduced the power considerably, particularly since 21 participants had dropped out by eighteen weeks. Significant effects may have consequently been missed.

Only nine participants were left hand dominant, and one of those had dropped out at six weeks. Five participants in the unilateral group demonstrated left hand dominance of whom two had right hemiplegia. In the bilateral group this number was three, two of whom had right hemiplegia. Conclusions based on such small sub-groups cannot be regarded as robust. Future research should examine effects of handedness and side of stroke with equivalent sized, adequately powered samples. Longitudinal studies should be conducted to determine the effects of handedness and side of stroke on UL recovery over time, with particular focus on individuals with left handedness. These should investigate how handedness and side of stroke influence recovery and responses to different types of UL training.

Participant handedness was examined by asking individuals which hand was used for writing. This approach to handedness assessment does not include the range of activities examined in formal assessments of handedness such as the Edinburgh Handedness Inventory (Oldfield 1971) which measures magnitude of laterality and accounts for ambidextrous individuals. Handedness in future studies should be identified using a standardised measure of laterality.

Development of new UL interventions should ensure that recovery of the non-dominant hand is addressed. Intervention activities should be appropriate to dominant and non-dominant side functions, for example, where the non-dominant hand is involved in stabilising and

supporting. Clearly this presents challenges for bilaterally identical activities, however investigation of effect of handedness on bilateral training outcomes should continue so that effects of hand dominance are quantified and understood. Sequencing of bilateral and unilateral activities to account for handedness may address this issue and should be explored during development of new bilateral interventions.

6.1.5 GENDER

6.1.5.1 Findings

Gender did not influence responses to bilateral compared to unilateral training. However there was a main effect of gender in which male participants demonstrated greater improvement in UL activity limitation than females between baseline and eighteen weeks. The same pattern of recovery existed for impairment and dexterity, but did not reach significance. Although secondary to the main analysis of bilateral training, findings will be briefly discussed here.

6.1.5.2 Previous literature and interpretation of findings

Findings are congruent with literature examining general stroke recovery. Several recent studies demonstrated higher disability levels in females at three months post-stroke, measured on the Barthel Index (Gargano et al. 2007) and Modified Rankin Scale (Di Carlo et al. 2003) and at six months on the Barthel Index (Kapral et al. 2005). Another study (Paolucci 2006), found that males recovered better in ADL, stair climbing and gait in a case control study of 220 male and 220 female participants who were matched on variables known to influence outcome.

In the present study, female participants (mean age 69.8±12.3 years) were not significantly older than males (mean age 66.4±11.1), ($t=-1.49$, $df=104$, $p=0.14$), making age an unlikely explanation for lower female recovery on the Action Research Arm Test. This is congruent with previous studies showing that training responses for older participants training do not differ from those of younger participants (Bagg et al. 2002, Fritz et al. 2006).

Depression may have influenced UL recovery in women. The present study showed that females demonstrated significantly higher depression scores on the Hospital Anxiety and Depression Scale than men at baseline (mean female score = 15.1±6.5; mean male score = 10.8±6.1; $F_{1, 105}$ =11.75, p=0.001) and eighteen weeks (mean female score = 12.1±6.2; mean male score = 8.8±7.4; $F_{1,84}$ =4.9; p=0.03). Findings are congruent with other studies in which females were more depressed and demonstrated poorer physical recovery in rehabilitation (Paolucci 2006). Lesion site, cognitive impairment, social factors, beliefs about stroke and stroke recovery and meaning ascribed by the patient to disability probably influence post-stroke depression (Gainotti and Marra 2002, Hackett and Anderson 2005) however no clear consensus exists of exactly how gender, depression and recovery are linked.

There may be biological explanations for women's poorer recovery. Large artery disease predominates in males, whereas females are more likely to suffer intra-cranial medium artery disease (Wyller et al. 1997), however whether this is the cause of gender differences in recovery or not is unclear and requires further investigation. Finally, females may be initially less strong than men, which may influence recovery and perhaps stamina to participate in rehabilitation activities (Paolucci 2006) leading to poorer outcomes, however this explanation also requires further investigation.

6.1.5.3 Study limitations and directions for future research

Gender bias within the UL training activities and outcome measures in the bilateral training study were not considered in the design of the study and may have influenced the findings. Future studies should investigate effects of gender bias in tests and interventions.

Findings were from post-hoc unplanned comparisons within an ANOVA. The study was not specifically powered for this analysis therefore findings should be interpreted cautiously since they may be spurious. Future studies should investigate the effect of gender on UL recovery in studies specifically designed to do so. These could investigate reasons for gender differences in UL recovery a priori using predictive modelling with adequately powered studies. Social, environmental, attitudinal and motivation factors that might differentially influence recovery in men and women as well as physical factors such as lesion site and stroke type should be examined to fully elucidate the reasons for gender differences in outcome.

Upper limb interventions should be developed to account for gender differences in recovery and these should be compared to non-gender specific activities to determine whether there is an advantage. Interventions should also account for individualised patient interests and leisure and life role activities, and should be developed through consultation with patients about their own gender-specific rehabilitation goals.

Studies should also be conducted to determine the neurophysiological and pathological mechanisms that might explain differences in gender recovery since these too are likely to inform development of specific therapeutic or medical interventions for men and women.

The next section discusses the implication of these findings for clinical practice and rehabilitation research.

6.1.6 CLINICAL AND DEMOGRAPHIC FACTORS: IMPLICATIONS FOR CLINICAL PRACTICE AND REHABILITATION RESEARCH

Severity of initial activity limitation

Clinically, participants with most severe movement dysfunction are those who recover least because they have greatest damage to motor cortical areas or descending motor pathways. Interventions that improve the movement dysfunction of this group of participants are therefore valuable to participants and therapists. Although it is not possible to be certain since findings were not significant, the current findings may indicate that for these participants bilateral training of proximal movements *may* be more effective than unilateral training. Before incorporating bilateral training for severely affected patients into usual physiotherapy programmes, further adequately powered studies should be conducted to determine if bilateral training is in deed effective with this sub-group of patients. Linking to the previous section, exploration of robotic devices used bilaterally might indeed be the most appropriate approach to provide these patients with opportunity to practice proximal movements bilaterally and provide an optimal training dose of therapy likely to make improvements, without placing undue burden on therapists' time. Work has already been conducted in this field using the MIME robotic device as discussed in Chapter 2, Section 2.2.5; however the advantage of bilateral over unilateral practice paradigms in this context still has to be established.

Severity sub-groups

Previous studies have mainly used regression analysis of data to *predict* recovery of large samples over time (Wade et al. 1983, Loewen and Anderson 1990, Feys et al. 2000a, Kwakkel et al. 2003, Kwakkel and Kollen 2007). The unique development in the present study was the creation of clinically identifiable patient groups using commonly used clinical measures to represent severity sub-groups. The analysis demonstrates that these groups are viable and do in fact discriminate different patterns of recovery in patients with mild, moderate and severe dysfunction in terms of clinically meaningful categories. The severity sub-groups may be used to target therapy appropriately and to determine likely recovery patterns of patient sub-groups. Clinical definition of sub-groups is more meaningful than the arbitrary but commonly used median split (Parry et al. 1999) for creation of sub-groups in research studies. Other researchers may therefore find the definitions useful for investigation of effects of interventions or recovery patterns since they are based on real clinical observation, and indeed this classification has already been implemented in another ongoing study (Rodgers et al 2008). The validity of these sub-groups for predicting recovery should therefore be investigated further.

Hand dominance

The findings suggest that side of lesion and hand dominance do not influence bilateral or unilateral training outcomes. An unexpected secondary finding showed that being left handed with right sided hemiplegia may however adversely influence outcomes irrespective of training intervention. In order to deliver and improve upon UL rehabilitation it is important for therapists to understand that handedness and side of stroke, specifically right hemiplegia in left handed patients may influence stroke recovery. This information should prompt therapists to consider targeting interventions appropriately for the differential functioning of each UL. Since the dominant and non-dominant ULs have different functions during bimanual tasks such as opening a jar or driving a car, consideration in therapy should be given to how training of function for each UL should be addressed, with specific reference to handedness, irrespective of which side is affected. A specific bank of activities and equipment should be available for left handed patients to ensure that the way in which the limbs interact normally is reflected in rehabilitation activities.

Left hand dominance in stroke rehabilitation is under-researched. The findings of this study suggest that more research should be conducted in collaboration with neuroscientists to determine the recovery patterns over time and the neural mechanisms underlying the effects

of hand dominance and side on stroke recovery for individuals who are left handed. This in turn may inform the development of appropriate interventions for handedness and side of stroke.

Gender

There was no impact of gender on bilateral compared to unilateral UL outcomes, however overall, women's UL outcomes improved less than men's. The findings add UL recovery to a general body of work pointing to different recovery patterns for men and women. Although secondary to the main bilateral training study this is an important finding which suggests that therapists should recognise and address gender differences in planning UL therapy. Once reasons for gender differences are more fully understood, it may be possible and appropriate to develop UL interventions and rehabilitation strategies to maximise recovery benefits for men and women. These are likely to involve the early diagnosis and treatment of depression, and will involve gender specific training activities that account for motivational, social environmental and attitudinal factors to ensure that participants of each gender are equally engaged in rehabilitation activities. Findings confirm previous research relating to gender in global functioning in stroke and therefore have implications for neuroscientists and motor control scientists investigating neurophysiological and pathological differences in UL recovery between men and women. Findings also have implications for health psychologists interested in the social, psychological and motivational differences between men and women and which might explain differences in recovery.

In conclusion, although no effect of clinical and demographic factors on bilateral training outcomes were demonstrated, unexpected findings from post-hoc analyses point to several areas requiring further investigation that also have important implications for clinical practice.

Moving on from the contralesional effects of training, the next section investigates the effect of bilateral training on ipsilesional UL activity limitation and dexterity.

6.1.7 IPSILESIONAL UPPER LIMB OUTCOMES

Continuing to examine effects of bilateral training compared to unilateral training, another study aim was to explore effects of bilateral training on ipsilesional UL activity limitation and dexterity compared to the unilateral group which received no specific ipsilesional UL training. Effects on gross and fine UL function were examined because standardised protocols determined that data was collected for both ULs on both the Action Research Arm Test and the Nine Hole Peg Test.

6.1.7.1 Findings

Before comparing effects of bilateral and unilateral training, preliminary analysis (Chapter 5, Sections 5.8.2.2 and 5.8.2.3) showed that ipsilesional dysfunction existed compared to published normal values for the measures, and that dysfunction improved significantly between baseline and six weeks for dexterity within the whole group. At eighteen weeks, the whole sample demonstrated scores approximating normal published values. This timescale for recovery is in line with other studies (Marque et al. 1997, Sunderland 2000). For activity limitation, fewer participants demonstrated sub-maximal scores at six and eighteen weeks compared to at baseline however the difference in scores between assessments was not significant (Chapter 5, Table 5.12). Ipsilesional dexterity but not activity limitation was also significantly associated with ADL independence at all assessments (Chapter 5, Table 5.15), indicating moderate but significant correlations (r=0.25 to 0.39) between ipsilesional dexterity and general functioning.

Having established that ipsilesional dysfunction was detectable on the selected measures, that it recovered significantly over time, and was associated with ADL independence, effects of bilateral compared to unilateral training were explored. In the complete case analysis, the between-group difference approached significance in favour of the bilateral group for short-term change in dexterity (Chapter 5, Table 5.17, Figure 5.8). This suggested an effect of bilateral training. The intention to treat analysis however did reach significance, suggesting that the complete case analysis was probably underpowered to detect the difference (ITT Table 20, Appendix 14). There was no overall significant effect of training on long-term change in dexterity between baseline and eighteen weeks.

6.1.7.2 Previous literature and interpretation of findings

The ipsilesional effect of bilateral training targeted at the hemiparetic UL is broadly congruent with another bilateral training study (McCombe-Waller and Whitall 2004) that demonstrated bilateral training effects on ipsilesional performance of finger tapping co-ordination tasks. In that study, ten participants with chronic stroke participated in six weeks BATRAC training. Significant improvements in ipsilesional finger tapping consistency were demonstrated in four participants after training. Like the present study, there was no impact of the training on hemiparetic UL performance and effects were demonstrated in fine finger control. Comparison between studies must be cautious since only three participants at baseline and four after six weeks training could complete the bilateral co-ordination assessment. Together however, these studies suggest that the effects of bilateral training on ipsilesional recovery require further exploration to determine optimal training characteristics and to determine the neurophysiological mechanisms underlying the effects.

DEXTERITY

In the present study, the magnitude of difference in change in dexterity between baseline and the end of the six weeks training period was very small, with a change of 0.05±0.08 pegs per second for the bilateral group (10% change from baseline) compared to 0.02±0.02 for the unilateral group (4% change from baseline. In terms of functional improvement, this was a small difference representing a percentage change difference of 6% between the groups which does not reach the difference of 10% considered to be clinically significant (Van der Lee et al. 2001). Ipsilesional UL dysfunction is subtle compared to contralesional dysfunction and it is nonetheless noteworthy that dexterity improved with a training programme designed to address dysfunction of the hemiparetic UL. Under bilateral conditions the ipsilesional limb is limited by the paretic limb's ability to move. The ipsilesional limb adopts similar timing and patterns of movement to the paretic limb and moves more slowly than its preferred natural rate (Rose and Winstein 2005). Improved ipsilesional dexterity occurred with bilateral training despite this constraint, therefore ipsilesional effects might not result from specificity of the tasks for functional use, but from another mechanism related to the bilateral nature of the training.

As discussed in relation to the contralesional side, repetitive, rhythmic bilateral practice may enhance neural efficiency through a centralised timing process. Enhanced neural efficiency developed in this way may lead to generalised improvements in *ipsilesional* performance such as dexterity, that are not necessarily specific to the characteristics of the trained tasks

(McCombe-Waller and Whitall 2004). This observation is also in line with the interlimb co-ordination models discussed in Chapter 1, Section 1.2.2.1. Specifically, dynamic systems models suggest that during bilateral rhythmic repetitive movement the limbs entrain to an in-phase co-ordination pattern that appears to be centrally controlled (Franz et al. 1991, Swinnen 2002). Movements in the present study were discrete rather than rhythmic with specific end-point goals however and participants experienced difficulty maintaining consistent interlimb coupling. However the bilateral interaction between the limbs may have been sufficient to access a central timing process that led to significant improvement in dexterity with task training that was ostensibly not optimal for ipsilesional improvement. Effects may have depended on conditions that *temporarily* adjusted interlimb interactions since the bilateral advantage for ipsilesional recovery of dexterity was lost for overall change between baseline and follow-up. Strategies to enhance long-term retention of effects require investigation.

An alternative explanation for the observed improved ipsilesional dexterity following bilateral training is alteration to interhemispheric inhibition. After stroke, interhemispheric inhibition from the damaged hemisphere to the undamaged hemisphere is reduced (Liepert, et al. 2000, Butefisch et al. 2003). Loss of normal inhibition between hemispheres is thought to lead to abnormally increased excitability of the non-damaged hemisphere (Cauraugh and Summers 2005). This altered balance of excitation and inhibition between hemispheres may also lead to the subtle ipsilesional dysfunction observed in the present study (Yarosh et al. 2004).

TMS studies show that bilateral mirror-symmetric activities can restore normal interhemispheric inhibition patterns after stroke (Stinear et al. 2008). Bilateral activities, albeit in this study not perfectly coupled interactions, probably increase transcallosal inhibition from the damaged to the undamaged hemisphere to restore the balance of excitation and inhibition towards normal. This in turn may lead to more normal output not only from the damaged hemisphere, but also from the undamaged hemisphere (Stinear et al. 2008, Stinear and Byblow 2004). The ipsilesional effect of training observed in the bilateral group of the present study may thus have emerged from a rebalancing of interhemispheric inhibition. However until neuroimaging studies have examined the phenomenon, it will remain a speculative explanation. The caveat is that it was difficult for participants to maintain simultaneous movement throughout task performance in practice. As with the

contralesional limb, this may have limited the potential for interhemispheric inhibition, and greater effects may have been observed had interlimb coupling been more tightly controlled.

Another potential explanation for the greater improvement in dexterity in the bilateral group was that compared to the unilateral group, participants in the bilateral group received training of the non-dominant ipsilesional upper limb. Participants, particularly those undertaking core tasks, were trained in some tasks that were not normally performed by the non-dominant UL, such as accurate targeting of small objects during peg placement, and touching small targets with pens. It was therefore possible that the greater improvement in the bilateral group during training may have occurred in the bilateral group through skill acquisition in the non-dominant ipsilesional UL. Data were examined to see if this was the case (Section 5.8.5.2), however the raw data showed that there was little difference between the dominant and non-dominant sides in either group in terms of improvement between baseline and six weeks, ruling out skill acquisition in the non-dominant UL as an explanation for the greater recovery in the bilateral group.

IPSILESIONAL ACTIVITY LIMITATION

In the present study, ipsilesional dexterity improved significantly with bilateral training to a degree approaching significance, whereas ipsilesional activity limitation did not. The most likely explanation for the finding is that it reflects the small number of participants with sub-maximal performance on the Action Research Arm Test. Compared to the contralesional side, participants also scored high, with the lowest recorded score of 42 out of a maximum of 57, leaving little scope for improvement on the measure and creating a ceiling effect that did not exist on the timed Nine Hole Peg Test.

An alternative explanation for the differential effect of bilateral training on ipsilesional dexterity compared to activity limitation may be neurophysiological. There is evidence of increased bilaterally distributed interrelated neural network activation with increased task complexity, such as during rapid dexterity tasks. This involves ipsilateral primary motor, sensory and premotor cortices as well as supplementary motor areas (Shibasaki et al. 1993, Winstein and Pohl 1995, Chen et al. 1997, Catalan et al. 1998). As discussed, functioning of these networks may be altered with stroke leading to the observed subtle ipsilesional impairments. Bilateral training may have contributed to restoration of these networks for complex ipsilesional performance. Training effects may have been most apparent on the Nine Hole Peg Test because the speed and complexity demands of the test activated these

networks which may not have been fully activated during the simpler tasks of the Action Research Arm Test where activity was not timed.

It is not clear why, when there was no advantage of bilateral training for the contralesional side, it appeared to have limited effects for the ipsilesional side. Effects may simply be due to additional practice compared to the unilateral group who received none targeted at the ipsilesional side. Alternatively, effects may have been observed on the ipsilesional side but not on the contralesional side because deficits to be overcome were much less severe.

IPSILESIONAL DEXTERITY AND ADL INDEPENDENCE

The association, as found in this study, between dexterity and ADL independence is of clinical relevance. The correlations were significant but moderate, and increased in strength over time from r=0.25 at baseline to r=0.40 eighteen weeks. The finding is in line with other research. Similar findings were reported by Desrosiers (Desrosiers et al. 1996), in longstanding stroke where performance on the Purdue peg test was associated with functional independence. Another study with 57 participants also demonstrated similar association between the Nine Hole Peg Test and the Barthel Index (de Groot-Driessen et al. 2006), which increased in strength over time in line with findings from the present study. A further study demonstrated associations between ipsilesional finger tapping and attainment of rehabilitation goals (Prigatano and Wong 1997).

The fine finger tasks in the present study and others require speed and accuracy. Increased task complexity in timed and sequenced activities is associated with bilateral cortical activation in various cortical areas including premotor cortices and parietal lobes (Baraldi 1999). Ipsilesional deficits in complex timed tasks probably reflect damage to bilaterally distributed functionally activated neural networks. The association with ADL performance, which requires more global functioning, suggests that ipsilesional UL performance of complex activities may be an indicator of the integrity of cortical functioning across both hemispheres.

The use of the Nine Hole Peg Test, a simple, bedside clinical test to indicate global functioning of an individual with stroke is an important and potentially useful clinical discovery. Given that the association was apparent at all assessments, future studies should explore the predictive strength over time of ipsilesional dysfunction for global functioning. Furthermore, the association between ipsilesional dexterity and ADL independence confirms

the clinical and functional relevance of ipsilesional dysfunction. The impact of that dysfunction and its perceived and actual effects on a broader range of activities should be explored further. Further work should be conducted to investigate the relationships between ipsilesional UL performance, ADL independence and the neural mechanisms underpinning their association.

6.1.7.3 Study limitations and implications for future research

Comparison to published norms

The presence of ipsilesional dysfunction on the Nine Hole Peg Test and Action Research Arm Test was established by comparison to published norms. Resources determined that it was not possible to statistically establish differences between healthy subjects and study participants which would have been a more robust approach. Caution should therefore apply to interpretation of findings. The existence of ipsilesional dysfunction on the selected measures should be confirmed through comparison to healthy age matched participants.

Training dose

Effects of bilateral training on ipsilesional dexterity may simply have resulted from the fact that the bilateral group received ipsilesional training whilst the unilateral group received none. Effects may therefore be related to dose of training and not to the bilateral component of training. Also, it was not possible to control for the duration, frequency and use of the ipsilesional limb by participants in either group, so it is possible that the training effect occurred because of increased use of the limb by the bilateral group. To establish that effects of bilateral training on dexterity were not simply due to additional therapy, this study should be extended by examining whether bilateral *or* unilateral task training is optimal for ipsilesional recovery using an RCT design with a bilateral training group, a control group receiving no additional intervention plus a unilateral group. The study should be sufficiently powered to detect significant differences on the Nine Hole Peg Test. Similarly, to account for usual activity, use of the ipsilesional limb in all groups could be monitored using movement monitors such as accelerometers.

Study power

The complete case analysis was probably underpowered to detect a significant difference, since the between groups difference in dexterity approached significance (Chapter 5, Section 5.8.5.1) and the bilateral advantage in dexterity was only apparent with intention to treat

analysis. That involved estimation of missing values therefore caution should apply in interpreting the findings.

Population

The study population was selected according to strict inclusion criteria for the contralesional effects of stroke, therefore findings may not apply to the ipsilesional side of participants selected from a more general stroke population. Furthermore, apraxia is a factor that may influence ipsilesional performance (Sunderland et al. 1999) however it was not measured in the present study, a consequence of the post-hoc nature of the analysis of ipsilesional data. It is possible that there was a difference in terms of apraxia between the groups that influenced outcomes. Future studies should examine effects of ipsilesional bilateral training in a more general stroke population, and assessment of apraxia should be carried out to establish its effects on outcomes. Comparison between acute and chronic stroke populations should also be conducted to determine relative effectiveness at different points in recovery.

Measures

The Nine Hole Peg Test was a narrow measure of dexterity that does not reflect the range of dexterity activities performed in everyday life. Clinically it may have been more relevant to use a measure involving a broader range of UL dexterity tasks. It would then have been possible to determine more fully the implications of ipsilesional dysfunction and impact of bilateral training in everyday usage and in tasks such as manipulation of small objects. Future studies should involve a broader variety of dexterity tasks as well as measures of impairment such as grip strength to fully explore the effects of ipsilesional bilateral training. Furthermore, effects of training on more subtle movement parameters such as velocity and acceleration at different points during task performance should also be examined and comparison made between unilateral and bilateral training.

Intervention

Bilateral training appeared to accelerate recovery between baseline and six weeks, however overall the change in pegs placed per second was lower (mean change = 0.04±0.11) than for the unilateral group (mean change =0.05±0.12), suggesting accelerated recovery with bilateral training that was lost at eighteen weeks. Future research should explore ways in which to maintain the training effect. This may involve development of equipment for home exercise and accompanying training programmes and examination of approaches to long-term adherence to the intervention that are relevant and applicable to clinical practice.

The intervention was designed to address contralesional UL dysfunction and not ipsilesional function. Although there was a significant effect for the bilateral group over the unilateral group in change in ipsilesional dexterity with the intention to treat analysis, this may have been greater if activities more appropriate to challenge the ipsilesional side had been selected. Specific activities for ipsilesional bilateral training should be further explored in future studies.

Congruent with the main contralesional study, the loss of tight interlimb coupling may also have influenced outcomes. The optimal practice mode for ipsilesional bilateral *or* unilateral training should be explored in future studies since the present training programme was designed primarily for the contralesional hemiparetic limb. Optimal coupling patterns and methods of entrainment for bilateral training should be compared, given that the ipsilesional limb will always be coupled with the mainly less dextrous contralesional limb factors. Approaches to training more complex activities which assist the contralesional limb whilst maintaining good interlimb coupling should be explored. Robotic devices might be helpful, however their development for distal activities is in its infancy and those that assist more proximal movement would not be appropriate for more complex and distally orientated ipsilesional tasks. Approaches to bilateral ipsilesional training that account for contralesional severity should be explored and a range of interventions involving augmented coupling and assistance should be investigated. The cost-benefits of extensive research programmes to investigate ipsilesional dysfunction should also be considered however particularly since the bilateral training effect demonstrated here did not reach clinical significance.

Specific task characteristics and factors such as speed, intensity, duration, and frequency of ipsilesional training should also be tested to ensure that ipsilesional training approaches relevant to clinical practice are developed and fully understood. These studies will also provide insight into motor control characteristics and may generate information that adds to knowledge about theoretical models of ipsilesional motor control. Future research should also examine how theoretical models of interlimb coupling, within the field of motor control science such as dynamic systems theory, can inform bilateral training parameters for the ipsilesional UL. This may lead to improved understanding of how interlimb co-ordination paradigms can be used to influence ipsilesional outcomes and generate new ideas about appropriate intervention characteristics for optimal effectiveness.

Neuroimaging

Neuroimaging and TMS should be used to provide information about the mechanisms underpinning ipsilesional effects of bilateral training. This should inform the development of training interventions that might provide sustained ipsilesional improvement, and provide an insight into causes of ipsilesional dysfunction and effects of training. Again, neuroimaging studies will make intervention trials more expensive however and costs of studying ipsilesional dysfunction need to be balanced against the relatively small clinical impact of ipsilesional dysfunction.

The first step in ipsilesional research has however to address a fuller understanding of the impact of ipsilesional dysfunction on functioning of the individual with stroke as a whole within his or her environment. In the current study, a small but significant association between ipsilesional dexterity and independence in ADL was found, however the real impact of ipsilesional impairment on how an individual functions within his environment is unclear. Ipsilesional dysfunction may otherwise be an academic finding of no real clinical interest and certainly not worth the investment in future research to investigate the clinical effects of interventions.

6.1.7.4 Implications for clinical practice and rehabilitation research

Although subtle and presenting a relatively minor rehabilitation problem, therapists should be aware of the parameters of normal performance by which to identify ipsilesional dysfunction and should consider including assessment and treatment of ipsilesional performance into clinical practice, particularly since the link, although moderate, between ipsilesional dexterity and ADL dysfunction has been confirmed in the present study. As previously highlighted, the current findings suggest clinically small but potentially useful improvements in performance of fine, rapid dexterity tasks can be achieved with bilateral task training, and that such training should be considered for incorporation into clinical practice. The evidence that dexterity and ADL independence are associated suggests that simple dexterity tests might be useful indicators of global cortical functioning and should be explored for their potential as clinical tools for predicting recovery.

Improving ipsilesional dexterity with bilateral task training may be of interest to motor control scientists. Findings support the existence of central control mechanisms accessed via

bilateral training that may influence ipsilesional performance. The movement parameters underpinning this observation should be explored further to determine why the effect occurred. The evidence might contribute to future theoretical development of models of bimanual co-ordination to explain ipsilesional motor control and central timing of movement. Neurophysiological investigation of mechanisms underpinning ipsilesional dysfunction should be further to examine the neural basis for training effects and the relationship between ADL functioning and ipsilesional dexterity.

Moving on from the effects of bilateral training on UL outcomes, the final physical outcomes section discusses findings relating to factors predictive of contralesional UL activity limitation.

6.1.8 PREDICTORS OF UPPER LIMB ACTIVITY LIMITATION

Clinically, the ability to predict UL recovery after stroke is important to therapists since it enables them to plan relevant treatment options and is important to patients to enable them to prepare for living with the consequences of stroke. Broadening the exploration of physical outcomes from the effects of bilateral versus unilateral training to examine UL recovery of the whole sample, this final section relating to physical outcomes discusses the exploratory analysis of predictors of contralesional UL activity limitation reported in Chapter 5, section 5.9). Here, after determining that training group did not influence predictions, clinical and demographic factors were entered into regression equations to determine the optimal predictors of activity limitation measured on the Action Research Arm Test at six and eighteen weeks.

6.1.8.1 Findings

Baseline variables were examined as predictors first. As expected, upper limb activity limitation measured on the Action Research Arm Test at baseline was the main predictor of activity limitation on the same measure at six weeks. Independence in ADL, days to initial assessment and presence of an anterior circulation stroke were also significantly predictive at six weeks. The baseline model predicted 68% of variance. When the Action Research Arm Test was removed from the model, dexterity measured on the Nine Hole Peg Test and independence in activities of daily living were the two strongest predictors, predicting the same proportion of variance (ß=0.38). Overall the model predicted 54% of variance in the ARAT. At eighteen weeks, upper limb activity limitation measured on the Action Research Arm Test at baseline was again the main predictor and the baseline model predicted 64% of variance in UL activity limitation. Without the Action Research Arm Test, 55% of variance was predicted with dexterity again the strongest predictor. Independence in ADL and days to initial assessment were also significant predictors. Of the six week variables, UL activity limitation was the only significant predictor of eighteen week UL activity limitation and explained 93% of the variance on the measure. With the Action Research Arm Test removed, dexterity explained most of the variance (ß=0.65), but independence in ADL was also a significant predictor (ß=0.27), together these variables explained 72% of variance.

6.1.8.2 Previous literature and interpretation of findings

Few studies have specifically examined predictors of later activity limitation. Most have examined predictors of impairment such as motor performance (Katrak et al. 1998, Gowland 1982). Where predictors of activity limitation have been examined, these have typically been conducted with a more general stroke population without any particular UL inclusion criteria (Wade et al. 1983, de Weerdt et al. 1987); with a very specific population with UL flaccidity (Kwakkel et al. 1999) or over a very short post-acute phase (Higgins et al. 2005). In line with the present study, one study examined a stroke population with a range of UL deficits over time from two to five weeks post-stroke (Feys et al. 2000a) but examined predictors of motor impairment and not activity limitation. Of those studies, two demonstrated impairment as the strongest predictor of activity limitation (Feys et al. 2000a, Kwakkel et al. 2003) over similar assessment periods to the present study, but activity limitation was not included as a predictor, making conclusions about the relative importance of impairment and activity limitation difficult. Activity limitation is important as an outcome since it is a measure of functional ability and is probably the most meaningful measure of recovery to participants and therapists.

Current findings are congruent with the only other study demonstrating early activity limitation as the strongest predictor of later activity limitation (Higgins et al. 2005). In line with the present study, it also demonstrated that dexterity and activity limitation were predictive of activity limitation, and that when gross activity limitation is removed from a predictive model, dexterity becomes predictive. That study was conducted over only five weeks, therefore timescales for prediction are not comparable, however together the findings show the importance of early activity limitation as a predictor of later activity limitation.

That early activity limitation predicts later activity limitation is unsurprising. However the relevance of examining the predictive strength of early activity limitation is to enable clinicians to predict likely recovery with a known degree of certainty.

ACTIVITY LIMITATION AS A PREDICTOR

One important and new finding from the present study stands out. There was little difference in terms of the amount of variance explained by baseline assessments at six weeks and that explained at eighteen weeks. Therefore baseline assessment, (at between two and four weeks after stroke) appears to predict activity limitation at six and eighteen weeks to approximately the same extent. Time, across the duration of the present study, does not

reduce the predictive strength of that assessment by a large magnitude. This finding is congruent with another study using motor impairment as the dependent variable (Feys et al. 2000a). The findings suggest that most recovery had occurred by the six week assessment in the current study (which occurred 8-10 weeks after stroke onset) and of important relevance to clinical practice, provide an indication of the degree of accuracy with which later outcomes can be predicted from baseline assessments.

In line with the finding that most recovery had occurred by six weeks, assessment at six weeks (between eight and ten weeks after stroke) provided the most accurate prediction of eighteen week outcome, explaining 93% of the variance in the ARAT when the ARAT itself was included, and 72% of variance with the ARAT excluded. Again this was in line with findings of another study (Feys et al. 2000a). Prediction at eight to ten weeks after stroke may be too late clinically for planning interventions and discharge, despite its greater accuracy. However, it does provide an indication of how much more recovery might be achieved after that point which is a very useful clinical tool.

Inclusion of the initial Action Research Arm Test score as an independent variable may have led to overestimation of explained variance however, since it was not entirely independent of the dependent variable (Higgins et al. 2005) therefore regression models were run with and without inclusion of that measure. Although the Action Research Arm Test explained more of the variance, results show that activity limitation measured with the Nine Hole Peg Test is also strongly predictive. The likely exaggeration of the predictive strength using the Action Research Arm Test means that although its predictive strength is less, the Nine Hole Peg Test is probably the most robust predictor of Action Research Arm Test score. It is also a clinical test more easily and more commonly used in practice and therefore probably has greater utility in practice as a predictive assessment than the Action Research Arm Test. However a large proportion of patients (n=78, 73.6%) could not perform the Nine Hole Peg Test at baseline making it less useful than might first appear. That the Nine Hole Peg Test *is* predictive of Action Research Arm Test score however is congruent with the fact that good finger function is required to score well on the Action Research Arm Test. Conducting the analysis with and without the Action Research Arm Test provides important clinical options for therapists. For patients with little or no dexterity, it is clear that the Action Research Arm Test provides a good assessment of likely outcome, with the caveat of autocorrelation. For patients able to perform the Nine Hole Peg Test, it provides a simpler bedside clinical assessment of likely future outcome.

OTHER PREDICTORS

ADL independence at baseline and six weeks was a significant predictor of activity limitation at six and eighteen weeks. That global functioning is related as a predictor to UL outcomes has been demonstrated in several other studies (Wade et al 1983; Kwakkel et al 1999, Feys et al. 2000a} and suggests that overall severity and extent of the lesion corresponds to global functioning and in turn UL functioning.

Presence of a total anterior circulation stroke was also predictive of outcome at six weeks, in line with other studies (Kwakkel et al. 2003, Feys et al. 2000b), although the added contribution to the explained variance of inclusion was small at only 0.5%. The presence of a TACS suggests a very large infarct incorporating cortical and sub-cortical areas, and these patients typically demonstrate poorest outcome (Bamford et al. 1991). Lesion site was no longer a significant predictor of UL AL at six months. This may be because in the long run clinical factors are more important in determining recovery, and responses to rehabilitation may override the impact of the lesion site in predicting UL outcomes.

The number of days to baseline assessment was also a significant predictor of UL activity limitation at six weeks with more days to assessment predictive of poorer activity limitation even when the Action Research Arm Test was removed from the equation. The time to assessment reflected how able and well patients were to participate in the trial. Those with more severe stroke were mainly recruited later to give them time to achieve the inclusion criteria for the trial. That this factor was no longer associated with activity limitation at six months suggests that other factors become more important as predictors over time.

In line with other studies (Wade et al. 1983, Kwakkel et al. 1999, Feys et al. 2000a) other factors such as age, sensation and anxiety and depression were not predictive of UL activity limitation. Overall, findings show unsurprisingly that activity limitation is the strongest predictor of later activity limitation, however the fact that it now does so to a known degree at different points in recovery is an important outcome of this analysis. Whilst other factors add to the explained variance, their contribution is relatively small.

6.1.8.3 Study limitations and implications for future research

Design

Participants received usual therapy and additional therapy as part of the bilateral training study. Duration, frequency intensity of therapy and environmental factors might have contributed to outcome but was not accounted for in the predictive models. Furthermore, baseline assessment was conducted between two to four weeks after stroke onset. This delay means that important information that may have strengthened prediction may have been lost. The number of assessments was low compared to some other studies (Kwakkel et al. 2006), which may have placed limitation of the information about recovery patterns and the predictive impact of time on UL activity limitation. Future studies should therefore account for the duration, intensity and frequency of therapy in predicting activity outcomes. Assessments should occur soon after stroke in order to account for natural recovery processes in predicting outcome and should be more frequent to account for the impact of time on recovery.

Population

Participants were specifically selected for inclusion to the bilateral training intervention, leading to limited potential for generalisation of the findings to the general stroke population. This study should be replicated with a study population that is not undergoing additional therapy within an RCT and that represents the general stroke population

Independent variables

Some potentially important clinical variables were not included in the predictive models. Sitting balance, muscle tone and hemi-inattention which have been demonstrated as predictors of motor impairment (Feys et al. 2000a), shoulder pain and grip strength (Feys et al. 2000a, Sunderland 1989) may have explained more of the variance and should be included in future studies.

It was not possible to examine motor impairment as a predictor in the present study. The Rivermead Motor Assessment, the impairment-orientated measure in the present study was too closely correlated with the Action Research Arm test to be included as an independent variable. The measures clearly examined constructs that were strongly related and this observation highlights the difficulty in distinguishing between the predictive strength of activity limitation and motor impairment within a predictive model. Future studies should select measures that clearly differentiate between motor impairment and activity limitation in

order to determine the predictive strength of each, and will provide important information to guide the targeting of therapy strategies for activity limitation.

Finally, it was not possible to examine the neural substrates involved in recovery patterns. It was not possible therefore to understand the relationship between physiological changes in neurotransmission and cortical activation patterns involved in recovery of activity limitation. The nature and predictive value of neural mechanisms underpinning recovery remain speculative (Kwakkel et al. 2006). However neurological indicators of recovery such as cortical activation patterns should be examined further. In line with other studies reporting the predictive relevance of systematic systems for delineating lesion location on CT scan on general functioning (Ng et al. 2007, Barber et al. 2000) and upper limb functioning (Shelton and Reding 2001) more detailed assessment of lesion location using CT scans is warranted. That approach is probably more reliable in determining lesion location than the clinical classification of the Oxfordshire Community Stroke Project used in the present study (Dewy et al. 1999) and should provide a more accurate indication of the predictive strength of lesion location than was possible in the present study. Furthermore, relationships between global functioning and recovery of UL functioning should also be examined in the context of the neurological indicators since the exact mechanisms by which they influence each other are unclear. This will requires multi-professional input from neuroradiologists and neurophysiologists in future studies which are large enough to allow for multiple factors to be included in regression modelling.

6.1.8.4 Implications for clinical practice and rehabilitation research

Findings are of considerable clinical relevance since the ability to predict future functional use of the UL is important for participants and therapists. Anecdotally, therapists do not tend to use predictive modelling to inform clinical practice, however this study provides accessible information over a timescale that is relevant to the usual rehabilitation period and should be useful to therapists working in stroke rehabilitation. Clinically, the Nine Hole Peg Test is probably the most useful predictor of future upper limb function because it is a simple commonly used and validated test with published normative data. However many patients are unable to perform this test at baseline. Findings show that clinicians can alternatively use the Action Research Arm Test, with the caveat that it may overestimate later prediction, as a predictive tool. That requires more time but does not have the floor effect demonstrated with the Nine Hole Peg Test. These findings broaden the range of available clinical tools

with which therapists can predict later outcome and appropriately target therapy to a known degree of certainty. This research makes predictive modelling accessible and useful to therapists who use these measures as clinical indicators of recovery in stroke rehabilitation. Future studies should seek to translate the predictive modelling into outcome scores that are meaningful for therapists. Useful clinical information would for example be " if a patient has scored *x* on the Action Research Arm Test by six weeks, there is a *y* chance that they will score *z* on that measure at six months".

The current findings which relate to UL activity limitation are particularly important in a field of rehabilitation research which has typically included impairment outcomes as dependent and independent variables. Discrimination between activity limitation and impairment in prediction of UL outcomes is important because it facilitates development of interventions targeted appropriately at specific outcomes. These findings will contribute to the development of interventions appropriate to the recovery patterns of activity limitation over time.

Having completed the section on from physical outcomes of the UL after stroke, the next section discusses the impact of bilateral training and UL recovery of the sample as a whole on the broader psychosocial outcomes of anxiety and depression and health related quality of life.

6.2 PSYCHOSOCIAL OUTCOMES: EFFECTS OF BILATERAL TRAINING AND PREDICTORS OF HEALTH RELATED QUALITY OF LIFE

6.2.1 INTRODUCTION

Stroke is a complex condition that affects many aspects of an individual's life and experience beyond physical dysfunction. Rehabilitation physiotherapy however typically focuses on reduction of impairment and restoration of function, and often fails to take account of what happens beyond simple physical recovery (McEwen et al. 2000). There is strong evidence that post-stroke depression and anxiety are common (Chemerinski and Robinson 2000, Hackett and Anderson 2005, Chemerinski and Levine 2006). Those psychological states have been associated in many studies with post-stroke disability (Chemerinski and Robinson 2000, Hackett and Anderson 2005). The full nature of the relationship between post-stroke physical dysfunction and depression and anxiety has not been fully explored, and it is not yet clear whether disability causes depression and anxiety or vice versa (Turner-Stokes and Hassan 2002). Little is known about the impact of UL dysfunction on anxiety and depression. This bilateral training study provided an opportunity to add to that body of knowledge by examining whether anxiety and depression were influenced differently by bilateral compared to unilateral training. .

Similarly, many studies show that HRQOL is adversely influenced by stroke (Mayo et al. 2002, Jonsson et al. 2005). Several UL studies have also examined the impact of interventions on HRQOL. However across those, findings have been equivocal. Some studies have demonstrated improved HRQOL with changes in UL measures (Dettmers et al. 2005, Butler et al. 2006, Wolf et al. 2006, Wu et al. 2007) and others have demonstrated no improvement in HRQOL (Kwakkel et al. 1999, Finley et al. 2005, Barnes et al. 2006), even where there has been an improvement in UL impairment or activity limitation as a result of training. It was therefore relevant to examine the impact of bilateral training compared to unilateral training on HRQOL. Findings are discussed in section 6.3.2.

Upper limb dysfunction also appears to be a predictor of HRQOL at different points in time after stroke (McEwen et al. 2000, Ones 2005, Wyller et al. 1997, Nichols-Larsen et al.

2005). It is not clear from this literature however, which domains of UL functioning - impairment, activity limitation or dexterity - are most influential in determining HRQOL because of the diversity of measures used. The aim of the second section within the psychosocial theme was therefore to determine which UL factors, from the selected measures, most influenced HRQOL for the *whole sample* at the follow-up assessment at eighteen weeks. Clinically this was an important area of investigation. Understanding the aspects of UL dysfunction which most influence patient perceptions of HRQOL could enable therapists to appropriately prioritise therapy to improve perceived quality of life. Findings are discussed in section 6.2.2.

6.2.2 EFFECTS OF BILATERAL TRAINING ON ANXIETY, DEPRESSION AND HEALTH RELATED QUALITY OF LIFE

6.2.2.1 Findings

There was no significant effect of bilateral compared to unilateral training on anxiety, depression or HRQOL at any of the assessments (Chapter 5 Section 5.9), suggesting that bilateral training did not differentially influence any of the psychosocial outcomes.

6.2.2.2 Previous literature and interpretation of findings

ANXIETY AND DEPRESSION

The rationale for this part of the thesis was that *if* UL recovery was improved through an intervention such as bilateral training, depression and anxiety *might* also be improved. The premise was appropriate since many studies have demonstrated associations between anxiety, depression and global physical outcomes (Shimoda and Robinson 1998, Hackett and Anderson 2005, Yanagita et al. 2006), but it remains unclear however whether depression and anxiety precede physical limitations or the other way round (Yanagita et al. 2006). Several studies have shown that treatment of depression with anti-depressants improves overall physical functioning after stroke, suggesting that depression influences physical outcomes (Chemerinski et al. 2001, Gainotti et al. 2001, van de Weg et al. 1999), but few studies have examined whether responses to physical interventions improve psychological outcomes.

Only one previous published study was found that examined relationships between depression and UL motor performance (Platz and Denzler 2002). That study examined the impact of depression on responses to sensorimotor training for motor performance in 33 individuals with mild paresis. Eight participants demonstrated paresis as a result of traumatic brain injury, however making comparison to the present stroke sample difficult. The intervention led to significant improvements in motor performance but depression predicted only 10% of variance in motor performance, suggesting that depression is of little consequence to UL recovery. However in that study the sample was well-recovered and demonstrated low depression scores. In contrast, the present study compared effects of unilateral or bilateral training depression and anxiety. Thus the studies examined the psychological outcomes from both perspectives – effects of depression on UL outcomes in the case of Platz (2002) and effects of UL training on depression in the present study. Neither study demonstrated a significant effect. Although conclusions must be tentative from so few studies, findings suggest that the relationship between depression and UL motor performance may be limited, irrespective of the effectiveness of interventions.

However, two potential explanations should be considered in relation to present findings. Firstly, UL recovery may potentially influence depression and anxiety, but with the exception of dexterity there were no significant differences in outcomes in the present study. It is unsurprising therefore given the very small physical difference between the groups, that anxiety and depression were not significantly different between the groups. The small difference between the groups in overall dexterity *was* however clinically and statistically significant. That anxiety and depression did not differ significantly between the groups in *spite of this difference* suggests that improved UL dexterity does not influence on anxiety and depression. It is not possible to determine which explanation is correct from the present study.

Until studies have been conducted with UL interventions that do influence motor performance more significantly than in the present study, it will not be possible to determine if changes in UL performance influence depression and anxiety. Whilst there is no evidence from the present study to show that UL recovery through bilateral training influences anxiety and depression, the existing literature highlights the need for UL intervention studies and indeed all rehabilitation studies to continue to include measures of anxiety and depression. It also highlights the need for rehabilitation therapists and clinical and health psychologists to

work together to fully understand the complex interactions between physical and psychological outcomes in stroke.

HEALTH RELATED QUALITY OF LIFE

Health related quality of life reflects perceptions of the impact of health conditions on the lives of individuals. The current study interventions demonstrated only a small difference in UL functioning that probably did not influence HRQOL. Conversely, several studies have demonstrated improved HRQOL with improved UL outcomes (Dettmers et al. 2005, Butler et al. 2006, Wolf et al. 2006, Wu et al. 2007). Those studies used the Stroke Impact Scale (Duncan et al. 1999), a stroke-specific measure of the perceived impact of stroke on functioning that included UL functioning as a specific domain. The difference in findings using the Stroke Impact Scale compared to the present study probably relate to the greater effectiveness of those interventions. The nature of the measures must also be considered however. The Stroke Impact Scale, which is in some articles presumed to measure HRQOL (Nichols-Larsen et al. 2005), probably in fact simply measures *perceived* health in certain domains relevant to stroke. These may or may not influence quality of life for individual patients (Hunt 1997) however the measure does specifically measure perceived UL function. The generic Nottingham Health Profile selected in the present study and another measure of perceived health status presumed to equate to HRQOL, may have insufficient construct validity for use in stroke UL recovery. The difference in measured constructs probably contributes to differences in findings between the present study and the others.

Furthermore, whilst improved UL outcomes are known to influence perceived well-being within and after the first year post-stroke (Wyller et al. 1997, Nichols-Larsen et al. 2005) the small difference in dexterity in the present study may have had relatively little impact on HRQOL in acute stroke when ambulation may be a greater concern to the patient (Shah et al. 1989). Several of the studies demonstrating improvements in HRQOL with UL interventions were conducted with participants in the chronic post-stroke period (Dettmers et al. 2005, Butler et al. 2006)when improvements in UL dysfunction for functional and leisure activities in individuals living in the community and functioning in their own environments may have a greater impact on perceived HRQOL.

6.2.2.3 Study Limitations and implications for future research

Analysis

Investigation of effects of anxiety and depression on UL recovery using factorial ANOVAS or regression analysis would have been appropriate in addition to comparing effects of training on those variables. This would have contributed more fully to the debate regarding the relationship between UL dysfunction and anxiety and depression. Although there was no effect of bilateral training compared to unilateral training on anxiety and depression in the present study, the literature shows that there may be a relationship between UL dysfunction and these variables (Wyller et al. 1997). Therefore, future research should continue to endeavour to determine the role of anxiety and depression in predicting UL recovery over time using predictive modelling or factorial ANOVAs in longitudinal studies. The relative importance of UL dysfunction in relation to anxiety and depression compared to more global effects of stroke on general functioning should also be discriminated using predictive modelling. In this way it will be possible to determine more clearly the relationship between physical and psychological outcomes.

Measures

Although widely used in stroke (Morrison et al. 2005), HADS is a screening tool for anxiety and depression, and its sensitivity and specificity for diagnosis have been challenged (Johnson 1995). This is particularly so since many of the post-stroke symptoms such as apathy, loss of concentration motor and speech disorders are also present in depression, which may lead to inflated depression scores which actually reflect the effects of stroke. Thus the study findings should be regarded with caution. Future studies should include assessment of anxiety and depression using more robust clinical measures than the HADS. This assessment should probably take place once the immediate symptoms of stroke have settled so that they are not mistaken for signs of depression. Study teams should include a clinical psychologist and or psychiatrist to provide more research expertise in depression than was available in the present study. A clinical assessment of depression and anxiety should also be included as part of the initial screening.

Findings for HRQOL may have been influenced by the use of generic HRQOL measure which did not include stroke specific outcomes. Comparison should be made between effects of UL interventions on generic and stroke specific HRQOL measures. In this way it will be possible to determine the relative validity of each.

Because of communicative and physical difficulties in completing the questionnaires, the raters read the questionnaires to patients and where necessary completed the forms. This may have influenced the way in which patients responded. The impact of rater completion of questionnaires should be evaluated for questionnaires used in future stroke studies to determine whether it influences the reliability and validity of outcomes. Rater recording of responses may lead to social desirability bias where participants respond as they think the rater wishes them to, rather than reflecting their own opinions (Bowling 2000).

6.2.2.4 Implications for clinical practice and rehabilitation research

The literature demonstrates that anxiety and depression influence physical outcomes in stroke, however little is known about whether physical recovery or responses to post-stroke rehabilitation influence anxiety and depression or vice versa. This study showed no significant differential effect of bilateral compared to unilateral training on anxiety and depression. In asking whether psychological variables respond to rehabilitation interventions however, the study points to a new field of research in stroke rehabilitation that combines investigation of physical and psychological outcomes. This is complementary to the field of exercise science in which much is now known about the positive impact of physical activity on depression in the general population (Mead 2008). Inclusion of psychological outcomes in future rehabilitation studies should provide a more holistic assessment of the relationship between physical outcomes and psychological variables and may lead to physical interventions that specifically influence anxiety and depression as well as physical outcomes.

Recovery from stroke is about return to participation in life roles and social and leisure activities beyond simple motor functions that make life worth living and contribute to quality of life. Return of patients to a life of quality is a key tenet of rehabilitation philosophy enshrined in health policies such as “Co-ordinated, integrated and fit for purpose: A Delivery Framework for Adult Rehabilitation in rehabilitation in Scotland” (Scottish Government, 2007). The interaction between upper limb dysfunction and quality of life is an important one for rehabilitation therapists. Upper limb dysfunction may interfere with many life roles, leisure and social activities beyond the simple functions measured in upper limb rehabilitation tests. Understanding the relationship between UL dysfunction after stroke and HRQOL is therefore an important one for therapists, since it may enable them to target interventions appropriately at what is important to patients for their quality of life. Equally, it is important to understand when continuing to spend health service resources on UL

dysfunction is *not* contributing to improved quality of life. Examination of the relationship between UL dysfunction and HRQOL provides an opportunity for appraisal of how the patient perceives the impact of stroke on his or her life. Therefore although the present study showed no effect of UL training on HRQOL, future studies should continue to include HRQOL as an outcome measure since it is only in this way the full impact of UL interventions will be understood.

In examining HRQOL in the present study questions have been raised about whether generic or stroke specific measures of HRQOL are most appropriate as stroke rehabilitation outcomes, since perceived physical effects of training, may have been missed with the selected generic measure.

The next section is the final one relating to psychosocial outcomes. It examines the role of UL dysfunction in predicting HRQOL at the eighteen week assessment which occurred approximately six months after stroke onset for the sample as a whole.

6.2.3 PREDICTORS OF PERCEIVED HEALTH RELATED QUALITY OF LIFE

In this final evaluation of the impact of UL recovery on psychosocial outcomes, the predictors of HRQOL at the eighteen week assessment (approximately six months after stroke onset) were explored to determine which, if any, of the three UL variables (i.e. activity limitation, dexterity and impairment) best predicted HRQOL measured on the Nottingham Health Profile for the whole sample, irrespective of intervention group. The eighteen week assessment was the dependent variable and demographic factors and eighteen week outcome measures were the independent variables. This assessment point was selected because by the time of follow-up assessment, most participants had been discharged home and the impact of stroke on quality of life within their own environment would be apparent.

6.2.3.1 Findings

It was only partly possible to determine the relative importance of different UL domains in predicting HRQOL. The dexterity measure, the Nine Hole Peg Test was not a significant correlate of the Nottingham Health Profile, suggesting that there was no relationship between dexterity and HRQOL. Dexterity was therefore excluded as a potential predictor of HRQOL. The Rivermead Motor Assessment, the measure of impairment and the Action Research Arm Test, the measure of activity limitation, demonstrated multicollinearity. The Action Research Arm Test was dropped from the model since it demonstrated a lower correlation with the Nottingham Health Profile than the Rivermead Motor Assessment.

Upper limb impairment measured on the Rivermead Motor Assessment was a significant predictor of total Nottingham Health Profile score at eighteen weeks. With anxiety and depression, UL impairment predicted 47% of the variance but was only a significant predictor with the intention to treat analysis (Table 29, ITT Appendix 14).

UL impairment was also a significant predictor of the Nottingham Health Profile sub-section Perceived Physical Activities at eighteen weeks. Independence in ADL was also a significant predictor of perceived physical activities and together these variables explained 36% of the variance.

Anxiety was the only significant predictor of the Nottingham Health Profile domains of Pain, Emotional Reactions, Sleep and Social Isolation, whilst anxiety and depression significantly predicted Energy Levels. The amount of variance predicted was relatively low however, ranging from 12% for Pain to 50% for Emotional Reactions.

Allocation to the bilateral or unilateral training group was not a significant correlate of HRQOL and was therefore not included in the regression model, as it was unlikely to influence findings.

6.2.3.2 Previous literature and interpretation of findings

UPPER LIMB IMPAIRMENT AS A PREDICTOR OF TOTAL HRQOL

The finding that UL impairment predicted total HRQOL score is in line with two other studies. In one, there was a modest association between UL motor performance and Nottingham Health Profile total score at six months post-stroke (Ones et al. 2005). That study did not conduct predictive analysis therefore direct comparison with the present study can only be limited, however it does similarly suggest a relationship between HRQOL and the UL using the same HRQOL measure. Wyller et al. (1997) demonstrated that UL impairment measured on the Sodring Motor Evaluation at one year was significantly predictive of HRQOL measured on the General Health Questionnaire. The measures in that study were different from the present study, and the time post-stroke was not specified, however the findings are broadly similar. Several studies have also demonstrated that UL activity limitation predicts HRQOL six months or more after stroke (McEwen et al. 2000; 2000, Nichols-Larsen et al. 2005). Together with the present study this body of evidence shows that that UL dysfunction, where it is included in predictive models, is important in determining HRQOL at six months after stroke and beyond.

It was not possible to determine the relative importance of UL activity limitation, motor impairment or dexterity in predicting HRQOL in the present study because of close correlation between UL measures. Fine dexterity measured on the Nine Hole Peg Test was not significantly correlated with the Nottingham Health Profile and was therefore excluded from the analysis. It can be concluded that, in the present study, dexterity did not influence HRQOL. Activity limitation and motor impairment demonstrated shared collinearity. Motor impairment demonstrated closest correlation to the HRQOL measure, and was retained

whilst activity limitation was removed from the model. This confirms other study findings (Platz et al. 2005) suggesting that activity limitation and motor impairment are constructs that are closely linked, making it difficult to determine their relative importance for HRQOL. It was considered important to distinguish their impact on HRQOL since therapy activities targeting each vary in nature (French et al. 2007). Activity limitation measures, including a broader range of everyday UL activities such as cooking, sewing, keyboard skills and use of tools, might distinguish relative importance of activity limitation from motor impairment in predicting HRQOL better than the relatively simple activities of the Action Research Arm Test. This may however best be done by asking patients themselves within a structured format, what activities are most important to their HRQOL, since it is likely to be an entirely personal perception. In this way it would be possible to determine which UL activities most influence HRQOL for individual patients. Therapists would then be able to better target UL therapy at activities and outcomes likely to influence HRQOL as perceived by individual patients.

Upper limb impairment predicted more of the variance in total HRQOL than independence in ADL, which was not a significant predictor. Although many studies show ADL as an important predictor of HRQOL (Mayo et al. 2002, Jonsson et al. 2005, MacKenzie and Chang 2002, Kim et al. 1999), unlike the present study, none included UL functioning as an independent variable, possibly skewing findings in favour of ADL as the only physical predictor of HRQOL. In line with Wyller et al. (1997), the present study shows that where UL functioning *is* included, it may be of greater importance than ADL functioning at six months in determining HRQOL. In the present study by eighteen weeks most participants had returned to the community and were relatively independent in ADL activities, with 82% demonstrating scores on the Modified Barthel Index of greater than 75. Consequently, the relative importance of UL dysfunction compared to ADL independence was probably greater because of the challenges faced in returning to life roles and functional, social and leisure activities, many of which require a high level of UL functioning.

UPPER LIMB IMPAIRMENT AS A PREDICTOR OF PHYSICAL ACTIVITIES

UL impairment predicted most of the variance in the Nottingham Health Profile sub-section perceived Physical Activities. ADL independence was also a significant predictor but predicted less variance. Together, the variables accounted for 36 % of the variance in Physical Activities. Findings suggest that UL impairment is a fairly important predictor of physical activities. This finding is in line with another study which examined the

relationship between UL impairment and HRQOL (McEwen et al. 2000). The selected measures differed from the present study, however in line with current findings, motor performance measures including UL measures and ADL performance explained 39% of the variance in HRQOL measured of the SF36, supporting the idea that UL impairment is an important physical co-determinant of physical aspects of HRQOL in long-term stroke. This again raises the question about how much HRQOL measures actually measure HRQOL and how much they simply measure perceived physical function. Similarly, another study of 216 participants between 3 and 9 months after stroke demonstrated that UL activity limitation measured on the Wolf Motor Function Test also significantly predicted the physical domain of the Stroke Impact Scale (Nichols-Larsen et al. 2005). The Stroke Impact Scale specifically measures perceived UL and hand function therefore it is not unexpected that UL functioning might influence this aspect of perceived physical functioning through autocorrelation. Nonetheless, together with the present study, that study and others suggest that UL performance is an important predictor of perceived HRQOL six months or more after stroke.

In the present study, UL impairment predicted more of the variance in physical activities than ADL independence which is surprising, given that of eight items only the dressing and reaching items in the physical activities section of the Nottingham Health Profile involve UL functioning. Other items involve standing and walking. Previous studies have shown that patients can be independent in ADL activities such as dressing with a dysfunctional UL however (Platz et al. 2005), suggesting that an intact UL is not necessary for independence in dressing. However the weighting in the Nottingham Health Profile given to dressing is higher than for four of the walking items, which may have skewed findings towards UL impairment as a predictor (The European Group for Quality of Life and Health Measurement, 1992). Irrespective of the reasons, clinically the relative importance of UL dysfunction in predicting performance of physical activities is an important finding since it provides an assessment from the perspective of the patient, of the impact of UL dysfunction on their perceived physical activities. It again highlights the importance for therapists of focusing rehabilitation on UL dysfunction as an important predictor of patients perceived physical activities.

ANXIETY AND DEPRESSION

Although UL impairment was a significant predictor of HRQOL, anxiety and depression predicted more variance of total HRQOL and were the only predictors of energy levels. Anxiety alone significantly predicted pain (12% of variance), emotional reactions (50% of variance), sleep (19% of variance) and social isolation (22.5% of variance). Many previous cross-sectional studies have demonstrated that anxiety and depression (Ahlsio et al. 1984, Fruhwald et al. 2001) or anxiety alone (Shimoda 1998, Wyller et al. 1998) are the most significant predictors of HRQOL. Several other studies demonstrated that depression alone is a strong predictor of HRQOL between six months and four years after stroke, amongst other factors (Niemi et al. 1988, King 1996, Kim et al. 1999, Jonsson et al. 2005, Robinson-Smith et al. 2000, Kauhanen et al. 2000, Ones et al. 2005). Most studies demonstrating depression as a significant predictor measured only depression, whereas in the present study it was possible to examine the relative importance of anxiety and depression. The findings in the present study suggest that anxiety was a relatively more important predictor of HRQOL than depression.

The findings show that emotional responses to stroke are the most important determinants of HRQOL at six months. They suggest that many patients are distressed after stroke and that this has a greater impact on their perceived quality of life than physical variables. A large body of literature shows that depression is very common following stroke (Chapter 3, Section 3.1), and there are many initiatives to develop care and treatment pathways to enable health professionals to recognize and manage depression (Turner-Stokes and Hassan 2002). There is less recognition of anxiety as a post-stroke disorder (Chemerinski and Levine 2006), and it is typically not recognized or managed in the context of rehabilitation. The present findings and findings from other studies (Morrison et al. 2005) indicate however that anxiety is indeed an important condition that adversely influences participants' post-stroke quality of life. Therapists and other health professionals should therefore be aware of the implications of anxiety for participants post-stroke, and management strategies should be developed to enable these health professionals to recognize and help participants to deal with anxiety as a priority.

Findings regarding anxiety and depression should be considered within the context of the debate regarding the concept of HRQOL. There is, as discussed in Chapter 3, debate in the literature regarding the theoretical constructs underpinning the concept of HRQOL. It has been suggested that many of the constructs examined in HRQOL measures are in fact

measuring anxiety and depression anyway. The strong predictive relationship between anxiety and depression measures and HRQOL measures may result from autocorrelation between the constructs of the Hospital Anxiety and Depression Scale and the Nottingham Health Profile (Fruhwald et al. 2001). Indeed, the constructs examined in the NHP subsections of pain, emotional reactions, sleep and social isolation have all been previously independently linked to the effects of depression or anxiety (Fruhwald et al. 2001). In particular, the NHP has been shown to actually measure depression in stroke and is suggested as a valid indicator of depression in stroke (Ebrahim et al. 1986) raising the question about what the NHP is measuring that is distinct from the psychological constructs of anxiety and depression. Until there is more distinction between psychological constructs and HRQOL, findings regarding HRQOL should be regarded cautiously.

6.2.3.3 Study Limitations and implications for future research

Population

The study population was selected specifically for an upper limb study and all participants demonstrated UL dysfunction. This may have led to an overestimation of the predictive strength of UL impairment for HRQOL. The potential bias caused by study selection criteria suggest that this study should be repeated with a more general stroke population that have not undertaken an UL training intervention before results can apply to the general stroke population.

Intention to treat analysis

UL impairment was a significant predictor of total NHP score, but only when the intention to treat analysis was applied, suggesting that the study power - where dropouts were not accounted for - might have been too low to detect UL impairment as a predictor of HRQOL. Caution needs to be applied in interpreting the ITT analysis however, since values for the missing data are estimated, although the estimate is conservative and gives some indication of the effects of missing data. Future studies should be adequately powered for the specific purpose.

Proportion of explained variance

The proportion of variance in total HRQOL explained by the variables in the present study was low, only 48%, suggesting that a considerable proportion of the variance of NHP total score was not explained by the included variables. This is unsurprising, since variables

relating to social and economic status, marital status, education, race, comorbidities, self-efficacy, memory and cognitive functioning were not included in the model. These factors have been shown to explain some of the variance in other studies (Ahlsio et al. 1984, Niemi et al. 1988, King 1996, Kim et al. 1999, McEwen et al. 2000, Robinson-Smith et al. 2000, Mayo et al. 2002, Jonsson et al. 2005), and inclusion of these factors would have provided a more complete picture of determinants of HRQOL. They were not included because this was a secondary analysis of data collected for the bilateral trial.

Future studies should include a wider range of demographic factors such as social support, marital status, and communication ability which are known to influence HRQOL and which may explore more variance in HRQOL than was achieved in this study.

The shared collinearity between the ARAT and the RMA means that they probably do not measure distinct UL constructs. Whilst the RMA examines some aspects of movement that could be categorised as impairment, it also examines several UL tasks or activities that could therefore be considered as measuring activity limitation which probably explains the close correlation with the ARAT. The close relationship between these measures and the consequent need to drop one measure from the model therefore made it difficult to discern which aspects of UL dysfunction – activity limitation or impairment - were most predictive of HRQOL. A wider range of UL measures of impairment and activity limitation should therefore be included in future studies of HRQOL. The measures should clearly measure separate UL constructs and should include a broad range of everyday activities and simple UL impairment outcomes such as muscle strength. In this way it might be possible to better discriminate between the impact of impairment and activity limitation on HRQOL. Stroke specific HRQOL measures should be used to capture the broad range of constructs of relevance.

Timing

The present study and others discussed above have examined the predictive strength of UL dysfunction at a single point in time, with most studies examining HRQOL six months or more after stroke (Chapter 2). It is unclear therefore how the relationship between HRQOL and UL dysfunction changes over time. Understanding how and when this relationship emerges and changes should be an important area for future study. Longitudinal studies examining the relationship between HRQOL and UL dysfunction should be conducted to investigate how the relationship changes over time.

HRQOL Measure

Although valid and widely used in stroke (Ebrahim et al. 1986), the Nottingham Health Profile does not examine many of stroke-specific issues, such as communication and cognitive functioning and even UL functioning that are of common concern after stroke, and therefore may have missed constructs that are very important to participants. Furthermore, HRQOL is conceptualised according to individualised perceptions of what it means (O'Connor 2004). The selected HRQOL and UL measures examine objective constructs from the perspective of the observer, which may be unrelated to the perception of the individual. Future consideration should therefore be given to the development of patient-centred measures that identify UL and HRQOL factors of concern to the individual. Although such individualised measures would present problems to researchers trying to aggregate data, for clinical purposes it may provide an individualized perspective to therapists about the problems that really matter to patients.

The finding in the present study that UL impairment influences HRQOL suggests that ways in which UL therapy interventions can best be targeted to influence HRQOL should be investigated. All UL intervention studies should include a measure of HRQOL, and different interventions should be compared in RCTs to investigate their impact on HRQOL.

6.2.3.4 Implications for clinical practice and rehabilitation research

Return of individuals with stroke to a life of quality and fulfillment is one of the main purposes of rehabilitation (Scottish Government 2007). The current findings, which highlight the impact that UL impairments still have on overall quality of life of patients at six months after stroke, have strong implications for therapy. Findings imply that even after most rehabilitation is over, UL impairment influences perceived quality of life. Therapy should therefore enable patients to continue to address UL impairment even after discharge from hospital since from the patients' perspective it is a very important outcome with implications for their life satisfaction after stroke. Findings also imply that therapy efforts should be targeted at UL activities that patients consider to be most important in influencing their own quality of life. Given that UL impairment appears more important to perceived HRQOL than ADL independence, UL impairments should be the priority for rehabilitation activities at this stage in recovery. Rehabilitation researchers should continue to develop and investigate UL interventions to maximize UL recovery in acute stage and more chronic stages of stroke, since it is now clear that UL impairments have implications for HRQOL.

Self-management interventions that enable patients to prioritise for themselves the most relevant UL activities for long term maintenance and improvement of UL recovery should be developed since these would be appropriate for the post-rehabilitation phase of recovery.

Anxiety and depression in the present study were the strongest predictors of all HRQOL domains except physical activities. The findings highlight the strong impact of emotional distress on perceived HRQOL. Although post-stroke depression is now recognised and protocols have been developed and applied in practice for prevention and management of the condition (Hackett 2008), the same is not so for anxiety which was shown to be the stronger predictor in the present study. The study points to the need for assessment and effective interventions to be developed and applied in stroke to address these psychological responses. Strategies to enable patients to cope with post-stroke anxiety and depression should therefore be developed, tested and applied during rehabilitation. The balance of rehabilitation activity should be shifted from purely physical recovery to include education of patients and their carers in recognition and management of anxiety and depression. Professional help from psychologists and other qualified health professionals should be available in the form of counselling (Kim et al.1999) and medical advice even after the end of rehabilitation to address these important issues which so strongly impact on HRQOL.

Development of such strategies will require collaboration between psychology researchers, rehabilitation scientists and therapists, nurses and medical staff if a more holistic approach towards dealing with the psychological impact of stroke on HRQOL is to be fully addressed.

The next section summarises and discusses some study limitations that apply across the thesis.

6.3. THESIS LIMITATIONS

Study limitations relevant to individuals sections of the thesis have been discussed however some study limitations apply across the whole study and are summarised and discussed below.

6.3.1 Recruitment

Although reasons for non-recruitment were documented for all participants, some patients appropriate for the study may have been missed because of the reliance on clinical opinion provided by clinical therapists for initial identification of potential participants.

6.3.2 Sample Characteristics

Although the sample population demonstrated heterogeneity in terms of severity of UL dysfunction, the generalisability of the findings of this study to the broader stroke population is limited. Inclusion criteria were set on practical grounds to ensure that individuals with UL impairment were included, but also so that they could participate adequately in testing and in completing the intervention. Because of the strict inclusion criteria, participants with communication and comprehension deficits were excluded, again limiting how well findings apply beyond the study population. In future studies, a speech and language therapist would be a valuable addition to the research team, and could provide a range of strategies to ensure that all of the procedures and the consent process were accessible by patients with communication limitations.

6.3.3 Use of statistical testing for baseline comparison

Statistical comparison for group equivalence at baseline using t-tests and non-parametric equivalents was conducted to verify whether randomisation had been successful, i.e. that groups were comparable and did not differ significantly at baseline. There are however some philosophical issues that should have been considered in relation to this decision. Firstly, any significant differences would necessarily be due to chance since randomisation, which was carefully conducted and concealed in the present study, should have accounted for biases that might have influenced participants' responses to the intervention (Altman

1985, 1991). With alpha set at 0.05, there is a one in twenty chance of finding a significant result by chance alone (Altman 1991). The total number of baseline tests that was conducted (n=21) makes it likely therefore that at least one significant finding would be found in any case by chance (Altman 1985).

Even where significant findings at baseline did not occur by chance, it is by no means certain that they were related to or influenced the trial outcomes. All that can be concluded therefore from the baseline comparison analyses is that the randomisation was fair, a finding that was not unexpected given that stratification was performed to minimise the effects of side of stroke, type of stroke and baseline upper limb severity that may have caused bias (Altman 1985). Analysis of association between and prognostically important variables, such as number of treatment sessions, that was *not* equivalently balanced between the groups but that may have influenced outcomes may have been a better approach (Altman 1985). This could have been performed using either clinical judgment, or as another purpose of the evaluation of variables for association with outcome variables presented in Chapter 5, Table 5.10.

Finally, notwithstanding the limitations of baseline testing, the relatively small sample size meant, according to central limit theorem (Polgar 1991), that variability was high in many of the measures at baseline because the sample size provided a limited estimate of the true population variability. The assumption of homoscedacity was tested and met using Levine's test for all variables, indicating equal variances. However the large sample variability may have led to type II errors with use of t-tests to assess baseline equivalence (Salkind 2005), in which significant findings were in fact missed. Use of non-parametric tests which do not make assumptions about variability may have been more appropriate in this instance.

6.3.4 Study design

Following on from the randomised controlled trial, a range of secondary statistical analyses were conducted on the data. In particular, the predictors of UL activity limitation and HRQOL were examined using the dataset from the RCT, therefore generalisation of study findings cannot extend beyond the selected study population who underwent additional therapy. A priori testing of predictors from a more general stroke population would have been a more robust study design for this purpose. Similarly, data from a more general stroke population may have facilitated a more robust examination of the relationship between anxiety and depression and the physical outcomes.

6.3.5 Measures

The UL measures were selected to assess various aspects of UL performance after stroke. The RMA was selected as a measure of impairment and the Action Research Arm Test as a measure of activity limitation. The Action Research Arm Test was selected because it is the most widely used dedicated UL outcome measure in stroke rehabilitation (Platz et al. 2005) which enables comparison with other studies. It became obvious during the course of analysis however that the Rivermead Motor Assessment and the Action Research Arm Test are closely associated, demonstrating strong correlation. It is clear therefore that they do not in fact measure distinct constructs as was assumed at the study design stage. This led to some loss of information and inability to address some research questions particularly in the regression analysis examining predictors of HRQOL.

The clinical data used in the analysis was also fairly limited. The NIH Stroke Scale was conducted as a screening tool for communication and neglect. However it was considered that the accuracy of the tool in identifying other clinical variables such as hemianopia and severity of initial neglect was limited since the data was collected as much as a month after stroke. Therefore data from the tool was not used in the predictive analyses of the study, leaving some important clinical factors unaccounted.

6.3.6 Raters and the role of the study author

The measurements were conducted by two independent raters, since one rater left during the study. Although every effort was made to ensure that the measures were conducted in a standardised way, and that there was good intra-rater reliability, it was only possible to test this with one measure, the ARAT (Chapter 4, Section 4.1.2.2). It is not possible to be entirely certain of the magnitude of error between the raters on the other measures, which may have influenced the results.

The study author was a potential source of bias. She designed the study and also provided the intervention to some study participants. Given her expectations about the effects of BT, she therefore had something of a vested interest in seeing participants within the bilateral group improving more. She was aware of this as a source of bias and therefore followed the protocol to the letter, ensuring that there was no difference between the intervention given to participants receiving bilateral and unilateral training. A more robust approach however

would have been to employ independent therapists to deliver the intervention, however given available resources this was not possible.

Linked to this, with the research physiotherapist, she was responsible for holding access to the web-based randomisation system, and for entering in the sequence of data for stratification. This meant that there was again potential for bias within the allocation process from the author who had a vested interest in the success of the bilateral intervention. She may have been more likely to include participants she felt were likely to do better with bilateral training in that group. The author was aware that she might be a possible source of bias and followed the web-based randomisation protocol strictly; nonetheless, the potential for bias existed. As a check, the statistician held a randomisation log, which indicated group allocation against the study identification number. Comparison with the paper logs was therefore possible to determine that the strata were correctly inputted against clinical information and that participants were allocated as determined by the web-based number generator, however that does not mitigate against bias in entering participant details into the system. Randomisation by a remote, centralised system or by another individual entirely uninvolved in the study would have been a safer approach to ensure that randomisation was concealed and robust.

6.3.7 Missing data

The sample size was based on an a priori power calculation to detect a minimal clinically significant difference on the Action Research Arm Test. The study was funded for recruitment of 53 participants per group. Drop-outs and loss of participants to follow-up clearly would have reduced the power to detect a significant difference on the primary outcome measure. This was particularly the case at eighteen weeks, where the sample size had been reduced to 85 (Bilateral group n=46, Unilateral group n=39. . An omission at the design stage was not to consider possible drop-out numbers. At the end of the study when the number of drop-outs was known, resources did not allow for further recruitment to address the effects of drop-outs.

Furthermore, as discussed in Chapter 4, the study was not powered for the secondary outcome measures and the exploratory analyses that were conducted on those measures, so it is likely that the study ran the risk of not detecting significant findings where they existed, thus possibly generating Type II errors. These more exploratory analyses were however useful in terms of identifying issues that lend themselves to further investigation.

6.3.8 Multiple comparisons

Multiple testing was a limitation of the thesis as a whole. The study was developed primarily to investigate effects of bilateral task training. Most of the analysis was therefore secondary to the main purpose of the study and was exploratory in nature. A large battery of tests was conducted on the data which may have led to significant findings occurring due to chance where no real effects exist (Type I error). ANOVAS and regression analysis were used where possible to minimise the risk of spurious findings, however the number of tests meant that this was still a possibility. As suggested in Chapter 4, Section 4.3.4.2, Bonferroni corrections could have been performed, however this approach was not chosen here as it is controversial. Adjusting p-values for multiple comparisons is known to be somewhat arbitrary and is likely to increase the chances of creating type II errors, where significant results might be missed (Perneger 1998, Feise 2002). To address the issue of multiple testing, all data and tests were presented and data were carefully inspected to ensure that the findings made logical sense (Feise 2002). Clearly the findings from exploratory analysis require confirmation and this should be conducted in future studies.

6.3.9 Follow-up Assessments

Follow-up at 18 weeks was selected because that was a point at which it was considered long enough to assess whether any effects of training had been maintained, and because of the financial restriction placed by the funders which meant that this period could not be extended. Given that there was a new significant difference at that point in terms of recovery of dexterity, in hindsight it would have been useful to be able to make longer-term follow-up at 1 and 2 years, and that is something that future studies should consider.

6.3.10 Ethical Considerations

In order to comply with ethical principles and rules concerning informed consent, only patients with full ability to communicate were included in the study. In doing so, some participants with communication difficulties were denied the opportunity to participate. This represents a violation of the equality principle in which all individuals should be offered an equal chance of participation (Mathers et al 1998). Effort should have been made to include

those participants using communication strategies devised by a speech and language therapist, as suggested in section 6.3.2 above.

A second ethical consideration relates to the situation in which patients developed shoulder pain. Shoulder pain was not examined as a specific outcome in this study, however Dromerick (2008) reported that self-reported shoulder pain is reported as many as 37% of cases. Where patients provided any report of shoulder pain, participation in the study was reviewed, however it was possible that these cases were not dealt with sufficiently quickly and daily assessment of shoulder pain using a standardised measure should have been conducted.

6.4 SUMMARY OF DISCUSSION

6.4.1 PHYSICAL OUTCOMES: CONTRALESIONAL EFFECTS OF BILATERAL TRAINING

This randomised controlled trial found no differences in terms of contralesional UL impairment, activity limitation, and ADL outcomes between bilateral and unilateral task training groups following a six week training intervention - however dexterity in the unilateral group was significantly better at follow-up assessment, a difference that was clinically significant.

Findings are inconsistent with other bilateral training research (Mudie and Matyas 1996, Mudie and Matyas 2000, Whitall et al. 2000, Cauraugh and Kim 2002, Lewis and Byblow 2004, Luft et al. 2004, Stinear and Byblow 2004, Stinear et al. 2008). The progressive programme of functionally orientated activities was more complex than previous studies and, from observation, participants in the bilateral group appeared to have some difficulty attending to both ULs and maintaining symmetrical and synchronous movement during practice. The high attentional demands probably led to limited strength of interlimb coupling and advantages of the *bilateral* characteristics of the intervention were not realised. That explanation is congruent with theoretical interlimb co-ordination models of dynamic systems theory and neural crosstalk, which suggest that for a bilateral advantage, identically timed, rhythmic, repetitive movement is optimal. Other explanations for findings include

sample heterogeneity, clinically poorer baseline performance of the bilateral group, limited standardisation of therapists' assistance for the most severely affected participants, lack of standardisation of usual therapy and low training dose. Finally, the relatively crude clinical measures may have missed subtle effects of training on kinematic parameters. For dexterity, bilateral training may not have been optimal because it did not account for the unilateral anatomical arrangement of cortical control of distal musculature.

Findings point to tension between rehabilitation literature highlighting task specificity as being effective for improvements in activity (Winstein et al. 2004, Dromerick et al. 2006); and maintenance of tight interlimb coupling using simple non-functional movements for a bilateral advantage highlighted in the motor control literature (Cardoso de Oliveira 2002, Cunningham et al. 2002). Findings suggest that further exploration of the optimal parameters of bilateral task training is required. Investigation of the relationship between *training tasks* and the *bilateral* nature of the training should be more fully investigated before bilateral task training can be rejected as an effective intervention for the contralesional UL.

Future studies should investigate approaches to auditory or visual cueing and use of robotic or mechanical devices to allow task performance whilst also maintaining tight interlimb coupling. Sequencing of bilateral with unilateral tasks within training sessions should also be examined. Effects of specific tasks for improved dexterity *and* gross arm function also require comparison. Future studies should include a wider range of clinical, kinematic and neurophysiological outcome measures than those selected for the present study. These might provide more insight into the effects and mechanisms underpinning contralesional bilateral training than was achieved in the present study. Neurophysiological assessments were not conducted in the present study and these should be undertaken in future to determine the mechanisms underlying responses and non-responses to bilateral training. In conclusion, although the present study demonstrated no advantage of bilateral task training, optimal parameters of bilateral task training still require to be determined through further investigation.

6.4.2 PHYSICAL OUTCOMES: EFFECTS OF CLINICAL AND DEMOGRAPHIC FACTORS

Initial severity of activity limitation, side of stroke and hand dominance, gender, age and proprioception did not significantly influence UL responses to bilateral compared to unilateral training. The finding suggests that none of the factors was important in determining training responses. However because there was no overall difference between the groups except on long-term dexterity, it was perhaps unlikely that any of the factors might influence outcomes. Additionally, the sub-group analysis was probably underpowered to detect significant effects.

Several observations relating to severity, handedness and gender from that analysis were however highlighted for discussion. Although not statistically significant, participants in the bilateral group with most severe initial UL dysfunction demonstrated more improvement in activity limitation and impairment than in the unilateral group suggesting that those patients *might* benefit more from bilateral training. This most severely affected group warrants further investigation for the effects of bilateral training on recovery. A secondary finding from post-hoc analysis showed that the three UL severity sub-groups developed for the study, which are standardised and reproducible, differed significantly in recovery on the UL measures with the moderate group demonstrating most recovery and the severe group demonstrating least. The groups might be useful in future for therapists and researchers wishing to define UL severity after stroke. The groupings may be of use in clinical practice in defining severity, predicting recovery and appropriately targeting interventions and should be investigated further.

Of the other factors investigated, findings regarding gender were of importance. Whilst it did not influence bilateral or unilateral training responses, post-hoc analysis of a significant main effect of gender provided interesting observations. Female participants recovered significantly less than males in terms of overall improvement in UL activity limitation. Although not significant, the same pattern existed for the other measures. The reasons for this finding are unclear; however males demonstrated better initial scores, were younger and were significantly less depressed than females. More research is required to fully account for the differences. The differences in recovery do suggest that specific approaches to UL rehabilitation that account for gender-related physical, social, environmental, attitudinal and motivation factors should be investigated.

In conclusion, although not significant, the findings suggest that patients with severe UL dysfunction *may* respond better to bilateral training than other patient groups, and that this an important area for future investigation. Furthermore, the severity sub-groupings created in the study are an important development relevant to clinicians and researchers and should be investigated more fully for validity and predictive strength. There was no effect of any of the selected variables on training responses, however important post-hoc observations were made that require more investigation but may in future influence the way in which therapists approach UL rehabilitation in severely affected and female and male patients. More research is required to investigate these phenomena to enable researchers to develop appropriate and demographic factor-specific interventions.

6.4.3 PHYSICAL OUTCOMES: IPSILESIONAL EFFECTS OF BILATERAL TRAINING

There was a small but statistically significant effect of bilateral training compared to unilateral training on ipsilesional dexterity in change between six and eighteen weeks, although this did nor reach the 10% difference considered to be clinically significant. The difference had disappeared by eighteen weeks. Effects may have resulted because the bilateral group received additional ipsilesional training where the unilateral received none. Alternatively, effects may have resulted from the bilateral repetitive component of training. More investigation is required to determine whether effects resulted from the bilateral component of training or simply from additional training itself, and to determine optimal characteristics for future ipsilesional training interventions.

The association between activity limitation and ipsilesional dexterity demonstrates the relevance of ipsilesional UL dysfunction to overall functioning and shows that it may be useful as a marker of global cortical dysfunction. The link between ipsilesional dexterity and ADL independence may be of clinical importance in predicting recovery, and of neuroscientific importance as a link between global and ipsilesional dysfunction. Future research should investigate the predictive value of ipsilesional dysfunction and the neurophysiological mechanisms underpinning it.

In conclusion, ipsilesional UL dysfunction in dexterity is detectable, clinically relevant and responds to bilateral training. Future studies are necessary to further investigate the clinical

consequences of ipsilesional dysfunction and to determine whether bilateral or unilateral training is most appropriate for ipsilesional dysfunction in different patient groups.

6.4.4 PHYSICAL OUTCOMES: PREDICTORS OF UPPER LIMB ACTIVITY LIMITATION

This strand of investigation was the first in the thesis to examine implications of the data for rehabilitation research more broadly than bilateral training outcomes. Here the predictors of activity limitation, irrespective if intervention group were examined over time. The findings showed that UL activity limitation is the strongest predictor of later activity limitation and the predictive strength depends whether gross activity limitation or dexterity is included as a predictor. Baseline assessment at ADL, days to initial assessment and whether the patient has a total anterior circulation stroke were significantly predictive, but only of early UL recovery at six weeks. There was little difference in predictive strength of the baseline variables for six and eighteen week variables suggesting that most recovery had occurred by the six week assessment.

The findings confirm and extend previous research. They are of important clinical relevance, providing information with which clinicians can predict UL functional recovery to a known extent from earlier assessments and to enable patients to plan for future outcome. They suggest that UL activity limitations including gross UL function and fine dexterity should be addressed in rehabilitation early after stroke since these are key indicators of later activity outcome. Further research is required to determine the relative importance of activity limitation and motor impairment as predictors of later activity limitation. Some important variables that were not assessed in the current study may have been missed as predictors and these should be included in future studies.

6.4.5 PSYCHOSOCIAL OUTCOMES: EFFECTS OF BILATERAL TRAINING

There was no effect of bilateral compared to unilateral training on anxiety, depression or HRQOL. The premise for this investigation was that improved UL recovery with bilateral training might improve psychosocial outcomes. The lack of an effect probably reflects the finding that there was only a small but clinically significant difference in dexterity outcomes

between the groups which may have been insufficient to influence psychosocial outcomes. Future studies employing more effective UL interventions than the present should continue to examine the direction of the relationship between these psychosocial outcomes and UL recovery, since the literature suggests it has not yet been fully addressed.

6.4.6 PSYCHOSOCIAL OUTCOMES: PREDICTORS OF PERCEIVED HEALTH RELATED QUALITY OF LIFE

In the second strand of the thesis to examine the impact of the data on broad health outcomes, UL predictors of HRQOL at eighteen weeks were explored, along with other potential predictors, for the whole sample. It was not possible to determine whether activity limitation or impairment were most important in predicting HRQOL and UL impairment was the only UL variable to significantly predict overall HRQOL at eighteen weeks. It was however significant only with the intention to treat analysis. UL impairment was also a significant predictor of the physical activities sub-domain of the Nottingham Health Profile and was a stronger predictor than ADL independence. These findings suggest that UL dysfunction represents an important factor that determines HRQOL approximately six months after stroke. Efforts to target improvements in performance of UL activities likely to influence HRQOL should therefore continue into this more chronic stage of recovery.

In line with many other studies, anxiety and depression were most important in predicting HRQOL however, indicating that physical recovery is secondary to psychological factors in predicting HRQOL. The amount of variance explained by the included variables was in most cases small and other important factors may have been missed that should be included in future studies.

In conclusion, findings point to the need for future studies to investigate how UL dysfunction influences HRQOL by exploring a wider range of UL variables as predictors, particularly those of relevance to UL activities involved in life roles and leisure and social activities. The importance of anxiety and depression in predicting HRQOL suggests that strategies for management of these conditions should be more fully integrated into rehabilitation to enable patients and their families to cope with and adjust better to the psychological impact of stroke.

Chapter 7 presents the thesis conclusions.

CHAPTER 7

CONCLUSIONS AND FUTURE DIRECTIONS

7.0 INTRODUCTION

This thesis was conducted in order to address gaps in the evidence for bilateral task training of the upper limb (UL) in stroke. In particular, methodological limitations meant that evidence for bilateral task training was limited and little was known about the effects of this intervention in acute stroke. The primary aim of this thesis was therefore to investigate effects of bilateral UL task training on physical and psychosocial outcomes in patients with acute stroke.

A second study aim was to investigate which demographic and clinical factors influence UL responses to bilateral task training. Broadening to examine UL recovery after stroke in general, the literature review demonstrated that evidence about the strength of UL activity limitation as a predictor of later activity limitation was limited; therefore another aim within the physical outcomes theme was to explore the predictors of UL activity limitation over time, for the whole sample, regardless of the type of intervention.

Evidence from one very small study suggested that bilateral training might influence ipsilesional UL performance however methodological limitations undermined the strength of that evidence. A further study aim was therefore to investigate the effects of bilateral training on ipsilesional motor outcomes. Another key aim within this strand was to examine the clinical relevance of ipsilesional dysfunction by investigating its relationship to ADL independence. Following on from this, and to acknowledge that physical outcomes after stroke are only part of the story, the second theme of the thesis investigated the effects of bilateral training and UL dysfunction on the psychosocial outcomes of anxiety, depression and health related quality of life.

Within this theme, the primary aim was to examine the differential effects of bilateral training on anxiety, depression and health related quality of life compared with unilateral

training. A secondary aim was to explore the role of UL dysfunction in predicting health related quality of life for the sample as a whole.

In this way, the thesis fulfilled a dual purpose by firstly investigating effects of a specific intervention on UL recovery, and secondly by examining broader aspects of UL recovery to add to the general body of rehabilitation knowledge relating to UL recovery after stroke. New knowledge has thus been generated that will both inform clinical practice in stroke rehabilitation *and* a range of topics in stroke rehabilitation research. The relationship between the study strands is illustrated in Figure7.1.

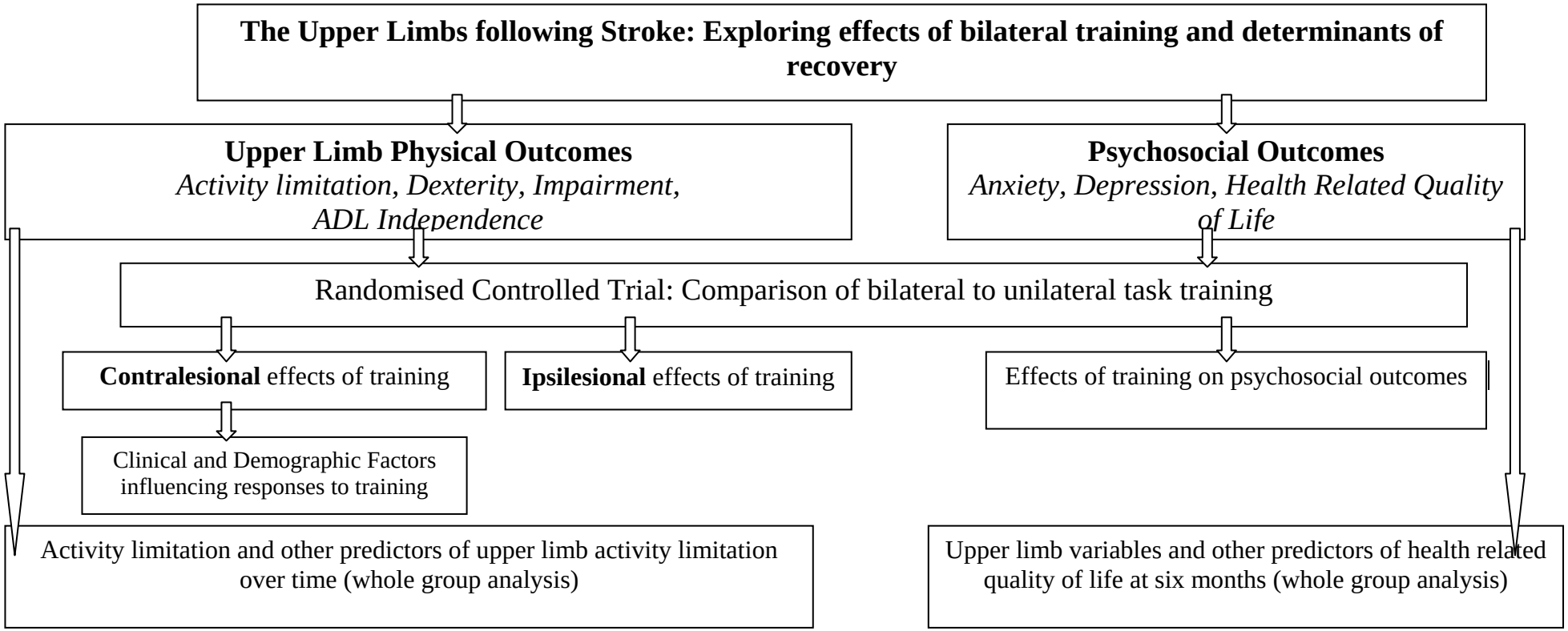


Figure 7.1 Overview of links between themes within the thesis

7.1 CONCLUSIONS AND FUTURE DIRECTIONS

7.1.1 EFFECTS OF BILATERAL TASK TRAINING ON PHYSICAL OUTCOMES

7.1.1.1 Contralesional Effects

Bilateral task training appears no more effective than unilateral training in terms of contralesional UL outcomes and ADL independence. Indeed for dexterity, unilateral task training appears to be more beneficial.

It is clear from the present study that bilateral task training is a complex intervention with many parameters that may influence outcomes. Functional relevant tasks were selected as the training tasks because of their good ecological validity. In selecting relatively complex tasks with high attentional demands however participants' ability to maintain tight interlimb coupling to achieve the *bilateral* advantage of training was probably compromised. Findings therefore probably reflect a tension between complex task training specific to UL functioning for everyday activities and tasks that have low enough attentional demand to maintain good interlimb coupling.

The first priority for further research is therefore to address the tension between the task characteristics and interlimb coupling. Approaches to strengthen interlimb coupling during bilateral task training should be investigated. These should include auditory and visual cueing for tasks and movements with many degrees of freedom. These tasks may be most appropriate for patients with good recovery. Attentional demands of different tasks should be investigated by analysis of eye movements and their effects on upper limb outcomes should be examined. Mechanical or robotic devices may be more appropriate to control degrees of freedom in patients with more severe UL dysfunction whilst tasks are practised.

Once these approaches to maintenance of good interlimb coupling have been established, the characteristics of the tasks should be considered. The effects of *task training* versus *simple movement* training should be compared for effects on a range of impairment and activity limitation outcomes in different patient populations since it is only in this way that it will be possible to discriminate which activities applied bilaterally are most effective in improving

UL recovery for patients with specific clinical characteristics. The present study indicated that dexterity may be differentially affected compared to gross UL function therefore in determining the optimal tasks for training, their effects on different domains of UL dysfunction should be discriminated.

Finally, optimal training dose and practice scheduling should be established. This should determine the optimal duration, intensity and frequency of training and the optimal scheduling of bilateral and unilateral practice *within* training programmes. Once these factors have been established it will then be appropriate to again compare unilateral and bilateral practice in a randomised controlled trial to determine which is most effective.

7.1.1.2 Ipsilesional Effects

Upper limb ipsilesional dysfunction is detectable on commonly used clinical activity limitation and dexterity outcome measures. Ipsilesional recovery of dexterity reflects contralesional recovery in terms of time, with most recovery occurring by the six week assessment. Furthermore and of particular clinical relevance, ipsilesional dexterity is moderately but significantly associated with independence in daily living suggesting that it reflects and has the potential as a clinical marker of global cortical functioning.

Bilateral training appears to influence the rate of recovery but not the overall outcome of ipsilesional dexterity compared to unilateral training in which no specific ipsilesional training occurs. The advantage appears to be small, is not clinically significant and may simply reflect the increased dose received by the bilateral group compared to the unilateral group who received no ipsilesional training. The small effect is of interest to clinicians and motor control scientists alike and is worth further investigation. Firstly however further investigation of effects of ipsilesional dysfunction in performance of a broader range of functional activities should be conducted to establish its clinical significance before funding should be allocated to investigating the small effect of bilateral training on ipsilesional performance. Secondly, the effects of unilateral training on ipsilesional performance should be investigated. Although bilateral training appeared advantageous, this was in comparison to no specific unilateral training. It is likely that unilateral training may be more effective for training ipsilesional dysfunction since training parameters appropriate to ipsilesional functioning such as fine dexterity and speed and direction will not be constrained by the

contralesional UL. Comparison between unilateral and bilateral training on a range of outcomes including gross UL functioning and fine dexterity and with stroke populations of differing severity should be investigated further.

7.1.2. FINDINGS OF GENERAL RELEVANCE TO UPPER LIMB REHABILITATION

7.1.2.1 Gender

The study shows that female patients performed more poorly than males in terms of UL recovery. This is a serendipitous but important finding that has implications for therapy and the way in which it is delivered in stroke. Reasons for the observation are not clear but may relate to the higher level of depression demonstrated in females at each assessment point. Neurological and physiological factors, physical, social, psychological and motivation factors might influence recovery and responses to rehabilitation differentially in male and female patients. The next step in investigating this phenomenon should be to conduct a longitudinal study which examines these factors as predictors of UL recovery in men and women. Once the relative importance of these factors has been established it will be important to develop interventions, probably physical and psychological, to address gender differences in recovery within the context of rehabilitation. This research will be multi-professional requiring expertise from health psychology, sociology and behavioural science and medicine as well as rehabilitation science.

7.1.2.2 Severity sub-groups and predicting UL activity limitation

The development of UL severity sub-groups in this thesis will inform clinical practice and researchers wishing to discriminate between patients with mild, moderate and severe UL dysfunction. These groupings should be investigated for their predictive validity in future studies so that therapists can predict with some certainty the likely outcomes for patients with UL dysfunction. The findings in the present study that early UL activity limitation predicted later activity limitation is a platform upon which to build this research. However since the regression analysis provides only limited clinical indication in terms of meaningful scores accessible to clinicians, the predictive analysis should be repeated in a longitudinal

study for each of the defined sub-groups. In this way it will be possible to determine whether the groupings have useful predictive validity.

In terms of prediction, upper limb activity limitation is predictive of later activity limitation outcomes, and the strength of prediction increases over time. The findings suggest that rehabilitation efforts should target activity limitation from an early stage since it is the most important factor in determining later outcome. The relative importance of activity limitation and motor impairment needs to be investigated further, since it was not possible to investigate those with the present measures. Discriminating between the two has important implications for therapists in targeting therapy at the dysfunctions most likely to influence activity outcomes. Future studies should include a much broader test battery of impairment, activity limitation and clinical variables to determine what variables best predict UL activity limitation.

7.1.3 PYSCHOSOCIAL OUTCOMES

Bilateral training appears not to influence the psychosocial outcomes of anxiety, depression and health related quality of life compared to unilateral training however the finding probably results from the small physical effect of the training. The study points to how little is known about the impact of physical recovery on psychological outcomes and HRQOL and highlights the need for health psychologists and rehabilitation scientists to collaborate to more fully understand the relationships between physical and psychological outcomes after stroke.

Although bilateral training did not influence psychosocial outcomes compared to unilateral training, the significant impact of UL impairment in predicting HRQOL is an important finding. It highlights the perceived importance of UL dysfunction on the lives of patients living at home with stroke. This is an important area which requires further investigation. A longitudinal study should be conducted using patient centered measures of UL dysfunction to determine more fully which UL activities, beyond the simple tests used in this study, are most important to the HRQOL of individual patients during stroke recovery. The next step is to develop effective interventions to enable patients to manage their UL recovery and to

target therapy activities at those UL activities that are most meaningful and relevant to patients' HRQOL.

Finally, anxiety and depression are the most important predictors of HRQOL, suggesting that rehabilitation interventions involving management and self-management of emotional responses to stroke should be developed and tested within the context of rehabilitation settings. This should be done in collaboration between rehabilitation scientists and health psychologists and its impact across physical psychological, social and leisure outcomes should be investigated along with its impact on the emotional health and stress of carers.

Overall this thesis provides a comprehensive assessment of the impact of an UL intervention in acute stroke on contralesional and ipsilesional physical outcomes and on psychosocial outcomes. It also provides a broad perspective of the determinants of UL recovery and how UL recovery influences important psychosocial outcomes and suggests future research that has emerged from the findings. In this way it should provide a valuable contribution to stroke rehabilitation research.

REFERENCES

ABDULLAEV, Y. and POSNER, M.I., 2005. How the brain recovers following damage. *Nature Neuroscience,* 8 (11), pp. 1424-1425.

ABEN, I., VERHEY, F., LOUSBERG, R., LODDER, J. and HONIG, A., 2002. Validity of the Beck Depression Inventory, Hospital Anxiety and Depression Scale, SCL-90, and Hamilton Depression Rating scale as screening instruments for depression in stroke patients. *Psychosomatics,* 43 (5), pp. 386-393.

ADA L, CANNING C, WESTWOOD P (1990). *The patient as an active learner. Key issues in neurological physiotherapy*. Butterworth Heinemann, Oxford.

ADAMS, S.A., ASHBURN, A., PICKERING, R.M. and TAYLOR, D., 1997. The scalability of the Rivermead Motor Assessment in acute stroke patients. *Clinical Rehabilitation,* 11(1), pp. 42-51.

ADAMSON, J., BESWICK, A. and EBRAHIM, S., 2004. Is stroke the most common cause of disability? *Journal of Stroke and Cerebrovascular Diseases,* 13 (4), pp. 171-177.

AHLSIO, B., BRITTON, M., MURRAY, V. and THEORELL, T., 1984. Disablement and quality of life after stroke. *Stroke,* 15 (5), pp. 886-890.

AHO, K., 1980. Cerebrovascular disease in the community: results of a WHO collaborative study. Geneva: World Health Organization.

ALTMAN, D.G (1985). Comparability of randomised groups. The Statistician; 34, pp 125-136.

ALTMAN, D.G (1991). Practical Statistics for Medical Research. Chapman and Hall, London.

AMERICAN PSYCHIATRIC ASSOCIATION (2000). The *Diagnostic and Statistical Manual of Mental Disorders* Fourth Edition (DSM-IV). Washington.

ANDERSON, K.L.R.N. and BURCKHARDT, C.S.R.N., 1999. Conceptualization and measurement of quality of life as an outcome variable for health care intervention and research. *Journal of Advanced Nursing,* 29 (2), pp. 298-306.

ARMITAGE P, BERRY G (1994). Statistical Methods in Medical Research, Blackwell Scientific Research, Oxford.

ASANUMA, H. and PAVLIDES, C., 1997. Neurobiological basis of motor learning in mammals. *Neuroreport,* 8 (4), pp i-vi.

ASTROM, M., 1996. Generalized anxiety disorder in stroke patients. A 3-year longitudinal study. *Stroke,* 27 (2), pp. 270-275.

BACH Y RITA, P 2000. Conceptual issues relevant to present and future neurologic rehabilitation. Functional recovery after stroke. In: LEVIN, H. S. & GRAFMAN, J. (Eds.) *Cerebral Reorganisation of Function after Brain Damage.* New York, Oxford University Press.

BADDELEY AD'LONGMAN DJA; (1978). The influence of length and frequency of training session on the rate of learning to type. Ergonomics, 21; 627-635; 3421.

BAER G, SMITH M, ROWE P, MASTERTON L (2003). Establishing the reliability of mobility milestones as an outcome measure for stroke. *Archives of Physical Medicine and Rehabilitation*; 84: 977-81.

BAGG, S., POMBO, A.P. and HOPMAN, W., 2002. Effect of age on functional outcomes after stroke rehabilitation. *Stroke,* 33(1), pp. 179-185.

BAMFORD, J., SANDERCOCK, P., DENNIS, M., BURN, J. and WARLOW, C., 1991. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet,* 337(8756), pp. 1521-1526.

BARALDI, P., 1999. Bilateral representation of sequential finger movements in human cortical areas. *Neuroscience Letters* 262(2) pp 55-96.

BARBER P.A., DEMCHUK A. M., ZHANG J, BUCHAN A. M., 2000. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. The Lancet, 355: 1670–74.

BARNES, C.L., SMITH, M.B., HASSET, E., KUNISH and A., 2006. A pilot study of bilateral arm training with repetitive auditory cueing in subjects with low functioning upper limb hemiparesis as a result of chronic stroke. Journal of Neurological Physiotherapy, 30 (4) 221.

BARRECA, S.R., STRATFORD, P.W., MASTERS, L.M., LAMBERT, C.L. and GRIFFITHS, J., 2006. Comparing two versions of the Chedoke Arm and Hand Activity Inventory with the Action Research Arm Test. *Physical Therapy,* 86(2), pp. 245-253.

BERGNER M, BOBBITT RA, CARTER WB. The Sickness Impact Profile: development and final revision of a health status measure. Medical Care 1981; 19:787-805.

BERNHARDT, J., BATE, P.J. and MATYAS, T.A., 1998. Accuracy of observational kinematic assessment of upper-limb movements. *Physical Therapy*, 78 (3), pp. 259-270.

BHAKTA, B.B., 2000. Management of spasticity in stroke. *British Medical Bulletin*, 56(2), pp. 476-485.

BJELLAND, I., DAHL, A.A., HAUG, T.T. and NECKELMANN, D., 2002. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of Psychosomatic Research*, 52(2), pp. 69-77.

BLAND M (1995). An introduction to medical statistics (2nd Edition). Oxford University Press, Oxford.

BOISSY, P., BOURBONNAIS, D., CARLOTTI, M.M., GRAVEL, D. and ARSENAULT, B.A., 1999. Maximal grip force in chronic stroke subjects and its relationship to global upper extremity function. *Clinical Rehabilitation*, 13(4), pp. 354-362.

BOLL, T.J., 1974. Right and left cerebral hemisphere damage and tactile perception: performance of the ipsilateral and contralateral sides of the body. *Neuropsychologia*, 12(2), pp. 235-238.

BOVEND'EERDT, T.J.H., DAWES, H., JOHANSEN-BERG, H. and WADE, D.T., 2004. Evaluation of the Modified Jebsen Test of Hand Function and the University of Maryland Arm Questionnaire for Stroke. *Clinical Rehabilitation*, 18(2), pp.195-202.

BOWLING, A., 2000. Research Methods in Health, Investigating health and Health services. Buckingham: Open University Press.

BOWLING A. WINDSOR J (2001). Towards the good life: A population survey of dimensions of quality of life. *Journal of Happiness studies 2*: 55-81.

BOWLING, A., 2005. Measuring Health: a review of quality of life measurement scales New York: Open University Press.

BRACE, N., KEMP, R. and SNELGAR, R., 2003. SPSS for Psychologists. A guide to data analysis using SPSS for Windows. 2nd Edition Basingstoke and New York: Palgrave MacMillan.

BRINKMAN, J. and KUYPERS, H.G., 1973. Cerebral control of contralateral and ipsilateral arm, hand and finger movement in the rhesus monkey. *Brain*, (96), pp. 653-674.

BRODAL, A., 1973. Self-observations and neuro-anatomical considerations after a stroke. *Brain*, 96(4), pp. 675-694.

BROEKS, J.G., LANKHORST, G.J., RUMPING, K. and PREVO, A.H.J., 1999. The long-term outcome of arm function after stroke: results of a follow-up study. *Disability and Rehabilitation*, 21(8), pp. 357-364.

BROTT T.G, ADAMS HP, OLINGER CP, MARLER JR, BARSAN WG, BILLER J, SPILKER J, HOLLERAN R, EBERLE R, HERTZBERG V, ET AL., 1989. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke.* 20, pp. 864-870.

BROWN J, BOWLING, A., Flynn, T. 2004. Models of quality of life: a taxonomy, overview and Systematic review of the literature. The European Forum for Population Aging Research.

BUCK, D., JACOBY, A., MASSEY, A. and FORD, G., 2000. Evaluation of measures used to assess quality of life after stroke. *Stroke*, 31(8), pp. 2004-2010.

BULLINGER M, ANDERSON R, CELLA D, AARONSON N. Developing and evaluating cross cultural instruments from minimum requirements to optimal models. *Quality of Life Research* 1993, (2) 451–459.

BURGAR, C.G., LUM, P.S., SHOR, P.C. and VAN DER LOOS, H.F.M., 2000. Development of robots for rehabilitation therapy: the Palo Alto VA/Stanford experience. *Journal of Rehabilitation Research and Development*, 37(6), pp. 663-673.

BUTEFISCH, C., HUMMELSHEIM, H., DENZLER, P. and MAURITZ, K.H., 1995. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. *Journal of the neurological sciences*, 130(1), pp. 59-68.

BUTEFISCH, C.M., NETZ, J., WESSLING, M., SEITZ, R.J. and HOMBERG, V., 2003. Remote changes in cortical excitability after stroke. *Brain*, 126(2), pp. 470-481.

BUTLER, A., BLANTON, S., ROWE, V. and WOLF, S., 2006. Attempting to improve function and quality of life using the FTM. Protocol: case report. *Journal of Neurologic Physical Therapy*, 30 (3), pp. 148-156.

BYL, N., RODERICK, J., MOHAMED, O., HANNY, M., KOTLER, J., SMITH, A., TANG, M. and ABRAMS, G., 2003. Effectiveness of sensory and motor rehabilitation of the upper limb following the principles of neuroplasticity: patients stable poststroke. *Neurorehabilitation & Neural Repair*, 17(3), pp. 176-191.

CALAUTTI, C. and BARON, J.C., 2003. Functional neuroimaging studies of motor recovery after stroke in adults: a review. *Stroke*, 34(6), pp. 1553-1566.

CALAUTTI, C., LEROY, F., GUINCESTRE, J.Y., MARIE, R.M. and BARON, J.C., 2001. Sequential activation brain mapping after subcortical stroke: changes in hemispheric balance and recovery. *Neuroreport*, 12(18), pp. 3883-3886.

CAMPBELL A, CONVERSE P. AND ROGERS WL. The quality of American life: perceptions, evaluations and satisfaction. New York: Russell Sage, 1976.

CAMPBELL M., FITZPATRICK R., HAINES, A., KINMONTH, A.L., SANDERCOCK, P., SPIEGELHALTER D., TYRER, P., 2002. Framework for design and evaluation of complex interventions to improve health. *BMJ*; 321;694-696.

CANNING, C.G., ADA, L., ADAMS, R. and O'DWYER, N.J., 2004. Loss of strength contributes more to physical disability after stroke than loss of dexterity. *Clinical Rehabilitation*, 18(3), pp. 300-308.

CARAMIA, M.D., PALMIERI, M.G., GIACOMINI, P., IANI, C., DALLY, L. and SILVESTRINI, M., 2000. Ipsilateral activation of the unaffected motor cortex in patients with hemiparetic stroke. *Clinical Neurophysiology*, 111(11), pp. 1990-1996.

CARDOSO DE OLIVEIRA, S., 2002. The neuronal basis of bimanual coordination: recent neurophysiological evidence and functional models. *Acta Psychologica*, 110(2-3), pp. 139-159.

CARR, A.J. and HIGGINSON, I.J., 2001. Are quality of life measures patient centred? *British Medical Journa*, 322(7298), pp. 1357-1360.

CARR, A.J., GIBSON, B. and ROBINSON, P.G., 2001. Measuring quality of life: Is quality of life determined by expectations or experience? *British Medical Journal*, 322(7296) pp 1240-3.

CARR J and SHEPHERD R (1998). *Neurological rehabilitation. Optimizing motor performance*. Butterworth Heinemann. Oxford.

CARR, J.H., SHEPHERD, R.B., NORDHOLM, L. and LYNNE, D., 1985. Investigation of a new motor assessment scale for stroke patients. *Physical Therapy*, 65(2), pp. 175-180.

CARROLL, D., 1965. A QUANTITATIVE TEST OF UPPER EXTREMITY FUNCTION. *Journal of chronic diseases, (*18), pp. 479-491.

CARSON, A.J., MACHALE, S., ALLEN, K., LAWRIE, S.M., DENNIS, M., HOUSE, A. and SHARPE, M., 2000. Depression after stroke and lesion location: a systematic review. *Lancet*, 356(9224), pp. 122-126.

CARSON, R.G. and SWINNEN, S.P., 2002. Coordination and movement pathology: models of structure and function. *Acta Psychologica*, 110(2-3), pp. 357-364.

CARSON, R.G., 2005. Neural pathways mediating bilateral interactions between the upper limbs. *Brain Research Reviews*, 49(3), pp. 641-662.

CATALAN, M.J., HONDA, M., WEEKS, R.A., COHEN, L.G. and HALLETT, M., 1998. The functional neuroanatomy of simple and complex sequential finger movements: a PET study. *Brain*, 121(2), pp. 253-264.

CAURAUGH, J.H. and KIM, S., 2002. Two coupled motor recovery protocols are better than one: electromyogram-triggered neuromuscular stimulation and bilateral movements. *Stroke*, 33(6), pp. 1589-1594.

CAURAUGH, J.H. and KIM, S.B., 2003a. Chronic stroke motor recovery: Duration of active neuromuscular stimulation. *Journal of the Neurological Sciences*, 215(1-2), pp. 13-19.

CAURAUGH, J.H. and KIM, S.B., 2003b. Stroke motor recovery: active neuromuscular stimulation and repetitive practice schedules. *Journal of Neurology, Neurosurgery & Psychiatry*, 74(11), pp. 1562-1566.

CAURAUGH, J.H. and SUMMERS, J.J., 2005. Neural plasticity and bilateral movements: A rehabilitation approach for chronic stroke. *Progress in Neurobiology*, 75(5), pp. 309-320.

CHEMERINSKI, E. and LEVINE, S.R., 2006. Neuropsychiatric disorders following vascular brain injury. *Mount Sinai Journal of Medicine*, 73(7), pp. 1006-1014.

CHEMERINSKI, E. and ROBINSON, R.G., 2000. The neuropsychiatry of stroke. *Psychosomatics*, 41(1), pp. 5-14.

CHEMERINSKI, E., ROBINSON, R.G., ARNDT, S. and KOSIER, J.T., 2001. The effect of remission of poststroke depression on activities of daily living in a double-blind randomized treatment study. *Journal of Nervous & Mental Disease*, 189(7), pp. 421-425.

CHEN, R., GERLOFF, C., HALLETT, M. and COHEN, L.G., 1997. Involvement of the ipsilateral motor cortex in finger movements of different complexities. *Annals of Neurology,* 41(2), pp. 247-254.

CHUA, K.S.G. and KONG, K., 1996. Functional outcome in brain stem stroke patients after rehabilitation. *Archives of Physical Medicine and Rehabilitation,* 77(2), pp. 194-197.

CLASSEN, J., LIEPERT, J., WISE, S.P., HALLETT, M. and COHEN, L.G., 1998. Rapid plasticity of human cortical movement representation induced by practice. *Journal of Neurophysiology,* 79(2), pp. 1117-1123.

COLLIN, C. and WADE, D., 1990. Assessing motor impairment after stroke: a pilot reliability study. *Journal of Neurology, Neurosurgery & Psychiatry,* 53(7), pp. 576-579.

CRAMER, S.C., 2004. Changes in motor system function and recovery after stroke. *Restorative Neurology & Neuroscience,* 22(3-5), pp. 231-238.

CROARKIN, E., DANOFF, J. and BARNES, C., 2004. Evidence-based rating of upper-extremity motor function tests used for people following a stroke. *Physical Therapy,* 84(1), pp. 62-74.

CUNNINGHAM, C.L., STOYKOV, M.E. and WALTER, C.B., 2002. Bilateral facilitation of motor control in chronic hemiplegic. *Acta Psychologica,* 110(2-3), pp. 321-337.

DE GROOT-DRIESSEN, D., VAN DE SANDE, P. and VAN HEUGTEN, C., 2006. Speed of finger tapping as a predictor of functional outcome after unilateral stroke. *Archives of Physical Medicine & Rehabilitation,* 87(1), pp. 40-44.

DE HAAN, R., AARONSON, N., LIMBURG, M., HEWER, R. and LANGTON VAN CREVEL, H., 1993. Measuring Quality of Life in Stroke. *Stroke,* 24(2), pp 320-327.

DE WEERDT, W., LINCOLN, N.B. and HARRISON, M.A., 1987. Prediction of arm and hand function recovery in stroke patients. *International Journal of Rehabilitation Research,* 10(4 Suppl 5), pp. 110-112.

DEAN, C.M. and SHEPHERD, R.B., 1997. Task-related training improves performance of seated reaching tasks after stroke. A randomized controlled trial. *Stroke,* 28(4), pp. 722-728.

DEBAERE, F., SWINNEN, S.P., BEATSE, E., SUNAERT, S., VAN HECKE, P. and DUYSENS, J., 2001. Brain areas involved in interlimb coordination: a distributed network. *NeuroImage,* 14(5), pp. 947-958.

DEBAERE, F., VAN ASSCHE, D., KIEKENS, C., VERSCHUEREN, S.M. and SWINNEN, S.P., 2001. Coordination of upper and lower limb segments: deficits on the ipsilesional side after unilateral stroke. *Experimental Brain Research,* 141(4), pp. 519-529.

DENNIS, M., O'ROURKE, S., LEWIS, S., SHARPE, M. and WARLOW, C., 2000. Emotional outcomes after stroke: factors associated with poor outcome. *Journal of Neurology, Neurosurgery & Psychiatry,* 68(1), pp. 47-52.

DESROSIERS J.; BOURBONNAIS, D.; CORRIVEAU, H.; GOSSELIN, S.; BRAVO, G. 2005. Effectiveness of unilateral and symmetrical bilateral task training for arm during the subacute phase after stroke: a randomized controlled trial. Clinical Rehabilitation, 19 (6), 581-593.

DESROSIERS, J., BOURBONNAIS, D., BRAVO, G., ROY, P.M. and GUAY, M., 1996. Performance of the 'unaffected' upper extremity of elderly stroke patients. *Stroke,* 27(9), pp. 1564-1570.

DETTMERS, C., TESKE, U., HAMZEI, F., USWATTE, G., TAUB, E. and WEILLER, C., 2005. Distributed form of constraint-induced movement therapy improves functional outcome and quality of life after stroke. *Archives of Physical Medicine & Rehabilitation,* 86(2), pp. 204-209.

DE WEERDT WJG, HARRISON MA. Measuring recovery of arm-hand functionin stroke patients: a comparison of the Brunstrom Fugl-Meyer test and the Action Research Arm Test. *Physiotherapy Canada*; 37: 65-70.

DEWEY, H., MACDONELL, R., DONNAN, G., MCNEIL, J., FREEMAN, E., THRIFT, A. C. SHARPLES, C., 2001. Inter-rater reliability of stroke sub-type classification by neurologists and nurses within a community-based stroke incidence study. Journal of Clinical Neuroscience; 8: 2001 14-17.DI CARLO, A., LAMASSA, M., BALDERESCHI, M., PRACUCCI, G., BASILE, A.M., WOLFE, C.D.A., GIROUD, M., RUDD, A., GHETTI, A. and INZITARI, D., 2003. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. Stroke, 34(5) pp 1114-9.

DIJKERS, M., 2007. "What's in a name?" The indiscriminate use of the "Quality of life" label, and the need to bring about clarity in conceptualizations. *International Journal of Nursing Studies,* 44(1), pp. 153-155.

DOBKIN B (1998) Activity dependent Learning contributes to Motor Recovery. *Annals of Neurology*; 44:158-160.

DOBKIN, B., 1995. The economic impact of stroke. *Neurology,* 45(2 Suppl 1), pp. S6-9.

DONCHIN, O., GRIBOVA, A., STEINBERG, O., BERGMAN, H. and VAADIA, E., 1998. Primary motor cortex is involved in bimanual coordination. *Nature,* 395(6699), pp. 274-278.

DROMERICK, A.W., EDWARDS, D.F. and HAHN, M., 2000. Does the application of constraint-induced movement therapy during acute rehabilitation reduce arm impairment after ischemic stroke? *Stroke,* 31(12), pp. 2984-2988.

DROMERICK, A.W., EDWARDS, D.F. and KUMAR, A., 2008. Hemiplegic shoulder pain syndrome: frequency and characteristics during inpatient stroke rehabilitation. *Archives of Physical Medicine and Rehabilitation,* 89(8) pp.1589-93.

DROMERICK, A.W., LUM, P.S. and HIDLER, J., 2006. Activity-based therapies. *NeuroRx,* 3(4), pp. 428-438.

DUNCAN, P.W., BODE, R.K., MIN LAI, S., PERERA, S. 2003. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. *Archives of Physical Medicine & Rehabilitation,* 84(7), pp. 950-963.

DUNCAN, P.W., GOLDSTEIN, L.B., MATCHAR, D., DIVINE, G.W. and FEUSSNER, J., 1992. Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. *Stroke,* 23(8), pp. 1084-1089.

DUNCAN, P.W., WALLACE, D., LAI, S.M., JOHNSON, D., EMBRETSON, S. and LASTER, L.J., 1999. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke,* 30(10), pp. 2131-2140.

EBRAHIM, S., BARER, D. and NOURI, F., 1986. Use of the Nottingham Health Profile with patients after a stroke. *Journal of Epidemiology & Community Health,* 40(2), pp. 166-169.

ELIASSEN, J.C., BAYNES, K. and GAZZANIGA, M.S., 2000. Anterior and posterior callosal contributions to simultaneous bimanual movements of the hands and fingers. *Brain,* 123 (12), pp. 2501-2511.

ENGSBERG, J.R., Van EMMERICK, R., ROSS, S.A., COLLINS, D.R 2008. Use of relative phase as a measure of motor control at the ankle in persons with cerebral palsy: a preliminary study. Journal of Applied Biomechanics, 24(4): 834-90.

ESSING, J.P., GERSTEN, J.W. and YARNELL, P., 1980. Light touch thresholds in normal persons and cerebral vascular disease patient: bilateral deficit after unilateral lesion. *Stroke,* 11(5), pp. 528-533.

EUROPEAN GROUP FOR QUALITY OF LIFE AND HEALTH MEASUREMENT1992. European Guide to the Nottingham Health Profile, 1989. Dauphin Conception, Montpellier.

FARNE, A., ROY, A.C., PAULIGNAN, Y., RODE, G., ROSSETTI, Y., BOISSON, D. and JEANNEROD, M., 2003. Visuo-motor control of the ipsilateral hand: evidence from right brain-damaged patients. *Neuropsychologia,* 41(6), pp. 739-757.

FEISE, R.J., 2002. Do multiple outcome measures require p-value adjustment? BMC Medical Research Methodology, (2), pp 8.

FEYDY, A., CARLIER, R., ROBY-BRAMI, A., BUSSEL, B., CAZALIS, F., PIEROT, L., BURNOD, Y. and MAIER, M.A., 2002. Longitudinal study of motor recovery after stroke: recruitment and focusing of brain activation. *Stroke,* 33 (6), pp. 1610-1617.

FEYS HM.WEERDT, W.J., SELZ, B.E., STECK, G.A.C., SPICHIGER, R., VEREECK, L.E., PUTMAN, K.D. and VAN HOYDONCK, A.V., 1998. Effect of a therapeutic intervention for the hemiplegic upper limb in the acute phase after stroke: a single-blind, randomized, controlled multicenter trial. *Stroke,* 29(4), pp. 785-792.

FEYS H.WEERDT, W., NUYENS, G., VAN DE WINCKEL, A., SELZ, B. and KIEKENS, C., 2000a. Predicting motor recovery of the upper limb after stroke rehabilitation: value of a clinical examination. *Physiotherapy Research International,* 5 (1), pp. 1-18.

FEYS, H., HETEBRIJ, J., WILMS, G., DOM, R. and DE WEERDT, W., 2000b. Predicting arm recovery following stroke: value of site of lesion. *Acta Neurologica Scandinavica,* 102(6), pp. 371-377.

FEYS H.WEERDT, W., VERBEKE, G., STECK, G.C., CAPIAU, C., KIEKENS, C., DEJAEGER, E., VAN HOYDONCK, G., VERMEERSCH, G. and CRAS, P., 2004. Early and repetitive stimulation of the arm can substantially improve the long-term outcome after stroke: a 5-year follow-up study of a randomized trial. *Stroke,* 35(4), pp. 924-929.

FIELDING, S., FAYERS, P.M., LOGE, J.H., JORDHØY, M.S. and KAASA, S., 2006. Methods for handling missing data in palliative care research. *Palliative Medicine* 20(8) pp 791-798.

FINLEY, FASOLI, S.E., DIPIETRO, L., OHLHOFF, J., MACCLELLAN, L., MEISTER, C., WHITALL, J., MACKO, R., BEVER CT, J., KREBS, H.I. and HOGAN, N., 2005. Short-duration robotic therapy in stroke patients with severe upper-limb motor impairment. *Journal of Rehabilitation Research and Development,* 42(5), pp. 683-691.

FITTS, P.M., & POSNER, M.I. (1967). Learning and skilled performance in human performance. Belmont CA: Brock-Cole.

FONTAINE, R.J., LEE, T.D. and SWINNEN, S.P., 1997. Learning a new bimanual coordination pattern: reciprocal influences of intrinsic and to-be-learned patterns. *Canadian Journal of Experimental Psychology,* 51(1), pp. 1-9.

FONTENOT, D.J. and BENTON, A.L., 1971. Tactile perception of direction in relation to hemispheric locus of lesion. *Neuropsychologia,* 9(1), pp. 83-88.

FORD, M.P. WAGENAAR , R.C., NEWELL, K.M., 2007. Phase manipulation and walking in stroke. *Journal of Neurologic Physical Therapy*. 31(2):85-91.

FRANZ, E.A. and ELIASSEN, J.C., 1996. Dissociation of spatial and temporal coupling in the bimanual movements of callosotomy patients. *Psychological Science,* 7(5; 5), pp. 306-310.

FRANZ, E.A., ZELAZNIK, H.N. and MCCABE, G., 1991. Spatial topological constraints in a bimanual task. *Acta Psychologica,* 77(2), pp. 137-151.

FRENCH, B., THOMAS, L.H., LEATHLEY, M.J., SUTTON, C.J., MCADAM, J., FORSTER, A., LANGHORNE, P., PRICE, C.I.M., WALKER, A. and WATKINS, C.L., 2007. *Repetitive task training for improving functional ability after stroke. Cochrane Database of systematic reviews.* Issue 4. Art.NoCD006073. DOI:10.1002/14651858.CD006073.pub2.

FRICKE, J. and UNSWORTH, C.A., 1997. Inter-rater reliability of the original and modified Barthel Index, and a comparison with the Functional Independence Measure. *Australian Occupational Therapy Journal,* 44(1), pp. 22-29.

FRITZ, S.L., LIGHT, K.E., CLIFFORD, S.N., PATTERSON, T.S., BEHRMAN, A.L. and DAVIS, S.B., 2006. Descriptive characteristics as potential predictors of outcomes following constraint-induced movement therapy for people after stroke. *Physical Therapy,* 86(6), pp. 825-832.

FRITZ, S.L., LIGHT, K.E., PATTERSON, T.S., BEHRMAN, A.L. and DAVIS, S.B., 2005. Active finger extension predicts outcomes after constraint-induced movement therapy for individuals with hemiparesis after stroke. *Stroke,* 36(6), pp. 1172-1177.

FRUHWALD, S., LOFFLER, H., EHER, R., SALETU, B. and BAUMHACKL, U., 2001; 2001. Relationship between depression, anxiety and quality of life: A study of stroke patients compared to chronic low back pain and myocardial ischemia patients. *Psychopathology,* 34(1), pp. 50-56.

FUGL-MEYER, A.R., JAASKO, L., LEYMAN, I., OLSSON, S. and STEGLIND, S., 1975. The post-stroke hemiplegic patient 1. A method for evaluation of physical performance. *Scandinavian Journal of Rehabilitation Medicine,* 7(1), pp. 13-31.

GAINOTTI, G., ANTONUCCI, G., MARRA, C. and PAOLUCCI, S., 2001. Relation between depression after stroke, antidepressant therapy, and functional recovery. *Journal of Neurology, Neurosurgery & Psychiatry,* 71(2), pp. 258-261.

GAINOTTI, G. and MARRA, C., 2002. Determinants and consequences of post-stroke depression. *Current Opinion in Neurology,* 15(1), pp. 85-89.

GARGANO, J.W., REEVES, M.J. and PAUL COVERDELL 2007. Sex differences in stroke recovery and stroke-specific quality of life: results from a statewide stroke registry. *Stroke,* 38(9), pp. 2541-2548.

GAUBERT, C.S. and MOCKETT, S.P., 2000. Inter-rater reliability of the Nottingham method of stereognosis assessment. *Clinical Rehabilitation,* 14(2), pp. 153-159.

GAUGGEL, S., HOOP, M. and WERNER, K., 2002. Assigned versus self-set goals and their impact on the performance of brain-damaged patients. *Journal of Clinical & Experimental Neuropsychology,* 24 (8), pp. 1070-1080.

GAUGGEL, S., LEINBERGER, R. and RICHARDT, M., 2001. Goal setting and reaction time performance in brain-damaged patients. *Journal of Clinical & Experimental Neuropsychology*, 23 (3), pp. 351-361.

GERLOFF, C. and ANDRES, F.G., 2002. Bimanual coordination and interhemispheric interaction. *Acta Psychologica*, 110 (2-3), pp. 161-186.

GILSON, B.S., GILSON, J.S., BERGNER, M., BOBBIT, R.A., KRESSEL, S., POLLARD, W.E. and VESSELAGO, M., 1975. The sickness impact profile. Development of an outcome measure of health care. *American Journal of Public Health*, 65(12), pp. 1304-1310.

GOLDIN-MEADOW, S., 2007. Pointing Sets the Stage for Learning Language and Creating Language. *Child Development*, 78(3), pp. 741-745.

GOWLAND, C., *1982* Recovery of motor function following stroke: profile and predictors. *Physiotherapy Canada. Mar-Apr; (34) 77-84*.

GRANGER CV, HAMILTON BB, LINACRE JM, HEINEMANN AW, WRIGHT BD (1993). Performance profiles of the Functional Independence Measure. *Archives of Physical*

GREEN, J., YOUNG, J., FORSTER, A., COLLEN, F. and WADE, D., 2004. Combined analysis of two randomized trials of community physiotherapy for patients more than one year post stroke. *Clinical Rehabilitation*, 18(3), pp. 249-252.

GRICE, K.O., VOGEL, K.A., LE, V., MITCHELL, A., MUNIZ, S. and VOLLMER, 2003. Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. *American Journal of Occupational Therapy*, 57(5), pp. 570-573.

HAALAND, K.Y. and HARRINGTON, D.L., 1989. Hemisphere control of the initial and corrective components of aiming movements. *Neuropsychologia*, 27(7), pp. 961-969.

HAALAND, K.Y. and HARRINGTON, D.L., 1994. Limb-sequencing deficits after left but not right hemisphere damage. *Brain & Cognition*, 24(1), pp. 104-122.

HAALAND, K.Y., PRESTOPNIK, J.L., KNIGHT, R.T. and LEE, R.R., 2004. Hemispheric asymmetries for kinematic and positional aspects of reaching. *Brain*, 127(5), pp. 1145-1158.

HACKETT ML, ANDERSON CS, HOUSE A, XIA J, 2008. Interventions for treating depression after stroke. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.CD003437. DOI: 10.1002/14651858.CD003437.pub3.

HACKETT, M.L. and ANDERSON, C.S., 2005. Predictors of depression after stroke: a systematic review of observational studies. *Stroke*, 36(10), pp. 2296-2301.

HAKEN H, KELSO J.A.S, BUNZ, H 1985. A theoretical model of phase transitions in human hand movements. Bilogical Cybernetics, 51, 347-356.

HAKEN H. 1975. Cooperative phenomena in systems far from thermal equilibrium and in nonphysical systems. *Reviews in Modern Physics. 47 (1), 67 – 121*.

HAKEN, H. and WUNDERLIN A., 1990. Synergetics and its paradigm of self-organisation in biological systems. IN: HTA Whiting, OG Meijer and PCW van Wieringen (eds). *The natural-physical approach to movement control.*, pp 1-36. Amsterdam: VU University Press.

HANLON, C.A., BUFFINGTON, A.L. and MCKEOWN, M.J., 2005. New brain networks are active after right MCA stroke when moving the ipsilesional arm. *Neurology*, 64(1), pp. 114-120.

HANLON, R.E., 1996. Motor learning following unilateral stroke. *Archives of Physical Medicine and Rehabilitation*, 77(8), pp. 811-815.

HARBOUR, R. and MILLER, J., 2001. A new system for grading recommendations in evidence based guidelines. *British Medical Journal*, 323(7308), pp. 334-336.

HARRINGTON, D.L. and HAALAND, K.Y., 1992. Motor sequencing with left hemisphere damage. *Brain*, 115(3), pp. 857-874.

HARRIS, J.E. and ENG, J.J., 2006. Individuals with the dominant hand affected following stroke demonstrate less impairment than those with the non-dominant hand affected. *Neurorehabilitation and Neural Repair*, 20(3), pp. 380-389.

HARRIS-LOVE, M.L., MCCOMBE WALLER, S. and WHITALL, J., 2005. Exploiting interlimb coupling to improve paretic arm reaching performance in people with chronic stroke. *Archives of Physical Medicine & Rehabilitation*, 86(11), pp. 2131-2137.

HELLER, A., WADE, D.T., WOOD, V.A., SUNDERLAND, A., HEWER, R.L. and WARD, E., 1987. Arm function after stroke: measurement and recovery over the first three months. *Journal of Neurology, Neurosurgery & Psychiatry*, 50(6), pp. 714-719.

HENDRICKS, H.T., VAN LIMBEEK, J., GEURTS, A.C. and ZWARTS, M.J., 2002. Motor recovery after stroke: a systematic review of the literature. *Archives of Physical Medicine & Rehabilitation*, 83(11), pp. 1629-1637.

HERMSDORFER, J., LAIMGRUBER, K., KERKHOFF, G., MAI, N. and GOLDENBERG, G., 1999. Effects of unilateral brain damage on grip selection, coordination, and kinematics of ipsilesional prehension. *Experimental Brain Research*, 128(1-2), pp. 41-51.

HERMSDORFER, J. and GOLDENBERG, G., 2002. Ipsilesional deficits during fast diadochokinetic hand movements following unilateral brain damage. *Neuropsychologia*, 40(12), pp. 2100-2115.

HERRMANN, N., BLACK, S.E., LAWRENCE, J., SZEKELY, C. and SZALAI, J.P., 1998. The Sunnybrook Stroke Study: a prospective study of depressive symptoms and functional outcome. *Stroke*, 29(3), pp. 618-624.

HESSE, S., SCHMIDT, H., WERNER, C. and BARDELEBEN, A., 2003. Upper and lower extremity robotic devices for rehabilitation and for studying motor control. *Current Opinion in Neurology*, 16(6), pp. 705-710.

HESSE, S., SCHULTE-TIGGES, G., KONRAD, M., BARDELEBEN, A. and WERNER, C., 2003. Robot-assisted arm trainer for the passive and active practice of bilateral forearm and wrist movements in hemiparetic subjects. *Archives of Physical Medicine & Rehabilitation*, 84(6), pp. 915-920.

HESSE, S., WERNER, C., POHL, M., RUECKRIEM, S., MEHRHOLZ, J. and LIGNAU, M.L., 2005. Computerized arm training improves the motor control of the severely affected arm after stroke: a single-blinded randomized trial in two centers. *Stroke*, 36(9), pp. 1960-1966.

HICKS CM 1988. *Practical research methods for physiotherapists*. Churchill Livingstone, Edinburgh.

HIGGINS, J., MAYO, N.E., DESROSIERS, J., SALBACH, N.M. and AHMED, S., 2005. Upper-limb function and recovery in the acute phase poststroke. *Journal of Rehabilitation Research and Development*, 42(1), pp. 65-76.

HÖRNQUIST JO 1982. The concept of quality of life. *Scandinavian Journal of Social Medicine*; 10:57-61.

HSIEH, C.L., HSUEH, I.P., CHIANG, F.M. and LIN, P.H., 1998. Inter-rater reliability and validity of the action research arm test in stroke patients. *Age & Ageing*, 27(2), pp. 107-113.

HSUEH, I.P. and HSIEH, C.L., 2002. Responsiveness of two upper extremity function instruments for stroke inpatients receiving rehabilitation. *Clinical Rehabilitation*, 16(6), pp. 617-624.

HUDLER M. AND RICHTER, R 2002. Cross-national comparison of the quality of life in Europe: inventory of surveys and methods. *Social Indicators Research*; 58:217-228.

HUNT, S.M. and MCEWEN, J., 1980. The development of a subjective health indicator. *Sociology of Health & Illness*, 2(3), pp. 231-246.

HUNT, S.M., 1997. The problem of quality of life. *Quality of Life Research*. 6(3) pp. 205-12.

IETSWAART, M., CAREY, D.P. and DELLA SALA, S., 2006. Tapping, grasping and aiming in ideomotor apraxia. *Neuropsychologia*, 44(7), pp. 1175-1184.

INGLEHART R AND RABIER JR, 1986. Aspirations adapt to situations - But why are the Belgians so much happier than the French? *A cross-cultural analysis of the subjective quality of life*. In: Andrews FM. (ed.). Research on the quality of life. Survey Research Center, Institute for Social Research University of Michigan, Michigan, 1986.

INSTITUTE OF MEDICINE (IOM) 2007. *The future of Disability in America*. Washington DC: The National Academies Press.

JACKSON, G.M., JACKSON, S.R., HUSAIN, M., HARVEY, M., KRAMER, T. and DOW, L., 2000. The coordination of bimanual prehension movements in a centrally deafferented patient. *Brain*, 123 (2), pp. 380-393.

JOHANSEN-BERG, H., DAWES, H., GUY, C., SMITH, S.M., WADE, D.T. and MATTHEWS, P.M., 2002. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain*, 125(12), pp. 2731-2742.

JOHANSEN-BERG, H., DAWES, H., GUY, C., SMITH, S.M., WADE, D.T. and MATTHEWS, P.M., 2002. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain, 125*(12), pp. 2731-2742.

JOHNSON, G., 1995. Screening instruments for depression and anxiety following stroke: experience in the Perth community stroke study. *Acta Psychiatrica Scandinavica*. 91(4), pp. 252-257.

JOHNSTON, M., POLLARD, B. and HENNESSEY, P., 2000. Construct validation of the Hospital Anxiety and Depression Scale with clinical populations. *Journal of Psychosomatic Research*, 48(6), pp. 579-584.

JONES, R.D., DONALDSON, I.M. and PARKIN, P.J., 1989. Impairment and recovery of ipsilateral sensory-motor function following unilateral cerebral infarction. *Brain*, 112(1), pp. 113-132.

JONSSON, A.C., LINDGREN, I., HALLSTROM, B., NORRVING, B. and LINDGREN, A., 2005. Determinants of quality of life in stroke survivors and their informal caregivers. *Stroke*, 36(4), pp. 803-808.

KANDEL, R.R., SCHWARTZ, J.H. and & JESELL, T.M., (Eds) 2000. *Principles of Neural Science*. New York: McGraw-Hill.

KAPLAN RM 1985. Quality of life measurement. In: Karloy P, Ed.Measurement Strategies in Health Psychology. New York, John Wiley.

KAPRAL, M.K., FANG, J., HILL, M.D., SILVER, F., RICHARDS, J., JAIGOBIN, C., CHEUNG, A.M. and INVESTIGATORS OF THE REGISTRY OF THE CANADIAN STROKE, NETWORK, 2005. Sex differences in stroke care and outcomes: results from the Registry of the Canadian Stroke Network. *Stroke*, 36(4), pp. 809-814.

KATRAK, P., BOWRING, G., CONROY, P., CHILVERS, M., POULOS, R. and MCNEIL, D., 1998. Predicting upper limb recovery after stroke: the place of early shoulder and hand movement. *Archives of Physical Medicine & Rehabilitation*, 79(7), pp. 758-761.

KAUHANEN, M.L., KORPELAINEN, J.T., HILTUNEN, P., NIEMINEN, P., SOTANIEMI, K.A. and MYLLYLA, V.V., 2000. Domains and determinants of quality of life after stroke caused by brain infarction. *Archives of Physical Medicine & Rehabilitation*, 81(12), pp. 1541-1546.

KELSO, J.A., SOUTHARD, D.L. and GOODMAN, D., 1979. On the coordination of two-handed movements. *Journal of Experimental Psychology: Human Perception & Performance*, 5(2), pp. 229-238.

KELSO, J.A., SOUTHARD, D.L. and GOODMAN, D., 1979. On the nature of human interlimb coordination. *Science*, 203(4384), pp. 1029-1031.

KIM, J.S. and CHOI-KWON, S., 1996. Discriminative sensory dysfunction after unilateral stroke... *Stroke*, 27(4), pp. 677-682.

KIM, J.S. and CHOI-KWON, S., 2000. Poststroke depression and emotional incontinence: correlation with lesion location. *Neurology*, 54(9), pp. 1805-1810.

KIM, P., WARREN, S., MADILL, H. and HADLEY, M., 1999; 1999. Quality of life of stroke survivors. *Quality of Life Research*, 8(4), pp. 293-301.

KIMURA, D., 1977. Acquisition of a motor skill after left-hemisphere damage. *Brain*, 100(3), pp. 527-542.

KING, R.B., 1996. Quality of life after stroke. *Stroke*, 27(9), pp. 1467-1472.

KIRKWOOD, B.R., STERNE J. (2003). Essential Medical Statistics, 2nd Edition, Blackwell Science, Oxford.

KNOPMAN, D.S. and RUBENS, A.B., 1986. The validity of computed tomographic scan findings for the localization of cerebral functions. The relationship between computed tomography and hemiparesis. *Archives of Neurology*, 43(4), pp. 328-332.

KWAKKEL, G. and KOLLEN, B., 2007. Predicting improvement in the upper paretic limb after stroke: a longitudinal prospective study. *Restorative Neurology & Neuroscience*, 25(5-6), pp. 453-460.

KWAKKEL, G., KOLLEN, B. and TWISK, J., 2006. Impact of time on improvement of outcome after stroke. *Stroke*, 37(9), pp. 2348-2353.

KWAKKEL, G., KOLLEN, B.J., VAN DER GROND, J. and PREVO, A.J., 2003. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke*, 34(9), pp. 2181-2186.

KWAKKEL, G., WAGENAAR, R.C., TWISK, J.W., LANKHORST, G.J. and KOETSIER, J.C., 1999. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. *Lancet*, 354(9174), pp. 191-196.

LACROIX, S., HAVTON, L.A., MCKAY, H., YANG, H., BRANT, A., ROBERTS, J. and TUSZYNSKI, M.H., 2004. Bilateral corticospinal projections arise from each motor cortex in the macaque monkey: a quantitative study. *Journal of Comparative Neurology*, 473(2), pp. 147-161.

LAI, S.M., PERERA, S., DUNCAN, P.W. and BODE, R., 2003. Physical and social functioning after stroke: comparison of the Stroke Impact Scale and Short Form-36. *Stroke,* 34(2), pp. 488-493.

LEHMAN, A.F. (1983). The well-being of chronic mental patients: assessing their quality of life. Archives of General Psychiatry; 40:369-373.

LEONARD, C.T., 1998. The neuroscience of human movement. Missouri: Mosby.

LEPPAVUORI, A., POHJASVAARA, T., VATAJA, R., KASTE, M. and ERKINJUNTTI, T., 2003. Generalized anxiety disorders three to four months after ischemic stroke. *Cerebrovascular Diseases,* 16(3), pp. 257-264.

LEVY, C.E., NICHOLS, D.S., SCHMALBROCK, P.M., KELLER, P. and CHAKERES, D.W., 2001. Functional MRI evidence of cortical reorganization in upper-limb stroke hemiplegia treated with constraint-induced movement therapy. *American Journal of Physical Medicine & Rehabilitation,* 80(1), pp. 4-12.

LEWIS, G.N. and BYBLOW, W.D., 2004. Neurophysiological and behavioural adaptations to a bilateral training intervention in individuals following stroke. *Clinical Rehabilitation,* 18(1), pp. 48-59.

LIEPERT, J., 2006. Motor cortex excitability in stroke before and after constraint-induced movement therapy. *Cognitive & Behavioral Neurology,* 19(1), pp. 41-47.

LIEPERT, J., BAUDER, H., WOLFGANG, H.R., MILTNER, W.H., TAUB, E. and WEILLER, C., 2000. Treatment-induced cortical reorganization after stroke in humans. *Stroke,* 31(6), pp. 1210-1216.

LIEPERT, J., MILTNER, W.H., BAUDER, H., SOMMER, M., DETTMERS, C., TAUB, E. and WEILLER, C., 1998. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neuroscience letters,* 250(1), pp. 5-8.

LIEPERT, J., UHDE, I., GRAF, S., LEIDNER, O. and WEILLER, C., 2001. Motor cortex plasticity during forced-use therapy in stroke patients: a preliminary study. *Journal of neurology,* 248(4), pp. 315-321.

LINCOLN, N. and LEADBITTER, D., 1979. Assessment of motor function in stroke patients. *Physiotherapy*. 65(2):48-51

LINCOLN, N., CROW, J.L., JACKSON, J.M., WATERS, G.R., ADAMS, S.A. and HODGSON, P., 1991. The Unreliability of Sensory Assessments. *Clinical Rehabilitation,* 5, pp. 273-274-282.

LINCOLN, N.B., JACKSON, J.M. and ADAMS, S.A., 1998. Reliability and revision of the Nottingham Sensory Assessment for stroke patients. *Physiotherapy,* 84(8), pp. 358-365.

LINCOLN, N.B., PARRY, R.H. and VASS, C.D., 1999. Randomized, controlled trial to evaluate increased intensity of physiotherapy treatment of arm function after stroke. *Stroke,* 30(3), pp. 573-579.

LOEWEN, S.C. and ANDERSON, B.A., 1990. Predictors of stroke outcome using objective measurement scales. *Stroke,* 21(1), pp. 78-81.

LUFT, A.R., MCCOMBE-WALLER, S., WHITALL, J., FORRESTER, L.W., MACKO, R., SORKIN, J.D., SCHULZ, J.B., GOLDBERG, A.P. and HANLEY, D.F., 2004. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. *JAMA,* 292(15), pp. 1853-1861.

LUM, P.S., BURGAR, C.G. and SHOR, P.C., 2004. Evidence for improved muscle activation patterns after retraining of reaching movements with the MIME robotic system in subjects with post-stroke hemiparesis. *IEEE Transactions on Neural Systems & Rehabilitation Engineering,* 12(2), pp. 186-194.

LUM, P.S., BURGAR, C.G., SHOR, P.C., MAJMUNDAR, M. and VAN DER LOOS, M., 2002. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. *Archives of Physical Medicine & Rehabilitation,* 83(7), pp. 952-959.

LYLE, R.C., 1981. A performance test for assessment of upper limb function in physical r rehabilitation treatment and research. *International Journal of Rehabilitation Research,* 4(4), pp. 483-492.

MACKENZIE, A.E. and CHANG, A.M., 2002; 2002. Predictors of quality of life following stroke. *Disability and Rehabilitation: An International Multidisciplinary Journal,* 24(5), pp. 259-265.

MALMGREN, R., BAMFORD, J., WARLOW, C., SANDERCOCK, P. and SLATTERY, J., 1989. Projecting the number of patients with first ever strokes and patients newly handicapped by stroke in England and Wales. *British Medical Journal*, 298(6674), pp. 656-660.

MALOUIN F, PICHARD L, BONNEAU C; DURAND A, CORRIVEAU D 1994. Evaluating motor recovery after stroke: comparison of the Fugl-Meyer assessment and the Motor Assessment Scale. *Archives of Physical Medicine & Rehabilitation*, 75:1206-12

MARIGOLD, D.S., ENG, J.J., DAWSON, A.S., INGLIS, J.T., HARRIS, J.E. and GYLFADOTTIR, S., 2005. Exercise leads to faster postural reflexes, improved balance and mobility, and fewer falls in older persons with chronic stroke. *Journal of the American Geriatrics Society*, 53(3), pp. 416-423.

MARQUE, P., FELEZ, A., PUEL, M., DEMONET, J.F., GUIRAUD-CHAUMEIL, B., ROQUES, C.F. and CHOLLET, F., 1997. Impairment and recovery of left motor function in patients with right hemiplegia. *Journal of Neurology, Neurosurgery & Psychiatry*, 62(1), pp. 77-81.

MARTENUIK R.G., MACKENZIE C.L. 1980. Infomation processing in movement orgaisation and execution. In R Nickerson (Ed). Attention and Performance VIII, pp29-57. Hillsdale, Erlbaum.

MASLOW, A 1968. *Toward a psychology of being*. 2nd ed. Princeton, New Jersey:Van Nostrand.

MATHERS, NIGEL; HOWE, AMANDA AND HUNN, AMANDA 1998. Trent Focus for Research and Development in Primary Health Care: Ethical Considerations in Research. Trent Focus.

MATHIOWETZ, V., VOLLAND, G., KASHMAN, N. and WEBER, K., 1985. Adult norms for the Box and Block Test of manual dexterity. *American Journal of Occupational Therapy*, 39(6), pp. 386-391.

MATTHEWS, P.M., JOHANSEN-BERG, H. and REDDY, H., 2004. Non-invasive mapping of brain functions and brain recovery: applying lessons from cognitive neuroscience to neurorehabilitation. *Restorative Neurology & Neuroscience*, 22(3-5), pp. 245-260.

MAYO, N.E., WOOD-DAUPHINEE, S., COTE, R., DURCAN, L. and CARLTON, J., 2002. Activity, participation, and quality of life 6 months post stroke. *Archives of Physical Medicine & Rehabilitation*, 83(8), pp. 1035-1042.

MAYSTON, M.J., HARRISON, L.M. and STEPHENS, J.A., 1999. A neurophysiological study of mirror movements in adults and children. *Annals of Neurology*, 45(5), pp. 583-594.

MAZEVET, D., MEUNIER, S., PRADAT-DIEHL, P., MARCHAND-PAUVERT, V. and PIERROT-DESEILLIGNY, E., 2003. Changes in propriospinally mediated excitation of upper limb motoneurons in stroke patients. *Brain*, 126(Pt 4), pp. 988-1000.

MCCOMBE WALLER, S. and WHITALL, J., 2004. Fine motor control in adults with and without chronic hemiparesis: baseline comparison to nondisabled adults and effects of bilateral arm training. *Archives of Physical Medicine & Rehabilitation*, 85(7), pp. 1076-1083.

MCCOMBE WALLER, S. and WHITALL, J., 2005. Hand dominance and side of stroke affect rehabilitation in chronic stroke. *Clinical Rehabilitation*, 19(5), pp. 544-551.

MCDOWD, J.M., FILION, D.L., POHL, P.S., RICHARDS, L.G. and STIERS, W., 2003. Attentional abilities and functional outcomes following stroke. *Journals of Gerontology Series B-Psychological Sciences & Social Sciences*, 58(1), pp. 45-53.

MCEWEN, S., MAYO, N. and WOODDAUPHINEE, S., 2000; 2000. Inferring quality of life from performance-based assessments. *Disability and Rehabilitation: An International Multidisciplinary Journal*, 22(10), pp. 456-463.

MCKENNA, S.P., HUNT, S.M. and MCEWEN, J., 1981. Weighting the seriousness of perceived health problems using Thurstone's method of paired comparisons. *International journal of epidemiology*, 10(1), pp. 93-97.

MEAD GE, MORLEY W, CAMPBELL P, GREIG CA, MCMURDO M, LAWLOR DA 2008. Exercise for depression. *Cochrane Database of Systematic Reviews*, Issue 4.

MELDRUM, D., PITTOCK, S.J., HARDIMAN, O., NI DHUILL, C. and O'REGAN, M., 2004. Recovery of the upper limb post ischaemic stroke and the predictive value of the Orpington Prognostic Score. *Clinical Rehabilitation*, 18(6), pp. 694-702.

MERCIER, C. and BOURBONNAIS, D., 2004. Relative shoulder flexor and handgrip strength is related to upper limb function after stroke. *Clinical Rehabilitation*, 18(2), pp. 215-221.

MICHALOS AC, ZUMBO BD, HUBLEY A, 2000. Health and the quality of life. *Social Indicators R esearch*; 51:245-286.

MILTNER, W.H., BAUDER, H., SOMMER, M., DETTMERS, C. and TAUB, E., 1999. Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke: a replication. *Stroke*, 30(3), pp. 586-592.

MOHER, D., SCHULZ, K.F., ALTMAN, D.G., 2001. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*; 357(9263):1191-1194

MOONS, P., BUDTS, W. and DE GEEST, S., 2006. Critique on the conceptualisation of quality of life: a review and evaluation of different conceptual approaches. *International Journal of Nursing Studies*, 43(7), pp. 891-901.

MORRIS JH, 2003. Motor performance and sensory discrimination in the ipsilateral upper limb in acute stroke, and effects of bilateral simultaneous upper limb task training. MSc. Queen Margaret University College, Edinburgh.

MORRISON V., POLLARD B., JOHNSTON M. and MACWALTER R., 2005. Anxiety and depression 3 years following stroke: demographic, clinical, and psychological predictors. Journal of Psychosomatic Research. 59(4), pp. 209-13.

MUDIE, M.H. and MATYAS, T.A., 1996. Upper extremity retraining following stroke: effects of bilateral practice. *Journal of neurologic rehabilitation*, 10(3), pp. 167-184.

Mudie H. 2000. Course Materials: Enhancing occupational performance after stroke with bilateral practice. A two day workshop. Glasgow Caledonian University 10th – 11th July 2000.

MUDIE, M.H. and MATYAS, T.A., 2000. Can simultaneous bilateral movement involve the undamaged hemisphere in reconstruction of neural networks damaged by stroke? *Disability and Rehabilitation*, 22(1/2), pp. 23-37.

MUDIE, M.H. and MATYAS, T.A., 2001. Responses of the densely hemiplegic upper extremity to bilateral training. *Neurorehabilitation and neural repair*, 15(2), pp. 129-140.

MURASE, N., DUQUE, J., MAZZOCCHIO, R. and COHEN, L.G., 2004. Influence of interhemispheric interactions on motor function in chronic stroke. *Annals of Neurology*, 55(3), pp. 400-409.

NAKAYAMA H, JORGENSON H.S, RAASCHOU H.O, OLSEN T.S, 1994. Recovery of upper extremity function in stroke patients: The Copenhagen stroke study. *Archives of Physical Medicine and Rehabilitation*, 75, pp. 394 - 398.

NANNETTI, L., PACI, M., PASQUINI, J., LOMBARDI, B. and TAITI, P.G., 2005. Motor and functional recovery in patients with post-stroke depression. *Disability & Rehabilitation*, 27(4), pp. 170-175.

NATIONAL AUDIT OFFICE, DEPARTMENT OF HEALTH., 2005. *Reducing Brain Damage: Faster access to better stroke care; HC 452 2005-2006.* London: National Audit Office.

NELLES, G., 2004. Cortical reorganization--effects of intensive therapy. *Restorative Neurology & Neuroscience*, 22(3-5), pp. 239-244.

NELLES, G., JENTZEN, W., JUEPTNER, M., MULLER, S. and DIENER, H.C., 2001. Arm training induced brain plasticity in stroke studied with serial positron emission tomography. *NeuroImage*, 13(6 Pt 1), pp. 1146-1154.

NETZ, J., LAMMERS, T. and HOMBERG, V., 1997. Reorganization of motor output in the non-affected hemisphere after stroke. *Brain*, 120(Pt 9), pp. 1579-1586.

NG, Y.S., STEIN J., NING, M., BLACK-SCHAFFER R.M., 2007. Comparison **of** Clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. *Stroke*;38:2309-2314.

NICHOLS-LARSEN, D.S., CLARK, P.C., ZERINGUE, A., GREENSPAN, A. and BLANTON, S., 2005. Factors influencing stroke survivors' quality of life during subacute recovery. *Stroke*, 36(7), pp. 1480-1484.

NIEMI, M.L., LAAKSONEN, R., KOTILA, M. and WALTIMO, O., 1988. Quality of life 4 years after stroke. *Stroke*, 19(9), pp. 1101-1107.

NUDO, R. J., BARBAY, S. & KLEIM, J. A. (2000) Role of Neuroplasticity in Functional Recovery after Stroke. In: LEVIN, H. S. & GRAFMAN, J. (Eds.) *Cerebral Reorganisation of Function after Brain Damage.* New York, Oxford University Press.

O'CONNOR, R., 2004. Measuring Quality of Life in Health. China: Elselvier.

OLDFIELD, R.C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia, (9), 97-113.

OLSEN, T.S., 1990. Arm and leg paresis as outcome predictors in stroke rehabilitation. *Stroke*, 21(2), pp. 247-251.

ONES, K., YILMAZ, E., CETINKA, B., CAGLAR, N, 2005. Quality of life for patients post stroke and the factors affecting it. *Journal of Stroke & Cerebrovascular Diseases,* 14(6), pp. 261-266.

PANDYAN, A.D., GREGORIC, M., BARNES, M.P., WOOD, D., VAN WIJCK, F., BURRIDGE, J., HERMENS, H. and JOHNSON, G.R., 2005. Spasticity: clinical perceptions, neurological realities and meaningful measurement. *Disability & Rehabilitation,* 27(1-2), pp. 2-6.

PANDYAN AD. VUADENS P. VAN WIJCK FM. STARK S. JOHNSON GR. BARNES MP 2002. Are we underestimating the clinical efficacy of botulinum toxin (type A)? Quantifying changes in spasticity, strength and upper limb function after injections of Botox to the elbow flexors in a unilateral stroke population. *Clinical Rehabilitation.* 16(6), pp. 654-60

PAOLUCCI, 2006. Is Sex a Prognostic Factor in Stroke Rehabilitation? A Matched Comparison. Stroke. 37(12) pp. 2989-94.

PAOLUCCI, S., ANTONUCCI, G., PRATESI, L., TRABALLESI, M., GRASSO, M.G. and LUBICH, S., 1999. Poststroke depression and its role in rehabilitation of inpatients. *Archives of Physical Medicine & Rehabilitation,* 80(9), pp. 985-990.

PARRY R.H., LINCOLN, N.B. and VASS, C.D., 1999. Effect of severity of arm impairment on response to additional physiotherapy early after stroke. *Clinical Rehabilitation,* 13(3), pp. 187-198.

PATRICK DL, ERICKSON P. What constitutes quality of life? Concepts and dimensions. *Drug Therapy Research* 1988; 13: 152–158.

PERNEGER, T.V., 1998. What's wrong with Bonferroni adjustments? BMJ. 316(7139):1236-8, London: British Medical Association.

PLATZ, T. and DENZLER, P., 2002. Do psychological variables modify motor recovery among patients with mild arm paresis after stroke or traumatic brain injury who receive the Arm Ability Training? *Restorative Neurology & Neuroscience,* 20(1-2), pp. 37-49.

PLATZ, T., BOCK, S. and PRASS, K., 2001. Reduced skilfulness of arm motor behaviour among motor stroke patients with good clinical recovery: does it indicate reduced automaticity? Can it be improved by unilateral or bilateral training? A kinematic motion analysis study. *Neuropsychologia,* 39(7), pp. 687-698.

PLATZ, T., PINKOWSKI, C., VAN WIJCK, F., KIM, I., DI BELLA, P. and JOHNSON, G., 2005a. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. *Clinical Rehabilitation,* 19(4), pp. 404-411.

PLATZ T. PINKOWSK C, VAN WIJCK F., 2005b. Arm Rehabilitation Measurement: Manual for Performance and Scoring. Berlin, Verlag.

POHJASVAARA, T., VATAJA, R., LEPPAVUORI, A., KASTE, M. and ERKINJUNTTI, T., 2001. Depression is an independent predictor of poor long-term functional outcome post-stroke. *European Journal of Neurology,* 8(4), pp. 315-319.

POHL, P.S. and WINSTEIN, C.J., 1999. Practice effects on the less-affected upper extremity after stroke. *Archives of Physical Medicine & Rehabilitation,* 80(6), pp. 668-675.

POHL, P.S., LUCHIES, C.W., STOKER-YATES, J. and DUNCAN, P.W., 2000. Upper extremity control in adults post stroke with mild residual impairment. *Neurorehabilitation & Neural Repair,* 14(1), pp. 33-41.

POIZNER, H., MERIANS, A.S., CLARK, M.A., MACAULEY, B., ROTHI, L.J. and HEILMAN, K.M., 1998. Left hemispheric specialization for learned, skilled, and purposeful action. *Neuropsychology,* 12(2), pp. 163-182.

POLGAR S, THOMAS, S (1991). Introduction to research in the health sciences, 2nd Edition. Churchill Livingstone, Melbourne.

POOLE, J.L. and WHITNEY, S.L., 2001. Assessments of motor function post stroke: a review. *Physical and Occupational Therapy in Geriatrics,* 19(2), pp. 1-22.

POWELL, J.M.C.S.P., PANDYAN, A.D., GRANAT, M., CAMERON, M.M.C.S.P. and STOTT, D.J., 1999. Electrical stimulation of wrist extensors in poststroke hemiplegia. *Stroke,* 30(7), pp. 1384-1389.

PRIGATANO, G.P. and WONG, J.L., 1997. Speed of finger tapping and goal attainment after unilateral cerebral vascular accident. *Archives of Physical Medicine and Rehabilitation,* 78(8), pp. 847-852.

RADOMSKI, M.V., 1995. There's more to life than putting on your pants. *American Journal of Occupational Therapy,* 49, pp. 487-490.

RAND, D., WEISS, P.L. and GOTTLIEB, D., 1999. Does proprioceptive loss influence recovery of the upper extremity after stroke? *Neurorehabilitation and Neural Repair*, 13(1), pp. 15-21.

RENWICK, R., BROWN, A. and NAGLER, M., Eds, 1996. *Quality of Life in Health Promotion and Rehabilitation: conceptual Approaches, Issues, and Applications*. London: Sage Publications.

RICE, M.S. and NEWELL, K.M., 2001. Interlimb coupling and left hemiplegia because of right cerebrovascular accident. *The Occupational Therapy Journal of Research*, 21(1), pp. 12-27.

ROBINSON, R.G., SHOEMAKER, W.J., SCHLUMPF, M., VALK, T. and BLOOM, F.E., 1975. Effect of experimental cerebral infarction in rat brain on catecholamines and behaviour. *Nature*, 255(5506), pp. 332-334.

ROBINSON-SMITH, G., JOHNSTON, M.V. and ALLEN, J., 2000. Self-care self-efficacy, quality of life, and depression after stroke. *Archives of Physical Medicine & Rehabilitation*, 81(4), pp. 460-464.

RODGERS, H, SHAW, L, PRICE C, VAN WIJCK F, BARNES M, GRAHAM L, et al (2008). Study design and methods of the BOTULS trial: a randomised controlled trial to evaluate the clinical effect and cost effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. Trials, (9), pp 59.

ROSE, D.K. and WINSTEIN, C.J., 2005. The co-ordination of bimanual rapid aiming movements following stroke. *Clinical Rehabilitation*, 19(4), pp. 452-462.

ROSSINI, P.M. and FORNO, G.D., 2004. Neuronal post-stroke plasticity in the adult. *Restorative Neurology & Neuroscience*, 22(3-5; 3-5), pp. 193-206.

RUDD, A.G., WOLFE, C.D., TILLING, K. and BEECH, R., 1997. Randomised controlled trial to evaluate early discharge scheme for patients with stroke. *British Medical Journal*, 315(7115), pp. 1039-1044.

RYAN, T., ENDERBY, P. and RIGBY, A.S., 2006. A randomized controlled trial to evaluate intensity of community-based rehabilitation provision following stroke or hip fracture in old age. *Clinical Rehabilitation*, 20(2), pp. 123-131.

SARTOR-GLITTENBERG, C. and POWERS, R., 1993. Quantitative measurement of kinesthesia following cerebral vascular accident. *Physiotherapy Canada*, 45(3), pp. 179-186.

SCHIEMANCK, S.K. KWAKKEL, G., POST, M.W., 2006. Predicting Long-Term Independency in Activities of Daily Living After Middle Cerebral Artery Stroke Does Information From MRI Have Added Predictive Value Compared With Clinical Information?

SCHMIDT, R.A., A schema of discrete motor skill learning, 1975. *Psychology Review*; 82: 225-260.

SCHMIDT, R. A., SHAPIRO, D. C., WINSTEIN, C. J., YOUNG, D. E., & SWINNEN, S, 1987. Feedback and motor skill training: Relative frequency of KR and summary KR (Contract No. MDA903-85-K-0225). Washington, DC: U.S. Army Research Institute. Cited in Schmidt RA(Ed) (1988). *Motor control and learning: A behavioural emphasis*. Champaign IL. Human Kinetics.

SCHMIDT RA(ED), 1988. *Motor control and learning: A behavioural emphasis*. Champaign Il. Human Kinetics.

SCHMIDT R.A. 1991 Contemporary *management of motor control problems.* In: LISTER MJ (Ed) Proceedings of the II STEP Conference, Foundations for physical therapy Fredricksburg VA

SCHMIDT, R.A. and WRISBERG, C.A., 2004. *Motor Learning and Performance.* Champaign, Ill: Human Kinetics.

SCHMIDT, R.C 1996. Dynamical perspective on motor learning in Zelanick HN (ed) Advances in motor learning and control. Human Kinetics Champaign, Illinois.

SCHMIDT R.A., Lee, T. 2005. *Motor Control and Learning: A behavioural emphasis.* Human Kinetics, Champaign Illinois.

SCHNITZLER, A., KESSLER, K.R. and BENECKE, R., 1996. Transcallosally mediated inhibition of interneurons within human primary motor cortex. *Experimental Brain Research*, 112(3), pp. 381-391.

SCHONER G, KELSO J.A.S. 1988. Dynamic pattern generation in behavioural and neural systems. *Science*, 239, 1513-1520

SCOTTISH EXECUTIVE (2007). Co-ordinated, integrated and fit for purpose: A Delivery Framework for Adult Rehabilitation in Scotland. A delivery framework for adult rehabilitation in Scotland. Scottish Executive, Edinburgh.

SCOTTISH GOVERNMENT Better Health, Better Care: Action Plan 2007. Scottish Government, Edinburgh.

SCOTTISH INTERCOLLEGIATE GUIDELINE NETWORK (2004). SIGN 50: A guideline developer's handbook. Available from http://www.sign.ac.uk/guidelines/fulltext/50/index.html (Accessed December 2006).

SERRIEN, D.J. and SWINNEN, S.P., 1999. Intentional switching between behavioral patterns of homologous and nonhomologous effector combinations. *Journal of Experimental Psychology: Human Perception & Performance,* 25(5), pp. 1253-1267.

SERRIEN, D.J., STRENS, L.H., CASSIDY, M.J., THOMPSON, A.J. and BROWN, P., 2004. Functional significance of the ipsilateral hemisphere during movement of the affected hand after stroke. *Experimental neurology,* 190(2), pp. 425-432.

SHAH, S., VANCLAY, F. and COOPER, B., 1989. Improving the sensitivity of the Barthes Index for stroke rehabilitation. *Journal of clinical epidemiology,* 42(8), pp. 703-709.

SHARPE, M., 2000. Depression after stroke and lesion location: a systematic review. *Lancet,* 356(9224), pp. 122-126.

SHEA CH, Kohl R; Indermill C (1990) Contextual interference: Contributions of Practice. Acta Psychologica, 73: 145-175

SHELTON, F.N. and REDING, M.J., 2001. Effect of lesion location on upper limb motor recovery after stroke. *Stroke,* 32(1), pp. 107-112.

SHIBASAKI, H., SADATO, N., LYSHKOW, H., YONEKURA, Y., HONDA, M., NAGAMINE, T., SHIMODA, K. and ROBINSON, R.G., 1998. Effects of anxiety disorder on impairment and recovery from stroke. *Journal of Neuropsychiatry & Clinical Neurosciences,* 10(1), pp. 34-40.

SHROUT, P.E. and FLEISS, J.L., 1979. Intraclass correlations: Uses in assessing rater reliability.Article. *Psychological bulletin,* 86(2), pp. 420-428.

SHUMWAY-COOKE A, WOOLLACOTT M; 1995. Chapter 2; *Motor Control Theory and practical application.* Williams and Wilkins, Baltimore.

SINGH, A., HERRMANN, N. and BLACK, S.E., 1998. The importance of lesion location in poststroke depression: a critical review. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie,* 43(9), pp. 921-927.

SINYOR, D., AMATO, P., KALOUPEK, D.G., BECKER, R., GOLDENBERG, M. and COOPERSMITH, H., 1986. Post-stroke depression: relationships to functional impairment, coping strategies, and rehabilitation outcome. *Stroke,* 17(6), pp. 1102-1107.

SMITH, K.W., AVIS, N.E. and ASSMANN, S.F., 1999. Distinguishing between quality of life and health status in quality of life research: a meta-analysis. *Quality of Life Research,* 8(5), pp. 447-459.

SONDE, L., 2001. Can the site of brain lesion predict improved motor function after low-TENS treatment on the post-stroke paretic arm? *Clinical Rehabilitation.* 15(5):545-51.

SPATT, J. and GOLDENBERG, G., 1997. Speed of motor execution and apraxia. *Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society,* 19(6), pp. 850-856.

SPAULDING, S.J., MCPHERSON, J.J., STRACHOTA, E., KUPHAL, M. and RAMPONI, M., 1988. Jebsen Hand Function Test: performance of the uninvolved hand in hemiplegia and of right-handed, right and left hemiplegic persons. *Archives of Physical Medicine & Rehabilitation,* 69(6), pp. 419-422.

STAINES, W.R., MCILROY, W.E., GRAHAM, S.J. and BLACK, S.E., 2001. Bilateral movement enhances ipsilesional cortical activity in acute stroke: A pilot functional MRI study. *Neurology,* 56(3), pp. 401-404.

STEULTJENS, E.M., DEKKER, J., BOUTER, L.M., VAN DE NES, J.C., CUP, E.H. and VAN DEN ENDE, C.H., 2003. Occupational therapy for stroke patients: a systematic review. *Stroke,* 34(3), pp. 676-687.

STINEAR, C.M., BARBER P.A., COXON, J.P., FLEMING, M.K. and BYBLOW, W.D., 2008. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. *Brain,* 131(Pt 5), pp. 1381-1390.

STINEAR, C.M., BARBER P.A., SMALE, P.R., COXON, J.P., FLEMING, M.K. and BYBLOW, W.D., 2007. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain,* 130(Pt 1), pp. 170-180.

STINEAR, C.M., WALKER, K.S. and BYBLOW, W.D., 2001. Symmetric facilitation between motor cortices during contraction of ipsilateral hand muscles. *Experimental Brain Research,* 139(1), pp. 101-105.

STINEAR, J.W. and BYBLOW, W.D., 2002. Disinhibition in the human motor cortex is enhanced by synchronous upper limb movements. *Journal of Physiology*, 543(1), pp. 307-316.

STINEAR, J.W. and BYBLOW, W.D., 2004. Rhythmic bilateral movement training modulates corticomotor excitability and enhances upper limb motricity poststroke: A pilot study. *Journal of Clinical Neurophysiology*, 21(2), pp. 124-131.

STUCKI, G., REINHARDT, J.D., GRIMBY, G., MELVIN, J. 2008. Developing research capacity in human functioning and rehabilitation research from the comprehensive perspective based on the ICF-model. *European journal of physical & rehabilitation medicine.* 44(3):343-51.

SUMMERS, J.J., KAGERER, F.A., GARRY, M.I., HIRAGA, C.Y., LOFTUS, A. and CAURAUGH, J.H., 2007. Bilateral and unilateral movement training on upper limb function in chronic stroke patients: A TMS study. *Journal of the Neurological Sciences*, 252(1), pp. 76-82.

SUMMERS, J.J., KAGERER, F.A., GARRY, M.I., HIRAGA, C.Y., LOFTUS, A. and CAURAUGH, J.H., 2007. Bilateral and unilateral movement training on upper limb function in chronic stroke patients: A TMS study. *Journal of the Neurological Sciences*, 252(1), pp. 76-82.

SUNDERLAND, A., 1989. Arm function after stroke. An evaluation of grip strength as a measure of recovery and a prognostic indicator. Journal of Neurology, Neurosurgery & Psychiatry. 52(11), pp.1267-1272

SUNDERLAND, A., BOWERS, M.P., SLUMAN, S.M., WILCOCK, D.J. and ARDRON, M.E., 1999. Impaired dexterity of the ipsilateral hand after stroke and the relationship to cognitive deficit.see comment. *Stroke*, 30(5), pp. 949-955.

SUNDERLAND, A., 2000. Recovery of ipsilateral dexterity after stroke. *Stroke*, 31(2), pp. 430-433.

SUNDERLAND, A., BOWERS, M.P., SLUMAN, S.M., WILCOCK, D.J. and ARDRON, M.E., 1999. Impaired dexterity of the ipsilateral hand after stroke and the relationship to cognitive deficit.see comment. *Stroke*, 30(5), pp. 949-955.

SUNDERLAND, A., FLETCHER, D., BRADLEY, L., TINSON, D., HEWER, R.L. and WADE, D.T., 1994. Enhanced physical therapy for arm function after stroke: a one year follow up study. *Journal of Neurology, Neurosurgery & Psychiatry*, 57(7), pp. 856-858.

SUWAZONO, S., MAGATA, Y., IKEDA, A. and MIYAZAKI, M., 1993. Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain*, 116(Pt 6), pp. 1387-1398.

SWINNEN, S.P. and WENDEROTH, N., 2004. Two hands, one brain: cognitive neuroscience of bimanual skill. *Trends in Cognitive Sciences*, 8(1), pp. 18-25.

SWINNEN, S.P., 2002. Intermanual coordination: from behavioural principles to neural-network interactions. *Nature Reviews Neuroscience*, 3(5), pp. 348-359.

TABACHNICK BG, FIDELL, LS (2001). Using Multivariate statistics (4th Edition). Allyn and Bacon, Boston.

TANJI, J., OKANO, K. and SATO, K.C., 1988. Neuronal activity in cortical motor Areas related to ipsilateral, contralateral, and bilateral digit movements of the monkey. *Journal of neurophysiology*, 60(1), pp. 325-343.

TAUB, E., USWATTE, G., KING, D.K., MORRIS, D., CRAGO, J.E. and CHATTERJEE, A., 2006. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. *Stroke*, 37(4), pp. 1045-1049.

TURNER-STOKES, L. and HASSAN, N., 2002. Depression after stroke: a review of the evidence base to inform the development of an integrated care pathway. Part 1: Diagnosis, frequency and impact. *Clinical Rehabilitation*, 16(3), pp. 231-247.

TURTON, A., FRASER, C., FLAMENT, D., WERNER, W., BENNET, K.M.B. and LEMON, R.N., 1994. *Spasticity: Mechanisms and Management.* Berlin: Springer Verlag, pp. 8 - 24.

TURTON, A., WROE, S., TREPTE, N., FRASER, C. and LEMON, R.N., 1996. Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. *Electroencephalography & Clinical Neurophysiology*, 101(4), pp. 316-328.

TURTON, A. 1998. Mechanisms for recovery of hand and arm function after stroke: a review of evidence from studies using non-invasive investigative techniques. *British Journal of Occupational Therapy*; 61, pp 359-364.

TURTON, A. and POMEROY, V., 2002. When should upper limb function be trained after stroke? Evidence for and against early intervention. *Neurorehabilitation*, 17(3), pp. 215-224.

VAN DE WEG, F.B., KUIK, D.J. and LANKHORST, G.J., 1999. Post-stroke depression and functional outcome: a cohort study investigating the influence of depression on functional recovery from stroke. *Clinical Rehabilitation,* 13(3), pp. 268-272.

VAN DER LEE JH.GROOT, V., BECKERMAN, H., WAGENAAR, R.C., LANKHORST, G.J. and BOUTER, L.M., 2001. The intra- and inter-rater reliability of the Action Research Arm test: a practical test of upper extremity function in patients with stroke. *Archives of Physical Medicine and Rehabilitation,* 82(1), pp. 14-19.

VAN PEPPEN, R.P., KWAKKEL, G., WOOD-DAUPHINEE, S., HENDRIKS, H.J., VAN DER WEES, P.J. and DEKKER, J., 2004. The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clinical Rehabilitation,* 18(8), pp. 833-862.

VAN WIJCK, F.M., PANDYAN, A.D., JOHNSON, G.R. and BARNES, M.P., 2001. Assessing motor deficits in neurological rehabilitation: patterns of instrument usage. *Neurorehabilitation & Neural Repair,* 15(1), pp. 23-30.

VIITANEN, M., FUGL-MEYER, K.S., BERNSPANG, B. and FUGL-MEYER, A.R., 1988. Life satisfaction in long-term survivors after stroke. *Scandinavian Journal of Rehabilitation Medicine,* 20(1), pp. 17-24.

WADE, D 1992; measurements in neurological rehabilitation; Oxford, Oxford University Press, 1992.

WADE, D.T., 1989. Measuring arm impairment and disability after stroke. *International Disability Studies,* 11(2), pp. 89-92.

WADE, D.T., LANGTON-HEWER, R., WOOD, V.A., SKILBECK, C.E. and ISMAIL, H.M., 1983. The hemiplegic arm after stroke: measurement and recovery. *Journal of Neurology, Neurosurgery & Psychiatry,* 46(6), pp. 521-524.

WAGENAAR, RC, HOLT, K.G., KUBO, M., HO, C., 2003. Gait risk factors for falls in older adults: a dynamic perspective. Generations, Winter 2002-3; 28-32.

WALLER, S.M. and WHITALL, J., 2004. Fine motor control in adults with and without chronic hemiparesis: baseline comparison to nondisabled adults and effects of bilateral arm training. *Archives of Physical Medicine and Rehabilitation,* 85(7), pp. 1076-1083.

WALLER, S.M. and WHITALL, J., 2005. Hand dominance and side of stroke affect rehabilitation in chronic stroke. *Clinical Rehabilitation,* 19(5), pp. 544-551.

WARE J.E. & SHERBOURNE CD.1992. The MOS 36-Item Short Form Health Survey (SF-36) I. Conceptual framework and item selection. *Med Care* 30: 473-483.

WATSON, D., WEBER, K., ASSENHEIMER, J.S., CLARK, L.A., STRAUSS, M.E. and MCCORMICK, R.A., 1995. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. *Journal of Abnormal Psychology,* 104(1), pp. 3-14.

WERRING, D.J., CLARK, C.A., BARKER, G.J., MILLER, D.H., PARKER, G.J.M., BRAMMER, M.J., BULLMORE, E.T., GIAMPIETRO, V.P. and THOMPSON, A.J., 1998. The structural and functional mechanisms of motor recovery: complementary use of diffusion tensor and functional magnetic resonance imaging in a traumatic injury of the internal capsule. *Journal of Neurology, Neurosurgery, and Psychiatry,* 65(6), pp. 863-869.

WETTER, S., POOLE, J.L. and HAALAND, K.Y., 2005. Functional implications of ipsilesional motor deficits after unilateral stroke. *Archives of Physical Medicine & Rehabilitation,* 86(4), pp. 776-781.

WHITALL, J., MCCOMBE WALLER, S., SILVER, K.H. and MACKO, R.F., 2000. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. *Stroke,* 31(10), pp. 2390-2395.

WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med.1998; 28:551–558

WHYTE, E.M. and MULSANT, B.H., 2002. Post stroke depression: epidemiology, pathophysiology, and biological treatment. *Biological psychiatry,* 52(3), pp. 253-264.

WINSTEIN, C.1991 *Contemporary management of motor control problems.* In: LISTER MJ(Ed) Proceedings of the II STEP Conference, Foundations for physical therapy Fredricksburg VA.

WINSTEIN, C.J. and POHL, P.S., 1995. Effects of unilateral brain damage on the control of goal-directed hand movements. *Experimental Brain Research,* 105(1), pp. 163-174.

WINSTEIN, C.J., 1991. Knowledge of results and motor learning-implications for physical therapy. *Physical Therapy,* 71(2), pp. 140-149.

WINSTEIN C.J., 1991. Designing practice for motor learning clinical implications: contemporary

management of motor control problems. In Lister MJ (ed) (1991) *Foundation for Physical Therapy*, Fredricksburg.

WINSTEIN, C.J., POHL, P.S. and LEWTHWAITE, R., 1994. Effects of physical guidance and knowledge of results on motor learning: support for the guidance hypothesis. *Research Quarterly for Exercise & Sport,* 65(4), pp. 316-323.

WINSTEIN, C.J., ROSE, D.K., TAN, S.M., LEWTHWAITE, R., CHUI, H.C. and AZEN, S.P., 2004. A randomized controlled comparison of upper-extremity rehabilitation strategies in acute stroke: A pilot study of immediate and long-term outcomes. *Archives of Physical Medicine & Rehabilitation,* 85(4), pp. 620-628.

WOLF, S.L., CATLIN, P.A., ELLIS, M., ARCHER, A.L., MORGAN, B. and PIACENTINO, A., 2001. Assessing Wolf Motor Function Test as Outcome Measure for Research in Patients after Stroke. *Stroke,* 32(7), pp. 1635-1639.

WOLF, S.L., NEWTON, H., MADDY, D., BLANTON, S., ZHANG, Q., WINSTEIN, C.J., MORRIS, D.M. and LIGHT, K., 2007. The Excite Trial: relationship of intensity of constraint induced movement therapy to improvement in the wolf motor function test. *Restorative Neurology & Neuroscience,* 25(5-6), pp. 549-562.

WOLF, S.L., WINSTEIN, C.J., MILLER, J.P., TAUB, E., USWATTE, G., MORRIS, D., GIULIANI, C., LIGHT, K.E., NICHOLS-LARSEN, D. and EXCITE, I., 2006. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA,* 296(17), pp. 2095-2104.

WOLFE, C.D., 2000. The impact of stroke. *British Medical Bulletin,* 56(2), pp. 275-286.

WOOD-DAUPHINEE, S., 1999. Assessing quality of life in clinical research: from where have we come and where are we going? *Journal of Clinical Epidemiology,* 52(4), pp. 355-363.

THE WORLD HEALTH ORGANIZATION, 1947. Constitution of the World Health Organisation. WHO: Geneva.

WORLD HEALTH ORGANISATION (WHO) 2001. International Classification of Functioning, Geneva.

WU, C.Y., CHEN, C.L., TSAI, W.C., LIN, K.C. and CHOU, S.H., 2007. A randomized controlled trial of modified constraint-induced movement therapy for elderly stroke survivors: changes in motor impairment, daily functioning, and quality of life. *Archives of Physical Medicine & Rehabilitation,* 88(3), pp. 273-278.

WYLLER, T.B., HOLMEN, J., LAAKE, P. and LAAKE, K., 1998. Correlates of subjective well-being in stroke patients. *Stroke,* 29(2), pp. 363-367.

WYLLER, T.B., SODRING, K.M., SVEEN, U., LJUNGGREN, A.E. and BAUTZ-HOLTER, E., 1996. Predictive validity of the Sodring Motor Evaluation of Stroke Patients (SMES). *Scandinavian Journalof Rehabilitation Medicine,* 28(4), pp. 211-216.

WYLLER, T.B., SØDRING, K.M., SVEEN, U., LJUNGGREN, A.E. and BAUTZ-HOLTER, E., 1997. Are there gender differences in functional outcome after stroke? Clinical Rehabilitation. 11(2):171-9, 1997.

WYLLER, T.B., SVEEN, U., SODRING, K.M., PETTERSEN, A.M. and BAUTZ-HOLTER, E., 1997. Subjective well-being one year after stroke. *Clinical Rehabilitation,* 11(2), pp. 139-145.

YANAGITA, M., WILLCOX, B.J., MASAKI, K.H., CHEN, R., HE, Q., RODRIGUEZ, B.L., UESHIMA, H. and CURB, J.D., 2006. Disability and depression: investigating a complex relation using physical performance measures. *American Journal of Geriatric Psychiatry,* 14(12), pp. 1060-1068.

YAROSH, C.A., HOFFMAN, D.S. and STRICK, P.L., 2004. Deficits in movements of the wrist ipsilateral to a stroke in hemiparetic subjects. *Journal of Neurophysiology,* 92(6), pp. 3276-3285.

YELNIK, A., BONAN, I., DEBRAY, M., LO, E., GELBERT, F. and BUSSEL, B., 1996. Changes in the execution of a complex manual task after ipsilateral ischemic cerebral hemispheric stroke. *Archives of Physical Medicine & Rehabilitation,* 77(8), pp. 806-810.

YOUDASJW, CAREY JR, GARRETT TR. Reliability of measurements of cervical spine range of motion – comparison of three methods. *Physical Therapy*; 71: 98-106.

ZIGMOND, A.S. and SNAITH, R.P., 1983. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica,* 67(6), pp. 361-370.

List of Appendices

Appendix 1

SIGN Checklist

SIGN

Methodology Checklist 2: Randomised Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

	In a well conducted RCT study…..	***In this study this criterion is::***	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed√ Poorly addressed	Not addressed Not reported Not applicable
1.2	The assignment of subjects to treatment groups is randomised	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	An adequate concealment method is used	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	How well was the study done to minimise bias? *Code ++, +, or –*	
2.2	If coded as +, or – what is the likely direction in which bias might affect the study results?	Results may be more negative than if groups had been better matched
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?	
SECTION 3: DESCRIPTION OF THE STUDY *(*The following information is required to complete evidence tables facilitating cross-study comparisons. Please complete all sections for which information is available). *PLEASE PRINT CLEARLY*		
3.1	How many patients are included in this study? *Please indicate number in each arm of the study, at the time the study began.*	
3.2	What are the main characteristics of the patient population? *Include all relevant characteristics – e.g. age, sex, ethnic origin, comorbidity, disease status, community/hospital based*	
3.3	What intervention (treatment, procedure) is being investigated in this study? *List all interventions covered by the study.*	
3.4	What comparisons are made in the study? *Are comparisons made between treatments, or between treatment and placebo / no treatment?*	
3.5	How long are patients followed-up in the study? *Length of time patients are followed from beginning participation in the study. Note specified end points used to decide end of follow-up (e.g. death, complete cure). Note if follow-up period is shorter than originally planned.*	
3.6	What outcome measure(s) are used in the study? *List all outcomes that are used to assess effectiveness of the interventions used.*	
3.7	What size of effect is identified in the study? *List all measures of effect in the units used in the study – e.g. absolute or relative risk, NNT, etc. Include p values and any confidence intervals that are provided.*	
3.8	How was this study funded? *List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*	
3.9	Does this study help to answer your key question? *Summarise the main conclusions of the study and indicate how it relates to the key question.*	

Appendix 2

Search Strategies

All searches were conducted between 1996 and 2006 in Medline, Embase. CINAHL and PSYCHINFO

Chapter 2

Search 1. Section 2.2 Search Strategy for Bilateral Training Studies

1. cerebrovascular disease.mp
2. cerebrovascular accident.mp
3. cerebrovascular disorders.mp
4. 1 or 2 or 3
5. stroke.mp
6. post-stroke.mp
7. poststroke.mp
8. cva.mp.
9. 5 and 6 and 7 and 8
10. 5 or 6 or 7 or 8
11. 4 or 10
12. hemiplegia.mp.
13. paresis.mp
14. 12 and 13
15. 13 or 14
16. 11 or 15
17. upper extremity.mp.
18. upper limb.mp
19. arm.mp
20. wrist.mp.
21. hand.mp
22. 17 or 18 or 19 or 20 or 21
23. rehabilitation mp
24. “recovery of function”.mp.
25. physical therapy.mp
26. exercise.mp
27. exercise therapy.mp
28. motor activity.mp.
29. motor learning.mp.
30. motor relearning. mp
31. motor skills.mp
32. “task performance and analysis.mp
33. occupational therapy.mp
34. 23 and 24 and 25 and 26 and 27 and 28 and 29 and 30 and 31 and 32 and 33
35. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
36. bimanual.mp
37. train.mp.
38. retrain.mp
39. train$.mp
40. retrain$.mp.
41. physiotherap$.mp.
42. physical therap$. mp.
43. 36 or 37 or 38 or 39 or 40 or 41 or 42
44. 34 or 35
45. 16 and 35 and 43

Search 2. Section 2.3 Search Strategy for factors likely to influence training responses and recovery

Combinations of the following search terms were entered:

1. cerebrovascular disease.mp
2. cerebrovascular accident.mp
3. cerebrovascular disorders.mp
4. 1 or 2 or 3
5. stroke.mp
6. post-stroke.mp
7. poststroke.mp
8. cva.mp.
9. 5 and 6 and 7 and 8
10. 5 or 6 or 7 or 8
11. 4 or 10
12. hemiplegia.mp.
13. paresis.mp
14. 12 and 13
15. 13 or 14
16. 11 or 15
17. upper extremity.mp.
18. upper limb.mp
19. arm.mp
20. wrist.mp.
21. hand.mp
22. 17 or 18 or 19 or 20 or 21
23. 16 and 22

23 was combined in turn with each of the following terms:

1. predict$.mp.
2. determin$.mp
3. dominance.mp. or exp Dominance, Cerebral/; or dominan$.mp.
4. sens$.mp.
5. exp Proprioception/ or exp proprioceptive or exp kinaesthesia 8. sensation/ or proprioception/ or kinesthesis/ or touch/
6. sensation disorders/ or exp somatosensory disorders/
7. stereognosis/ or agnosia/
8. two point discrimination.tw.
9. position sense.tw.
10. exp Gender/ or exp sex /
11. exp Age Factors/.
12. lesion.mp. or exp Brain Ischemia/
13. Lesion site.mp.
14. Lesion side.mp.
15. Lesion location.mp.
16. Tone.mp./or muscle tone.mp./or exp muscle spasticity

Search 3. Section 2.4 Search strategy for ipsilesional dysfunction

1. cerebrovascular disease.mp
2. cerebrovascular accident.mp
3. cerebrovascular disorders.mp
4. 1 or 2 or 3
5. stroke.mp
6. post-stroke.mp
7. poststroke.mp
8. cva.mp.
9. 5 and 6 and 7 and 8
10. 5 or 6 or 7 or 8
11. 4 or 10
12. hemiplegia.mp.
13. paresis.mp
14. 12 and 13
15. 13 or 14
16. 11 or 15
17. upper extremity.mp.
18. upper limb.mp
19. arm.mp
20. wrist.mp.
21. hand.mp
22. 17 or 18 or 19 or 20 or 21
23. rehabilitation mp
24. “recovery of function”.mp.
25. physical therapy.mp
26. exercise.mp
27. exercise therapy.mp
28. motor activity.mp.
29. motor learning.mp.
30. motor relearning. mp
31. motor skills.mp
32. “task performance and analysis.mp
33. occupational therapy.mp
34. 23 and 24 and 25 and 26 and 27 and 28 and 29 and 30 and 31 and 32 and 33
35. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
36. 34 or 35
37. 16 and 36
38. ipsilateral.mp
39. ipsilesional.mp
40. “unaffected”mp
41. 36 or 37 or 38
42. 37 and 41

Chapter 3

Search 4. Section 3.1 Search strategy for anxiety and depression

1. cerebrovascular disease.mp
2. cerebrovascular accident.mp
3. cerebrovascular disorders.mp
4. 1 or 2 or 3
5. stroke.mp
6. post-stroke.mp
7. poststroke.mp
8. cva.mp.
9. 5 and 6 and 7 and 8
10. 5 or 6 or 7 or 8
11. 4 or 10
12. hemiplegia.mp.
13. paresis.mp
14. 12 and 13
15. 13 or 14
16. 11 or 15
17. upper extremity.mp.
18. upper limb.mp
19. arm.mp
20. wrist.mp.
21. hand.mp
22. 17 or 18 or 19 or 20 or 21
23. rehabilitation mp
24. “recovery of function”.mp.
25. physical therapy.mp
26. exercise.mp
27. exercise therapy.mp
28. motor activity.mp.
29. motor learning.mp.
30. motor relearning. mp
31. motor skills.mp
32. “task performance and analysis.mp
33. occupational therapy.mp
34. 23 and 24 and 25 and 26 and 27 and 28 and 29 and 30 and 31 and 32 and 33
35. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
36. 34 or 35
37. 16 and 36
38. exp depression
39. depressive disorder mp
40. severe depression.mp.
41. depressive disorder, major mp
42. 38 or 39 or 40 or 41
43. 37 and 42
44. exp anxiety
45. anxiety disorder mp
46. severe anxiety
47. anxiety disorder, major
48. 44 or 45 or 46 or 47
49. 37 and 48

Search 5. Section 3.2 Search strategy for health related quality of life

1. cerebrovascular disease.mp
2. cerebrovascular accident.mp
3. cerebrovascular disorders.mp
4. 1 or 2 or 3
5. stroke.mp
6. post-stroke.mp
7. poststroke.mp
8. cva.mp.
9. 5 and 6 and 7 and 8
10. 5 or 6 or 7 or 8
11. 4 or 10
12. hemiplegia.mp.
13. paresis.mp
14. 12 and 13
15. 13 or 14
16. 11 or 15
17. upper extremity.mp.
18. upper limb.mp
19. arm.mp
20. wrist.mp.
21. hand.mp
22. 17 or 18 or 19 or 20 or 21
23. rehabilitation mp
24. “recovery of function”.mp.
25. physical therapy.mp
26. exercise.mp
27. exercise therapy.mp
28. motor activity.mp.
29. motor learning.mp.
30. motor relearning. mp
31. motor skills.mp
32. “task performance and analysis.mp
33. occupational therapy.mp
34. 23 and 24 and 25 and 26 and 27 and 28 and 29 and 30 and 31 and 32 and 33
35. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
36. 34 or 35
37. 16 and 36
38. quality of life.mp.
39. exp "Quality of Life"
40. exp Health Status/
41. "health related quality of life".mp
42. "well-being".mp
43. 38 or 39 or 40 or 41 or 42
44. 37 and 43

Appendix 3

Tables summarising the literature

Table 1 Summary of studies demonstrating impairment as a predictor of activity outcomes

Study	Population	Predictive Variable	Outcome Variable	Outcome Domain
Loewen (1990) Observational cohort study	N=57	Motor Assessment Scale (UL) <4days, 1 week and 1 month post-onset	Motor Assessment Scale at discharge	Motor Impairment. Upper arm scores predictive at 1 week (r^2=0.84) and 1 month (r^2=0.91) ($p<0.0001$)
Duncan (1992) Observational cohort study	N=54	FM <24 hours post-onset	Fugl Meyer (FM) scores at 5, 30, 90 and 180 days	Motor Impairment: 53.2% of variance explained by initial FM; 74.2% at 5 days; 86.2% at 30 days
Nakayama (1994) Observational cohort study	N=421	Paresis 13 hours post-onset	Paresis (Scandinavian Stroke Scale) weekly until 12 weeks Barthel grooming and feeding	Motor Impairment: 56% of patients with initial impairment demonstrated impairment at 12 weeks Activity: Functional recovery significantly better where motor recovery occurred ($p=0.02$)
Katrak (1998) Observational cohort study	N=71	Shoulder shrug or abduction at 11 days; lesion side, sensation, age, gender	Hand movement and hand function at three months	Impairment: Odds ratio for good recovery 7.3 for initial shrug, 7.5 for abduction; 10.0 for hand movement
Broeks (1999) Observational cohort study	N=54	FM, Ashworth, cutaneous sensation, proprioception at 3-8 weeks post-onset	Fugl Meyer at 4 years	Impairment: Correlation with initial FM ($r2=0.83$; $p<0.001$)
Feys (2000a) Observational cohort study	N=100	FM, Ashworth, Tactile sensation score 2-5 weeks post onset	Change in FM at 2, 6 and 12 months	Impairment: Predictive variables: 69% of variance at 2 months, 57.8% at 6 months

Table 2. Summary of studies demonstrating impairment as a predictor of activity outcomes

Study	Population	Predictive Variable	Outcome Variable	Outcome Domain
Wade (1983) Observational cohort study	N=92	Motor deficit, Joint Position Sense 1-3 weeks post-onset	Frenchay Arm Test over 1- month – 2 years	Activity: Motor deficit significantly correlated with FAT at 2 years (X^2=5.74; p<0.02)
Olsen (1990) Observational cohort study	N=68	Paresis at admission to rehabilitation (MRC Scale)	Grooming and feeding on Barthel Index at discharge	Activity: Baseline Paresis correlated significantly with activity score at discharge (r^2=0.65; p=0.01)
Rand (1999) Observational cohort study	N=40	FM, Proprioception and light touch <20days post-onset	FM Frenchay Arm Test at 6 weeks	Activity: impairment significantly correlated with activity limitation at six weeks (r^2>0.88; p<0.001) irrespective of presence of sensory impairment at baseline
Kwakkel (2003) Observational cohort study	N=102, flaccid UL	FM, lesion type, proprioception at 4 weeks	Action Research Arm Test (ARAT) at 6 months	Activity: FM scores at 4 weeks most predictive of ARAT at 6 months (94% positive predictive value)

FM denotes Fugl Meyer Test

Table 3. Summary of impairment factors influencing outcomes in the context of therapeutic interventions

Study	Design	Population	Intervention	Outcome Variable	Factor influencing outcome
Feys (1998)	RCT	N=100 3 weeks post-onset	Sensorimotor stimulation or usual care	FM at post-treatment and six and twelve month follow-up assessments	Patients with most severe paresis improved most. No effect of side
Parry (1999)	RCT	N=282 1-5 weeks post stroke	10 hours additional therapy	Recovery on the ARAT and RMA	Initial motor impairment (RMA)
Winstein (2004)	RCT	N=64 <20 days post-onset	Task training, strength training or usual care	FM, UL functional test, of the hemiplegic upper extremity	Less severe impairment on Orpington Prognostic Scale improved most
Fritz (2005)	Pre/post Test	N=55 Longstanding stroke	CIMT over 10 days plus mitt wearing	Wolf Motor Function Test	Initial finger extension and grasp/release

FM denotes Fugl Meyer Test

Table 4. Summary of activity limitation factors influencing outcomes in the context of therapeutic interventions

Study	Design	Population	Intervention	Outcome Variable(s)	Factor influencing outcome
Sunderland (1992)	RCT	N=137 <11 days post onset	Enhanced therapy compared to usual care	Nine hole peg, Extended Motricity Index, Motor club assessment	Patients with better FAT scores at baseline performed best at 1&6 months
Platz (2002)	Pre/post test	N=33 Sub-acute, mild impairment	Arm Ability Training	TEMPA	Patients with poorer TEMPA scores pre-training improved most. Baseline TEMPA predicted 70% of variance of outcome scores

Table 5. Summary of effects of hand dominance on impairment and activity outcomes

Study	Population	Predictive Variable	Outcome Variable	Outcome Domain
Harris (2006) Observational cohort study	N=93, chronic stage	Dominance predictive Dominance not predictive	Tone, grip, strength, pain Chedoke Arm and Hand Activity Inventory, Motor Activity Log	Impairment and Activity

Table 6. Summary of effects of lesion side or hand dominance on responses to therapeutic interventions

Study	Design	Population	Intervention	Outcome Variable(s)	Factor influencing outcome
Byl (2003)	Crossover RCT	N=18 Chronic stage	8 weeks Home based motor and sensory training in line with principles of neuroplasticity	Wolf Motor Function Test	Dominance and side no effect
Miltner (1999)	Pre/post test	N=15 Chronic stage	14 days constraint induced movement therapy	WMFT Motor Activity Log	No effect of side of lesion
Friz (2006)	Pre/post test	N=55 Chronic Stage	14 days constraint induced movement therapy	WMFT Motor Activity Log	No effect of dominance
McCombe (2005)	RCT	N=22 Chronic stage	6 weeks x 20 minutes of BATRACT	FM, UL Strength, WMFT, University of Maryland Arm Questionnaire for Stroke	Effects of right side dominant vs Left side dominance

FM denotes Fugl Meyer Test, WMFT denotes Wolf Motor Function Test

Table 7. Summary of effects of proprioception on impairment outcomes

Study	Design	Population	Predictive Variable	Outcome Variable	Outcome Domain
Gowland (1982)	Observational cohort study	N=233	Proprioception and touch at admission	FM at discharge	Impairment
Meldrum (2004)	Observational cohort study	N=114	Proprioception <48hours post-onset	RMA at 6 months and 2 years	Impairment

Table 8. Summary of ipsilesional activity limitations.

Study	Design	Participants	Time post-Stroke	Ipsilesional dexterity deficit	Hemispheric differences	Follow-up
Spaulding 1988	Observational cohort	49 CVA compared to normative data from Jebsen hand function test,	Not provided Mixed aetiology	Poorer performance than controls on JHFT	Significant slowing with LHD ($p>0.01$)	None
Yelnick (1996)	Two trial observation	18 (L) CVA 18(R)CVA 86 Controls	Mean 60 days post stroke	L and RHD slower than controls and significantly correlated with age on 9HPT	When 9 participants with apraxia removed (L)CVA better than (R) CVA ($p<0.05$)	None
Desrosiers (1996)	Observational cohort	43 CVA 43 controls	Mean time 25.1 months	Poorer performance than controls on TEMPA, Box and Block Test, Purdue Peg Test	No difference between RHD and LHD	None
Marque (1997)	Cohort Study	15 CVA 16 matched healthy controls	20 days and 90 days	Participants significantly impaired compared to controls at 20 and 90 days on 9HPT	n/a	None
Sunderland (1999)	Cohort Study	30 CVA 34 matched healthy controls	1-31 days	Deficit on JHFT compared to controls	LHD significantly poorer than controls particularly in 7 apraxic participants. RHD no difference	None
Sunderland (2000)	Cohort Study, follow-up from Sunderland (1999)	24 CVA from above study	6 months	Significant recovery JHFT	Recovery greatest for LHD($p<0.05$) but remained slower than controls($p<0.001$)	None
Wetter (2005)	CVA n=59 Controls n=67	59 CVA 67 Controls	Mean 5.1 years post stroke	(L) CVA and (R)CVA participants slower than controls on JHFT	No hemispheric differences (L) apraxic group worse than non apraxic and controls on JHFT total and writing ($p<0.01$).	None

JHFT denotes Jebsen Hand Function Test; CVA denotes Cerebrovascular accident; RHD denotes right hemisphere damage; LHD denotes left hemisphere damage; 2PD denotes two point discrimination. All reported deficits were significant at $p<0.05$

Table 9. Summary of studies examining ipsilesional finger tapping

Study	Design	Participants	Time post-Stroke	Finger Tapping Speed	Hemispheric differences	Follow-up
Harrington (1992)	Observational cohort	(R) CVA n=16 Controls n=17	Not provided	Reduced	No, but apraxic participants slower	None
Prigatano (1997)	Observational cohort	CVA n=51	12.6 days	Significantly faster in those who achieved rehab goals and those who did not	No	None
Marque (1997)	Cohort Study	15 (L) CVA Matched healthy controls n=16	20 and 90 days	No deficit	Not examined	No difference in findings at 90 days
McCombe Waller (2004)	Cohort study and single group pre and post training	10 CVA 10 controls	>6months	No unilateral tapping deficits compared to controls Bilateral tapping defict	Not examined	none
De Groot Driessen (2006)	Prospective cohort	CVA n=57 Matched controls n=42	Admission	Reduced compared to controls	Participants with LHD slower	Improved at 4 weeks. Baseline tapping associated with ADL performance at 3 months
Ietswaart (2006)	Observational cohort	(L) CVA n=10 Controls n=10	51-241 days	Participants lower tapping rate that correlated with apraxia severity	Not examined	None

CVA denotes Cerebrovascular accident; RHD denotes right hemisphere damage; LHD denotes left hemisphere damage; 2PD denotes two point discrimination. All reported deficits were significant at $p<0.05$.;

Table 10. Summary of studies examining ipsilesional grip strength

Study	Design	Participants	Time post-stroke	Ipsilesional Grip strength deficit	Hemispheric differences	Follow-up
Jones (1989)	Cohort Study	8 CVA 8 matched healthy controls	11 days	Mild significant deficit at 11 days	Not examined	12 months grip strength normal
Desrosiers (1996)	Cohort Study	43 CVA 43 matched healthy controls	25.1 months	No deficit	None	None
Marque (1997)	Cohort Study	15 CVA 16 matched healthy controls	20 days	Significant deficit compared to controls	Not examined	Significant improvement by day 90
Sunderland (1999)	Cohort Study	30 CVA 34 matched healthy controls	1-31 days	Deficit compared to controls	L side poorer but not significantly ($p=0.07$)	See study below
Sunderland (2000)	Cohort Study, follow-up from Sunderland (1999)	24 CVA from above study	6 months	Significant improvement compared to controls	None	

CVA denotes Cerebrovascular accident; RHD denotes right hemisphere damage; LHD denotes left hemisphere damage.
All reported deficits were significant at $p<0.05$.

Table 11. Summary of ipsilesional sensory impairment

Study	Design	Participants	Time post-Stroke	Ipsilesional Sensory Domain	Hemispheric differences	Follow-up
Boll (1974)	Observational cohort	30 (LHD) 30 (RHD) Range of aetiologies	Not reported	Tactile localisation, number perception, Form recognition. No comparison to controls	Tactile perception errors greater with RHD	None
Fontenot (1971)	Observational cohort	20 (LHD) 20 (RHD) 20 controls Range of aetiologies	Not reported	Errors of ipsilesional tactile perception of direction	Participants with RHD poorer	None
Essing (1980)	Observational cohort	30 CVA 55 controls	1month-4years	All had light touch deficits but worse in participants with severe contralateral deficit	None	None
Caselli (1991)	Observational cohort	30 CVA	Not provided	Tactile and visual object recognition	RHD with neglect greater deficit despite normal somatosensory function	
Sartor-Glittenberg (1993)	Observational cohort	20 CVA 20 controls	Not provided	Deficits in movement discrimination in participants but not on clinical tests of proprioception	Not reported	None
Kim (1996)	Observational cohort	67 CVA 32 controls	1 week	Deficits in texture discrimination, point localisation, stereognosis	None	None
Desrosiers (1996)	Observational cohort	43 CVA 43 controls	Mean time 25.1 months	No tactile deficits Proprioception reduced compared to controls	No difference between RHD and LHD	None
Morris (2003)	Observational cohort	10 CVA	2-4 weeks	Deficits in tactile localisation, stereognosis	Greater deficit frequency with RHD	None

CVA denotes Cerebrovascular accident; RHD denotes right hemisphere damage; LHD denotes left hemisphere damage; 2PD denotes two point discrimination. All reported deficits were significant at $p<0.05$.;

Table 12 Consequences of post-stroke depression for recovery and rehabilitation

Study	Design	Population	Depression Measure	Rehabilitation Outcome Measures	Results
Sinyor (1986)	Cohort	N=64	Zung Depression Measure,Nurses Rating Scale, Composite Depression Index, Hopkins Symptom Checklist, Beck Hopelessness Scale	Impairment and Activity: Patient Evaluation conference System at admission to rehab and discharge At admission and discharge from rehabilitation	PSD N=32 PSD patients had lower functional scores than non-depressed ($p<0.05$) at all time points but recovery was not significantly different. After discharge PSD patients demonstrated significant declines in function compared to non-PSD ($P<0.02$)
Pohjasvaara (2001)	Cohort	N=390	Beck's Depression Inventory at 3 and 15 months	Barthel Index	PSD at 3 months N=171 Major depression at 3 months correlated to poor functional outcome at 15 months ($p=0.03$). Poor functional outcome at 3 months more often depressed at 15 months ($p<0.001$)
Van de Weg (1999)	Cohort	N=85	Geriatric Depression Scale/DSM-IV criteria	Activity: FIM Rehabilitation Activities Profile at 3-6 weeks and 6 months post-stroke	PSD N=30 PSD patients showed significantly lower scores at admission and follow up ($p<0.05$) but no significant difference in improvement Mean improvement in function of 30% in 6 patients treated with antidepressants
Paolucci (1999)	Cohort	N=470	Hamilton Rating Scale for Depression	Activity: Rivermead Mobility Index, Barthel Index at admission and discharge from rehab	PSD N=129 (27.4%) PSD associated with lower ADL at discharge ($p<0.05$)
Nannetti (2005)	Cohort	N=117	Geriatric Depression Scale/DSM-IV criteria	Impairment: FM Activity: Barthel Index at admission, 2 weeks and 4 weeks post-stroke	PSD n=49 Group with PSD significantly poorer than non PSD group on FM at all assessment points ($p<0.05$). Both groups improved significantly on both measures ($p<0.001$) but patients with PSD significantly poorer in functional recovery between all assessment points

Table 13 Effects of antidepressant treatment on physical outcomes of stroke

Study	Design	Population	Methods	Measures	Results
Gainotti (2001)	Retrospective between group comparison	N=49 patients with depression on Hamilton Depression Rating Scale meeting DSM-III-R criteria	PSD treated with antidepressant therapy (n=24) compared to untreated PSD (N=25) on rehabilitation outcomes before during and end of rehabilitation	Barthel Index (BI) Canadian Neurological Scale (CNS) Rivermead Mobility Index (RMI)	Baseline physical scores worse for depressed patients. For all physical scales, improvement was significantly higher for non-PSD and treated PSD than for non treated PSD. Significance highest for RMI (P<0.0001)
Chemerinski (2001)	Double blind RCT	N=23 Depression diagnosed using the Present State Examination and DSM-IV criteria	Patients randomised to receive nortrypilene or placebo using double blind methods. Comparison made on ADL indices of patients who reduced depression and those who did not	ADL: John Hopkins Functioning Inventory at 12 weeks	Remission of depression group (n=11) demonstrated improved ADL (p<0.02) over assessment period where non-responders (n=12) did not demonstrate improvement

Table 14. Factors influencing health related quality of life in stroke

Study	Population	Time of assessment post-stroke	HRQOL Measure	Determinants of HRQOL
Ahlsio (1984)	N=96 Mixed severity	Discharge, 6 months and 4 years	Visual analogue self-rating of QOL	↑ADL independence ↓Anxiety and depression ↓Age
Niemi (1988)	N=46 Mild to moderate	Discharge and 4 years	Unvalidated measure	*HRQOL had deteriorated by 4 years* ↑ADL independence ↑Mobility ↑Memory ↓Depression
King (1996)	N=86 Moderate severity	1-3 years	Ferrans and Powers QOL Index (Stroke)	Depression Perceived Social Support Functional Ability
Wyller (1997)	N=60 Severity not indicated	One year	General Health Questionnaire	*HRQOL ↓ at 1 year compared to norms* Gender (males ↑ HRQOL) UL Function Motor Function
Wyller (1998)	N=1417 Mild severity	Various	Subjective well-being questionnaire (unvalidated)	Presence of stroke Sex (HRQOL higher in women) Age (higher with age) ↑General health ↓Anxiety ↑ ↑Social support ↓Loneliness ↑Sleep

QOL denotes Quality of Life, HRQOL denotes Health Related Quality of Life; ADL denotes Activities of Daily Living;UL denotes Upper Limb;
↑ denotes increased; ↓ denotes decreased; reported findings significant at $p<0.05$

Table 14 (cont) .Factors influencing health related quality of life in stroke

Study	Population	Time of assessment post-stroke	HRQOL Measure	Predictors of HRQOL
Kim (1999)	N=50 Moderate Severity	1-3 years post-discharge	Ferrans and Powers QOL Index (Stroke)	*HRQOL relatively low* ↓Depression Marital status ↑Social support ↑ADL
Robinson Smith (2000)	N=77 Moderate severity	1 and 6 months	QOL Index	1 month: family, home, emotional support, self-care self-efficacy 6months: depression, self-care self-efficacy, functional ability
Kauhanen (2000)	N = 106 Mild to moderate severity	Admission, 3 months,12 months	RAND Health Survey	↓ Depression Being Married ↓ Age
McEwen (2000)	N=43 Mild severity	14 months post-stroke	SF-36	↑ADL/IADL Gender UL Dexterity Motor impairment
Mackenzie 2002	N=215 Severity not reported	2 weeks and 3 months	Sickness Impact Profile	↑ADL independence ↑Satisfaction with social support

Table 14 (cont) .Factors influencing health related quality of life in stroke

Study	Population	Time of assessment post-stroke	HRQOL Measure	Predictors of HRQOL
Mayo (2002)	N=434 Mild to moderate severity	6 months post-stroke	SF-36 Visual analogue Scale	*Persons with stroke had poorer HRQOL than matched peers* Basic ADL IADL Reintegration
Jonsson (2005)	N=416 Mild to moderate severity	4 and 16 months	SF-36	↓Depression ADL independence ↓Age Female
Ones (2005)	N=88 Mild to moderate	>6months	Nottingham Health Profile	Functional Ability Cognitive ability Upper Extremity FM scores Hand FM Scores Depression
Nichols-Larsen (2005)	N=229 Mild severity	3-9months	Stroke Impact Scale	↓Age Gender Stroke type Dominant hand affected UL motor function

ADLdenotes Activities of Daily Living; IADL denotes Instrumental Activities of Daily living; FM denotes Fugl Meyer Teat

Table 15. Upper limb rehabilitation and health related quality of life

Study	Population	Design	Intervention and Effects on UL Outcomes (measures)	HRQOL Measure	Impact on aspects of HRQOL
Kwakkel (1999)	N=101 14 days post-stroke Severe UL severity	RCT	Intensive UL or LL training vs control ↓ UL activity limitation (ARAT) arm and leg group compared to control	Nottingham Health Profile	No significant effect of UL training on HRQOL
Dettmers (2005)	N=11 >12 months post stroke Moderate UL severity	Single group, pre and post training testing	Distributed Constraint Therapy ↓ impairment (grip strength, spasticity) ↓Activity limitation (MAL, WMFT, FAT) following training	Stroke Impact Scale	Significant improvements in SIS, perceived overall physical function and hand, strength, ADL, mobility sub-components baseline to post-treatment. Significant improvements in social participation and communication baseline to 6 month follow-up
Finley (2005)	N=13 Longstanding stroke Severe	Single group, pre and post training testing	Robot-assisted training ↓impairment (FM, Motor power) =Activity limitation (WMFT)	Stroke Impact Scale	No impact on physical domain of scale despite significant improvements in UL motor impairment and strength
Butler (2006)	N=1 Post-rehabilitation Moderate severity	Single case	Saboflex + strength and function training ↓ impairment (FM) ↓ activity limitation (WMFT)	Stroke Impact Scale	Change in perceived: strength =43%, communication = 29%, social participation =33% Hand function = 33%

RCT denotes randomised controlled trial; ARAT denotes Action Research Arm Test; MAL denotes Motor Activity Log; WMFT denotes Wolf Motor Function Test; FAT denotes Frenchy Activity Test; FM denoted Fugl-Myer test. ↑ denotes greater; ↓denotes lower; = denotes no change

Table 15 (cont). Upper limb rehabilitation and health related quality of life

Study	Population	Design	Intervention and Effects on UL Outcomes (measures)	HRQOL Measure	Impact on HRQOL
Barnes (2006, poster abstract only)	N=4 Longstanding stroke Severe	Single group	BATRAC ↓ impairment (grip strength, elbow ROM) =Activity limitation (WMFT)	Stroke Impact Scale	No impact on HRQOL in spite of improved perceived grip strength and range of movement
Wolf (2006)	N=222 Severity?	Multi-site RCT	Constraint Induced Movement Therapy ↓activity limitation (WMFT, MAL)	Stroke Impact Scale	Significant improvement in perceived hand function domain at 12 month follow-up. No impact on other HRQOL domains
Wu (2007)	N=26 >6 months post-stroke Moderate severity	RCT	Modified Constraint Induced Movement Therapy ↓ impairment (FM) ↓ activity limitation (MAL)	Stroke Impact Scale	Significantly improvement for overall Stroke Impact Scale for mCIMT group, also significant differences on perceived strength, ADL and IADL domains.

RCT denotes randomised controlled trial; ARAT denotes Action Research Arm Test; MAL denotes Motor Activity Log; WMFT denotes Wolf Motor Function Test; FAT denotes Frenchy Activity Test; FM denoted Fugl-Myer test. ↑ denotes greater; ↓denotes lower; = denotes no change

Appendix 4

Ethical Approval

Our Ref: 171/01

Tayside Committee on Medical Research Ethics

Level 9
Ninewells Hospital & Medical School
Dundee
DD1 9SY
Tel: 01382 632701/425598
Fax: 01382 496207
Email: fiona.bain@tuht.scot.nhs.uk

5 September, 2001

Response Form for Applicants

Reference Number: **171/01**

Title of Proposal: An investigation of bilateral simultaneous upper limb task training

First Researcher: Dr R S MacWalter, Consultant Physician, Medicine & Cardiovascular Department, Ninewells Hospital & Medical School

Documentation Reviewed:

Proposal Form
Subject Consent Form(s)
Subject Information Sheet(s)
Letter to General Practitioner

This application has been considered and the Tayside Committee on Medical Research Ethics would like to make the following comments:

No comments were made.

APPROVAL IS GIVEN SUBJECT TO THE CONDITIONS SET OUT BELOW

Date of Review: 31 August 2001

List of Members in attendance: Mr A MacConnachie; Mr P K Brown; Dr B Green; Mr A S Jain; Mr G MacLaren; Dr H Staines

Conditions of Approval

- You should follow the protocol agreed and advise the Committee of any proposed amendments – no significant changes to the protocol should be made without the Ethics Committee/Chairman's approval.

- You must promptly inform the Ethics Committee of deviations from or changes to the protocol which are made to eliminate immediate hazards to the research subject; of any changes that increase the risk to subjects and/or affect significantly the conduct of the research; all adverse events that are both serious and unexpected; new information that may adversely affect the safety of the subjects or the conduct of the research; if the research is abandoned for any reason.

- Each research proposal will be subject to a follow-up review and may be selected for a monitoring visit on behalf of the Tayside Trusts.

- You must start the project within three years of the date approval is given or the approval expires; extensions can be applied for; you are required to notify the Committee of the termination of the study.

It would be helpful if in the event of there being any future correspondence about this study, you could quote Ref: 171/01.

Signed

Secretary
On behalf of the Tayside Committee on Medical Research Ethics

Appendix 5

Test administration instructions

BILATERAL UPPER LIMB TASK TRAINING

1.0 INTRODUCTION:

1.1 ADMINISTRATION INSTRUCTIONS FOR ASSESSOR:

- Following confirmation of a subject being recruited to the study please arrange a time for baseline assessment with the subject and/or carers.
- Please arrange appointment time for 6-week assessment following confirmation of the date for the end of intervention.
- 3-month assessment should be arranged with the subject (+/- carers) 3-months following the end of the intervention period.
- Always record date, subject number, affected UL and assessment type (eg baseline, 6-weeks OR 3-months) on cover sheet and every page thereafter.

- Always conduct the tests in the same order as follows:

  1. Action Research Arm Test (ARAT)
  2. Hospital Anxiety and Depression Score (HADS)
  3. Nine Hole Peg Test (9HPT)
  4. Modified Barthel Index (MBI)
  5. Rivermead Motor Assessment (Upper Limb) (RMA)
  6. Nottingham Health Profile (NHP)
  7. Nottingham Sensory Assessment (NSA)

- Please ensure adequate rest between tests.
- Remember to score the unaffected side on the ARAT, 9HPT and NSA.
- The unaffected side should be tested first on all applicable tests.
- If a subject reports not being able to do a certain task, the task should still be attempted. The outcome should be observed and not just stated.
- If the subject is unable to complete the test in one session, the remaining tests should be completed no later than the following day.

1.2 INSTRUCTIONS/EXPLANATION TO SUBJECT PRIOR TO ASSESSMENT:

BASELINE:

Firstly, I would like to thank you for taking part in this study. My job today is to do some tests with you so we have some information about you and your arm. We will then do the same tests in 6 weeks time and then 3 months after that. We can use this information from each test to see any changes in your recovery. The information will also help us determine the best ways to treat peoples' arm following stroke.

"We have a series of tests that usually take approximately an hour to complete. If at any time you feel that you need a rest or wish to stop please let me know. Some of the tests look at the movement in your arm, some look at how you feel inside (for example your emotions) and the last test looks at the feeling in your arm (we call this sensation). Most of the tests look at both arms even though you are only experiencing difficulty with your R/L."

I have some water here if you need a drink at any time (swallowing ability is confirmed prior to this, otherwise water is not offered)."

Do you have any questions before we start?

6 WEEKS/3-MONTHS:

Do you remember the tests that I did with you last time we met.

"YES": Well we are going to do the same tests today … repeat paragraph in italics.

"NO" or "only a little": repeat above paragraph in italics.

2.0 ACTION RESEARCH ARM TEST (ARAT):

2.1 ADMINISTRATION INSTRUCTIONS FOR ASSESSOR:

Items within each subscale are ordered in such a way that if a subject accomplishes the most difficult item (the first item of each subscale), then this predicts success with all the less difficult subscale items. Thus, the subject is credited with all the items of the subscale for that limb. On the other hand, failure with the easiest item, (the second item of the first three subscales and the first item of the fourth subscale) predicts failure with all items of greater difficulty on that subscale. The scores on the different items are added to give a maximum score of 57 on each side.

Scoring: **0 = Can perform no part of the test**
1 = Performs test partially
2 = Completes test, but takes abnormally long time or has great difficulty
3 = Performs test normally

Throughout testing the subject sits on a chair, the table being close to the subject's chest. Test items are placed on the table in front of the upper-limb (UL) being tested. Both UL's are tested for each subject, for each sub-test. The non-affected UL is tested first. The starting position for the first 3 sub-tests is with the tested UL placed on the wooden platform. For sub-test 4 the UL should be in the subjects lap or by their side. (For table/chair dimensions and equipment specifications: see 9.0 equipment).

The subject is allowed to rest between the tasks. The subject does not receive therapeutic interventions to reduce the muscle tone. The objects listed under each item of each subtest are presented one at a time (unaffected UL first, then affected UL). There is no quantitative time limit for performing the test. The subject is allowed one trial only- practice is allowed but the score is based on this one trial.

2.2 INSTRUCTIONS TO SUBJECT:

"OK, for the first test, I am going to ask you to lift a variety of objects from the table to the shelf above. We will start with your R/L (unaffected) arm first (often touch the dorsum of hand or forearm to indicate which arm you are speaking about) and then move to you R/L (affected). If you have any pain please tell me".

SUB-SCALES:

A	Grasp	B	Grip
C	Pinch	D	Gross

A: *Grasp*

The subject is required to pick up wooden blocks and a stone from the table and put on a shelf situated 37cm above the table. The stone must be grasped by lateral prehension. The test items are placed on the table in front of the UL tested, apart from this there is no specific starting and destination location for any of the test items. Once the subject has completed an item it is taken away by the assessor. A score of 1 is assigned if the subject can grasp the item but cannot raise it because the necessary upper arm and shoulder function has been impaired.

	Evaluation	
1 woodblock 10cm (If score =3, total = 18 and go to grip)	Left	Right
2 Woodblock 2.5cm (if score = 0, total = 0 and go to grip)		
3 Woodblock 5cm		
4 Woodblock 7.5cm		
5 Cricketball 7.5cm diameter		
6 Stone 10 x 2.5 x 1cm		
SUBTOTAL Grasp	/18	/18

B: *Grip*

The subject is required to pour water from one glass to another, lift aluminum tubes forward on the table and pick up an iron washer and place it over a bolt.

The water is poured from the tumbler into a second tumbler using a motion involving pronation of the hand. The tumblers are placed in front of the subject on either side of the subject's midline. The tumblers stand close together at no fixed distance but do not touch. The tumblers are half full of water. The subject is allowed to fix the second tumbler in a vertical position.

The two tubes of different sizes (see below) are placed over the vertical peg closest to the subject. The subject is asked to move the tube and place it over the vertical peg positioned further forward on the table.

The washer is to be picked up and placed over the vertical bolt, positioned further forward on the table. (The subject is not allowed to slide the washer off the table in order to grasp it).

	Evaluation	
	Left	Right
1 Pour water from glass to glass (pronation) (If score =3, total = 12 and go to gross movement)		
2 Tube 2.25cm (if score = 0, total = 0 and go to gross mvt)		
3 Tube 1cm		
4 Washer over bolt		
Subtotal *Grip*	/12	/12

C: *Pinch*

The subject is required to pick up small ball bearings or marbles from the table and put them in a tray on the shelf above the table.

There is a tray to contain the spheres which are to be moved one at a time in strict order to a similar tray on the shelf.

	Evaluation	
	Left	Right
1 Ball bearing, 6mm, 3rd finger (ring) and thumb (if score =3, total =18 and go to gross mvt)		
2 Marble, 1.5cm, 1st finger (index) and thumb (if score = 0, total =0 and go to gross mvt)		
3 Ball bearing, 2nd finger (middle) and thumb		
4 Ball bearing 1st finger (index) and thumb		
5 Marble, 3rd finger (ring) and thumb		
6 marble 2nd finger (middle) and thumb		
SUBTOTAL *Pinch*	/18	/18

D. Subtest Gross Movement

In order to achieve a 3 the hand must be placed behind the head and not the neck. Similarly the hand must be place on the top of the head, not on the forehead for item 2. The starting position of the Ul is either lying on the subjects lap or at their side.

	Evaluation	
	Left	Right
1 Place hand behind head (if score =3, total = 9 and finish, if score = 0, total = 0 and finish		
2 Place hand on top of head		
3 Hand to mouth		
Subtotal *Gross Movement*	/9	/9

ACTION RESEARCH ARM TEST
TOTAL SCORE

TOTAL SCORE	/57	/57

2.3 SCORING SHEET:

ACTION RESEARCH ARM TEST (ARAT):

Patient ID:

Date: Subject:

Scoring:

0 = Can perform no part of the test
1 = Performs test partially
2 = completes test, but takes abnormally long time or has great difficulty
3 = performs test normally

Subtest Grasp

	Evaluation	
1 woodblock 10cm (If score =3, total = 18 and go to grip)	Left	Right
2 Woodblock 2.5cm (if score = 0, total = 0 and go to grip)		
3 Woodblock 5cm		
4 Woodblock 7.5cm		
5 Cricketball 7.5cm diameter		
6 Stone 10 x 2.5 x 1cm		
SUBTOTAL Grasp	/18	/18

Subtest Grip

	Evaluation	
	Left	Right
1 Pour water from glass to glass (pronation) (If score =3, total = 12 and go to gross movement)		
2 Tube 2.25cm (if score = 0, total = 0 and go to gross mvt)		
3 Tube 1cm		
4 Washer over bolt		
Subtotal *Grip*	/12	/12

Subtest Pinch

	Evaluation	
	Left	Right
1 Ball bearing, 6mm, 3rd finger and thumb (if score =3, total =18 and go to gross mvt)		
2 Marble, 1.5cm, index finger and thumb (if score = 0, total =0 and go to gross mvt)		
3 Ball bearing, 2nd finger and thumb		
4 Ball bearing 1st finger and thumb		
5 Marble, 3rd finger and thumb		
6 marble 2nd finger and thumb		
SUBTOTAL *Pinch*	/18	/18

Gross Movement

	Evaluation	
	Left	Right
1 Place hand behind head. If score =3, total = 9 and finish. If score = 0, total = 0 and finish		
2 Place hand on top of head		
3Hand to mouth		
Subtotal *Gross Movement*	/9	/9

ACTION RESEARCH ARM TEST
TOTAL SCORE

TOTAL SCORE	/57	/57

3.0 HOSPITAL AND ANXIETY DEPRESSION SCALE (HADS):

3.1 INSTRUCTIONS TO ASSESSOR:

This scale is designed to be completed by the subject. If the subject is physically unable to underline the questions, then it is acceptable for the assessor to do this for the subject. Similarly, if the subject is unable to read the questions, it is acceptable for the assessor to read them to the subject.

3.2 INSTRUCTIONS TO SUBJECT:

The assessor reads the following blurb to the subject prior to completion. (It is recommended that this be done slowly with sufficient pauses).

> *"We are aware that emotions play an important part in most illnesses. This questionnaire is designed to help us know how you feel. Ignore the numbers printed on the left of the questionnaire. Read each item and underline the reply which comes closest to how you have been feeling in the* ***past week****. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response."*

(NB This information is part of the questionnaire and is printed at the top of the document for clarification).

HOSPITAL AND ANXIETY DEPRESSION SCALE (HADS):

Patient ID:
Date: Examiner:

We are aware that emotions play an important part in most illnesses. This questionnaire is designed to help us know how you feel. Ignore the numbers printed on the left of the questionnaire. Read each item and underline the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

A	**I feel tense or wound up:**
3	Most of the time
2	A lot of the time
1	From time to time, occasionally
0	Not at all

D	**I still enjoy things I used to enjoy:**
0	Definitely as much
1	Not quite so much
2	Only a little
3	Hardly at all

A	**I get a sort of frightened feeling as if something awful is about to happen:**
3	Very definitely and quite badly
2	Yes but not too badly
1	A little, but it doesn't worry me
0	Not at all

D	**I can laugh and see the funny side of things:**
0	As much as I always could
1	Not quite so much now
2	Definitely not so much now
3	Not at all

A	**Worrying thoughts go through my mind:**
3	A Great deal of the time
2	A lot of the time
1	From time to tome but not too often
0	Only occasionally

D	**I feel cheerful:**
3	Not at all
2	Not often
1	Sometimes
0	Most of the time

A	**I can sit at ease and feel relaxed:**
0	Definitely
1	Usually
2	Not often
3	Not at all
D	**I feel as if I am slowed down**:
3	Nearly all of the time
2	Very often
1	Sometimes
0	Not at all
A	**I get a sort of frightened feeling like "butterflies" in the stomach:**
0	Not at all
1	Occasionally
2	Quite often
3	Very often
D	**I have lost interest in my appearance:**
3	Definitely
2	I don't take as much care as I should
1	I may not take as much care
0	I take just as much care as ever
A	**I feel restless as if I have to be on the move:**
3	Very much indeed
2	Quite a lot
1	Not very much
0	Not at all
D	**I look forward with enjoyment to things:**
0	As much as I ever did
1	Rather less than I used to
2	Definitely less than I used to
3	Hardly at all
A	**I get sudden feelings of panic**:
3	Very often indeed
2	Quite often
1	Not very often
0	Not at all
D	**I can enjoy a good book or radio or TV programme:**
0	Often
1	Sometimes
2	Not often
3	Very seldom

Hospital Anxiety and Depression Scale
(Circle Scores)

Anxiety	**Scores**
I feel tense and wound up	0 1 2 3
I get a sort of frightened feeling/something awful	0 1 2 3
Worrying thoughts go through my mind	0 1 2 3
I can sit at ease and feel relaxed	0 1 2 3
I get a sort of frightened feeling/butterflies	0 1 2 3
I feel restless	0 1 2 3
I get sudden feelings of panic	0 1 2 3
TOTAL Anxiety	
Depression Score	
I still enjoy things I used to enjoy	0 1 2 3
I can laugh and see the funny side of things	0 1 2 3
I feel cheerful	0 1 2 3
I feel as if I am slowed down	0 1 2 3
I have lost interest in my appearance	0 1 2 3
I look forward with enjoyment to things	0 1 2 3
I can enjoy a good book/radio/tv programme	0 1 2 3
TOTAL Depression	

0-7 = Normal
8-10 = Borderline
11-21 = Abnormal

4.0 NINE HOLE PEG TEST (9HPT):

4.1 INSTRUCTIONS TO ASSESSORS:

Subjects are asked to place 9 pegs in the holes (see figure). The subject is timed by the assessor from the time the 1st peg is touched until the last peg is placed. If the time exceeds 50 seconds, the subject is stopped and the number of pegs placed is recorded.

Two practice attempts for each UL are made before scoring on the third attempt. Subjects may choose to forgo practise if their arm tires easily or increased tone with activity is a problem.

Results are recorded as number of seconds to place each peg.
-for example:

if 9 pegs are placed in 12 seconds – 9/12 = 0.75 pegs per second
OR
if 5 pegs are placed in 50 seconds – 5/50 = 0.1 pegs per second.

4.2 INSTRUCTIONS TO SUBJECTS:

"This next test looks at your hand function. We will start with your R/L (unaffected) and I want to you place all the pegs in the holes as quickly as you can. You get 2 practices and then on your 3rd attempt I am going to time you with this stopwatch. OK. Are you ready……. Go!

..Ok, now we will do exactly the same thing with R/L (affected). Ok. Are you ready….. Go!

4.3 NINE HOLE PEG TEST SCORE SHEET:

Patient ID:

Date: **Examiner:**

9 hole Peg Test	**Right**	**Left**
Total time to completion, if < 50 seconds		
Number of pegs placed, if > 50 seconds		
Pegs per second		

5.0 MODIFIED BARTHEL INDEX (MFI):

5.1 INSTRUCTIONS FOR ASSESSOR:

The MBI is used to assess the subject's functional ability. The assessor should assign the score in order to reflect what the subject does, not of what a subject could do. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason and the need for supervision renders the subject not independent.

The score should be established using the best available evidence. Asking the subject, friends, relatives and nurses are the usual sources, but direct observation and common sense are also important. However, direct testing is not required. Usually the subject's performance over the preceding 24-48 hours should be used, but occasionally longer periods will be relevant. The use of aids to be independent is allowed.

The following guidelines should be used by the assessor when rating subjects using the MBI:

5.1.1 Guidelines for the MBI Functions

Shah,S, Vanclay F, Cooper B (1989) Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J. Clinical Epidemiology, 42 (8): 703-709.*

Personal Hygiene

1. The patient is unable to attend to personal hygiene, and is dependent in all aspects.
2. Assistance is required in all steps of personal hygiene.
3. Some assistance is required in one or more steps of personal hygiene.
4. Patient is able to conduct his/her own personal hygiene but requires minimal assistance before and/or after the operation.
5. The patient can wash his/her hands and face, comb hair, clean teeth and shave. A male patient may use any kind of razor but must insert the blade, or plug in the razor without help, as well as retrieve it from the drawer or cabinet. A female patient must apply her own make-up, if used, but need not braid or style her hair.

Bathing Self

1. Total dependence in bathing self.
2. Assistance is required in all aspects of bathing.
3. Assistance is required with either transfer to shower/bath or with washing or drying, including inability to complete task because of condition or disease etc.
4. Supervision is required for safety in adjusting the water temperature, or in the transfer.
5. The patient may use a bath tub, a shower, or take a complete sponge bath. The patient must be able to do all the steps of whichever method is employed without another person being present.

Feeding

1. Dependent in all aspects and needs to be fed.
2. Can manipulate an eating device, usually a spoon, but someone must provide active assistance during the meal.
3. Able to feed self with supervision. Assistance is required with associated tasks such as putting milk/sugar into tea, salt, pepper, spreading butter, turning a plate or other "set-up" activities.

4. Independence in feeding with prepared tray except may be cut meat, open milk carton, jar lid etc.
5. The patient can feed self from a tray or table when someone puts the food within reach. The patient must put on an assistive device if needed, cut the food, and if desired, use salt and pepper, spread butter etc.

On and Off the Toilet

1. Fully dependent in toileting.
2. Assistance required in all aspects of toileting.
3. Assistance may be required with management of clothing, transferring, or washing hands.
4. Supervision may be required for safety with normal toilet. A commode may be used at night but assistance is required for emptying or cleaning.
5. The patient is able to get on and off the toilet, fasten and unfasten clothes, prevent soiling of clothes and use toilet paper without help. If necessary, the patient may use a bed pain or commode, or urinal at night, but must be able to empty it, and clean it.

Stairs

1. The patient is able to climb the stairs.
2. Assistance is required in all aspects of stair climbing, including assistance with walking aids.
3. The patient is able to ascend/descend but is unable to carry walking aids, and needs supervision and assistance.
4. Generally no assistance is required. At times supervision is required for safety due to morning stiffness, shortness of breath etc.
5. The patient is able to go up and down a flight of stairs safely without help or supervision. The patient is able to use hand rails, cane, or crutches when needed and is able to carry these devices as he/she ascends or descends.

Dressing

1. The patient is dependent in all aspects of dressing and is unable to participate in the activity.
2. The patient is able to participate to some degree, but is dependent in all aspects of dressing.
3. Assistance is needed in putting on, and/or removing any clothing.
4. Only minimal assistance is required with fastening clothing, such as buttons, zips, bra, shoes etc.
5. The patient is able to put on, remove, and fasten clothing, tie shoelaces, or put on, fasten, remove corset, braces as prescribed.

Bowels

1. The patient is bowel incontinent.
2. The patient needs help to assume appropriate position, and with bowel movement facilitatory techniques.
3. The patient can assume appropriate position, but cannot use facilitatory techniques, or clean self without assistance and has frequent accidents. Assistance is required with incontinence aids such as pads etc.
4. The patient may require supervision with the use of suppository or enema and has occasional accidents.
5. The patient can control bowels and has no accidents, can use suppository, or take an enema when necessary.

Bladder

1. The patient is dependent in bladder management, is incontinent, or has indwelling catheter.
2. The patient is incontinent but is able to assist with the application of an internal or external device.
3. The patient is generally dry by day, but not at night, and needs some assistance with the devices.
4. The patient is generally dry by day and night, but may have an occasional accident, or need minimal assistance with internal or external devices.
5. The patient is able to control bladder day and night, and/or is independent with internal or external devices.

Chair/Bed Transfers

1. Unable to participate in a transfer. Two attendants are required to transfer the patient with or without a mechanical device.
2. Able to participate but maximum assistance of one other person is required in all aspects of the transfer.
3. The transfer requires the assistance of one other person. Assistance may be required in any aspect of the transfer.
4. The presence of another person is required either as a confidence measure, or to provide supervision for safety.
5. The patient can safely approach the bed in a wheelchair, lock the brakes, lift the footrests, move safely to the bed, lie down, come to a sitting position on the side of the bed, change the position of the wheelchair, transfer back into it safely. The patient must be independently in all phases of this activity.

Ambulation

1. Dependent in ambulation.
2. Constant presence of one or more assistants is required during ambulation.
3. Assistance is required with reaching aids and/or their manipulation. One person is required to offer assistance.
4. The patient is independent in ambulation but unable to walk 50 yards/metres without help, or supervision is needed for confidence or safety in hazardous situations.
5. The patient must be able to wear braces if required, lock and unlock these braces, assume standing position, sit down and place the necessary aids into position for use. The patient must be able to use crutches, canes, or a walkerette, and walk 50 metres/yards without help or supervision.

Wheelchair Management (alternative to ambulation)

Only use this item if the patient is rated "1" for Ambulation, and then only if the patient has been trained in wheelchair management.

1. Dependent in wheelchair ambulation.
2. Patient can propel self short distances on flat surface, but assistance is required for all other steps of wheelchair management.
3. Presence of one person is necessary and constant assistance is required to manipulate chair to table, bed etc.
4. The patient can propel self for a reasonable duration over regularly encountered terrain. Minimal assistance may still be required in "tight corners".
5. To propel wheelchair independently, the patient must be able to go around corners, turn around, manoeuvre the chair to table, bed, toilet, etc. The patient must be able to push a chair at least 50 metres/yards.

5.2 MODIFIED BARTHEL INDEX (MFI SCORE SHEET):

Patient ID:

Examiner: **Date:**

	Code				
Items	1 Unable to perform Task	2 Substantial help required	3 Moderate help required	4 Minimal help required	5 Fully Independent
Personal hygiene	0	1	3	4	5
Bathing self	0	1	3	4	5
Feeding	0	2	5	8	10
Toileting	0	2	5	8	10
Stair Climbing	0	2	5	8	10
Dressing	0	2	5	8	10
Bowel control	0	2	5	8	10
Bladder Control	0	2	5	8	10
Ambulation	0	3	8	12	15
Wheelchair *	0	1	3	4	5
Chair/bed transfer	0	3	8	12	15
Range	0				100
Subtotal	∑	∑	∑	∑	∑

TOTAL SCORE	/100

* Score only if Ambulation coded “1” (unable to perform task) and subject trained in wheelchair management

6.0 RIVERMEAD MOTOR ASSESSMENT SCALE (RMA): UPPER LIMB:

6.1 INSTRUCTIONS FOR ASSESSOR:

Items are presented in order of difficulty. A subject achieves a score of 1 if they can perform the activity and a score if 0 of they cannot. Up to 3 tries are allowed, however after 3 consecutive failures the subject is asked to stop. Add up the number of items achieved and assign the total score. There is no need to proceed beyond this point as items are hierarchical.

No feedback should be given. General encouragement is permitted.
Repeat instructions and demonstrate the task to the subject if required. All items should be carried out independently unless otherwise stated. The affected UL only is tested.

6.2 INSTRUCTIONS TO SUBJECTS:

This test looks again at what you can manage to do with your arm. However, this time we are only going to look at your R/L (affected) arm. I will ask you step by step if you can manage to do certain movements. If you can manage these we might move on to some tasks. OK, are you ready?

6.3 RIVERMEAD MOTOR ASSESSMENT SCALE (RMA) SCORE SHEET: UPPER LIMB:

Patient ID: **Date :**

Examiner:

Arm Section	Score 0 or 1
Item	
1) Lying protract shoulder girdle with arm in elevation. ***Arm may be supported***	
2) Lying, hold extended arm in elevation (some external rotation) for at least 2 sec. ***Physiotherapist should place arm in position and patient must maintain position with some external rotation. Do not allow pronation. Elbow must be held within 30° of full extension***	
3) Flexion and extension of elbow with arm as in 2 above. ***Elbow must extend to at least 20° of full extension. Palm should not face outward during any part of the movement.***	
4) Sitting, elbow into side, pronation and supination. ***Three quarters range is acceptable, with elbow unsupported and at right angles.***	
5) Reach forward, pick up large ball with both hands and place down again. ***Ball should be on table so far in front of patient that he has to extend arms fully to reach it. Shoulders must be protracted, elbows extended, wrists neutral or extended and fingers extended throughout movement. Palms should be kept in contact with the ball.***	
6) Stretch arm forward, pick up tennis ball from table, release on mid-thigh. Repeat 5 times. ***Shoulder must be protracted, elbow extended and wrist neutral or extended during each phase***	
7) Same exercise as 6 but with a pencil. ***Patient must use thumb and fingers to grip***	
8) Pick up piece of paper from table in front and release five times. ***Patient must use thumb and fingers to pick up paper and not pull it to edge of table. Arm positioned as in 6***	
9) Cut putty with knife and fork on plate with non-slip mat and put pieces into container on side of plate. ***Bite sized pieces***	
10) Stand on spot, ***maintain upright position, pat large ball on floor with palm for 5 continuous bounces.***	
11) Continuous opposition of thumb and each finger more than 14 times in 10sec. ***Must do movements in in consistent sequence. Do not allow thumb to slide from one finger to the other.***	
12) Supination and pronation on to palm of affected hand 20 times in 10 sec. ***Arm must be away from body, palm and dorsum of hand must touch palm of good hand. Each tap counts as one. This is similar to 4 but introduces speed***	
13) Stand, affected arm abducted to 90°with palm flat against wall. Maintain arm in position. Turn body towards wall and as far as possible towards arm ie rotate body beyond 90°. ***Do not allow flexion at elbow, and wrist must be extended with palm fully in contact with wall***	
14) Place string around head, tie bow at back. Do not allow neck to flex. ***Affected hand must be used for more than just supporting string. This tests function of hand without help of sight***	

15) Pat a cake 7 times in 15 sec. ***Mark crosses o wall at shoulder level. Clap both hands together(both hands touch crosses – clap-one hand touches opposite cross). Must be in correct order. Palms must touch. Each sentence counts as one. Give patient three tries. This is a complex pattern which involves co-ordination, speed and memory, as well as good arm function***.	

7.0 NOTTINGHAM HEALTH PROFILE (NHP):

7.1 INSTRUCTIONS FOR ASSESSOR:

This scale is designed to be completed by the subjects themselves. If the patient is physically unable to tick the appropriate response, then it is acceptable for the assessor to do this for the subject. Similarly, if the subject is unable to read the questions, it is acceptable for the assessor to read them to the subject.

7.2 INSTRUCTIONS TO SUBJECTS:

The following blurb is read to the subjects:

> "Listed below are some problems people have in their daily life. Although some of our previous conversations already tell me some of the answers to these questions, for the purpose of this project it is important that everyone answers the same questions. So I apologise in advance that this is a bit repetitive.
>
> OK, so what I would like you to do is to look down the list and put a tick under "Yes" for any problem you may have at the moment. Tick under "No" for any problem you do not have. *Please answer every question.* If you are not sure whether to answer yes or no, tick whichever answer you think is nearly right at the moment".

7.3 NOTTINGHAM HEALTH PROFILE (NHP)SCORE SHEET:

Patient ID: **Date:**

Examiner:

Statement	Yes	No	Cat
I'm tired all of the time			EL
I have pain at night			P
Things are getting me down			ER
I have unbearable pain			P
I take tablets to help me sleep			S
I have forgotten what it is like to enjoy myself			ER
I'm feeling on edge			ER
I find it painful to change position			P
I feel lonely			SI
I can only walk about indoors			PA
I find it hard to bend			PA
Everything is an effort			EL
I'm waking up in the early hours of the morning			S
I'm unable to walk at all			PA
I'm finding it hard to make contact with people			SI
The days seem to drag			ER
I have trouble getting up and down stairs/steps			PA
I find it hard to reach for things			PA
I am in pain when I walk			P
I lose my temper easily these days			ER
I feel there is nobody I am close to			SI
I lie awake for most of the night			S
I feel as if I am losing control			ER
I'm in pain when I am standing			P
I find it hard to dress myself			PA
I soon run out of energy			EL
I find it hard to stand for long (for example at the kitchen sink, waiting for a bus)			PA
I am in constant pain			P
It takes me a long time to get to sleep			S
I feel I am a burden to people			SI
Worrying is keeping me awake at night			ER
I feel that life is not worth living			ER
I sleep badly at night			S

I am finding it hard to get on with people			SI
I need help to walk about outside (for example a walking aid or someone to support me)			PA
I'm in pain going up and down stairs			P
I wake up feeling depressed			ER
I'm in pain when I am sitting			P

NOTTINGHAM HEALTH PROFILE (NHP)SCORE SHEET (2):

Energy Level	**Yes**	**Weight**
I soon run out of energy		24.00
Everything is an effort		36.80
I'm tired all of the time		39.20
No statement applicable		0
Energy Level total		/100

Pain	**Yes**	**Weight**
I'm in pain when going up and down stairs		5.83
I'm in pain when I'm standing		8.96
I find it painful to change position		9.99
I'm in pain when I am sitting		10.49
I'm in pain when I walk		11.22
I have pain at night		12.91
I have unbearable pain		19.74
I'm in constant pain		20.86
No statement applicable		0
Pain Total		/100

Emotional Reactions	**Yes**	**Weight**
The days seem to drag		7.08
I'm feeling on edge		7.22
I've forgotten what it is like to enjoy myself		9.31
I lose my temper easily these days		9.76
Things are getting me down		10.47
I wake up feeling depressed		12.01
Worry is keeping me awake at night		13.95
I feel as if I am losing control		13.99
I feel that life is not worth living		16.21
No statement applicable		0
Emotional Reactions Total		/100

Sleep	**Yes**	**Weight**
I'm waking in the early hours of the morning		12.57
It takes me a long time to get to sleep		16.10
I sleep badly at night		21.70
I take tablets to help me sleep		22.37
I lie awake for most of the night		27.26
No statement applicable		0
Sleep Total Weighting		/100

Social Isolation		**Yes**	**Weight**
I'm finding it hard to get on with people		15.97	
I'm finding it hard to make contact with people		19.36	
I feel there is nobody I am close to		20.13	
I feel lonely		22.01	
I feel I am a burden to people		22.53	
No statement applicable		0	
Social Isolation Total Weighting		/100	

Physical Abilities		**Yes**	**Weight**
I find it hard to reach for things		9.30	
I find it hard to bend		10.57	
I have trouble getting up and down stairs and steps		10.79	
Ifind it hard to stand for long		11.20	
I can only walk about indoors		11.54	
I find it hard to dress myself		12.61	
I need help to walk about outside		12.69	
I'm unable to walk at all		21.30	
No statement applicable		0	
Physical Abilities total Weighting		/100	

Section	**Section Scores**
Energy level	
Pain	
Emotional Reactions	
Sleep	
Social Isolation	
Physical Abilities	
TOTAL NHP SCORE	

8.0 NOTTINGHAM SENSORY ASSESSMENT (NSA):

8.1 INSTRUCTIONS FOR ASSESSOR:

The Nottingham Sensory assessment will be used to assess sensation of the UL. The assessment is divided into tactile sensation (including light touch, pressure, pin-prick, temperature, tactile localisation and bilateral simultaneous touch), kinaesthetic awareness, stereognosis and 2-point discrimination. Each test is described and demonstrated to the subject before he or she is blindfolded. The blindfold is removed regularly throughout the test to avoid the subject becoming disorientated.

A: Tactile Sensation

The subject is asked to indicate, either verbally or by a body movement, whenever he feels the test sensation. For each test the skin is touched with the appropriate test item in a **random order** ie start with the hand and randomly apply each sensation to the hand, then move on to the wrist, then elbow then shoulder. All test sensations are applied in an on/off pattern.

The **Unaffected side** is tested for light touch and temperature. If these are normal, only the affected side is tested on other items.

For each section test **hand and wrist** first.

If hand and wrist both score 2 give 2's for elbow and shoulder.

Scoring Criteria

0= Absent:	Fails to identify the test sensation on three occasions
1= Impaired:	Identifies the test sensation, but not on all three occasions in each region of the body
2= Normal:	Correctly identifies the test sensation on all three occasions
N/A =	Unable to test

Light Touch: Touch, not brush, the skin lightly with a cotton wool ball.

Pressure: Press the skin just enough to deform the skin contour using the index finger.

Pinprick: Prick the skin with a neurotip, maintaining even pressure.

Temperature: Touch the skin with the side of one of two test-tubes, one filled with hot water and one filled with cold water (use the sides, not the base of the tubes). Apply hot and cold tubes in random order.

Tactile Localisation:

Repeat the pressure test with the index finger tip coated with talcum to mark the spot touched and ask the subject to point to the exact spot that has been touched. If communication permits, this test may be combined with the pressure test. 2cm of error are allowed.

Bilateral Simultaneous Touch:

Touch corresponding sites on one or both sides of the body using the fingertips and ask the subject to indicate if both or one (and which) have been touched.

B: Kinaesthetic Sensations

All three aspects of movement are tested: appreciation of movement, its direction and accurate joint position sense are assessed simultaneously. The limb on the affected side of the body is supported and moved by the examiner in various directions but movement is only at one joint at a time. The subject is asked to mirror the change of movement with the other limb. Three practice movements are allowed before the blindfolding. The reverse procedure, supporting and moving the unaffected arm, is attempted if there is a good recovery of movement in the affected limb.

If hand and wrist score 3 give 3's for elbow and shoulder without further testing.

Scoring

0= *Absent*	No appreciation of movement taking place
1= A*ppreciation of movement taking place*	Subject indicates on each occasion that a movement takes place but the direction is incorrect
2=Direction of movement sense	Subject is able to appreciate and mirror the direction of the test movement taking place each time, but is inaccurate in its new position
3=Joint position Sense	Accurately mirrors the test movement to within 10° of the new test position
N/A =	*Unable to test*

C: Stereognosis

Various objects are placed in the subject's hand for a maximum time of 15 seconds. Identification is by naming, description or by pair-matching with an identical set. The object may be moved around the affected hand by the examiner. First answer only is accepted.

Scoring for each object

2= Normal	Item is correctly named or matched
1= Impaired	Some features of object identified or attempts at descriptions of objects
0= Absent	Unable to identify the object in any manner
N/A	Unable to test

D: Two-point discrimination

Set dividers at decreasing intervals. Apply two points simultaneously to the skin horizontally for approximately 0.5 seconds. Ask subject to indicate if one or two points are felt. Record the last interval at which two points are felt.

Test a) index finger b) thenar crease

Scoring – Record minimum interval (mm) where two separate points are detected

2 Less than 3mm at finger tips or 8mm on palm

1 Greater than 3mm at finger tips or 8mm on palm

0 Unable to detect two points

8.2 INSTRUCTIONS TO SUBJECT:

"This is the final test. In this test we have a series of small tests that will give us information about the feeling in your arm.

Light touch: What I am going to ask you to do is to wear this blindfold. When you are blind folded I am going to touch you hand, then your wrist and possibly further up you arm with this cotton wool. I want you to say "Yes" each time you feel me touch. OK lets make a start."

(Blind fold is taken off in between each test and further explanation is given).

Light Touch: The next one I am going to do is press on you arm with my finger. Can you tell me "Yes" each time you feel me touch

Pressure: This next one uses a small pin to touch your skin. It won't and should not hurt. Can you tell me "yes" each time you feel it.

Temperature: I now have 2 test tubes. One is hot and one is cold. Can you tell me hot or cold when I place it on your skin?

Tactile Localisation: This time I am going to press your arm with my finger. I then want you to reach across with the opposite hand and touch the spot that I touched. Try and be as accurate as possible.

Bilateral Simultaneous touch: Now I am going to touch you arms or hands either separately or together. I need you to answer left, right OR both. If you are not very clear with your left and right just raise the hand or hands that I have touched.

Kinaesthetic awareness: This is one of the more difficult tests. I am going to place your hand/arm in a certain position, for example like this (cup holding positioning) and I want you to copy this position with your other hand. The trick is that I want you to try and do this with your blindfold on. We will start with your hand, then your wrist and progress up your arm if needed. Lets try.

Stereognosis: OK, after you have put the blindfold on, I am going to put an object in your hand. I would like you to tell me what the object is OR if you can not manage this, I would like you to try and describe it. OK…

2-point discrimination: This is the last part of this test. I am going to use these little pins on your palm and thumb. Can you tell me if you feel 2 points or 1.

9.0 EQUIPMENT:

ARAT: (figure 1 and 3)

- Table (100cm width, 60cm depth, 76.5cm height)
- Shelf (37cm high)
- wheelchair/chair (44cm +/- 2cm)
- Wooden blocks (10cm, 7.5cm, 5cm, 2.5cm - squared)
- Stone 10 x 2.5 x 1cm
- Cricketball 7.5cm diameter
- 2 x glass
- Tube 2.25cm
- Tube 2.5cm
- 2 prongs x 2.25cm
- 2 prongs x 1cm
- washer (3cm diameter)
- ball-bearing 6mm diameter
- Marble 1.5cm diameter

HADS:

- Pen or pencil

9HPT: (figure 2)

- Nine hole peg test (see photo)
- Non-slip mat
- Stopwatch

MBI

- Pen or pencil

RMA:

- Table (100cm width, 60cm depth, 76.5cm height),
- wheelchair/chair (44cm +/- 2cm),
- bean bag,
- large ball (20cm diameter),
- tennis ball,
- pencil,
- piece of paper (A5,)
- thera-putty,
- knife and fork,
- non-slip mat
- ball of string,
- chalk
- crosses (8cmx8cm) made from cardboard and stuck onto wall with blue-tac.

NHP:

- Pen or pencil

NSA:

- Blindfold
- cotton wool ball
- Neurotip

- two test tubes
- hot and cold water
- talcum powder
- 2p and 10p coins
- ballpoint pen
- pencil
- comb
- scissors
- sponge
- flannel
- cup
- glass
- blunt dividers
- ruler

Figure 1: Table and shelf , with ARAT apparatus.

Figure 2: Nine Hole Peg Test apparatus.

Figure 3: Closer view of ARAT apparatus.

Appendix 6

Permission to use the Nottingham Health Profile

Enterprise House, Manchester Science Park,
Lloyd Street North, Manchester, M15 6SE, UK.

Telephone: +44 (0)161 226 4446
Facsimile: +44 (0)161 226 4478

GALEN RESEARCH

Ref: 9907as034

Jacqui Morris
Clinical Research Fellow, PhD student
Alliance for Self-Care Research
University of Dundee
Dundee
DD1 4HJ

18th July 2007

Dear Ms Morris,

Ref: The Nottingham Health Profile

Thank you for your application to use the NHP. Permission has been granted for the use in your study of an 'upper limb intervention for patients in the sub-acute stage of stroke'. I am enclosing an invoice for your attention. On receipt of payment I will forward the measure and scoring manual to you.

If you have any questions please do not hesitate to contact me.

Best regards.

Yours sincerely

Kate Firth
Finance Manager

Enc.

Appendix 7

Bilateral upper limb task training study recruitment and randomisation procedures

RECRUITMENT

1. Identifying potential patients
Preliminary stages of screening are conducted in collaboration with the Stroke Team Physiotherapists, who review all patients admitted to the Medical receiving ward with a preliminary diagnosis of stroke.

Details of patients admitted to the acute Medical receiving ward, ward 15, are collected by the research physiotherapists in collaboration with the Stroke Team physiotherapists for all patients with a preliminary diagnosis of stroke. This includes preliminary diagnoses such as:

- TIA
- Left or Right sided weakness
- CVA/?CVA
- Stroke

Patient records are reviewed two days after admission, and scan reports are checked for confirmation of new unilateral stroke, characterised by infarct or haemorrhage on the scan.

Patients discharged home within the first two weeks with full scores on the Motor Assessment Scale, as assessed by the stroke team therapists are noted by the Research Physiotherapists, but these patients are not followed up for inclusion to the study.

2. Between Admission and Week Two
Patients discharged from hospital with less than full scores on the Motor Assessment Scale, as assessed by the stroke team physiotherapists, within the first two weeks after stroke, are contacted at home between two and four weeks after stroke, by the research physiotherapists for repeat Motor Assessment Scale and full screening.

For other patients, progress of upper limb recovery and progress to rehabilitation or home of all in-patients at physiotherapy is monitored by the research physiotherapists in collaboration with the Stroke Team physiotherapists.

3. At Two Weeks
Research physiotherapists review patients still in hospital.

An indication of the patient's ability to participate in normal physiotherapy sessions is provided by the Stroke Team physiotherapists.

Patients who can actively participate in 30 minute physiotherapy sessions according to the stroke physiotherapists' assessments and who according to the physiotherapy records score <6 on the upper limb sections of the MAS are screened by the research physiotherapists using the

- Motor Assessment Scale – repeat assessment conducted by the research physiotherapists
- NIH Stroke Scale
- Timed measurement of ability to sit unsupported for one minute

Patients with MAS scale scores of <6 on any of the upper limb sections, and who score 0 or 1 on the communication or neglect items of the NIH Stroke Scale are eligible for inclusion.

Patients are asked if they had any problems in using their upper limbs prior to the stroke, either due to previous stroke, or because of any other problems or pain.

Where there is any uncertainty about what the patient was previously unable to do with their upper limb, where possible, relatives or carers are contacted for more information, with permission of the patient.

The patient is also asked to indicate if they have experienced any shoulder pain since stroke, and medical records are checked for evidence of this. Patients with previous functional impairment of the upper limb prior to stroke, and those experiencing significant hemiplegic shoulder pain are excluded.

4. Obtaining Informed Consent
Patients meeting criteria at two weeks following stroke are provided with the patient information sheet. The research therapist explains the study to the patient and goes over the information sheet with the patient. The patient is instructed that he should read it and discuss it with their family or carers if they wish.

The research therapist returns within two days to answer any questions the patient may have and to invite the patient to participate. The patient is then asked to complete the consent form. Where there is any question about the patient's ability to understand the concept of informed consent, the speech and language therapist is contacted for her opinion, and a relative or carer is consulted with the permission of the patient to ensure that informed consent is provided.

5. Rescreening
Patients who are unable for any reason to participate at two weeks following stroke because they do not meet inclusion criteria or because of illness, are reviewed again in collaboration with the physiotherapists at three and four weeks, using the same procedure.

6. Baseline Measurements
The blinded rater is informed that the patient has consented to participate, and conducts baseline measurements with the patient prior to the four week deadline for recruitment.

7. Randomisation
Following the randomisation protocol (below), the patient is randomised following baseline assessment.

8. Undertaking the Intervention
The patient starts the intervention protocol within two days of baseline assessment.

Control and experimental treatment is delivered for twenty minutes on weekdays whilst the patient is in hospital. If discharged during the six-week period, the treatment is continued in the patient's home, but reduced to twice per week.

Patients may miss treatments because of transfer to rehabilitation or home, because of illness or the need to attend tests, home visits or because the research therapists are absent due to public holidays or annual leave. Where possible, the therapists will cover each other to ensure that treatments are not missed. When any of the above occur, the therapists will add the missed treatments onto the end of the intervention period to ensure that time spent in intervention is uniform.

The blinded rater is informed of the date of the last treatment and conducts the six-week measurements within five days of the last intervention in hospital, or in the patient's home.

The delay of five days will be avoided where possible but will occur occasionally because the rater works on the study for only six hours over two days per week.

RANDOMISATION PROCEDURE

Randomisation is conducted using a web based, computerised system that is housed in the remote computer of Dundee University, and that is administered by Simon Ogston, statistician for the study.

1. Procedure for Randomisation

- Randomisation is conducted after consent to participate has been obtained from the patient, and after baseline measurement has been conducted by the blinded rater.

- Prior to randomisation it has been established:

    - Which is the hemiplegic side (R or L)
    - Whether the stroke is lacunar or non-lacunar
    - Whether the patient has scored 5 or less, or 6 or more, on the ARAT, the primary outcome measure

Decision about whether the stroke is lacunar or not is made by the consultant physician, Dr Ron MacWalter according to the Oxfordshire Stroke Classification, and can be determined by the results of the NIH stroke scale at screening, the findings of the initial examination on admission to hospital reported in the medical records, and results of the CT scan.

The blinded rater will provide the result of the total ARAT score after baseline assessment.

The file for randomisation is accessed electronically via a password, available only to the lead researcher, Jacqui Morris.

Enter the patient ID number and other information as prompted for each patient then press submit.

The output will provide details of allocation and the patient is allocated as follows:

Treatment 1 = Unilateral Control group
Treatment 2 = Bilateral Experimental group

Simon Ogston alone has access to the electronic log details, but opening the file “showlog” shows the number of patients in each stratum. The blinded rater has no access to any of this information.

Written information about the allocation is recorded in the patient record file, which is stored in a locked cabinet when not in use. Locked cabinets have been made available in each of the physiotherapy departments where the therapists are conducting the intervention – Ninewells Hospital, Royal Victoria Hospital Rehabilitation, Royal Victoria Hospital Centre for Brain Injury Rehabilitation and Stracathro Hospital.

The blinded rater has no access to the records containing information about allocation.

Appendix 8

Patient Screening Sheet

Screening Sheet

Patient ID:

Date: **Examiner:**

Inclusion Criteria:

1. **2-4 weeks since stroke onset at start of intervention?**

Date of Stroke Onset	
Date of inclusion to trial	

CT Scan

Date of Scan	
Report	

2. **MAS Scores (> 48 hours post stroke onset)**

Date of Assessment	
Upper Arm Function Score	
Hand Movement Score	
Advanced Hand Activities Score	
Total Upper Limb Score	**/18**

3. Can sit unsupported for > 1 minute? Tick yes ☐

4. Able to participate in standard 30 minute therapy sessions as reported by regular therapist? ☐

NIH Scores

Date of Assessment	
Consciousness	
Communication	
Neglect	

Exclusion Criteria **:**

	Yes	**No**
Previous stroke with resultant disability?		
Able to provide informed consent? (check with SALT if unclear)		
Premorbid UL impairment or HSP?		

Patient ID: Date: Examiner:

NIH Stroke Scale

1a Level of Consciousness	Alert Not alert, rousable with minor stimulation Not alert, requires repeated stimulation to attend, or painful stimuli Coma ,resonds only with reflex motor or autonomic effectss, unresponsive, flaccid	0 1 2 3
1b Ask patient the month and their age	Answers both correctly Answers one correctly Both incorrect	0 1 2
LOC Ask patient to open and close eyes	Obeys both correctly Obeys one correctly Both incorrect	0 1 2
2 Best Gaze (horizontal eye movement)	Normal Partial Gaze Palsy Forced deviation or total gaze paresis not overcome by oculocephalic manoeuvre	0 1 2
3 Visual field testing	No visual field loss Partial hemianopia Complete hemianopia Bilateral hemianopia (blind including cortical blindness)	0 1 2 3
4 Facial Paralysis	Normal symmetrical movement Minor paralysis (asymmetry on smiling) Partial paralysis (total or near of lower face) Complete paralysis of one or both upper and lower face	0 1 2 3

	NIH Stroke Scale	
5 Motor function Arm R……. L……	Normal – no drift limb holds 90° for10 sec Drift holds 90° but drifts down before full 5sec does not hit bed Some effort against gravity, limb cannot get to or maintain 90,(if cued 90° drifts but some effort against gravity) No effort against gravity No movement Untestable (joint fused or limb amputated)	0 1 2 3 4 9
Motor Leg R…… L…….	No drift – limb holds 45° for full 5 seconds Drift-limb holds 45°but drifts down before full 5 secs,does not hit bed Some effort against gravity limb cannot get to or maintain 45° (if cued 45°drifts,but some effort against gravity) No effort against gravity No movement Amputation, joint fusion	0 1 2 3 4 9
Limb Ataxia Finger/Nose Heel/Shin	Absent Present in one limb Present in two limbs	0 1 2
Sensory	Normal Mild to moderate, dullness to pinprick Severe to total sensory loss	0 1 2
Best Language	No aphasia Mild to moderate aphasia Severe aphasia Mute global dysphasia	0 1 2 3

	NIH Stroke Scale	
Dysarthria	Normal Mild to moderate – slurs some words Severe – slurred to unintelligible Intubated or physical barrier	0 1 2 3
Extinction and inattention	No abnormality Visual, tactile, auditory, spatial or personal inattention or extinction to bilateral simultaneous stimulation Profound hemi-inattention	0 1 2

Patient ID: **Date:**

Examiner:

Motor Assessment Scale (amended version (1994). Carr J, and Shepherd R. School of Physiotherapy, Faculty of Health Sciences University of Sydney

Scoring:

- Repeat each item three times unless otherwise stated, scoring on best performance. Score between 0 and 6.
- Equipment: Stopwatch, polystyrene cup, 8 jelly beans, 2 teacups, rubber ball 5" in diameter, comb, pen top, dessert spoon, water, sheet prepared for drawing lines, pencil, cylindrical object such as jar
-

Upper Arm Section

Instructions	Score
Unable to perform any of the activities	0
Lying, protract shoulder girdle with arm in elevation (therapist places arm in position and supports it with elbow extension)	1
Lying, hold extended arm in 90° of shoulder flexion for 2 seconds (therapist should place arm in position and patient must maintain position with some (45°) external rotation. Elbow must be held within 20° of full extension)	2
Flexion and extension of elbow to take palm to forehead with arm as in 2 (therapist may assist supination of forearm)	3
Sitting, hold extended arm in forward flexion at 90 to body for 2 secs. (therapist should place arm in position and patient maintains position. Patient must hold arm in mid-ratation (thumb pointing up). Do not allow excess shoulder elevation)	4
Sitting, patient lifts arm to above position, holds there for 10 seconds and then lowers it (patient must maintain position with some external rotation. Do not allow pronation)	5
Standing, hand against wall. Maintain arm position while turning body towards wall (have arm abducted to 90 with palm flat against the wall)	6

Patient ID: **Date:**

Examiner:

Hand Movements

Unable to perform any of the activities	0
Sitting, extension of wrist. Therapist should have patient sitting at table with forearm resting on table. Therapist places cylindrical object in palm of patient's hand. Patient is asked to lift object off table by extending the wrist. Do not allow elbow flexion.	1
Sitting, radial deviation of wrist. Therapist should place forearm in mid pronation – supination,ie resting on ulnar side, thumb in line with forearm and wrist in extension, fingers round cylindrical object. Patient is asked to lift hand off table. Do not allow elbow flexion or pronation.	2
Sitting, elbow into side. Pronation and supination, elbow unsupported and at right angle. Three quarter range is acceptable.	3
Reach forwards, pick up a large ball of 14cm (5") diameter with both hands and put it down. Ball should be on table so far in front of patient that he has to extend his arms fully to reach it. Shoulders must be protracted, elbows extended, wrist neutral or extended. Palms should be kept in contact with the ball.	4
Pick up polystyrene cup from the table and put it on table across other side of body. Do not allow alteration in shape of cup.	5
Continuous opposition of thumb and each finger more than 14 times in 10 seconds. Each finger in turn taps the thumb, starting with the index finger. Do not allow thumb to slide from one finger to the other to go backwards.	6

Patient ID: .....Date: .....Examiner.....

Advanced Hand Activities

Unable to perform any activities	0
Picking up the top of a pen and putting it down again. Patient stretches arm forward, picks up pen top and releases it on table close to body	1
Picking one jelly bean from a cup and placing it in another cup. Teacup contains 8 jelly beans. Both cups must be at arms length. Left hand takes jelly bean from cup on right and releases it in cup on left	2
Drawing horizontal lines to stoop at vertical line 10 times in 20 seconds. At least 5 lines must touch and stop at vertical line. Lines of at least 10cm in length	3
Holding pencil, making rapid consecutive dots on a sheet of paper. Patient must do at least 2 dots a second for 5 seconds. Patient picks pencil up and positions it without assistance. Patient must hold pencil as for writing. Patient must make a dot not a stroke	4
Taking a dessert spoon of liquid to the mouth. Do not allow head to lower towards the spoon. Do not allow liquid to spill	5
Holding a comb and combing hair at back of head (shoulder must be externally rotated, abducted to at least 90°. Head erect.	6

MAS Score Sheet **(R) Hemiplegia/(L) Hemiplegia (delete)**

Score	0	1	2	3	4	5	6
Upper Arm Function							
Hand Movements							
Advanced Hand Activities							
Total UL	/18						

Patient ID: **Date:**

Examiner:

Procedure:

Patient provided with information sheet(tick)…… Consent for participation obtained(tick)……..

Discussed with patient/Carers (tick)…….. GP/Consultant record sent (tick)…….

Demography:

Sex: M/F Age: …….. (years) (R) Hemiplegia / (L) Hemiplegia

Date commenced Study Intervention…….. Time from stroke onset to start of BSULTT (Days)…….

TACS/PACS/POCS/LACS (Bamford 1991)…… Ischaemic/Haemorrhagic (delete)

Physio
Report…….

……..

Relevant PMH/Current condition of relevance
…….

……
……

Randomisation: Intervention/Control (Delete)

Other:

Discharge Date from Ninewells: ……. Discharged to:……

Date of completion of intervention……

Dropped out? Date……..

Reason……
……

Destination at end of intervention (6 weeks)…… Planned Date for 3 month follow-up……

Independent Rater informed of follow-up date?…….(tick)

Destination at 3
months……..

Therapy records checked? Confounding variables……

Record of Intervention

Patient ID: **Date:**

Examiner:

Record whether intervention carried out according to protocol, general observations, untoward effects, general changes in patient condition etc)

Date	**Comments**

Appendix 9

Participant information sheet

UPPER LIMB TASK TRAINING

We invite you to participate in a research project. We believe it to be of potential importance. However before you decide whether or not you wish to participate, we need to be sure that you fully understand firstly why we are doing it, and secondly what it would involve if you agreed. We are therefore providing you with the following information. Read it carefully and be sure to ask any questions you have, and, if you want, discuss it with others. We will do our best to explain and provide any further information you may ask for now or later. You do not have to make an immediate decision

BACKGROUND

What is this research about?

This research is investigating physiotherapy treatment for arm recovery in the early stages following stroke, in which patients practise useful tasks either using both arms together, each arm performing the task at the same time but independently or using the arm affected by the stroke only.

Why is this research being done?

As many as 1300 people per year in Scotland suffer a new stroke, and many of those will suffer some sort of lasting disability.

We know that arm recovery after a stroke can be particularly poor, with as few as 20% of sufferers regaining full use of the affected arm

Physiotherapy is known to be helpful in improving arm recovery, and is a major part of the rehabilitation process. As yet however, no single type of exercise for the arm is thought to better than another.

This research aims to investigate a promising new technique. The results of the study will give us new information about the effectiveness of this type of exercise, and important knowledge about how recovery from stroke occurs.

Who is sponsoring this research?

The Chief Scientist's Office at the Scottish Office is funding the study, and paying for the research physiotherapist.

Why have I been chosen as a possible participant in the research?

We are looking for patients like yourself, who have recently had a new stroke, and who are experiencing difficulty in using their stroke arm. As long as you are able to participate in normal physiotherapy rehabilitation sessions, we would like to invite you to participate in our study.

How many other people have been asked to consider participating?

We hope to recruit 106 people in total

WHAT DOES THE STUDY ENTAIL?

Will I have to come back to the clinic more often or remain in hospital longer than would normally be the case?

No. The treatment will be carried out daily whilst you are undergoing normal rehabilitation in hospital. Should you be discharged home before the end of your participation in the study, the research physiotherapist would visit you at home twice a week until the end of the study. In addition, an occupational therapist will visit you at home to carry out some tests to examine what you can do with your affected arm. These visits will be before, immediately after and 3 months after the treatment.

What will I be asked to do on each treatment session?

To practice activities with your affected arm, or with both arms. The daily sessions will last 15-20 minutes, and will be in addition to your normal therapy. The activities include reaching, pointing, taking a glass to your mouth, and moving objects from one place to another. You will be given opportunity to rest between activities, and if you cannot perform the tasks by yourself, the therapist will help by moving your arm with you.

How long will my participation in the study last?

The treatment will last 6 weeks with follow-up as mentioned above.

What procedures will I be asked to submit to, and what will they be like?

Apart from the treatment, you will be asked to perform some tests to examine how well you can use your arm, and to test if the stroke has affected your ability to feel touch and movement. We will also test how the stroke has affected you generally, in your ability to move around. In addition, we will ask you some short questions about how you are feeling.

What treatment will I get if I do take part? Will this be different to the treatment I would get otherwise?

If you decide to take part, you would continue with normal physiotherapy. The research treatment will be in addition to this.

Will the decisions about my treatment be made by my usual doctor and therapist or by someone else?

Decisions about your treatment will continue to be made by the doctors and therapists who normally look after you.

Will all patients receive active treatment, or will some receive dummy treatment? If so, what is the chance that I would receive dummy treatment?

There is a 50% chance that you would receive dummy treatment. However, both the treatment and the group receiving dummy treatment will receive additional therapy. The additional therapy will be slightly different in each case though.

Were I to feel severe discomfort or pain during the study would I be able to take any relief medication?

Yes. If the discomfort were thought to be related to the exercise, we would withdraw you from the study.

Is there any chance that the proposed research will be of benefit to me personally, or to patients in the future?

We know from other research that additional exercise is of benefit to arm recovery in stroke, so that even if the new treatment does not prove more beneficial, having more therapy anyway is likely to be of benefit to you. Future patients will also benefit.

Were the new treatment to be of benefit to me, could I continue it after the trial?

No

If not, what care and follow-up will I receive after the trial?

You would continue with the normal rehabilitation process, in hospital, at day hospital, or with the community rehabilitation team.

WHAT ARE THE DISCOMFORTS, RISKS AND SIDE EFFECTS?

Will there be any discomforts such as additional needle pricks or biopsies or pain, and if so, how much and for how long?

There should be no additional discomfort.

Are there likely to be side effects from what will be done to me in the research, and if so, what are they?

There should be no side effects, however as you will be having additional treatment, you may feel more tired than otherwise. The research physiotherapist will discuss this with you regularly, and if you are finding the additional therapy too much, you can of course withdraw from the study.

Some people with stroke suffer from shoulder pain on the affected arm. This treatment has no additional risk of causing pain, but should you experience any shoulder pain, we would immediately stop the treatment and refer the problem to your doctor and regular physiotherapist.

Who should I contact if I am worried about any side effects?

You can contact Dr MacWalter at 01382-633883, Jacqui Morris or Rachel Mills, Research Physiotherapists at 01382-660111 ext33331.

Is there any chance of something going wrong, and if so, what are the risks compared to everyday activities?

There is virtually no risk of anything going wrong.

Would I be withdrawn from the study if my condition became worse or if any extra risks came to light during the course of it?

Immediately

Are there any activities I should refrain from during and in the period following the research and for how long?

None

WHAT WILL HAPPEN TO THE INFORMATION COLLECTED IN THE STUDY?

How will my confidentiality be protected i.e., who will have access to the records generated and what steps will be taken to ensure that they will only be seen by those authorised to see them?

Only the researchers will see records. As far as possible, information will be coded so that individual patients cannot be identified.

Will my GP be informed that I am taking part in the study, and the results of my participation?

Yes.

If any illness of which I am presently unaware is found as a result of the study, will I be told and receive any treatment?

Yes

Will I be informed of the results of the study?

Yes.

WHAT ARE MY RIGHTS?

How can I obtain more information if I wish?

By contacting either DR MacWalter or Jacqui Morris at the numbers above.

Can I discuss the study with my friends and relatives, or my GP before deciding whether to take part?

Yes

Can I refuse to take part or change my mind later even if I agree to take part now?

Certainly. You can withdraw from the study at any time you wish.

If I do refuse to take part or change my mind later, will I still get the treatment my usual doctor or physiotherapist thinks is right for me?
Yes.

Will I get travelling expenses or any payment?
No.

Participation in this study is entirely voluntary and you are free to refuse to take part or withdraw from the study at any time without having to give a reason, and without this affecting your future medical care or therapy or your relationship with medical staff of physiotherapists looking after you.

The Tayside Committee on Medical Research Ethics, which has responsibility for scrutininsing all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics.

Appendix 10

Participant Consent Form

UPPER LIMB TASKS TRAINING IN ACUTE STROKE

PARTICIPANT CONSENT FORM

(The patient should complete this form himself/herself)

	PLEASE CROSS OUT AS NECESSARY
Have you read the Patient Information Sheet?	**YES/NO**
Have you had an opportunity to ask questions and discuss this study?	**YES/NO**
Have you received satisfactory answers to all of your questions?	**YES/NO**
Have you received enough information about the study?	**YES/NO**
Who have you spoken to? Dr./Mr./Mrs. ……..	
Do you understand that participation is entirely voluntary?	**YES/NO**
Do you understand that you are free to withdraw from the study: • **at any time?** • **without having to give a reason for withdrawing?** • **without this affecting your future medical care?**	**YES/NO**
Do you agree to take part in this study?	**YES/NO**

Patient's Signature ……. Date ……..

Patient's name in block letters …….

Telephone number where patient can be contacted:

……. (Home) …… (Work)

Research Physiotherapist's signature ……
Date ……..……..

Appendix 11

Intervention Protocol

1. GENERAL PROCEDURES

EQUIPMENT

Patients will be seated on a chair (seat height 45cm) with armrests, at a table (76cm high, 100 cm wide, 60 cm deep). The table has been designed with a detachable, adjustable height shelf, which is fixed 47cm from front of table onto a sliding frame which allowed adjustment of vertical height (Figure 1).

If a chair of suitable height is not available then a wheelchair should be used (height may vary between 47 and 51 cm, depending on depth of cushion).

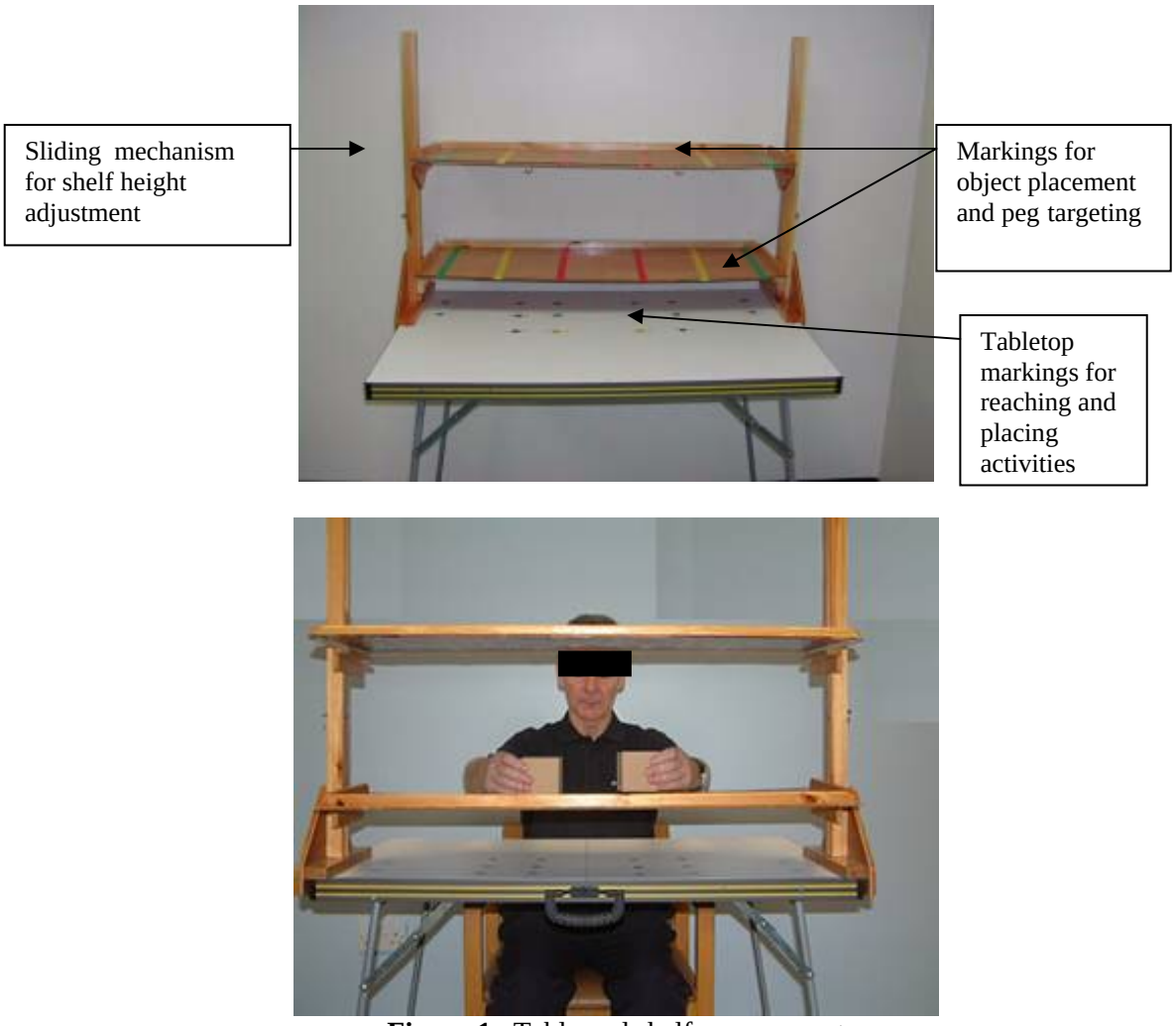


Figure 1. Table and shelf arrangement

Additional equipment comprises:

Task 1. Two mobile vertical target boards, each 17.5 cm square, and fixed to stand 30cm in height

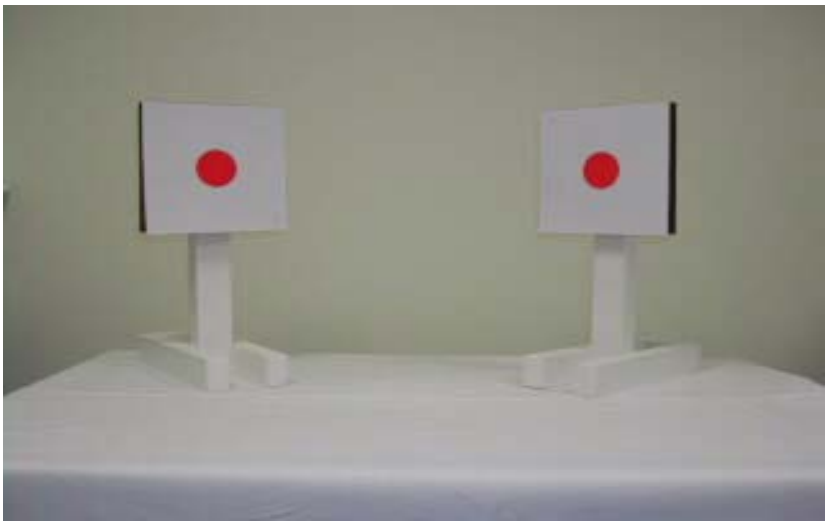


Figure 2. Vertical target boards for Task 1

Task 2. Round dowelling pegs 2cm diameter x 4 cm long, round dowelling pegs 6mm x4cm, plastic cups 1cm x 7.5cm, china cups 7.5 cm x 7.5 cm, hooks and keys, Velcro, clothes pegs and string, weighted cylinders

Figure 3. Equipment for Task 2

Task 3. 7.5cm^3 wooden cube and everyday objects of varying shapes and sizes.

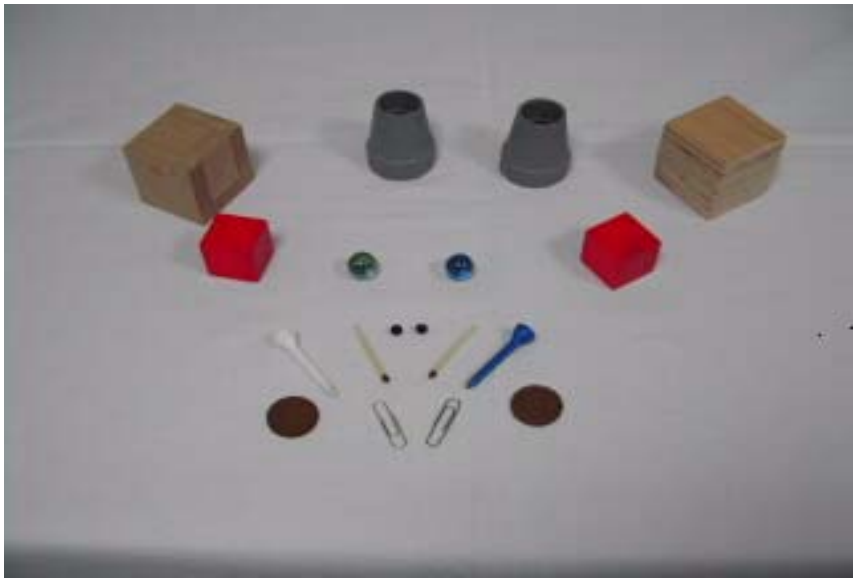


Figure 4. Equipment for Task 3

Task 4. Two drinking glasses (7.5 cm high, 7.5 cm diameter at widest part) and various everyday objects of varying shapes and sizes

Figure 5. Equipment for Task 4

PROCEDURE

Bilateral and Unilateral Groups
Patients randomized to treatment group one (unilateral) will practice all tasks with the affected arm only. Patients allocated to group two (bilateral) will practice with both arms, performing the activities independently but simultaneously.

Patients in group two (bilateral) will be instructed to move both arms simultaneously and to achieve the tasks with both arms at the same time. Say to the patient:

> "I would like you to bring both glasses to your mouth/reach to touch the yellow dots etc. Move both arms together at the same time, but do not allow the stronger to assist the other"

Duration of sessions
Daily sessions last 20 minutes. Within this time the patient should attempt as many trials as possible within the blocked/random schedule detailed below.

FIRST SESSION
At the first treatment session patients should be assessed performing each of the core activities.

The core activities comprise:
1. Reach to touch targets: raised 30cm, placed 40 cm from the front of table and placed 40cm to left and 40cm to right of midline. When reaching to the front, touch one target with either one or both hands, depending on the group allocation. When reaching to left and right, those in group one reach to the hemiplegic side only, group two reach to both targets simultaneously.

2. Move a peg 2x4cm from the table to touch the underside of a shelf placed at eye level

3. Grasp a glass, take to the mouth and return to midline

4. Move a $7.5cm^3$ block from table onto a shelf at shoulder height

If the patient **can** perform part of the task, or is judged able to perform with practice, then start the task, following the **Core Protocol Progression.**

If the patient **cannot** perform the task or any part of the task and lacks motor control to attempt the task actively, start with the **Modified Protocol Progression** of that task.

The patient can be assisted to perform tasks by the therapist but the therapist must withdraw assistance as the patient regains control. This ensures that the patient performs as actively as possible at all times.

PRACTICE SCHEDULE
Both protocols start with the easiest activity and progress to those more difficult as illustrated in Figure 1.

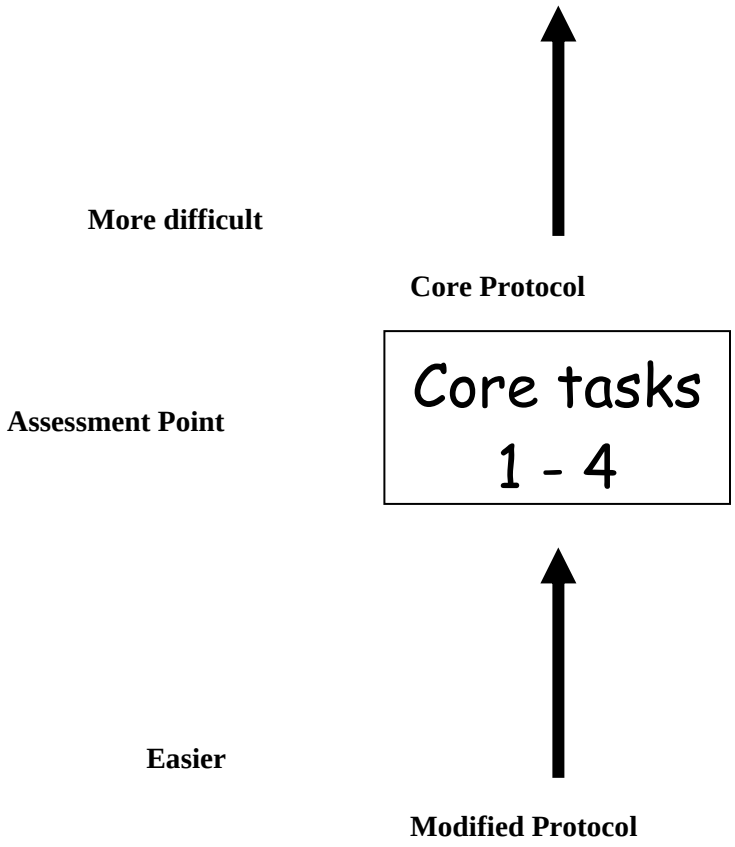


Figure 1. Representation of Task Progression

Blocked and random practice
Sheets of randomised numbers 1-4 representing each task (1-4) are used for task order. For each task, practice in **blocks** of 10 trials is interspersed randomly with identical blocks of 10 trials of the other three tasks until the patient is able to perform any of the tasks five times in a row (within a block of ten) with **reasonable** accuracy. The accuracy does not have to be perfect but the patient must take the object or his/her hand and be able to at least touch the target point/point of goal achievement.

Thereafter continuing to use the randomization sheet to determine order, single trials should be interspersed randomly with the other three tasks, resting after five trials, to a maximum of 120 blocked or randomised trials in any one 20 minute session.

Progression to next level of difficulty
Progression to the next level of difficulty for each task in the protocol will occur once that patient is accurate on **75%** of random single trials.

If the patient is able to complete all trials of any task in the block phase with 100% accuracy, random practice can be omitted and the patient can proceed straight to the next task. This process can be repeated until the patient reaches a task that they cannot perform with 100% accuracy on all blocked trials.

Feedback
General verbal **encouragement** should be given to encourage patients to achieve the tasks, and to maintain symmetry of movement during bilateral tasks.

Summary feedback about performance should be provided after 5 trials. This should relate to both the number of accurate trials and to the movement patterns being used.

After five trials, **random or blocked,** during a short break to give feedback**,** the patient should be told **how many** of trials were accurately achieved and the goal met.

" Of these five trials, you achieved three accurately. In the other two you missed the target"

The number of trials in which the goal was actually achieved should be recorded on the randomised number sheet.

Feedback should also relate to the **motor performance** or movement patterns. If the patient is displaying movement errors during the task, he should be told:

"you are not moving your wrist back sufficiently or opening your finger enough when you are trying to grasp the glass"

Or

"Try not to lift your elbow out to the side as you lift the block onto the shelf"

Example of a practice schedule:

The session might run like this:

Task 1 Block of 5 trials, feedback, block of 5 trials feedback
Task 2 Block of 5 trials feedback, block of 5 trials feedback
Task 3 Block of 5 trials feedback, block of 5 trials feedback
Task 4 Block of 5 trials feedback, block of 5 trials feedback

Task 2, 5 trials in a row accurate, progress to single random

Task 4 Block of 5 trials feedback, block of 5 trials feedback
Task 4 Block of 5 trials feedback, block of 5 trials feedback
Task 3 Block of 5 trials feedback, block of 5 trials feedback
Task 2 single trial

Task 3, 5 trials in a row accurate, progress to single random

Task 4 Block of 5 trials feedback, block of 5 trials feedback
Task 3 single trial

Task 1 Block of5 feedback, block of 5 trials feedback
Task 2 single trial

Provide feedback after 5 single trials

Once the single task trials are 75% accurate across the session, progress to the next task progression. Start with block practice whilst continuing with blocks or single trials of practice of the tasks that have not been practiced accurately on 5 consecutive trials or with 75% accuracy during single random trials.

GOALS
Within the protocol there are points at which the patient can choose what he or she wishes to practice using the available tasks and equipment for that task.

"Please choose what tasks you feel you would like to try, using any of the equipment that we have here"

ADVERSE EVENTS
Always ask the patient if they are well and if they are experiencing any pain or discomfort prior to starting that day's intervention

If the patient complains of upper limb pain during the intervention stop and report it to the regular physiotherapist and to the lead researcher.

START POSITION
For all tasks start position is with hands flat on table with manual support to do this if required

Figure 6. Start position for all tasks

2. TASK 1: CORE PROGRESSION

Touching Target Boards

For all trials, the patient should perform the tasks at a speed that is comfortable to them. Use block and random practice with feedback as described on page 3: when patient performs the task accurately on at least 75% of single randomised trials in a practice session, progress to the next protocol.

Task 1 (easiest in the core protocol)
Protocol 1
Start and finish position of each trial with hands flat on table (Figure 6)
Patient to reach to touch **target board/s** raised 30 cm from table and positioned at midline and 40cm apart (20cm to the right and/or 20cm to the left of midline), and 40cm from the front of the table (blue square marked 40/40). Touch midline target with index finger(s) followed by lateral targets. Hands return to table between midline and lateral trials. Target/s are red circles, of 5cm diameter positioned in the middle of the board. When patient accurately reaches the red circle on 75% of single randomized trials in one practice session, progress to **Task 1 Protocol 2**

Task 1
Protocol 2
Start position as for Protocol 1, same task, use lateral and midline target board/s, 40cm from edge of table.
Wider position of **target boards** to 80 cm apart/40cm to R and/or L of midline side (blue square marked 80/40)
When patient accurately reaches the red circle on 75% of single randomised trials in one session progress to **Task 1, Protocol 3**

Task 1
Protocol 3
Start position as for Protocol 1, same task, use only lateral target board/s, 40cm from edge of table
Target boards positioned as for **Protocol 1, 20cm to R or L of midline**, (blue square marked 40/40), using only lateral target(s) this time. Targets are blue circles, of 4 cm diameter, positioned in upper right or left quadrant of target board. Progress to target boards at 80cm apart/40cm to R and/or L of midline (blue square marked 80/40). Once patient is able to accurately reach target, in both positions on 75% of single randomized trials in one entire practice session progress to Task 1 Protocol 4.

Task 1
Protocol 4
Start position as for Protocol 1, same task, use only lateral target board/s
2 **target boards**, 20cm to R and/or L of midline (blue square marked 40/40). Change targets on each board to two pink and yellow circles (2cm in diameter). Patient to touch each circle accurately with index finger, returning hands to table between trials. Once patient is able to alternately reach pink and yellow target circles on 75% of single randomized trials in one entire practice session, progress to wider placement of the **target boards to** 80cm apart, (blue square marked 80/40) again progressing to next task when performing accurately on 75% of single randomized trials in one session. Progress to practising random targeting of both circles between both distances

Task 1
Protocol 5
Start position as for Protocol 1, same task, use only lateral target board/s
2 target boards, 40cm apart/20 cm to R and/or L of midline (blue square marked 40/40). Targets are six coloured circles of 2cm in diameter. Patient to touch coloured circles when colour called out randomly by therapist. Ask patient to carefully locate colour on each board before reaching to touch. Once patient accurately reaches each colour, on 75% of single randomised trials of one session progress to **Task 1 Protocol 6**

Task 1
Protocol 6
Start position as for Protocol 1, same task, use only lateral target board/s
Start position with pens on table. Patient to pick up pen(s) from table, grip as able**. Target board(s)** 40cm apart/20 cm to R and/or L of midline, (square blue mark 40/40). Touch anywhere on target board with marker pen to make a dot. Once patient is able to touch board anywhere on 75% of single randomised trials in one session progress to **Task 1 Protocol 7.**

Task 1
Protocol 7
Start position as for Protocol 1, same task, use only lateral target board/s
Target board(s) touching or just lateral to midline on hemiplegic side for unilateral group (square blue mark 20/40). Reach with pen to make dots inside pink circle, 2cm diameter in the middle of the board. Once patient is able to make dot in circle on 75% of single randomised trials in one session, widen target board(s) to 80 cm apart/40cm to R and/or L of midline, (square blue mark 80/40) and repeat same task. Once able to accurately perform task on 75% of single randomised trials progress to **Task 1 Protocol 8.**

Task 1
Protocol 8
Start position as for Protocol 1, same task, use only lateral target board/s
Target boards 40 cm apart/20cm to R and/or L of midline, (square blue mark 40/40) start position hands flat on table. Patient to pick up key(s), if able. If unable, keys can be placed in patient's hand by therapist. Hang key(s) on target board(s). Once able to hang key(s) on 75% of single randomised trials in one session, widen target boards to 80 cm apart /40cm to R or L of midline (square blue mark 80/40). Once able to hang key(s) on 75% of single randomised trials in one session, at 80 cm apart, progress to **Task 1 Protocol 9.**

Task 1
Protocol 9
Start position as for Protocol 1, same task, use only lateral target board/s
Target boards 40 cm apart/20 cm to R and/or L of midline (square blue mark 40/40). Start position hands flat on table. Patient to pick up drawing pin and pin into blue TAC placed in the middle of target board. If unable to pick pin up, it may be placed in patient's hand. Once able to stick pin into Blu Tac on 75% of single randomised trials in one session, progress to 80cm apart/40cmto side (square blue mark 80/40).

Once able to stick pin into BluTac on 75% of single randomised trials in one session, ask patient what they feel they would like to achieve along the same lines. Other objects such as pins to stick in Blu Tac, paper clips to hang on hooks, smaller target circles or ball pens instead of markers can be used, and progress make through variation in position and task difficulty applied as for the rest of the protocol. At this stage consideration should be made of what the patient feels is of importance, but the same basic movement strategy of reach must apply. Move randomly between tasks at different widths and different speeds

3. TASK 1: MODIFIED PROGRESSION

Like the core progression, this progression of activities starts with the easiest tasks. Follow the progression of blocked and random practice on page 3: when patient performs the task accurately on at least 75% of single randomised trials in a practice session, progress to the next protocol.

Protocol M1
Start position hands flat on table. Upper limb support can be given, but active movement must be encouraged.

Patient to slide hand(s) forward to touch mark 30 cm in from front edge of table and 20 cm apart/10cm to R and/or L of midline (yellow circle 20/30)
Once patient can perform this accurately on 75% of single randomised trials trial during one practice session, increase distance to touch red mark at 50cm from edge of table (red circle 20/50). Once performing accurately at each distance on 75% of single randomised trials in one session, progress by increasing distance to touch purple mark at 40cm (purple circle 40/50) and then green mark at 80 cm apart (green circle 80/50). Once patient performs accurately on 75% of single randomised trials in one session at the widest width, progress to **Task 1 protocol M2.**

Task 1
Protocol M2
Start position hands flat on table
Reach forward, lifting hand/s off table and extending elbow to touch yellow mark on table 30cm from front edge of table and 20cm apart/10cm to R and/or L of midline (yellow circle 20/30). Patient should lift hand off table and attempt to point. Once patient can perform this accurately on 75% of single randomised trials in one practice session, increase distance to touch red mark at 50cm from edge of table (red circle 20/50). Progress by lifting hand/s to touch purple and green marks at 40cm apart/20cm to R or L of midline (purple circle 40/50) and 80cm apart/40cm to L and/or R of midline (green circle 80/50) respectively until patient performs accurately on 75% of single randomised trials in one practice session at the widest width. Progress to **Task 1 Protocol M4**

Task 1
Protocol M3
Start position hands flat on table
Target board/s 20cm apart/10cm to L and/or R of midline and 40cm from front edge of table. (blue square 40/40). Patient to lift arm off table through shoulder flexion, external rotation and elbow extension try to touch target board anywhere (including base), using any part of the hand. Mark touch point with chalk, or note where touch point is, so that the patient can try to increase height towards the red circle until performing it accurately on every trial in one practice session. With boards at same distance work to touch red target with index finger only. Therapist to note where touch has been made. Once patient performs task accurately on 75% in one session progress to core protocol progression.

4. TASK 2: CORE PROGRESSIONS

Peg Targeting

Position: patient to be seated as for task 1 at table**.** Patient should be able to pick up peg using opposition grip with thumb, index and middle fingers.

The primary task is to target peg/s onto the underside of the shelf at eye level (40cm), and return hands to start position. The top of the peg has Velcro attached, and the underside has Velcro targets at widening distances underneath**.**

The protocol starts with the primary task. Use block and random practice with feedback as described on page 3: when patient performs the task accurately on at least 75% of single randomised trials in a practice session, progress to the next protocol.

Task 2
Protocol 1
Start position hand/s flat on table.
Attach peg 2x4cm to underside of shelf, targets 20cm apart/10cm R and/or L from midline (at red line). Once patient able to do this accurately on 75% of single randomised trials in one session, progress to wider placement – 50cm /25cm (yellow line) then 80cm/40cm (green line). On each width, progress when patient performs accurately on 75% of single randomised trials in one session. When able to accurately target pegs at the widest width on 75% of single randomised trials in one session, progress to **Task 2 Protocol 2.**

Task 2
Protocol 2
Start position hand/s flat on table.
Patient should attach and detach the peg at 20cm apart/10cm R and/or L of midline (under red line) return peg to table and reposition on table. Patient should attempt to stand peg upright but will not fail if placed lengthways. Once able to perform task accurately on 75% of single randomised trials in one session, widen to 50cm (yellow line) then 80cm (green line), progressing to **Task 2 Protocol 3**, once accurately performing on 75% of single randomised trials in one session.

Task 2
Protocol 3
Start position hand/s flat on table.
Repeat protocol 1 with doweling peg of 6mm diameter, progressing to **Task 2 Protocol 4**, once accurately performing on 75% of single randomised trials in one session.

Task 2
Protocol 4
Start position hand/s flat on table.
Hang plastic cups (10 cm high x 7.5 cm in diameter) onto hooks at 40cm wide/20cm to R and/or L of midline and 14 cm from front of shelf on underside of shelf. Once able to perform this accurately on 75% of single randomised trials in one session repeat process with china cups. (7.5 cm high x 7.5 cm in diameter). Once able to perform with china cups accurately on 75% of single

randomised trials in one session, hang keys on the hooks. Once able to perform this accurately on 75% of single randomised trials progress to **Task 2 Protocol 5**

Task 2
Protocol 5
Start position hand/s flat on table.
Stick small piece of felt onto Velcro on underside of shelf at 20cm(red line), 50cm (yellow line) and 80cm, (green line) progressing to wider widths once patient can perform accurately on 75% of single randomised trials on one session at that width. Once accurate at the widest width on 75% of single randomised trials in a session, progress to **Task 2 Protocol 6.**

Task 2
Protocol 6
Start position hand/s flat on table.
Fasten clothes pegs onto string tied between two hooks 40 cm apart, 14 cm from front of shelf on underside of shelf. Once patient able to perform at shoulder width accurately on 75% of single randomised trials of one session, progress to vary width along string. Once performing accurately on 75% of single randomised trials along width of string, Progress to **Task 2 Protocol 7.**

Task 2
Protocol 7
Start position hand/s flat on table.
Using weighted cylinders (24 cm high, 6.5 cm diameter), touch underside of shelf at 20cm (red line.) Once performing this accurately on 75% of single randomised trials in one session, widen to 50cm (yellow line) then 80cm, (green line) progressing to wider width once patient able to perform accurately on 75% of single randomised trials of one session at that width. Progress by increasing cylinder weight and repeat protocol as above until performing accurately at each width with the heavier weight on 75% of single randomised trials at that width.

One completed all activities; ask patient for his or her ideas about what they feel is relevant to practice. Activities such as screwing a nut onto a screw on the underside of the shelf, targeting with a pen to accurately make marks on a target stuck to the shelf etc may be suggestions. Random practice of the different tasks at different widths would be an appropriate practice session for those patients skilled in all tasks and at the end of the protocol.

5. TASK 2: MODIFIED PROGRESSION

Start with Protocol L1, which is the easiest and progress from there through the other protocols. Use block and random practice with feedback as described on page 3: when patient performs the task accurately on at least 75% of single randomised trials in a practice session, progress to the next protocol.

Task 2
Protocol M1
Patient positioned with forearms supported on table, pronated position, passively if necessary. Beanbags (15 cm x 12 cm) placed on table on lateral side of hand. Patient to supinate and to try to depress beanbag with back of hand. Once patient performing this for 75% of single randomised trials in one session progress to **Task 2, Protocol M2**

Task 2
Protocol M2
Patient positioned with forearms supported on table, supinated position, passively if necessary. Doweling of 2cm diameter and 21 cm long, coloured at one end. Therapist to assist patient to grasp doweling in supinated position, but start task with hands pronated. Patient to attempt to supinate to touch table with coloured end of doweling, and return to pronated position. Once patient able to do this accurately on 75% of single randomised trials in one session, progress to **Task 2, Protocol M3**.

Task 2
Protocol M3
Patient positioned with forearms supported on table, supinated position, passively if necessary. Grasping doweling in hand as above, with help from therapist if required, start with hands in pronated position. Patient to attempt to place doweling upright on theraputty making circular mark, and return to pronated position. Putty placed 30cm from front edge of table/10cm to R or L of midline (yellow circle 20/30). Once able to do this accurately on 75% of single randomised trials in a session increase width to 20 cm either side of midline (blue circle 40/30). Once performing accurately on 75% of single randomised trials in one session, progress to **Task 2, Protocol M4**.

Task 2
Protocol M4
Start position, forearms resting on table, elbows supported, hands pronated. Shelf 20cm high. Patient to flex elbow and supinate to touch underside of shelf with palm of hand at 20cm (red line). Talc may be used on fingers to mark shelf and assess accuracy. Once performing this accurately on 75% of single randomised trials in one session progress to 50 cm (yellow line) then 80 cm wide (green line). Once performing this accurately on 75% of single randomised trials in one session, at the widest width, progress to **Task 2, protocol** M**5**

Task 2
Protocol M5
Start position, forearms resting on table, elbows supported, hands pronated. Repeat L4 by grasping large cylinder, 20 cm high, and 6 cm in diameter in hand (large Smarty Tube with Velcro on top). Shelf at 40 cm height so patient can reach with elbows supported on table, but if able encourages lifting entire arm off table. Stick tube onto Velcro at 20cm mark, (red line). Progressions as for L4.

Once performing this accurately on 75% of single randomised trials in one session, at the widest width, progress to **Task 2, protocol M6**

Task 2
Protocol M6
Start position, forearms resting on table, elbows supported, hands pronated. Repeat L4 with hollow plastic cylinder (9 cm high and 3 cm in diameter). Shelf at eye level. Progressions as for L3. Once performing accurately as specified, progress to **Task 2, protocol M7**

Task 2
Protocol M7
Start position, forearms resting on table, elbows supported, hands pronated. Using doweling from L2 and 3, in pinch grip, **not** palmar grasp and in mid prone, patient to touch underside of shelf to touch with flat end of doweling at 20cm (red line) 50cm (yellow line) and 80 cm (green line) wide progressing to wider width once patient able to perform accurately on 75% of single randomised trials in one practice session. Progress to core protocol progression.

6. TASK 3: CORE PROGRESSION

Placing objects onto shelf

Start position: forearms supported on table, hands flat. All activities in this section are fundamentally the same – grasp object on the tabletop and move onto the shelf. For each object follow the same protocol.

Use block and random practice with feedback as described on page 3: when patient performs the task accurately on at least 75% of single randomised trials in a practice session, progress to the next protocol.

Task 3
Protocol
Start position: forearms supported on table, hands flat.
The shelf is to be positioned at 10cm from tabletop height to start. The patient is required to grasp object and move from tabletop to place the object onto marks on the shelf at 20cm apart/10cm R and/or L of midline (red line). Once patient is able to position object accurately on 75% of single randomised trials in one session, widen target position to 50cm (yellow line) then 80cm (green line). Once accurately placing at widest width on 75% of single randomised trials of one session, raise shelf to 20cm and repeat process with same object and to the same positions. Once performing accurately on 75% of single randomised trials, progress to next object on list.

Task 3
Objects
Start with hierarchy, but within each session give patient a choice from the available objects, or allow them to suggest their own object with which they wish to practice. Include the object for several trials over several sessions until they perform accurately with the object.

1. 7.5 cm wooden cube
2. Smaller wooden cube– 2.6cm
3. Sponge (rectangular – 7.5 cm x 13 cm)
4. Smaller oblong block (6 x 3 x 1 cm)
5. Ferrule (5 x 4 cm at widest part)
6. Small cylinder (yoghurt drink tub) (10 x 3.5 cm)
7. Teacup – grip with handle
8. Teacup with water - grip with handle
9. Teacup – grasp with cylindrical grasp
10. Teacup with water - grasp with cylindrical grasp
11. Walnut
12. Pegs (plastic, spring hinge, 9.5 cm x 1cm x 1.5cm)
13. Cotton wool ball
14. Polystyrene cup – do not deform (8.5cm x 7cm at widest part)
15. Polystyrene cup with water – half full
16. Polystyrene cup with water – almost full
17. Pencil
18. Key

19. Golf tees
20. Allan keys
21. Marble
22. Coin (2 pence piece)
23. Matches
24. Paperclip
25. Ball bearings (0.5 cm in diameter)

Once patient is performing all these tasks accurately on 75% of single randomised trials in one session, continue to practice by switching randomly between objects and widths.

7. TASK 3: MODIFIED PROTOCOL

Start Position: forearms flat on table.

Use block and random practice with feedback as described on page 3: when patient performs the task accurately on at least 75% of single randomised trials in a practice session, progress to the next protocol.

Task3
Protocol M1
Start Position: forearms flat on table. Patient to slide hand/s forward to touch beanbag/s on table positioned 20cm apart and 40 cm from front of table (blue square marked 20/40). Therapist should position the beanbag so the patient must reach to touch. Once able to touch accurately on 75% of single randomised trials of one session increase width to 40cm, (blue square marked 40/40) then 80cm (blue square marked 80/40) until accurate on 75% of single randomised trials in one session. Once able to do this accurately on 75% of single randomised trials in one session progress to **Task 3 protocol M2**

Task3
Protocol M2
Start Position: forearms flat on table. Beanbag in start position as before. Patient to reach and place hand on top of beanbag. Follow protocol for progression as above. Once able to perform progressions accurately on 75% of single randomised trials in one session progress to **Task 3 Protocol M3**

Task3
Protocol M3
Start Position: forearms flat on table. Therapist to place hollow plastic cylinder ((9 cm high x 3 cm diameter) in patient's hand if unable to grasp actively. If able to grasp, therapist to encourage simultaneous opening of hand aperture and reach. Patient to lift hollow plastic cylinder and place in front of beanbag. Follow protocol for widths as 1. Once able to do this accurately on 75% of single randomised trials in one session progress to **Task 3 Protocol M4**

Task3
Protocol L4
Start Position: forearms flat on table. Patient to grasp and lift hollow plastic cylinder onto beanbag. Progress widths as protocol 1. Once able to perform progressions accurately on 75% of single randomised trials in one session progress to **Task 3 Protocol L5**

Task3
Protocol M5
Start Position: forearms flat on table. Patient to grasp and lift hollow plastic cylinder over beanbag, progressing as Protocol 1 but continuing until patient is able to release container independently on 75% of single randomised trials. Once able to perform progressions accurately on 75% of single randomised trials in one session progress to **Task 3 Protocol M6**

Task3
Protocol M6
Start Position: forearms flat on table. Patient to grasp and move large cylinder (Smartie tube 20 cm high, 6 cm diameter) forward to mark at 20cm width, 40cm from front of table (blue square marked 20/40). Progress widths as protocol 1. Once able to perform progressions accurately on 75% of single randomised trials in one session progress to **Task 3 protocol M7**

Task3
Protocol M7
Start Position: forearms flat on table. Patient to grasp and move large cylinder (Smartie tube, 20 cm high, 6 cm diameter) onto shelf at 10cm height, initially at 20cm width, 10cm to R or L of midline (red line). Increase width to 50cm (yellow line) and 80cm, (green line), progressing to wider width once patient performs task accurately on 75% of single randomised trials. Once performing at widest width on 75% of single randomised trials in one session progress to **Task 3 Protocol M8**.

Task3
Protocol M8
Start Position: forearms flat on table. Patient to grasp and move glass onto shelf at 10cm height, at 20cm width, (red line) Progress widths as protocol 7. Once accurate on 75% of single randomised trials in one session, progress to core progression protocol.

8. TASK 4: CORE PROGRESSION

Glass to Mouth

Start position: hands flat on the table. The object/s to be taken to the mouth should be placed on the table in front of the patient, approximately 20cm apart and returned to same position.

Use block and random practice with feedback as described on page 3: when patient performs the task accurately on at least 75% of single randomised trials in a practice session, progress to the next protocol.

Task 4
Protocol 1
Start position: hands flat on the table. Patient to grasp a glass, take it to the mouth and return to starting position. Once able to do this accurately on 75% of single randomised trials in one session, progress to **Task 4 protocol 2**

Task 4
Protocol 2
Start position: hands flat on the table. Patient to grip a plastic cup (10 cm high x 7.5 cm in diameter) by the handle and take to the mouth and return to table.
Once able to do this accurately on 75% of single randomised trials in one session progress to **Task 4 Protocol 3**

Task 4
Protocol 3
Start position: hands flat on the table. Plastic cup filled with water to ¾ full. Patient to take to mouth and return to table without spilling. Once able to do this accurately on 75% of single randomised trials progress to **Task 4 protocol 4**

Task 4
Protocol 4
Start position: hands flat on the table. Patient to grasp a polystyrene cup (8.5cm high x 7cm diameter at widest part) that is half full and take to the mouth and return to the table. Once able to do this accurately on 75% of single randomised trials in one session, progress to **Task 4 Protocol 5**

Task 4
Protocol 5
Start position: hands flat on the table. Patient to grasp an empty polystyrene cup and take to the mouth and return to start position. Do not allow the cup to become deformed. Once able to do this accurately on 75% of single randomised trials in one session, progress to **Task 4 Protocol 6**

Task 4
Protocol 6
Start position: hands flat on the table. Patient to take a piece of theraputty from the table to the mouth by grasping between finger and thumb, and return to start position. Once able to do this accurately on 75% of single randomised trials in one session progress to **Task 4 Protocol 7**

Task 4
Protocol 7
Start position: hands flat on the table. Patient to take a jellybean from the table to the mouth by grasping between finger and thumb, and return to table. Once able to do this accurately, on 75% of single randomised trials in one session, progress to **Task 4 protocol 8.**

Task 4
Protocol 8
Start position: hands flat on the table. Patient to pick up fork from table, hold by stabilising handle against palm, take to mouth and return to table. Once able to do this accurately on 75% of single randomised trials in one session, progress to **Task 4 protocol 9**

Task 4
Protocol 9
Start position: hands flat on the table. Patient to jab theraputty with fork with above hold, take to mouth and return to table. Once able to do this accurately on 75% of single randomised trials in one session, progress to **Task 4 protocol 10.**

Task 4
Protocol 10
Start position: hands flat on the table. Bowl of dried beans on table, patient to scoop beans with spoon and take to mouth. Return spoon to table. Once able to do this accurately and without spilling, on 75% of single randomised trials in one session, continue random practice of tasks, varying start position. Ask patient for their suggestions about what they would like to practice doing, along these lines – bean to mouth, smartie to mouth, water on spoon etc the task must involve moving object to mouth.

9. TASK 4: MODIFIED PROGRESSION

Start position with hands flat on table.

Use block and random practice with feedback as described on page 3: when patient performs the task accurately on at least 75% of single randomised trials in a practice session, progress to the next protocol.

Task 4
Protocol M1
Start position: hands flat on the table. Therapist to place hollow plastic cylinder (9 cm high x 3 cm in diameter) in patient's hand, ask patient to grasp as actively as possible. Start in pronated position. Supinate to midline. Once able to do this accurately on 75% of single randomised trials in one session, progress to **Task 4, Protocol M2.**

Task 4
Protocol M2
Start position: hands flat on the table. As for protocol 1, but in addition, patient to lift ulnar side of hand off table flexing elbow as far towards mouth as possible. Once able to lift hand off table, whilst holding cylinder, on 75% of single randomised trials in one session, progress to **Task 4, Protocol M3.**

Task 4
Protocol M3
Start position: hands flat on the table. Maintaining mid prone position, patient to open hand and reach towards glass 10 cm either side of midline and 40cm from front edge of table (blue square marked 20/40). Hand may slide along table. Once able to grasp and release glass accurately on 75% of single randomised trials in one session, progress to **Task 4, protocol M4.**

Task 4
Protocol M4
Start position: hands flat on the table. Patient to take a stack of 10 plastic tumblers (each 11cm high x 7 cm diameter) towards mouth to touch either side of chin. Once able to do this accurately on 75% of single randomised trials in one session, progress by reducing number of tumblers in stack by 2. Once able to do this accurately on 75% of single randomised trials in one session continue reducing stack by 2 until patient able to take single cup to mouth. Once accurate on 75% of single randomised trials, progress to core protocol

Appendix 12

Task Randomisation Sheet

3	3	3	3	3	4	1	2	3	1
2	3	3	3	2	2	3	1	1	2
4	1	1	2	1	4	4	3	1	2
1	4	3	3	2	4	1	4	1	1
1	1	1	3	2	2	4	1	2	1

3	2	3	3	1	4	2	2	2	2
3	4	3	2	3	1	2	4	3	3
4	3	4	4	4	1	3	1	1	3
1	2	4	1	1	1	3	1	4	2
1	4	2	2	2	4	4	2	1	2

Appendix 13

Data Appendix

Table 1. Summary of measures for whole sample at T1 and follow-up assessments; number, range, mean (standard deviation), distributions and outliers

Measures	*Possible score*	*Time*	*n*	*Mean (sd)*	*Range*	*Skewness*	*z Skewness*	*Kurtosis*	*z Kurtosis*	*Outliers*	
										low	*high*
ARAT	Min=0	T1	106	15.8 (16.3)	0.0-54.0	0.76	3.20	-0.70	-1.49	0	0
	Max=57	T3	97	30.9 (19.8)	0.0-57.0	-0.26	-1.06	-1.27	-2.70	0	0
		T3	85	32.9 (18.6)	0.0-57.0	-0.39	-1.49	-1.37	-2.90	0	0
RMA	Min=0	T1	106	3.8 (3.2)	0.0-10.0	-0.42	1.77	-1.04	-2.20	0	0
	Max=15	T3	97	6.2 (3.7)	0.0-15.0	0.03	0.11	-0.70	-1.49	0	0
		T3	85	6.6 (4.1)	0.0-15.0	-0.09	-0.33	-0.92	-1.91	0	0
9HPT	Pegs/	T1	106	0.03 (0.07)	0.0-0.42	2.91	12.37*	9.18	19.5*	0	2
	second	T3	97	0.12 (0.15)	0.0-0.70	1.48	6.00*	1.77	3.62*	0	2
		T3	85	0.15 (0.17)	0.0-0.63	0.99	3.78*	-0.17	0.36	0	0
MBI	Min=0	T1	106	61.9 (24.6)	12.0-98.0	-0.28	-1.17	-1.05	-1.61	2	0
	Max=100	T3	97	84.0 (17.6)	19.0-100.0	-1.54	-6.88*	1.94	4.13*	2	0
		T3	85	86.0 (18.7)	15.0-100.0	-2.17	-8.30*	4.49	9.55*	2	0
NHP	Min=0	T1	106	177.0 (119)	0.0-460.0	0.47	1.99	-0.68	-1.44	0	0
	Max=600	T3	97	116.0 (94)	0.0-414.0	0.94	3.85*	0.28	0.56	0	0
		T3	85	108.0 (102)	0.0-432.0	1.32	5.07*	1.14	2.42	0	0
Anxiety	Min=0	T1	106	6.3 (4.1)	0.0-19.0	0.52	2.21	-0.08	-0.17	0	0
	Max=21	T3	97	5.4 (4.0)	0.0-16.0	0.64	2.61	-0.40	-0.83	0	0
		T3	85	5.1 (4.1)	0.0-17.0	0.72	2.74	-0.23	-0.48	0	0
Depression	Min=0	T1	106	6.4 (3.4)	0.0-14.0	0.31	1.31	-0.73	-1.52	0	0
	Max=21	T3	97	5.8 (3.4)	0.0-15.0	0.52	2.21	-0.26	-0.54	0	0
		T3	85	5.0 (3.5)	0.0-17.0	0.81	3.11	0.37	0.77	0	1
NSA	Min=0	T1	106	68.1(17.3)	0.0-83.0	-1.90	-9.40*	3.69	6.94*	2	0
	Max=84	T3	97	69.4(18.5)	0.0-84.0	-2.42	-11.45*	5.68	10.72*	3	0
		T3	85	73.7(12.3)	2.0-84.0	-3.37	-16.84*	15.70	29.62*	1	0

* z skewness >3.29; p>0.001. ARAT denotes Action Research Arm Test;RMA denotes Rivermead Motor Assessment Scale; 9HPT denotes Nine Hole PegTest; ADL denotes Activities of Daily Living; MBI denotes Modified Barthel Index; NHP denotes Nottingham Health Profile; HADS denotes Hospital Anxiety and Depression Scale;NSA denotes Nottingham Health Profile; ITT denotes intention to treat analysis

Table 2. Summary of change scores for ARAT, RMA and 9HPT for whole sample T1 to T2, T1 to T3; number, range, mean (standard deviation), distributions and outliers.

Measures	*Possible score*	*Time (weeks)*	*n*	*Time (weeks)*	*Mean (sd)*	*Range*	*Skewness*	*z Skewness*	*Kurtosis*	*z kurtosis*	*Outliers*	
											low	*high*
ARAT	Min=0	0-6	97	0-6	14.8 (12.9)	-4.0-52.0	0.64	2.59	0.04	0.06	0	0
	Max=57	0-18	85	0-18	16.3 (14.0)	-16.0-57.0	0.33	1.26	-0.38	-0.73	0	0
RMA	Min=0	0-6	97	0-6	2.3 (2.5)	-2.0-8.0	0.64	2.19	-0.78	1.63	0	0
	Max=15	0-18	85	0-18	2.6 (3.0)	-5.0-9.0	0.63	2.24	-0.19	0.37	0	0
9HPT	Pegs/	0-6	97	0-6	0.09 (0.13)	-0.06-0.62	1.61	6.44*	2.53	5.16*	0	1
	second	0-18	85	0-18	0.12 (0.14)	-0.06-053	0.97	4.51*	0.63	1.21	0	0

* z skewness >3.29; p>0.001 ARAT denotes Action Research Arm Test;RMA denotes Rivermead Motor Assessment Scale; 9HPT denotes Nine Hole Peg Test

Table 3. Summary of missing data: Percentage missing, reasons and plan

MEASURES with missing data	**Percentage missing**	**Reasons (N)**	**Plan**
DEMOGRAPHIC			
Days to hospital discharge	11.3%	Data unavailable (12)	Nothing
Days from stroke to start of intervention	0.9%	Administrative error (1)	Nothing
UPPER LIMB MEASURES			
ARAT T1	0%		
ARAT T3	8.5%	Withdrawal (9)	Complete case analysis and ITT using imputed data
ARAT T3	19.8%	Withdrawal (21)	Complete case analysis and ITT using imputed data
Nine Hole Peg Test T1	0%		
Nine hole peg test T3	9.4%	Withdrawal (9) Patient unable because of pain (1)	Complete case analysis and ITT using imputed data
Nine hole peg test T3	19.8%	Withdrawal (21)	Complete case analysis and ITT using imputed data
RMA T1	0%		
RMA T3	8.5%	Withdrawal (9)	Complete case analysis and ITT using imputed data

NB. Withdrawals included loss to follow-up

Table 3 **(cont).** Summary of missing data: Percentage missing, reasons and plan

MEASURES with missing data	**Percentage missing n=106**	**Reasons**	**Plan**
RMA T3	19.8%	Withdrawal (21)	Complete case analysis and ITT using imputed data
Nottingham Sensory Assessment Total T1	23.6%	Patients unable to complete items (25)	Sub-analysis only
Nottingham Sensory Assessment Total T3	21.7%	Withdrawal (9) Patients unable to complete items (14)	Sub-analysis only
Nottingham Sensory Assessment Total T3	29.2%	Withdrawal (21) Patients unable to complete items (10)	Sub-analysis only
Nottingham Sensory Assessment Tactile Sub-Score T1	18%	Patients unable to complete items (20)	Sub-analysis only
Nottingham Sensory Assessment Tactile Sub-Score T2	12.3%	Withdrawal (9) Unable to complete items (4)	Sub-analysis only
Nottingham Sensory Assessment Tactile Sub-Score Score T3	26.4%	Withdrawal (21) Unable to complete items (7)	Omit
Nottingham Sensory Assessment Stereognosis Sub-Score T1	11.3%	Unable to complete items (12)	Sub-analysis only
Nottingham Sensory Assessment Stereognosis Sub-Score T2	13.2%	Withdrawal (9) Unable to complete items (5)	Sub-analysis only
Nottingham Sensory Assessment Stereognosis Sub-Score T3	22.6%	Withdrawal (21) Unable to complete items (3)	Sub-analysis only
Nottingham Sensory Assessment Proprioception Sub-Score T1	16%	Unable to complete items (17)	Sub-analysis only
Nottingham Sensory Assessment Proprioception Sub-Score T2	19.8%	Withdrawal (9) Unable to complete (12).	Sub-analysis
Nottingham Sensory Assessment Proprioception Score T3	24.5%	Withdrawal (21) Unable to complete (5).	Sub-analysis

NB. Withdrawals included loss to follow-up

Table 3 (cont). Summary of missing data: Percentage missing, reasons and plan

OTHER MEASURES	Percentage missing n=106	Reasons	Plan
Modified Barthel Index T1	0.9%	Administrative error (1)	Complete case analysis and ITT using imputed data
Modified Barthel Index T3 (Total Score)	8.5%	Withdrawal (9)	Complete case analysis and ITT using imputed data
Modified Barthel Index T3(Total Score)	19.8%	Withdrawal (21)	Complete case analysis and ITT using imputed data
Nottingham Health Profile T1	0.9%	Patient upset (1)	Complete case analysis and ITT using imputed data
Nottingham Health Profile T3 (Total Score)	8.5%	Withdrawal (9)	Complete case analysis and ITT using imputed data
Nottingham Health Profile T3 (Total Score)	19.8%	Withdrawal (21)	Complete case analysis and ITT using imputed data
HADS Anxiety T1	0.9%	Patient unable to complete (1)	Complete case analysis and ITT using imputed data
HADS Anxiety T3	8.5%	Withdrawal (9)	Complete case analysis and ITT using imputed data
HADS Anxiety T3	19.8%	Withdrawal (9)	Complete case analysis and ITT using imputed data
HADS Depression T1	0.9%	Patient unable to complete (1)	Complete case analysis and ITT using imputed data
HADS Depression T3	8.5%	Withdrawal (9)	Complete case analysis and ITT using imputed data
HADS Depression T3	19.8%	Withdrawal (9)	Complete case analysis and ITT using imputed data

NB. Withdrawals included loss to follow-up

Table 4 (a). Comparison of completers and non-completers: Mann-Whitney U Tests

	Withdrew before end of Intervention (n=9)	**Completed Intervention (n=97)**	**Mann Whitney U Test**	
T1 Measure	**Median (Range)**	**Median (Range)**	**U**	**p**
Age	66 (59 -94)	69 (36 – 91)	421.0	0.86
Days to start of intervention	23 (15 – 30)	23 (12 – 30)	362.0	0.75
MAS (min=0, max=18)	4.5 (0.0 -13.0)	4.0 (0.0 -14.0)	361.0	0.75
ARAT (min=0, max=57)	4 (0 – 53)	2 (0 – 56)	405.0	0.72
RMA (min=0, max=15)	3 (0 – 10)	4 (0 – 10)	392.0	0.61
9HPT (Pegs/second)	0.00 (0.00 - 0.14)	0.00 (0.00 - 0.42)	412.5	0.72
MBI (min=0, max=100)	62 (20- 87)	67 (12- 98)	364.0	0.41
NHP (min=600, max=0)	162.7 (34.8 - 428.5)	163.9 (0.0 - 460.6)	430.0	0.94
HADS: Anxiety (min=0, max=21)	6 (0 – 19)	6 (0- 16)	403.0	0.74
HADS: Depression (min=0, max=21)	6 (3- 14)	6 (0- 13)	390.0	0.63
NSA (UL) (min=0, max=84)	63 (45 – 75)	77 (0 -84)	317.0	0.17

Table 4 (b) Comparison of completers and non-completers: Chi-square tests

Characteristic	*Withdrew before end of Intervention**(n=9)***	*Completed Intervention **(n=97)***	*N*	*df*	χ^2	*p*
Group (Unilateral/Bilateral)	4/5	46/51	106	1	Fishers	1.00
Gender (Male/Female)	6/3	55/42	106	1	Fishers	0.73
Side of Hemiplegia (R/L)	3/6	49/48	106	1	Fishers	0.48
Handedness (R/L)	7/2	90/7	106	1	Fishers	0.17
Stroke Type (Ischaemic/Haemorrhagic)	8/1	84/13	106	1	Fishers	1.00

ARAT denoted Action Research Arm Test;RMA denotes Rivermead Motor Assessment Scale; 9HPT denotes Nine Hole Peg Test; ADL denotes Activities of Daily Living; MBI denotes Modified Barthel Index; NHP denotes Nottingham Health Profile; HADS denotes Hospital Anxiety and Depression Scale; NSA denotes Nottingham Health Profile

Table 5 (a). Comparison of patients who were discharged home and those who remained in hospital during the intervention: Chi Square Tests

Characteristic	BT Group patients discharged during intervention (n=19)	UT Group patients discharged during intervention (n=27)	n	df	χ^2	p
Gender (Male/Female)	12/7	16/11	46	1	0.07	0.79
Side of Hemiplegia (R/L)	11/8	11/16	46	1	1.32	0.25
Handedness (R/L)	18/1	23/4	46	1	1.05	0.31
Stroke Type (Ischaemic/Haemorrhagic)	17/2	24/3	46	1	0.00	0.95

Table 5 (b). Comparison of patients who were discharged home and those who remained in hospital during the intervention: Median, range, Mann Whitney U Tests

T1 Measures	*BT Group patients discharged during intervention **(n=19)*** Median (Range)	*UT Group patients discharged during intervention **(n=27)*** Median (Range)	*Mann Whitney U Test* *U*	*p*
Age	72 (36-83)	67 (47-85)	215.5	0.36
Days to start of intervention	21 (14-33)	23 (12-31)	233.0	0.60
UL Screening Tool : MAS (min=0, max=18)	11 (0-14)	9 (0-12)	196.5	0.18
UL Activity: ARAT (min=0, max=57)	25 (0-45)	27 (0-53)	237.0	0.66
Impairment: RMA (min=0, max=15)	8 (0-10)	6 (0-10)	229.5	0.54
Dexterity: 9HPT (Pegs/second)	0.02 (0.00-0.42)	0.00 (0.00 -0.30)	249.5	0.86
Independence in ADL: MBI (min=0, max=100)	83 (43-98)	81 (20 -81)	222.5	0.45
Quality of Life: NHP (min=600, max=0)	130 (23-397)	133 (10 – 415)	231.0	0.57

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment Scale; 9HPT denotes Nine Hole Peg Test; ADL denotes Activities of Daily Living; MBI denotes Modified Barthel Index; NHP denotes Nottingham Health Profile; HADS denotes Hospital Anxiety and Depression Scale; NSA denotes Nottingham Health Profile

Table 6. Post Hoc Bonferroni pairwise comparisons for main effect of time on total ARAT scores

Comparison	Mean Difference	Std. Error	p	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
T1:T2	-14.690	1.270	<0.001*	-17.793	-11.587
T1:T3	-16.482	1.514	<0.001*	-20.181	-12.782
T2:T3	-1.792	0.787	0.08	-3.715	0.131

*Significant at $p \leq 0.05$

Table 7. Post Hoc Bonferroni pairwise comparisons for main effect of time on ARAT grasp scores

Comparison	Mean Difference	Std. Error	p	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
T1:T2	-4.411	0.509	<0.001*	-5.656	-3.167
T1:T3	-4.688	0.562	<0.001*	-6.062	-3.314
T2:T3	-0.276	0.362	1.000	-1.162	0.610

*Significant at $p \leq 0.05$

Table 8. Post Hoc Bonferroni pairwise comparisons for main effect of time on ARAT grip scores

Comparison	Mean Difference	Std. Error	p	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
T1:T2	-3.215	0.312	<0.001*	-3.978	-2.452
T1:T3	-3.319	0.344	<0.001*	-4.161	-2.478
T2:T3	-0.104	0.187	1.000	-0.563	0.354

*Significant at $p \leq 0.05$

Table 9. Post Hoc Bonferroni pairwise comparisons for main effect of time on ARAT gross scores

Comparison	Mean Difference	Std. Error	p	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
T1:T2	-1.758	0.240	<0.001*	-2.344	-1.172
T1:T3	-1.700	0.246	<0.001*	-2.302	-1.098
T2:T3	5.857	0.177	1.000	-0.374	0.491

*Significant at $p \leq 0.05$

Table 10. Post Hoc Bonferroni pairwise comparisons for main effect of time on ARAT pinch scores

Comparison	Mean Difference	Std. Error	p.	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
T1:T2	-5.193	0.586	<0.001*	-6.626	-3.759
T1:T3	-6.777	0.675	<0.001*	-8.428	-5.127
T2:T3	-1.584	0.427	<0.001*	-2.629	-0.540

*Significant at $p \leq 0.05$

Table 11. Post Hoc Bonferroni pairwise comparisons for main effect of time on 9HPT scores

Comparison	Mean Difference	Std. Error	p	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
T1:T2	-0.170	0.266	<0.001*	-2.929	-1.629
T1:T3	-2.575	0.330	<0.001*	-3.383	-1.768
T2:T3	-0.296	0.240	0.664	-0.884	2.929

*Significant at $p \leq 0.05$

Table 12. Post Hoc Bonferroni pairwise comparisons for main effect of time on RMA scores

Comparison	Mean Difference	Std. Error	p	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
T1:T2	-.159	0.021	<0.001*	-0.210	-0.108
T1:T3	-.208	0.021	<0.001*	-0.260	-0.155
T2:T3	-4.874	0.014	<0.01*	-8.249	-1.499

*Significant at $p \leq 0.05$

Table 13. Post Hoc Bonferroni pairwise comparisons for main effect of time on MBI scores

Comparison	Mean Difference	Std. Error	p	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
T1:T2	-20.466	1.701	<0.001*	-24.621	-16.310
T1:T3	-21.531	2.209	<0.001*	-26.930	-16.133
T2:T3	-1.066	1.285	1.000	-4.206	2.075

*Significant at $p \leq 0.05$

Table 14. Post Hoc Bonferroni pairwise comparisons for main effect of ARAT Level: Change in total ARAT between T1 and T2

Comparison		Mean Difference	Std. Error	Sig.	95% Confidence Interval	
ARAT level	ARAT level				Lower Bound	Upper Bound
1	2	-10.3203	2.89324	<0.01*	-17.3785	-3.2621
1	3	-3.4919	3.31485	0.885	-11.5787	4.5948
2	3	6.8284	3.26255	0.118	-1.1308	14.7875

*denotes significance at $p<0.05$

Table 15. Post Hoc Bonferroni pairwise comparisons for main effect of ARAT Level: Change in RMA between T1 and T2

Comparison		Mean Difference	Std. Error	Sig.	95% Confidence Interval	
ARAT level					Lower Bound	Upper Bound
1	2	-.9289	.58125	0.042	-2.3466	.4888
1	3	-.1006	.67008	1.000	-1.7350	1.5337
2	3	.8283	.65632	0.630	-.7725	2.4291

*denotes significance at p<0.05

Table 16. Post Hoc Bonferroni pairwise comparisons for main effect of ARAT Level: Change in 9HPT between T1 and T2

Comparison ARAT Level		Mean Difference	Std. Error	Sig.	95% Confidence Interval for difference	
ARAT level					Lower Bound	Upper Bound
1	2	-.08592	.025225	<0.01	-.14746	-.02438
1	3	-.18668	.028901	<0.001	-.25718	-.11617
2	3	-.10075	.028445	<0.01	-.17015	-.03136

* denotes significance at p<0.05

Table 17. Post Hoc Bonferroni pairwise comparisons for main effect of ARAT Level: Change in total ARAT between T1 and T3

Comparison		Mean Difference	Std. Error	Sig.	95% Confidence Interval	
ARAT level					Lower Bound	Upper Bound
1	2	-10.7303	3.38215	<0.01*	-19.0031	-2.4575
1	3	-4.5333	3.76331	0.696	-13.7385	4.6718
2	3	6.1970	3.69023	0.291	-2.8294	15.2234

*Significant at p≤0.05

Table 18. Post Hoc Bonferroni pairwise comparisons for main effect of ARAT Level: Change in RMA between T1 and T3

Comparison		Mean Difference	Std. Error	Sig.	95% Confidence Interval	
ARAT level	ARAT level				Lower Bound	Upper Bound
1	2	-.4212	.77863	1.000	-2.3258	1.4833
1	3	-.0879	.86638	1.000	-2.2071	2.0313
2	3	.3333	.84956	1.000	-1.7447	2.4114

Table 19. Post Hoc Bonferroni pairwise comparisons for main effect of ARAT level: Change in 9HPT between T1 and T3

		Mean Difference	Std. Error	Sig.	95% Confidence Interval for difference	
ARAT level	ARAT level				Lower Bound	Upper Bound
1	2	-.09457	.030229	<0.01	-.16851	-.02063
1	3	-.19497	.033636	.000	-.27724	-.11270
2	3	-.10040	.032983	.010	-.18107	-.01972

*Significant at p≤0.05

Table 20. Post Hoc Bonferroni pairwise comparisons for main effect of side and dominance on the RMA between T1 and T3

		Mean Difference	Std. Error	Sig.	95% Confidence Interval	
SIDE DOMINANCE	SIDE DOMINANCE				Lower Bound	Upper Bound
Left hemiplegia dominant side affected	Left hemiplegia non-dominant side affected	-0.0064	1.54979	1.000	-4.0718	4.0590
Left hemiplegia dominant side affected	Right t hemiplegia dominant side affected	-0.9868	1.55168	0.920	-5.0572	3.0835
Left hemiplegia dominant side affected	Right hemiplegia non-dominant side affected	3.0000	2.08730	0.480	-2.4754	8.4754
Left hemiplegia non-dominant side affected	Right hemiplegia dominant side affected	-0.9804	.67285	0.468	-2.7454	.7846
Left hemiplegia non-dominant side affected	Right hemiplegia non-dominant side affected	3.0064	1.54979	0.220	-1.0590	7.0718
Right hemiplegia dominant side affected	Right hemiplegia non-dominant side affected	3.9868	1.55168	0.052	-0.0835	8.0572

Table 21. Patient characteristics for whole sample at T1: Frequencies, mean (sd), Range

Characteristic	Total
n	106
Gender M/F	61/45
Age (mean, SD)	67.9 (11.7)
Side of hemiplegia R/L	52/54
Handedness prior to stroke R/L	97/9
Dominant side affected Y/N	52/54
Type of Stroke	
TACS	5
PACS	59
LACS	38
POCS	3
Ischaemic/haemorrhagic Stroke	92/14
Days to initial assessment- (mean, SD)	23.1(6.3)
MAS Score (Median, Range)	4 (0,14)

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; PACS denotes anterior circulation stroke; POCS denotes posterior circulation stroke; MAS denotes Motor Assessment Scale

Table 22. Collinearity between T1 measures and participant characteristics for regression

	TACS	LACS	PACS	POCS	ARAT T1	RMA T1	9HPT T1	MBI T1	Anxiety T1	Depression T1
TACS	1.00									
LACS	-0.19	1.00								
PACS	-0.25	-0.86**	1.00							
POCS	-0.34	-0.12	-0.16	1.00						
ARAT T1	-0.23	0.24	-0.12	0.07	1.00					
RMA T1	-0.26	0.21	-0.12	0.12	0.89**	1.00				
9HPT T1	-0.14	0.09	-0.05	0.08	0.70	0.69	1.00			
MBI T1	-0.28	0.31	-0.22	0.14	0.53	0.56	0.31	1.00		
Anxiety T1	0.20	-0.16	0.08	-0.05	-0.20	-0.25	-0.15	-0.28	1.00	
Depression T1	0.03	-0.18	0.16	0.01	-0.24	-0.28	-0.18	-0.45	0.53	1.00
Days to initial assessment	0.05	0.04	-0.02	-0.11	-0.25	-0.35	-0.22	-0.07	0.09	0.11

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; Days denotes days from stroke onset to initial assessment; ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; ** denotes collinearity between independent variables defined by correlation coefficient >0.70

Table 23. Prediction of ARAT at T2: Beta values, t-test statistics and significance levels for independent T1 variables

Step	Predictor Variable	Beta	t	p	95% CI	Adjusted R^2 after each step
1	ARAT T1	0.65	6.23	<0.001*	0.58 to 1.12	
	MBI T1	0.21	2.77	0.01*	0.05 to 0.31	
	9HPT T1	-0.02	-0.26	0.80	-9.63 to 7.43	0.670
	Days to initial assessment	-0.15	-2.43	0.02*	-0.95 to -0.10	
	Anxiety T1	-0.06	-0.86	0.39	-1.05 to 0.41	
	Depression T1	0.03	0.42	0.67	-0.72 to 1.11	
2	ARAT T1	0.64	6.01	<0.001*	0.55 to 1.09	
	MBI T1	0.18	2.26	0.03*	0.02 to 0.29	0.675
	9HPT T1	-0.02	-0.20	0.84	-9.39 to 7.65	
	Days to initial assessment	-0.15	-2.48	0.02*	-0.96 to -0.11	
	Anxiety T1	-0.03	-0.44	0.66	-0.91 to 0.58	
	Depression T1	-0.00	0.04	0.97	-0.91 to 0.95	
	OCSPC					
	TACS	-0.13	-2.10	0.04*	-24.07 to -0.65	
	LACS	0.00	0.04	0.97	-5.29 to 5.51	
	POCS	-0.01	-0.18	0.86	-19.00 to 15.90	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index.* denotes significance at $p \leq 0.05$

Table 24. Prediction of ARAT at T2: Beta values, t-test statistics and significance levels for independent T1 variables with ARAT T1 excluded

Step	Predictor Variable	Beta	t	p	95% CI	Adjusted R^2 after each step
1	MBI	0.44	5.37	<0.001*	0.23 to 0.51	
	9HPT	0.39	5.17	<0.001*	11.22 to 25.26	
	Days to initial assessment	-0.23	-3.09	<0.01*	-1.28 to -0.28	0.531
	Anxiety	-0.07	-0.87	0.39	-1.26 to 0.49	
	Depression	0.06	0.65	0.52	-0.73 to 1.45	
2	MBI	0.38	4.37	<0.001*	-0.18 to 0.47	
	9HPT	0.38	5.11	<0.001*	10.90 to 24.76	
	Days to initial assessment	-0.23	-3.20	<0.01*	-1.30 to 0.30	
	Anxiety	-0.34	-0.41	0.69	-1.06 to 0.70	
	Depression	0.03	0.30	0.77	-0.94 to 1.27	
	OCSPC					0.544
	TACS	-0.16	-2.10	0.04*	-28.41 to -0.73	
	LACS	0.05	0.73	0.47	-4.02 to 8.65	
	POCS	-0.03	-0.40	0.69	-24.77 to 16.52	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; HADS denotes Hospital Anxiety and Depression Scale, *Denotes significance at the $p \leq 0.05$ level

Table 25. Beta values, t- test statistics and significance levels for independent T1 variables tested for prediction of ARAT at T3

Step	Predictor Variable	Beta	t	p	95% CI	Adjusted R^2 after each step
1	ARAT T1 Score	0.53	-4.52	<0.001*	0.41 to 1.04	
	MBI	0.26	2.91	0.01*	0.07 to 0.39	
	9HPT	0.06	0.62	0.54	-6.69 to 12.68	0.636
	Days to initial assessment	-0.16	-2.18	0.03*	-1.05 to -0.05	
	Anxiety	-0.09	-1.24	0.23	-1.39 to 0.32	
	Depression	0.03	0.40	0.69	-0.89 to 1.34	
2	ARAT T1 Score	0.53	-4.42	<0.001*	0.40 to 1.05	
	MBI	0.21	2.15	0.04*	0.01 to 0.35	
	9HPT	0.06	0.55	0.58	-7.08 to 12.47	
	Days to initial assessment	-0.15	-2.06	0.04*	-1.03 to -0.02	0.635
	Anxiety	-0.07	-0.84	0.40	-1.26 to 0.51	
	Depression	-0.02	-0.19	0.85	-1.30 to 1.08	
	OCSPC					
	TACS	0.12	-1.64	0.11	-27.78 to 2.68	
	LACS	0.01	-0.16	0.88	-6.99 to 5.97	
	POCS	-0.12	0.24	0.81	-17.32 to 22.04	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; HADS denotes Hospital Anxiety and Depression Scale.

Table 26. Beta values, t-test statistics and significance levels for independent T1 variables tested for prediction of ARAT at T3 with ARAT T1 excluded

Step	Predictor Variable	Beta	t	p	95% CI	Adjusted R^2 after each step
1	MBI	0.44	4.96	<0.001*	0.23 to 0.55	
	9HPT	0.39	5.02	<0.001*	11.39 to 26.35	0.546
	Days to initial assessment	-0.23	-3.03	<0.01*	-1.37 to -0.28	
	Anxiety	-0.12	-1.34	0.18	-1.65 to 0.31	
	Depression	0.60	0.60	0.55	-0.87 to 1.62	
2	MBI	0.37	3.74	<0.001*	0.15 to 0.51	
	9HPT	0.39	4.90	<0.001*	10.94 to 25.97	
	Days to initial assessment	-0.23	-2.97	<0.001*	-1.36 to -0.27	
	Anxiety	-0.08	-0.90	0.37	-1.44 to 0.54	
	Depression	0.01	0.06	0.95	-1.29 to 1.37	
	OCSPC					0.545
	TACS	-0.13	-1.56	0.12	-30.31 to 3.70	
	LACS	0.04	0.48	0.63	-5.43 to 8.86	
	POCS	0.02	0.03	0.97	-21.60 to 22.31	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; HADS denotes Hospital Anxiety and Depression Scale, *Denotes significance at the p,0.05 level

Table 27. Collinearity between descriptive and T2 independent variables for regression with ARAT scores at T3

	TACS	LACS	PACS	POCS	ARAT T2	RMA T2	9HPT T2	MBI T2	Tactile Sensation T2	NSA Total T2	Proprioception T3
TACS	1.00										
LACS	-0.17	1.00									
PACS	-0.25	-0.86	1.00								
POCS	-0.04	-0.13	-0.17	1.00							
ARAT T2	-0.34	0.23	-0.09	0.08	1.00						
RMA T2	-0.35	0.17	-0.05	0.13	0.89**	1.00					
9HPT T2	-0.28	0.12	-0.04	0.13	0.69	0.73**	1.00				
MBI T2	-.20	0.11	-0.04	0.07	0.50	0.47	0.28	.00			
Tactile Sensation T2	-.29	0.20	-0.04	-0.10	0.11	0.17	0.15	0.20	1.00		
NSA Total T2	-.31	0.17	-0.03	-0.03	0.18	0.23	0.21	0.23	0.95**	1.00	
Proprioception T3	-.17	0.09	-0.04	0.10	0.26	0.31	0.14	.31	0.67	0.79**	1.00

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; Days denotes days from stroke onset to initial assessment; ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (UL section); 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; HADS denotes Hospital Anxiety and Depression Scale, ** denotes collinearity between independent variables defined by correlation coefficient >0.70

Table 28. Beta values, test statistics and significance levels for independent T2 variables tested for prediction of ARAT at T3

Step	Predictor Variable	Beta	t	p	95% CI	Adjusted R^2 after each step
1	ARAT T2	0.83	14.53	< 0.001*	0.73 to 1.02	
	MBI T2	-0.06	-1.64	0.10	-6.14 to 1.46	
	9HPT	0.10	1.94	0.06	-0.43 to 10.28	0.925
	NSA Proprioception T2	-0.03	-0.67	0.51	-5.86 to 5.14	
	NSA Tactile Total T2	-0.03	-0.87	0.39	-6.72 to 2.50	
2	ARAT T2	0.86	14.20	<0.001*	0.73 to 1.04	
	MBI T2	-0.06	-1.48	0.14	-6.12 to 1.62	
	9HPT	0.08	-1.53	0.13	-1.11 to 9.97	
	NSA Proprioception T2	-0.01	-0.28	0.78	-5.45 to 6.23	0.925
	NSA Tactile Total T2	-0.06	-1.33	0.19	-8.36 to 2.40	
	OCSPC					
	TACS	-0.02	0.41	0.69	-9.01 to 9.45	
	LACS	-0.05	1.36	0.18	-5.90 to 17.47	
	POCS	0.06	1.61	0.11	-2.82 to 4.14	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NSA denotes Nottingham Sensory Assessment

Table 29. Beta values, t-test statistics and significance levels for independent T2 variables tested for prediction of ARAT at T3 with ARAT T2 excluded

Step	Predictor Variable	Beta	t	p	95% CI	Adjusted R^2 after each step
1	MBI	0.28	4.25	<0.001*	-17.86 to -6.18	
	9HPT	0.68	10.58	<0.001*	23.77 to 35.46	0.719
	Proprioception	-0.08	-1.06	0.23	-12.39 to 6.80	
	Tactile sensation	-0.03	-0.40	0.75	-11.15 to 5.31	
2	MBI	0.27	4.11	<0.001*	-17.29 to -5.80	
	9HPT	0.65	9.87	<0.001*	22.48 to 34.21	
	Proprioception	-0.09	-1.21	0.23	-13.50 to 5.47	0.723
	Tactile sensation	-0.02	0.32	0.75	-8.19 to 9.28	
	OCSPC					
	TACS	-0.13	-1.82	0.07	-28.35 to 0.69	
	LACS	-0.09	-1.40	0.78	-21.86 to 15.98	
	POCS	-0.02	-0.28	0.17	-10.88 to 0.41	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NSA denotes Nottingham Sensory Assessment

Table 30. Ipsilesional scores for whole sample at T1, T2 and T3; mean (sd), range, skewness, z skewness and kurtosis scores and outliers

Measures	*Possible score*	*Time*	*n*	*Mean (sd)*	*Range*	*Skewness*	*Z Skewness*	*Kurtosis*	*Z kurtosis*	*Outliers*	
										low	*high*
ARAT	Min=0	T1	106	56.7 (1.8)	42 – 57	-6.6	28.2*	49.3	104.9*	2	0
	Max=57	T3	97	56.9 (0.1)	48 – 57	-8.5	33.9*	75.4	153.8*	1	0
		T3	85	57.0 (0.2)	56 – 57	-5.2	19.8*	25.2	49.4*	0	0
9HPT	Time to completion	T1	106	20.4 (7.9)	11.5 – 50.0	2.2	9.1*	5.6	3.2	0	0
		T3	97	18.4 (7.3)	9.6 – 50.0	2.6	10.4*	8.2	12.1*	0	0
		T3	85	17.9 (5.6)	9.4 – 36.4	1.1	4.2*	1.0	12.3*	0	0
9HPT	Pegs/	T1	106	0.48 (0.15)	0.02 – 0.78	-0.5	2.1	0.8	1.9	0	0
	second	T3	97	0.53 (0.15)	0.10 – 0.94	-0.4	1.5	0.4	0.9	0	0
		T3	85	0.55 (0.15)	0.25 – 0.96	0.2	0.8	-0.4	0.8	0	0
NSA	Min=0	T1	81	74.9 (5.2)	58 – 80	-1.6	3.4*	3.2	3.6*	1	0
	Max=84	T3	83	76.4 (4.2)	57 – 80	-2.7	8.2*	8.7	13.4*	1	0
		T3	75	76.0 (5.6)	53 – 80	-2.4	7.3*	6.4	9.9*	1	0

* z skewness >3.29; p>0.001

Table 31. Summary of missing ipsilesional data; percentage missing, reasons and actions

MEASURES	Percentage missing	Reasons (N)	Plan
ARAT T3	10.4%	Withdrew (n=9) Administrative error (2)	Complete case analysis and imputation
ARAT T3	18.9%	Withdrew (n=21)	Complete case analysis and analysis with imputation
Nine hole peg test T1 (pegs/second)	0.9%	Administrative error (n=1)	Nothing
Nine hole peg test T2 (pegs/second)	8.5%	Withdrew (n=9)	Complete case analysis and analysis with imputation
Nine hole peg test T3(pegs/second)	19.8%	Withdrew (n=21)	Complete case analysis and analysis with imputation
Nottingham Sensory Assessment Total T1	75.5%	Unable to complete all items (n=80)	Unable to use
Nottingham Sensory Assessment Total T2	50.9%	Withdrew (n=9) Unable to complete all items (n=45)	Unable to use
Nottingham Sensory Assessment Total T3	50.9%	Withdrew (n=21) Unable to complete all items (n=33)	Unable to use
Nottingham Sensory Assessment Stereognosis Sub-Score T1	14.2%	Unable to complete (n=15)	Sub-analysis with complete cases only

Table 31. (cont). Summary of missing ipsilesional data; percentage missing, reasons and actions

MEASURES	Percentage missing	Reasons (N)	Plan
Nottingham Sensory Assessment Stereognosis Sub-Score T2	14.2%	Withdrew (n=9) Unable to complete (n=6)	Sub-analysis with complete cases only
Nottingham Sensory Assessment Stereognosis Sub-Score T3	25.5%	Withdrew (n=21) Unable to complete (n = 6)	Unable to use
Nottingham Sensory Assessment Proprioception Sub-Score T1	69.8%	Unable to complete all items (n = 74)	Unable to use
Nottingham Sensory Assessment Proprioception Sub-Score T2	39.6%	Withdrew (n=9) Unable to complete (n=33)	Unable to use
Nottingham Sensory Assessment Proprioception Score T3	25.5%	Withdrew (n=21) Unable to complete all items (n = 6)	Unable to use
Nottingham Sensory Assessment Tactile Sub-Score T1 Light touch Temperature Two point discrimination Tactile localisation	64.2% 5.7% 9.4% 17% 57.5%	Unable to complete all items (n=68)	Sub-analysis with complete cases only
Nottingham Sensory Assessment Tactile Sub-Score T2 Light touch Temperature Two point discrimination Tactile localisation	43.3% 12.3% 12.3% 15.1% 38.7%	Withdrew (n=9) Unable to complete all items (n=37)	Sub-analysis with complete cases only
Nottingham Sensory Assessment Tactile Sub-Score Score T3 Light touch Temperature Two point discrimination Tactile localisation	44.3% 23.6% 23.6% 15.1% 42.5%	Withdrew (n=21) Unable to complete all items (n=25)	Sub-analysis with complete cases only

Table 32. Post Hoc Bonferroni pairwise comparisons for main effect of time on depression

		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
Comparison					Lower Bound	Upper Bound
T1	T2	0.439	0.344	0.618	-0.402	1.280
T1	T3	1.169	0.347	0.003*	0.322	2.016
T2	T3	0.731	0.294	0.045	1.302	1.448

*denotes $p \leq 0.05$

Table 33. NHP scores: Mean (sd), Range, skewness, z skewness, kurtosis and z kurtosis for the whole sample at T1, T2 and T3

	Time	*Mean Score (SD)*	*Range*	*Skewness*	*Z skewness*	*Kurtosis*	*Z kurtosis*
Total NHP (max=600)	T1	177.0 119)	0, 460	0.47	1.99	-0.68	-1.44
	T2	116.0 (94)	0, 414	0.94	3.85*	0.28	0.56
	T3	108.0 (102	0, 432	1.32	5.07*	1.14	2.42
Energy Levels	T1	41.1 (35.2)	0, 100	0.34	1.44	-1.09	2.32
	T2	27.1 (32.4)	0, 100	1.03	4.20*	-0.04	0.08
	T3	24.4 (31.2)	0, 100	1.08	4.15*	0.11	0.21
Pain	T1	13.8 (21.8)	0, 94	1.77	7.16*	2.63	5.59*
	T2	11.6 (17.9)	0, 80	1.77	7.08*	2.91	6.06*
	T3	10.6 (16.6)	0, 94	2.21	8.50*	6.60	12.90
Emotional Reactions	T1	21.4 (23.6)	0, 100	1.27	5.29*	1.11	2.36*
	T2	13.4 (20.6)	0, 86	2.03	8.12*	3.45	7.18*
	T3	12.4 (22.9)	0, 100	2.32	8.92*	4.68	9.00*
Sleep	T1	34.9 (33.6)	0, 100	0.60	2.50	-1.05	-2.23
	T2	21.8 (26.6)	0, 100	1.24	4.96*	0.48	0.89
	T3	17.8 (25.5)	0, 100	1.65	6.34*	2.00	3.92
Social Isolation	T1	19.7 (23.1)	0, 100	1.33	5.54*	1.50	3.19
	T2	10.2 (17.6)	0, 100	2.11	8.70*	4.98	10.14*
	T3	12.5 (19.2)	1, 100	1.58	6.07*	1.96	3.92*
Physical Activities	T1	48.4 (25.0)	0, 89	-0.17	0.74	-0.87	1.85
	T2	31.5 (24.4)	0, 78	0.35	1.40	-0.98	-2.00
	T3	30.6(22.0)	0, 78	0.32	1.23	-1.02	1.96

NHP denotes Nottingham Health Profile; * denotes z skewness >3.29; p>0.001.

Table 34. Bonferroni pairwise comparisons for main effect of time on total NHP score

		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
TIME	TIME				Lower Bound	Upper Bound
T1	T2	2.608	.487	0.000	1.418	3.799
T1	T3	3.142	.537	0.000	1.830	4.454
T2	T3	.534	.443	0.695	-0.549	1.616

Table 35. Post Hoc Bonferroni pairwise comparisons for main effect of time on NHP emotional reactions score

		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
TIME	TIME				Lower Bound	Upper Bound
T1	T2	5.352	1.980	0.025	.514	10.191
T1	T3	6.316	2.248	0.019	.822	11.810
T2	T3	.964	1.615	1.000	-2.983	4.910

Table 36. Post Hoc Bonferroni pairwise comparisons for main effect of time on NHP energy level score

		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
TIME	TIME				Lower Bound	Upper Bound
T1	T2	1.313	0.414	0.006	.302	2.324
T1	T3	1.908	0.450	0.000	.809	3.007
T2	T3	.595	0.390	0.394	-.359	1.549

Table 37. Post Hoc Bonferroni pairwise comparisons for main effect of time on NHP sleep score

Comparison		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
TIME	TIME				Lower Bound	Upper Bound
T1	T2	1.321	.395	0.004	.355	2.288
T1	T3	1.961	.438	0.000	.892	3.030
T2	T3	.640	.312	0.131	-.123	1.403

Table 38. Post Hoc Bonferroni pairwise comparisons for main effect of time on NHP social isolation score

Comparison		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
TIME	TIME				Lower Bound	Upper Bound
T1	T2	1.334	.351	0.001	.477	2.192
T1	T3	1.130	.371	0.010	.222	2.038
T2	T3	-1.334	.351	0.001	-2.192	-.477

Table 39. Post Hoc Bonferroni pairwise comparisons for main effect of time on NHP physical activities

Comparison		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
TIME	TIME				Lower Bound	Upper Bound
T1	T2	16.343	2.707	0.000	9.726	22.960
T1	T3	16.257	2.610	0.000	9.876	22.639
T2	T3	-8.548	2.075	1.000	-5.159	4.988

Table 40. Patient characteristics and scores for whole sample (mean, sd) for all measures at T3

Characteristic	Frequency/mean (SD)	Median (Range)
n	85	-
Gender M/F	49/36	
Mean (SD)Age	67.6 (11.4)	69 (36,88)
Side of hemiplegia R/L	43/42	-
Handedness R/L	78/7	-
Dominant side affected Y/N	42/43	-
Type of Stroke TACS PACS LACS POCS	 4 45 34 2	-
Ischaemic/haemorrhagic Stroke	76/9	-
Days to initial assessment	22.8 (6.2)	23 (12,39)
Bilateral/UT Group	46/39	-
MAS Score	5.4(4.6)	5.0 (0, 14)
UL Activity Limitation: ARAT (max = 57)	32.9 (28.9)	36 (0, 57)
UL Impairment: RMA (max = 15)	6.6(4.1)	8 (0, 15)
Dexterity:9HPT Pegs/s	0.15 (0.17)	1.00 (0.00, 0.63)
Sensation: Nottingham Sensory Assessment (max = 84) Proprioception (max = 12) Tactile sensation (max = 48) Stereognosis (max = 20)	73.8(12.4) 9.1 (3.6) 44.9 (8.3) 15.4 (6.0)	77 (2, 84) 10 (0, 12) 10 (0, 12) 18 (0, 20)
Independence in activities of daily living: Modified Barthel Index (Max=100)	85.9(18.7)	92 (15, 100)
Quality of Life: NHP Total Max=600 (indicating poorer HRQOL) Energy Levels Pain Emotional Reactions Sleep Social Isolation Physical Activities (max =100)	108.5(102.8) 24.5 (31.2) 10.9 (16.7) 12.4 (22.9) 17.8 (25.5) 12.5 (19.2) 30.7 (22.1)	81.0 (0.0, 432.2) 0.0 (0.0, 100.0) 0.0 (0.0, 94.2) 0.0 (0.0, 100.0) 12.6 (0.0, 100.0) 0.0 (0.0, 79.9) 24.6 (0, 78.7)
HADS: Anxiety	5.2 (4.1)	4 (0, 17)
Depression	5.0 (3.5)	4 (0, 17

*Denotes critical value for skewness p>0.0005

Appendix 14

Data Appendix

Intention to Treat Analysis

Table 1. Repeated measures ANOVA: ARAT total and ARAT sub-sections and 9HPT

Measure	Time	BT Group N=55	UT Group N=50	Source of variance		df	F	p
ARAT	T1	13.6 (15.3)	18.5 (17.2)	Within Subject	Time	1.65	124.62	<0.001*
	T2	28.4 (19.3)	34.4 (19.8)		Time x Group	1.65	0.73	0.46
	T3	29.4 (19.7)	37.2 (18..9)					
				Between Subject	Group	1	3.45	0.07
Grasp				Within Subject	Time	1.87	74.61	<0.001*
	T1	5.1(6.0)	6.7(6.5)		Time x Group	1.87	0.21	0.80
	T2	9.9 (6.7)	11.7(6.8)					
	T3	9.9(6.7)	11.7(6.8)	Between Subject	Group	1	1.72	0.19
Grip	T1	2.7(3.3)	4.0(4.0)	Within Subject	Time	1.68	111.64	<0.001*
	T2	6.3(4.3)	7.6(4.3)		Time x Group	1.47	1.68	0.35
	T3	6.0(4.2)	8.0(4.2)					
				Between Subject	Group	1	3.85	0.06
Pinch	T1	2.6(4.3)	2.8(4.8)	Within Subject	Time	1.76	92.71	<0.001*
	T2	7.2(6.9)	8.6(6.9)		Time x Group	1.76	3.24	0.05*
	T3	7.8(7.6)	11.1(7.4)					
				Between Subject	Group	1	2.86	0.09
Gross	T1	3.65(3.2)	4.6(3.1)	Within Subject	Time	1.89	48.07	<0.001*
	T2	5.5(3.3)	6.3(3.1)		Time x Group	1.89	0.41	0.65
	T3	5.6(3.1)	6.2(3.0)					
				Between Subject	Group	1	1.90	0.17
9HPT	T1	0.02 (0.08)	0.04 (0.07)	Within Subject	Time	1.75	94.32	<0.001*
	T2	0.11 (0.17)	0.19(0.15)		Time x Group	1.75	4.43	0.02*
	T3	0.12 (0.14)	0.19 (0.16)					
				Between Subject	Group	1	4.50	0.04*†

*denotes $p \leq 0.05$ † denotes a difference in terms of significance between Complete Case Analysis and Intention to Treat Analysis

Table 2. Repeated measures ANOVA: RMA and MBI

Measure		BT Group N =56	UT Group N =50	Source of variance		df	F	p
RMA	T1	3.4(3.3)	4.3 (3.1)	Within Subject	Time	1.85	70.71	<0.001*
	T2	5.5(3.5)	7.1(3.8)		Time x Group	1.85	2.77	0.46
	T3	6.0(4.1)	7.3 (4.0)					
				Between Subject	Group	1	3.57	0.06
MBI	T1	59.0(25.2)	65.7(23.5)	Within Subject	Time	1.57	107.39	<0.001*
	T2	83.7(15.6)	85.1(19.2)		Time x Group	1.57	3.29	0.06
	T3	86.8(13.8)	86.1(18.5)					
				Between Subject	Group	1	0.39	0.53

*denotes $p \leq 0.05$

Table 3. Change Scores for UT and BT groups for effects of severity on ARAT, RMA and 9HPT, T1 -T3

		UT Group			BT Group			Factorial ANOVA			
Measure	***ARAT Sub-group***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T2	**Sub-group1 (0-3)**	**13**	9.0	11.7	**24**	11.5	14.8	Main Effects: Group	1, 104	0.06	0.82
	Sub-group2 (4-28)	**23**	20.2	12.9	**19**	19.3	10.4	ARAT Level	2, 104	6.27	<0.01*
	Sub-group3 (29-57)	**14**	13.6	7.8	**12**	13.7	7.9	Group x ARAT Level	2, 104	0.20	0.82
RMA T1-T2	**Sub-group1 (0-3)**	**13**	1.8	2.9	**24**	2.1	2.7	Main Effects: Group	1, 104	2.48	0.12
	Sub-group2 (4-28)	**23**	3.6	2.5	**19**	2.0	1.7	ARAT Level	2, 104	4.12	0.03*
	Sub-group3 (29-57)	**14**	2.6	2.2	**12**	1.5	1.8	Group x ARAT Level	2, 104	1.30	0.22
9HPT T1-T2	**Sub-group1 (0-3)**	**13**	0.01	0.02	**24**	0.02	0.04	Main Effects: Group	1, 104	0.52	0.52
	Sub-group2 (4-28)	**23**	0.11	0.12	**19**	0.09	0.11	ARAT Level	2, 104	19.59	<0.001*
	Sub-group3 (29-57)	**14**	0.16	0.11	**12**	0.21	0.18	Group x ARAT Level	2, 104	0.94	0.40

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test;
*denotes significant result $p \leq 0.05$

Table 4. Change Scores for UT and BT groups for effects of severity on ARAT, RMA and 9HPT, T1 -T3

		UT Group			BT Group			Factorial ANOVA			
Measure	***ARAT Sub-group***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T3	**Sub-group1 (0-3)**	**13**	11.0	13.1	**24**	121	15.6	Main Effects: Group	1, 104	0.56	0.46
	Sub-group2 (4-28)	**23**	23.9	12.1	**19**	17.4	12.2	ARAT Level	2, 104	5.36	<0.01*
	Sub-group3 (29-57)	**14**	15.7	6.6	**12**	15.7	5.3	Group x ARAT Level	2, 104	1.04	0.36
RMA T1-T3	**Sub-group1 (0-3)**	**13**	2.3	3.4	**24**	2.5	3.6	Main Effects: Group	1, 104	0.30	0.59
	Sub-group2 (4-28)	**23**	3.3	2.5	**19**	2.1	2.3	ARAT Level	2, 104	3.27	0.04*
	Sub-group3 (29-57)	**14**	2.4	2.2	**12**	2.6	1.6	Group x ARAT Level	2, 104	0.70	0.50
9HPT T1-T3	**Sub-group1 (0-3)**	**13**	0.05	0.06 0.14	**24**	0.04	0.06	Main Effects: Group	1, 104	2.11	0.15
	Sub-group2 (4-28)	**23**	0.15	0.14	**19**	0.09	0.12	ARAT Level	2, 104	17.2	<0.001*
	Sub-group3 (29-57)	**14**	0.22		**12**	0.21	0.11	Group x ARAT Level	2, 104	0.65	0.52

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test;
*denotes significant result $p \leq 0.05$

Table 5. ARAT, RMA and 9HPT, T1-T2:Mean change scores, standard deviation and factoral ANOVA for UT and BT groups for side of hemiplegia and hand dominance

Measure				n	Mean	SD	*Source of Variance.*	*df*	*F*	*p*
ARAT T1-T2	UT Group	Right Side Affected	non-dominant dominant	2 21	9.5 17.3	7.8 14.5	**Main Effects :** Group	1	0.66	0.42
							Side	1	0.00	0.99
		Left Side Affected	non-dominant dominant	23 4	14.1 16.0	10.4 11.2	Dominance	1	0.50	0.48
							Interaction Effects: Group x Side	1	0.13	0.72
	BT Group	Right Side Affected	non-dominant dominant	3 26	21.9 15.8	6.2 13.8	Group x dominance	1	0.11	0.74
							Side x dominance	1	0.28	0.59
		Left Side Affected	non-dominant dominant	25 1	12.3 22.0	11.4 -	Group x side x dominance	1	1.36	0.25
RMA T1-T2	UT Group	Right Side Affected	non-dominant dominant	2 21	1.5 2.6	2.1 2.5	**Main Effects :** Group	1	0.01	0.94
							Side	1	0.66	0.42
		Left Side Affected	non-dominant dominant	23 4	3.2 2.6	2.9 2.4	Dominance	1	0.41	0.52
							Interaction Effects: Group x Side	1	0.01	0.92
	BT Group	Right Side Affected	non-dominant dominant	3 26	2.4 2.0	0.5 2.5	Group x dominance	1	0.13	0.72
							Side x dominance	1	0.08	0.78
		Left Side Affected	non-dominant dominant	25 1	1.7 4.0	2.1 -	Group x side x dominance	1	1.40	0.24
9HPT T1-T2	UT Group	Right Side Affected	non-dominant dominant	2 21	0.04 0.13	0.03 0.14	**Main Effects :** Group	1	0.14	0.71
							Side	1	0.05	0.83
		Left Side Affected	non-dominant dominant	23 4	0.08 0.08	0.10 0.05	Dominance	1	1.44	0.23
							Interaction Effects: Group x Side	1	0.11	0.74
	BT Group	Right Side Affected	non-dominant dominant	3 26	0.06 0.11	0.06 0.16	Group x dominance	1	0.09	0.77
							Side x dominance	1	0.04	0.85
		Left Side Affected	non-dominant dominant	25 1	0.06 0.16	0.10 0.10	Group x side x dominance	1	0.58	0.45

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test; *denotes significant result $p \leq 0.05$

Table 6. ARAT, RMA and 9HPT, T1-T3: Mean change scores, standard deviation and factoral ANOVA for UT and BT groups for side of hemiplegia and hand dominance

Measure				n	Mean Change	SD	*Source of Variance.*	*df*	*F*	*p*
ARAT T1-T3	UT Group	Right Side Affected	non-dominant	2	13.0	12.7	**Main Effects :** Group	1	0.15	0.70
			dominant	21	18.5	12.6	Side	1	1.24	0.27
		Left Side Affected	non-dominant	23	18.7	12.4	Dominance	1	1.41	0.24
			dominant	4	16.8	12.5	**Interaction Effects:** Group x Side	1	0.46	0.50
	BT Group	Right Side Affected	non-dominant	3	13.7	22.6	Group x dominance	1	0.66	0.42
			dominant	26	14.9	12.7	Side x dominance	1	0.25	0.62
		Left Side Affected	non-dominant	25	13.9	15.3	Group x side x dominance	1	1.60	0.21
			dominant	1	32.0	-				
RMA T1-T3	UT Group	Right Side Affected	non-dominant	2	1.0	1.4	**Main Effects :** Group	1	1.89	0.17
			dominant	21	3.2	2.8	Side	1	0.14	0.71
		Left Side Affected	non-dominant	23	2.6	2.7	Dominance	1	1.23	0.27
			dominant	4	3.0	2.2	**Interaction Effects:** Group x Side	1	0.07	0.79
	BT Group	Right Side Affected	non-dominant	3	-1.1	3.5	Group x dominance	1	0.02	0.88
			dominant	26	3.0	2.8	Side x dominance	1	3.99	0.04*
		Left Side Affected	non-dominant	25	2.2	2.5	Group x side x dominance	1	1.21	0.27
			dominant	1	0.0	-				
9HPT T1-T3	UT Group	Right Side Affected	non-dominant	2	0.11	0.07	**Main Effects :** Group	1	0.47	0.49
			dominant	21	0.15	0.17	Side	1	0.51	0.47
		Left Side Affected	non-dominant	23	0.14	0.11	Dominance	1	0.14	0.59
			dominant	4	0.15	0.12	**Interaction Effects**: Group x Side	1	0.30	0.70
	BT Group	Right Side Affected	non-dominant	3	0.08	0.08	Group x dominance	1	0.15	0.95
			dominant	26	0.08	0.11	Side x dominance	1	0.01	0.94
		Left Side Affected	non-dominant	25	0.10	0.13	Group x side x dominance	1	0.25	0.62
			dominant	1	0.16	-				

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test;
***denotes significant result, p≤0 05**

Table 7. ARAT, RMA and 9HPT T1-T2: Change scores for BT and UT groups for effect of gender

		UT Group			BT Group			Factorial ANOVA			
Measure	***Gender***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T2	**Male** **Female**	27 23	17.2 13.3	10.9 13.4	33 23	14.4 15.1	11.1 14.5	Group Gender Group x Gender	1, 104 1, 104 1, 104	0.05 0.40 0.90	0.83 0.53 0.35
RMA T1-T2	**Male** **Female**	27 23	3.0 2.6	2.5 2.7	33 23	2.0 1.8	2.2 2.2	Group Gender Group x Gender	1, 104 1, 104 1, 104	3.36 0.54 0.06	0.07 0.46 0.81
9HPT T1-T2	**Male** **Female**	27 23	0.12 0.08	0.11 0.11	33 23	0.10 0.07	0.15 0.11	Group Gender Group x Gender	1, 104 1, 104 1, 104	0.33 1.85 0.00	0.56 0.18 1.00

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test;
***denotes significant result, p≤0 05**

Table 8. ARAT, RMA and 9HPT T1-T3: Change scores for UT and BT groups and effect of gender

		UT Group			BT Group			Factorial ANOVA			
Measure	***Sex***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T3	**Male**	27	22.3	12.2	33	15.3	11.0	Group	1, 104	1.92	0.17
	Female	23	13.5	10.6	23	13.7	15.5	Gender	1, 104	4.71	0.03*
								Group x Gender	1, 104	2.18	0.14
RMA T1-T3	**Male**	27	3.1	2.6	33	2.6	2.6	Group	1, 104	0.77	0.38
	Female	23	2.5	2.8	23	1.9	3.0	Gender	1, 104	1.31	0.26
								Group x Gender	1, 104	0.00	0.98
9HPT T1-T3	**Male**	27	0.18	0.13	33	0.10	0.11	Group	1, 104	4.40	0.06
	Female	23	0.11	0.14	23	0.09	0.12	Gender	1, 104	2.04	0.16
								Group x Gender	1, 104	1.02	0.31

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test; *denotes significant result, $p \leq 0.05$

Table 9. ARAT, RMA and 9HPT T1-T2: Change scores for UT and BT groups for effect of age

		UT Group			BT Group			Factorial ANOVA			
Measure	***Age***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T2	**≤ 69**	29	16.7	12.5	26	15.2	12.4	Group	1, 104	0.04	0.84
	> 69	21	13.7	11.6	30	14.2	12.7	Age	1, 104	0.66	0.42
								Group x Age	1, 104	0.19	0.66
RMA T1-T2	**≤ 69**	29	2.7	2.5	26	1.8	2.3	Group	1, 104	3.69	0.06
	> 69	21	2.9	2.9	30	2.0	2.2	Age	1, 104	0.23	0.67
								Group x Age	1, 104	0.02	0.96
9HPT T1-T2	**≤ 69**	29	0.09	0.11	26	0.06	0.10	Group	1, 104	0.34	0.56
	> 69	21	0.10	0.12	30	0.11	0.15	Age	1, 104	1.38	0.24
								Group x Age	1, 104	0.67	0.42

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test; ***denotes significant result, p≤ 0.05**

Table 10. ARAT, RMA and 9HPT T1-T3: Change scores for UT and BT groups and effect of age

		UT Group			BT Group			Factorial ANOVA			
Measure	***Age***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T3	**≤ 69**	29	19.1	13.1	26	13.4	10.5	Group	1, 104	1.93	0.17
	> 69	21	17.1	11.0	29	16.0	14.7	Age	1, 104	0.03	0.92
								Group x Age	1, 104	1.08	0.36
RMA T1-T3	**≤ 69**	29	2.7	2.5	26	2.5	3.2	Group	1, 104	0.68	0.41
	> 69	21	3.0	3.0	29	2.2	2.4	Age	1, 104	0.00	0.99
								Group x Age	1, 104	0.24	0.63
9HPT T1-T3	**≤ 69**	29	0.14	0.13	26	0.05	0.06	Group	1, 104	5.94	0.02*
	> 69	21	0.16	0.14	29	0.13	0.14	Age	1, 104	4.56	0.04*
								Group x Age	1, 104	2.19	0.14

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test; *denotes significant result, $p \leq 0.05$

Table 11. Change scores for UT and BT groups for proprioception levels on ARAT, RMA and 9HPT, T1-T2

		BT Group			Unilteral Geoup			Factorial ANOVA			
Measure	***Proprioception Sub-group***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T2	**Impaired Proprioception**	43	17.9	14.0	37	13.0	11.4	Group	1	0.13	0.72
								Proprioception.Level	1	0.05	0.83
	Intact Proprioception	13	13.4	11.9	13	16.2	12.4	Group x Level	1	1.95	0.16
RMA T1-T2	**Impaired Proprioception**	43	1.8	2.5	37	2.3	3.0	Group	1	1.96	0.16
								Proprioception .Level	1	0.50	0.48
	Intact Proprioception	13	1.9	2.5	13	3.0	2.5	Group x Level	1	0.31	0.58
9HPT T1-T2	**Impaired Proprioception**	43	0.07	0.14	37	0.09	0.11	Group	1	0.07	0.80
								Proprioception .Level	1	0.00	0.99
	Intact Proprioception	13	0.10	0.12	13	0.10	0.13	Group x Level	1	0.21	0.65

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test; *denotes significant result $p \leq 0.05$

Table 12. Change scores for UT and BT groups for proprioception levels on ARAT, RMA and 9HPT, T1-T3

		BT Group			UT Group			Factorial ANOVA			
Measure	***Proprioception Sub-group***	**N**	**Mean Change**	**SD**	**N**	**Mean Change**	**SD**	***Source of Variance***	***df***	***F***	***p***
ARAT T1-T3								Group	1	0.18	0.67
	Impaired Proprioception	13	21.0	16.8	13	17.1	12.5	Proprioception .Level	1	1.54	0.22
	Intact Proprioception	43	12.5	11.0	37	18.7	12.3	Group x Level	1	3.18	0.08
RMA T1-T3								Group	1	0.13	0.72
	Impaired Proprioception	13	3.0	3.1	13	2.7	3.5	Proprioception .Level	1	0.34	0.56
	Intact Proprioception	43	2.1	2.6	37	2.8	2.4	Group x Level	1	0.61	0.44
9HPT T1-T3								Group	1	3.16	0.08
	Impaired Proprioception	13	0.13	0.14	13	0.17	0.19	Proprioception .Level	1	2.52	0.12
	Intact Proprioception	37	0.08	0.11	37	0.14	0.14	Group x Level	1	0.14	0.71

ARAT denotes Action Research Arm Test; RMA denotes Rivermead Motor Assessment (Upper Limb section); 9HPT denotes Nine Hole Peg Test; ***denotes significant result $p \leq 0.05$**

Table 13. Beta values, t-test statistics and significance levels for independent T1 variables tested for prediction of ARAT at T2

Step	Predictor Variable	Beta	t	p	95% Confidence interval for Beta	Adjusted R^2 after each step
1	ARAT T1	0.56	5.56	<0.001*	0.43 to 0.91	
	MBI	0.22	2.74	0.01*	0.05 to 0.30	
	9HPT	-0.06	-0.70	0.46	-9.98 to 4.76	0.62
	Days to initial assessment	-0.18	-2.78	0.01*	-1.01 to -0.17	
	Anxiety	-0.01	-0.14	0.89	-0.73 to 0.63	
	Depression	-0.01	-0.07	0.95	-0.86 to 0.92	
2	ARAT T1	0.54	5.59	<0.001*	0.43 to 0.90	
	MBI	0.19	2.32	0.02*	0.02 to 0.28	0.64
	9HPT	-0.07	-0.80	0.42	-10.07 to 4.26	
	Days to initial assessment	-0.18	-2.94	<0.01*	-1.02 to -0.20	
	Anxiety	0.01	0.19	0.85	-0.61 to 0.73	
	Depression	-0.01	-0.17	0.86	-0.96 to 0.80	
	OCSPC					
	TACS	-0.16	-2.58	0.01*	-26.52 to -3.44	
	LACS	0.02	0.25	0.80	-4.51 to 5.83	
	POCS	-0.08	-1.34	0.18	-24.26 to 4.73	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; POCS denotes posterior circulation Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NSA denotes Nottingham Sensory Assessment

Table 14. Beta values, t-test statistics and significance levels for independent T1 variables tested for prediction of ARAT at T2 without T1 ARAT as an independent variable

Step	Predictor Variable	Beta	t	p	95% Confidence interval for Beta	Adjusted R^2 after each step
1	MBI	0.42	5.21	<0.001*	0.21 to 0.47	
	9HPT	-0.39	-5.09	<0.001*	-22.55 to -9.91	
	Days to initial assessment	-0.25	-3.57	<0.001*	-1.31 to -0.37	0.50
	Anxiety	-0.40	-0.49	0.62	-0.96 to 0.58	
	Depression	0.09	1.00	0.32	-0.49 to 1.49	
2	MBI	0.37	4.39	<0.001*	0.16 to 0.43	
	9HPT	-0.39	5.17	<0.001*	-22.34 to -9.96	0.53
	Days to initial assessment	-0.25	-3.69	<0.001*	-1.31 to -0.39	
	Anxiety	-0.01	-0.15	0.88	-0.82 to 0.71	
	Depression	-0.06	0.71	0.48	-0.64 to 1.35	
	OCSPC					
	TACS	-0.18	-2.50	0.01*	-29.80 to -3.40	
	LACS	0.04	0.56	0.57	-4.24 to 7.57	
	POCS	-0.06	-0.91	0.37	-24.18 to 8.97	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NSA denotes Nottingham Sensory Assessment

Table 15. Beta values, t-test statistics and significance levels for independent T1 variables tested for prediction of ARAT at T3

Step	Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2 after each step
1	ARAT T1 Score	0.46	4.30	<0.001*	0.30 to 0.82	
	MBI	0.20	2.38	0.02*	0.03 to 0.30	
	9HPT	-0.09	-0.96	0.34	-11.76 to 4.12	0.56
	Days to initial assessment	-0.21	-3.09	<0.01*	-1.16 to -0.25	
	Anxiety	-0.05	-0.62	0.53	-0.96 to 0.05	
	Depression	-0.02	-0.25	0.80	-1.08 to 0.83	
2	ARAT T1 Score	0.45	4.19	<0.001*	0.29 to 0.81	
	MBI	0.17	1.19	0.04*	-0.01 to 0.28	
	9HPT	-0.10	-1.01	0.32	-11.92 to 3.88	0.56
	Days to initial assessment	-0.21	-3.13	<0.001*	-1.16 to -0.26	
	Anxiety	-0.03	-0.35	0.73	-0.87 to 0.61	
	Depression	-0.04	-0.47	0.64	-1.20 to 0.74	
	OCSPC					
	TACS	-0.13	-1.87	0.06	-24.71 to 0.74	
	LACS	0.03	0.40	0.69	-4.56 to 6.84	
	POCS	-0.03	-0.46	0.64	-19.73 to 12.22	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NSA denotes Nottingham Sensory Assessment

Table 16. Beta values, t-test statistics and significance levels for independent T1 variables tested for prediction of ARAT at T3 without T1 ARAT as an independent variable

Step	Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2 after each step
1	MBI	0.37	4.51	<0.001*	0.17 to 0.43	
	9HPT	-0.36	-4.65	<0.001*	-21.63 to -8.69	0.48
	Days to initial assessment	-0.27	-3.79	<0.001*	-1.39 to -0.44	
	Anxiety	-0.07	-0.88	0.38	-1.14 to 0.44	
	Depression	0.05	-053	0.60	-0.75 to 1.29	
2	MBI	0.32	3.67	<0.001*	0.12 to 0.40	
	9HPT	-0.36	-4.61	<0.001*	-21.41 to -8.52	0.48
	Days to initial assessment	-0.27	-3.80	<0.001*	-1.39 to -0.44	
	Anxiety	-0.05	-0.57	0.57	-1.03 to 0.57	
	Depression	0.02	0.24	0.81	-0.91 to 1.16	
	OCSPC					
	TACS	-0.14	-1.92	0.06	-27.07 to 0.42	
	LACS	0.05	0.64	0.53	-4.18 to 8.12	
	POCS	-0.02	-0.23	0.82	-19.24 to 15.29	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NSA denotes Nottingham Sensory Assessment

Table 17. Beta values, t-test statistics and significance levels for independent T2 variables tested for prediction of ARAT at T3

Step	Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2 after each step
1	ARAT T2	0.81	11.31	<0.001*	0.67 to 0.95	
	MBI T2	-0.02	-0.47	0.64	-4.82 to 2.97	0.84
	9HPT	-0.09	-1.44	0.15	-9.25 to 1.47	
	NSA Proprioception T2	-0.02	-0.31	0.76	-6.31 to 4.60	
	NSA Tactile Total T2	-0.08	-1.69	0.10	-8.25 to 0.67	
2	ARAT T2	0.83	11.01	<0.001*	-0.68 to 0.98	
	MBI T2	-0.02	-0.48	0.63	-4.90 to 2.99	0.84
	9HPT	-0.08	-1.23	0.22	-8.79 to 2.08	
	NSA Proprioception T2	-0.01	0.12	0.91	-5.31 to 5.98	
	NSA Tactile Total T2	-0.12	-2.15	0.03	-10.58 to -0.42	
	OCSPC					
	TACS	0.05	1.00	0.32	-4.45 to 13.56	
	LACS	0.01	1.46	0.15	-2.66 to 17.61	
	POCS	0.01	0.16	0.87	-3.32 to 3.86	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NSA denotes Nottingham Sensory Assessment

Table 18. Beta values, t-test statistics and significance levels for independent T2 variables tested for prediction of ARAT at T3 with ARAT T1 excluded

Step	Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2 after each step
1	MBI	-0.25	-3.56	<0.001*	-15.16 to -4.32	
	9HPT	-0.63	-9.65	<0.001*	-31.96 to -21.06	0.62
	Proprioception	-0.09	-1.17	0.24	-13.03 to 3.37	
	Tactile sensation	-0.04	-0.57	0.57	-8.68 to 4.80	
2	MBI	-0.25	-3.61	<0.001*	-15.30 to -4.44	
	9HPT	-0.61	-8.88	<0.001*	-30.85 to -19.58	
	Proprioception	-0.09	-1.26	0.24	-13.67 to 3.06	0.63
	Tactile sensation	-0.01	0.07	0.78	-7.24 to 7.73	
	OCSPC					
	TACS	-0.16	-1.49	0.61	-22.74 to 3.25	
	LACS	0.01	0.11	0.57	-14.30 to 16.00	
	POCS	-0.11	-1.69	0.59	-9.65 to 0.78	

TACS denotes Total Anterior Circulation Stroke; LACS denotes Lacunar Stroke; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; MBI denotes Modified Barthel Index; NSA denotes Nottingham Sensory Assessment

Table 19. Ipsilesional Data: Mean, Range, all measures at T1, T2 and T3 and repeated measures tests for differences over time

Measure	***Possible score***	***n***	***Time***	***Mean (sd)***	***Range***	*% of patients scoring less than -maximally*	***Friedman's Test*** X^2	***df***	***p***
ARAT	Min=0 Max=57	106 106 106	T1 T2 T3	56.7(1.7) 56.9(0.9) 57.0(0.2)	(42,57) (48,57) (56,57)	5.7% 2.8% 4.7%	3.2	2	0.19
NSA									
Light Touch	Min=0 Max=8	106 106 106	T1 T2 T3	7.9 (0.5) 8.0 (0.0) 8.0 (0.0)	(4.0, 8.0) (8.0, 8.0) (8.0, 8.0)	6.6% 0.0% 0.0%	0.56	2	0.06
Temperature	Min=0 Max=8	106 106 106	T1 T2 T3	7.7 (1.0) 7.8 (1.0) 7.9 (0.1)	(0.0, 8.0) (0.0, 8.0) (7.0, 8.0)	16% 15.1% 18.9%	0.7	2	0.70
Two Point Discrimination	Min=0 Max=4	106 106 106	T1 T2 T3	2.7 (1.2) 2.6 (0.1) 2.6 (0.9)	(0.0, 4.0) (1.0, 4.0) (1.0, 4.0)	73.6% 75.5% 80.2%	0.56	2	0.76
Stereognosis	Min=0 Max=20	106 106 106	T1 T2 T3	17.4 (2.2) 18.1 (1.2) 18.5 (1.0)	(8.0, 20.0) (15.0, 20.0) (15.0, 20.0)	91..5% 84.9% 85.8%	33.9	2	<0.001*
							F	*df*	*p*
9HPT	Peg/sec	106 106 106	T1 T2 T3	0.48(0.14) 0.53(0.15) 0.53(0.15)	(0.03,0.78) (0.10,0.94) (0.25,0.96)	-	20.79	2, 105	<0.001*

ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test; *denotes significant result $p \leq 0.05$

Table 20. Ipsilesional Data: Post hoc comparisons for ITT data

Measure	Bonferroni Comparison		p
9HPT	T1: T2 T1: T3 T2: T3		<0.001 <0.001 1.000
	Wilcoxon paired tests	*z*	*p*
Stereognosis	T1:T2 T1:T3 T2:T3	-3.10 -4.66 -1.36	<0.01 <0.001 0.14

ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test

Table 21. Ipsilesional ARAT, 9HPT and NSA: Mean scores (SD), range and comparisons between patients with right and left sided hemispheric damage

Measure	*Time*	*Hemiplegic side: Right*			*Hemiplegic side: Left*			*Kruskall Wallis Tests*		
		n	*Mean (sd)*	*Range*	*n*	*Mean (sd)*	*Range*	X^2	*df*	*p*
ARAT	T1	52	56.8 (1.1)	(51,57)	54	56.6 (2.2)	42, 57	0.00	1	0.98
	T2	52	56.9 (0.4)	(54,57)	54	56.8 (1.2)	48, 57	0.00	1	0.99
	T3	52	56.9 (0.2)	(56,57)	54	56.9 (0.1)	56, 57	0.01	1	0.91
NSA										
Light Touch	T1	52	7.9 (0.6)	(4.0, 8.0)	54	7.9 (0.4)	(5.0, 8.0)	1.12	1	0.29
	T2	52	8.0 (0.0)	(8.0, 8.0)	54	8.0 (0.0)	(8.0, 8.0)	0.00	1	1.00
	T3	52	8.0 (0.0)	(8.0, 8.0)	54	8.0 (0.0)	(8.0, 8.0)	0.00	1	1.00
Temperature	T1	52	7.8 (0.7)	(4.0, 8.0)	54	7.7 (1.3)	(0.0, 8.0)	0.52	1	0.47
	T2	52	7.9 (0.6)	(4.0, 8.0)	54	7.6 (1.3)	(0.0, 8.0)	1.56	1	0.21
	T3	52	8.0 (0.1)	(7.0, 8.0)	54	8.0 (0.1)	(7.0, 8.0)	0.00	1	0.98
Two Point Discrimination	T1	52	2.7 (1.2)	(0.0, 4.0)	54	2.7 (1.3)	(0.0, 4.0)	1.00	1	0.32
	T2	52	2.7 (1.0)	(1.0, 4.0)	54	2.6 (1.0)	(1.0, 4.0)	0.75	1	0.39
	T3	52	2.6 (0.8)	(1.0, 4.0)	54	2.6 (0.9)	(1.0, 4.0)	0.01	1	0.97
Stereognosis	T1	52	17.5 (2.0)	(8.0, 20.0)	54	17.3 (2.4)	(9.0, 20.0)	0.01	1	0.92
	T2	52	18.0 (1.0)	(15.0, 20.0)	54	18.3 (1.3)	(15.0, 20.0)	3.04	1	0.08
	T3	52	18.4 (0.8)	(17.0, 20.0)	54	18.5 (1.1)	(15.0, 20.0)	0.12	1	0.72
								Independent samples t-test		
								t	*df*	*P(95% CI)*
9HPT (pegs/sec)	T1	52	0.48 (0.13)	(0.14, 0.75)	54	0.49 (0.15)	0.03, 0.78	0.19	104	0.85 (-0.05 to 0.06)
	T2	52	0.52 (0.15)	(0.16, 0.94)	54	0.53 (0.15)	0.10, 0.79	0.29	104	0.77 (-0.05 to 0.06)
	T3	52	0.53 (0.14)	(0.25, 0.96)	54	0.54 (0.16)	0.26, 0.83	0.44	104	0.66 (-0.04 to 0.07)

ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test

Table 22. Associations between the ARAT and 9HPT and MBI at T1, T2, T3: Correlation coefficients and p values

N=106	MBI Score(SD)		ARAT T1	9HPT (pegs/sec) T1	ARAT T2	9HPT (pegs/sec) T2	ARAT 18 week	9HPT (pegs/sec) 18 weeks
MBI T1	61.9 (24.6)	Correlation coefficient *P*	0.02 0.84	0.27 0.01*				
MBI T2	84.1 (18.0)	Correlation coefficient *P*			-0.06 0.58	0.29 0.00*		
MBI T3	84.9 (19.6)	Correlation coefficient *P*					-0.01 0.93	0.43 0.00*

MBI denotes Modified Barthel Index; ARAT denotes Action Research Arm Test; 9HPT denotes Nine Hole Peg Test

Table 23. Ipsilesional effects of BT and UT training on change in activity limitation: Mean, median, standard deviation, between group comparison for the ARAT

ARAT Total T1, T2, T3 Change T1 to T2 and T1 to T3 *(max=57)*	*BTTraining (n=51) Mean(Median)*	*SD*	*UTTraining (n=46) Mean(Median)*	*SD*	X^2	*df*	*p*
T1	56.9 (57.0)	0.7	56.4 (57.0)	2.4	1.02	1	0.31
T2	56.9 (57.0)	0.4	56.8 (57.0)	1.3			
T3	57.0 (57.0)	0.2	57.0 (57.0)	0.1			
ChangeT1-T2	0.1(0.0)	0.4	0.4(0.0)	2.2	0.50	1	0.48
ChangeT1-T3	0.1 (0.0)	0.6	0.4 (0.0)	2.2	0.15	1	0.70

Table 24. Ipsilesional effects of BT and UT training on change in dexterity: Mean, median, standard deviation, between group comparison for the 9HPT pegs/sec

9HPT T1, T2, T3 Change T1 to T2 and T1 to T3	*BTTraining (n=51) Mean(Median)*	*SD*	*UTTraining (n=46) Mean(Median)*	*SD*	*t*	*df*	*P (95% confidence interval for difference in means)*
T1	0.54(0.54)	0.15	0.51 (0.52)	0.14	0.15	104	0.88 (-0.05 to 0.06)
T2	0.54(0.54)	0.15	0.51(0.53)	0.14			
T3	0.53(0.52)	0.16	0.54 (0.53)	0.14			
ChangeT1-T2	0.06(0.07)	0.09	0.02 (0.02)	0.09	-2.08	104	0.04*† (-0.07 to -0.00)
ChangeT1-T3	0.04(0.04)	0.10	0.05 (0.04)	0.11	0.18	104	0.86 (-0.04 to 0.05)

* indicates $p \leq 0.05$ † indicates difference in significance in terms of $p \leq 0.05$ with compared to Intention to Treat Analysis

Table 25. Repeated Measures ANOVA: HADS

Measure	Time	BT Group N=45	UT Group N=39	Source of variance		df	F	p
HADS Depression	T1	6.1(3.2)	6.6(3.6)	Within Subject	Time	2	11.04	<0.001
	T2	5.8(3.3)	5.7(3.6)		Time x Group	2	1.33	0.27
	T3	5.2(3.5)	4.7(2.9)					
				Between Subject	Group	1	0.06	0.94
HADS Anxiety	T1	6.5(4.1)	5.9(3.3)	Within Subject	Time	2	5.29	0.01*†
	T2	5.7(3.9)	5.6(3.9)		Time x Group	2	1.72	0.18
	T3	5.1(4.0)	4.9(3.2)					
				Between Subject	Group	1	0.05	0.81

HADS denotes Hospital Anxiety and Depression Scale

*denotes $p \leq 0.05$ † denotes a difference in terms of significance between Complete Case Analysis and Intention to Treat Analysis

Table 26. Mixed ANOVA: NHP total score and sub-sections

Measure	Time	BT Group N=45	UT Group N=39	Source of variance		df	F	p
NHP Total	T1	180.4(121.3)	174.3 (118.1)	Within Subject	Time	2	35.04	<0.001
	T2	126.1(105.9)	103.9 (89.2)		Time x Group	2	1.45	0.49
	T3	122.6(110.3)	91.9 (91.8)					
				Between Subject	Group	1	1.04	0.31
Emotional Reactions	T1	23.1(25.3)	19.6(21.9)	Within Subject	Time	2	5.99	<0.001
	T2	14.8(23.6)	11.7(16.9)		Time x Group	2	0.19	0.83
	T3	14.2(25.5)	10.1(19.5)					
				Between Subject	Group	1	1.46	0.23
Energy Levels	T1	42.5(36.6)	39.9 (33.9)	Within Subject	Time	2	13.64	<0.001
	T2	30.8(35.7)	22.9(28.2)		Time x Group	2	0.70	0.50
	T3	28.3(34.1)	19.8 (27.1)					
				Between Subject	Group	1	0.81	0.37
Sleep	T1	33.8(35.1)	36.2 (32.1)	Within Subject	Time	1.81	17.16	<0.001
	T2	20.3(27.3)	23.5 (26.0)		Time x Group	1.76	0.87	0.41
	T3	20.4(28.8)	14.8(21.0)					
				Between Subject	Group	1	0.37	0.54
Social Isolation	T1	20.5(23.7)	18.9(22.5)	Within Subject	Time	1.88	11.77	<0.001
	T2	11.7(19.8)	8.6(14.9)		Time x Group	1.88	1.73	0.18
	T3	16.7(20.9)	7.7(15.8)					
				Between Subject	Group	1	2.26	0.24
Pain	T1	12.2(19.5)	15.6 (24.3)	Within Subject	Time	1.88	0.31	0.72
	T2	14.6(20.9)	8.2 (13.2)		Time x Group	1.88	2.15	0.12
	T3	10.2(17.5)	10.9 (15.6)					
				Between Subject	Group	1	0.02	0.88
Physical Activity	T1	51.7(24.2)	44.7(25.7)	Within Subject	Time	1.83	39.19	<0.001
	T2	33.8(24.4)	28.8(24.4)		Time x Group	1.83	0.04	0.96
	T3	33.3(20.7)	27.6(23.4)					
				Between Subject	Group	1	1.98	0.16

NHP denotes Nottingham Health Profile

Table 27. Predictors of Total NHP Score at T3: beta, significance and adjusted R^2

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.43	4.57	0.00*	0.30 to 0.75	0.479
Depression	0.26	2.83	0.01*	0.11 to 0.62	
MBI	0.06	0.67	0.49	-0.45 to 0.93	
RMA	-0.19	-2.51	0.01*†	-0.42 to -0.05	
Hand dominance	-0.13	-1.75	0.08	-2.45 to 0.15	
Gender	-0.07	-1.03	0.30	-2.07 to 0.65	

NHP denotes Nottingham Health Profile, RMA denotes Rivermead Motor Assessment, MBI denotes Modified Barthel Index
† denotes a difference in terms of significance between Complete Case Analysis and Intention to Treat Analysis

Table28. Predictors of NHP Energy at T3: beta, significance and adjusted R^2

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.41	3.78	0.00*	0.17 to 0.55	0.302
Depression	0.26	2.46	0.02*	0.05 to 0.49	
MBI	-0.17	1.90	0.06	-0.02 to 1.05	

MBI denotes Modified Barthel Index

Table 29. Predictors of NHP Pain at T3: beta, significance and adjusted R^2

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.32	2.68	0.01*	0.01 to 0.09	0.116
Depression	0.04	0.34	0.74	-0.04 to 0.05	

Table 30. Predictors of NHP Emotional Reactions at 18 weeks: beta, significance and adjusted R^2

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.45	4.72	0.00*	0.04 to 0.11	0.406
Depression	0.16	1.64	0.10	-0.07 to 0.07	
Hand dominance	-0.17	-1.33	0.19	-0.54 to 0.12	
Side of stroke	0.11	0.85	0.40	-0.18 to 0.46	

Table 31. Predictors of NHP Sleep at 18 weeks: beta, significance and adjusted R^2 at each step

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.26	0.28	0.02*	0.01 to 0.10	0.094
Depression	0.19	0.04	0.75	-0.05 to 0.06	
MBI	0.15	0.08	0.45	-0.18 to 0.40	

Table 32. Predictors of NHP Social Isolation at 18 weeks: beta, significance and adjusted R^2 at each step

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Anxiety	0.30	2.70	0.01*	0.02 to 0.10	0.222
Depression	0.15	1.32	0.19	-0.02 to 0.08	
MBI	0.02	0.22	0.83	-0.11 to 0.13	
Side of stroke	0.07	0.47	0.64	-0.30 to 0.49	
Dominant side affected	-0.20	-1.36	0.18	-0.67 to 0.13	

† denotes difference in significance from the complete case analysis

Table 33. Predictors of NHP physical activity at 18 weeks: beta, significance and adjusted R^2

Predictor Variable	Beta	t	p	95% Confidence Interval for B	Adjusted R^2
Age	0.19	2.21	0.03*	0.03 to 0.61	0.369
Gender	-0.16	-1.98	0.05*	-13.23 to 0.01	
Days to hospital discharge	-0.02	-0.27	0.79	-0.03 to 0.02	
RMA	-0.34	-3.79	0.00*	-2.77 to -0.86	
MBI	-0.13	-1.35	0.18	-5.85 to 1.12	
Anxiety	0.17	1.66	0.10	-0.18 to 2.05	
Depression	0.14	1.38	0.17	-0.38 to 2.13	
Proprioception	-0.01	-0.16	0.87	-0.04 to 0.05	

Appendix 15

Proposal funded by the Chief Scientist Office

TITLE An Investigation of Bilateral Simultaneous Upper Limb Task Training in Acute Stroke: A Randomised Controlled Trial

1. INTRODUCTION

Stroke is the main cause of adult disability, with approximately 13000 people in Scotland treated for stroke in hospital annually (1). Accounting for 5.5% of total hospital costs, stroke presents a considerable cost challenge to health and social services (2). Dependence resulting from stroke means that the cost of care is considerable. Lifetime costs for those with major impairment, including rehabilitation and nursing home care have been estimated at £76,000 per person and at £28,000 per person for minor impairment (3). Epidemiological studies show that 30-40% of patients remain dependent in activities of daily living, and that few return to previous vocational or leisure activities (4). Dependence in activities of daily living adversely influences quality of life for stroke sufferers, and between 23 and 27% suffer from depression after stroke (5).

Carers of those discharged home from hospital with disability in skills of daily living suffer disruption to social and leisure activities and are also influenced emotionally. Depression and emotional distress in carers is common, and more likely when the stroke sufferer has a poor physical outcome (6). Activities of everyday living that cause most distress to carers who assist in these tasks, were shown in one study to be bathing and continence. Grooming and feeding, activities whose performance requires good arm function, were also found to be distressing for carers (7).

Arm recovery following stroke is typically poor, with studies indicating that the upper limb remains with incomplete function in between 27 and 60% of cases, depending on initial weakness, with only 5-20% of cases demonstrating full recovery (8).

Physiotherapy plays a major role in the rehabilitation of stroke patients, and many treatment approaches to enhance arm recovery are currently available. There is some evidence that treatments such as electromyographic biofeedback (9), motor and sensory stimulation (10) and forced use (11) can enhance upper limb recovery, but many of these studies demonstrate methodological weaknesses such as small numbers of patients and inadequate controls. Exercise is more commonly used in physiotherapy to enhance arm recovery, and a recent systematic review suggested that increased intensity of exercise is beneficial (12). Although it is not yet clear which type of exercise is most beneficial, specific training of everyday reaching tasks, often found difficult by stroke patients, has in one randomised, controlled trial been shown to lead to improvements in performance of the specific tasks being trained (13).

A potentially important approach to training of everyday upper limb tasks after stroke, that has as yet received little attention, is bilateral simultaneous task training, in which both limbs simultaneously but independently perform identical functional tasks. Clinically observed immediate changes in movement timing and quality seem to occur immediately in the affected arm when practising tasks in this way. Whilst in daily life it is uncommon for each arm to perform exactly the same task independently but simultaneously, there is some theoretical support for use of this

technique as part of a rehabilitation programme for retraining arm function in stroke patients.

It has been proposed that in stroke, neural pathways descending from the ipsilateral, undamaged side of the brain may be activated during performance of simultaneous identical bilateral tasks (14,15). This hypothesis is supported by studies using neuroimaging techniques such as functional MRI and positron emission tomography, which indicate that activity patterns in the brain reorganise following stroke, and that the undamaged side of the brain becomes more active than normal during use of the affected arm. This increased activity on the undamaged side of the brain may represent an important component of motor recovery in stroke (16). Performance of tasks using both arms simultaneously may harness this reorganisation to facilitate functional recovery of the affected arm early after stroke, but the effectiveness of the technique has not yet been evaluated in acute patients. Since most arm recovery occurs between three weeks and three months after onset of stroke (17), intervention aimed at maximising function in the acute phase is critical.

Studies using bilateral simultaneous approach in therapy to date have shown promising results, but only with patients with longstanding stroke. Two small studies using single case series design (14, 15) demonstrated improved task performance, measured using standardised motion analysis, following bilateral simultaneous training of the tasks, compared to practice with one arm only, hands linked or each arm performing different tasks. In some patients, following bilateral practice, movement parameters were brought to within normal range, a change in performance that could be considered clinically significant. In an uncontrolled single group study, clearly a design with methodological limitations, Whitehall et al (18), using bilateral reaching with auditory cueing, demonstrated improved functional performance and, of clinical significance, these patients with stroke of more than 6 months duration, reported increased daily use of the arm.

It is not known if this approach is effective in improving upper limb function soon after stroke, nor whether it is most beneficial for patients with greater or lesser initial weakness. The purpose of this study is therefore to investigate the effectiveness of simultaneous bilateral upper limb task training on upper limb disability in acute stroke patients.

3. RESULTS OF PILOT STUDY

Ninewells Hospital admits approximately 400 stroke patients annually all of whom are routinely assessed by the physiotherapists for participation in rehabilitation. To establish the feasibility of a study to examine the effectiveness of bilateral simultaneous task training, we conducted a small pilot to examine firstly, what proportion of our patients would meet the inclusion criteria for the study, and secondly, whether patients would be willing to participate in such a study. The pilot was conducted over two months, and patients were assessed on admission by the physiotherapists on the acute stroke team, using the screening tools that we plan to use in the study. Of 73 patients admitted during the pilot phase, 12 patients met our inclusion criteria on initial assessment and all agreed to participate in such a study. Other upper limb studies with similar populations and inclusion criteria indicate likely recruitment rates of between 10 and 22% (19, 20), with 1% of patients refusing

to participate. Taking account of these studies, and our pilot study, we have assumed that we might recruit approximately 16% of patients. Recruitment will be carried out over 27 months, which on this basis would enable us to recruit 146 potential patients, which accounting for attrition and refusal to participate would enable us to fulfil our sample requirements of 106.

4. AIMS

a) To establish if simultaneous bilateral task training of the hemiplegic upper limb in acute stroke improves functional upper limb recovery more than unilateral training; **b)** to investigate whether the training is most beneficial for patients with more or less severe initial impairment; **c)** to establish if the intervention has any impact on post-stroke depression and quality of life.

5. RESEARCH QUESTIONS

Primary Research Question: Does bilateral simultaneous upper limb task training improve upper limb disability, dexterity and impairment in acute stroke more than unilateral task training?

Secondary research questions: a) Do patient sub-groups identified by severity of initial impairment respond differently to this training? **b)** Does bilateral upper limb task training improve quality of life and depression in these patients more than unilateral training?

We hypothesise that bilateral, simultaneous task training of the hemiplegic upper limb in the acute post-stroke period is significantly better than unilateral task training in reducing upper limb disability and impairment, and in improving dexterity.

6. PLAN

This study will be a randomised, controlled trial with blinded outcome assessment.

SAMPLE

The acute Medical Unit in Ninewells Hospital admits 400 new stroke patients annually, and the sample will be drawn from consecutively admitted stroke patients. Potential subjects for the study will be identified through screening of medical records of all admitted stroke patients. The research physiotherapists will screen likely participants following admission with stroke and will recruit patients meeting the following **Inclusion Criteria:**

1. Acute unilateral stroke, confirmed by CT scan carried out between 2 and 7 days after onset. Patients will be recruited between 2 and 4 weeks after stroke onset provided they meet all other inclusion criteria.
2. Persistent upper limb motor impairment lasting 48 hours or more, defined by scores of < 6 on any of the upper limb sections of the **Motor Assessment Scale.**
3. Ability to participate in standard 30-minute physiotherapy sessions defined by a) evidence of preserved cognitive function, indicated by scores of 0 or 1 on consciousness, communication and neglect items of the **NIH Stroke Scale** and b) the ability to sit unsupported for 1 minute.

Exclusion Criteria:

1. Previous stroke resulting in residual disability
2. Inability to provide informed consent due poor comprehension or communication

3. Premorbid upper limb impairment or hemiplegic shoulder pain

RECRUITMENT

The Motor Assessment Scale upper limb Sections and NIHSS will be used as screening tools for inclusion to the study, and will be carried out by the research physiotherapists following admission. Ability to tolerate normal physiotherapy sessions will be confirmed in liaison with the patient's normal physiotherapist between 2 and 4 weeks after stroke onset. Provided the patient fulfils all inclusion criteria, they will be asked to consent to participate in the study.

RANDOMISATION

Patients recruited to the trial will be randomised into either a control group or a bilateral task training group using web based computer randomisation. To ensure equal numbers of patients with left and right-sided hemiplegia in each group, stratification will be applied based on side of hemiplegia.

SAMPLE SIZE

We intend to use change in the Action Research Arm Test (ARAT) score as response variable. Van der Lee (1999) suggests that a difference of 10% of maximum action Research Arm Test may represent a minimal clinically significant difference. This is approximately 6 units. Powell (1999) shows changes in standard deviation of the ARAT of 12.7 and 9.0 in study groups. Assuming an average standard deviation of 11 units suggests that sample sizes of 53 in each group will have 79% power to detect a difference in means of 6 units at 5% significance level

BASELINE AND OUTCOME DATA COLLECTION

Will be carried out by an independent rater who is blinded to the treatment allocation and not otherwise involved in the study. The rater will be a stroke research nurse with many years of experience of this type of data collection with acute stroke patients. Baseline measurements will be carried out on all patients in hospital prior to intervention. All patients will then receive six weeks of control or experimental intervention. Those patients discharged home within the six weeks intervention period will continue to receive the intervention until six weeks from commencement, but twice per week instead of daily. Measurements will be carried out for all patients at the end of the six weeks intervention and three months following the end of intervention.

MEASURES

Patient Characteristics

Age, Sex, Handedness, Ischaemic or Haemorrhagic stroke, Side of Hemiplegia.

All outcome measures are standardised tests, widely used in stroke trials, with established reliability and validity.

Primary Outcome Measure

Upper Limb Disability: **The Action Research Arm Test**

Secondary Outcome Measures

Motor Impairment: **The Rivermead Motor Assessment**

Dexterity: **The Nine Hole Peg Test**

Sensory deficit: **The Nottingham Sensory Assessment**
Activities of Daily Living: **The Barthel Index**
Quality of Life: **The Nottingham Health Profile**
Depression and Anxiety: **The Hospital Anxiety and Depression Scale**
Time to Discharge: **Number of days spent in hospital**

TREATMENT

Timing

The total study duration will be 36 months. Patients will be recruited and start intervention if they meet inclusion criteria between 2 and 4 weeks after stroke onset. Intervention will be every weekday for 6 weeks. Initial intervention will take place in Ninewells Hospital, and will continue at the rehabilitation hospital, Ashludie Hospital, 10 miles away if patients are transferred there within the intervention period. Recruited patients who are discharged home within the intervention period will continue the 6 weeks study intervention at home with treatment twice per week.

Intervention

To ensure that improved upper limb function as a result the experimental intervention is not due simply to increased intensity of therapy, patients in both groups will receive the experimental or control treatment in addition to standard intervention from their normal therapist. Standard upper limb treatment is based on an approach which encourages normal movement, and in which any treatment is conducted unilaterally.

Bilateral Task Training Group

Patients in this group will undertake bilateral simultaneous practice of the tasks in the experimental training protocol, using both arms independently but simultaneously.

Control Group

Patients in this group will undertake unilateral practice of the tasks in the experimental training protocol, using the hemiplegic arm only.

Experimental Training Protocol

1. Intervention will be shared by two research physiotherapists both of whom have experience in stroke treatment and have received the standard training for therapists working in this speciality.
2. The treatment will be carried out in a room away from the normal treatment area. Rooms are available both in Ashludie Hospital and in Ninewells Hospital for this purpose and their use has been agreed with physiotherapy managers.
3. Activities (a-d) described below, and representing essential reaching, grasping and pointing tasks found difficult by stroke patients comprise the experimental intervention. These tasks are similar to those used by Mudie (18) in their bilateral training study.
4. The therapist will carry out the activities passively where the patient has insufficient activity in the affected arm to participate actively; encouraging participation until independent movement is regained.
5. All activities will be carried out 30 times each, interspersed by rest after 10 trials.
6. To identify any confounding variables, normal therapy interventions will be monitored through review of therapy records for each patient at the end of the experimental treatment.

Patients will be withdrawn from the trial if they develop upper limb or shoulder discomfort or if they find the experimental treatment too tiring. It is envisaged that each daily intervention will take approximately 20 minutes.

Activities – these will be carried out at a table using equipment that can be transported to each site and the patient's home. Starting positions and seating will be standardised.

a) Reach to point to 3 targets raised 30cm from the table and positioned in front, 50cm to the right and 50cm to the left of midline.
b) Grasp a cup, take to the mouth and return to starting position
c) Move a 7cm block from table onto a shelf at shoulder height
d) Move a peg 2x4cm from table to touch underside of a shelf placed at eye level.

ANALYSIS

Data will be analysed using SPSS. The differences in scores on primary and secondary outcome measures will be analysed using two sided t-tests and confidence limits for differences in means. For some scales, equivalent non-parametric tests will be used. Motor Assessment upper limb scores from initial screening will be used to categorise severity of impairment for sub-group analysis.

To ensure data quality, two persons, the independent rater and one of the researchers will independently code, enter and input data to the computer. A third researcher will check the data for inconsistencies.

EXPERTISE AVAILABLE

The research team involves a consultant physician (RSM) with extensive experience in conducting and supervising quantitative trials of stroke treatment. Two research physiotherapists, one of whom is a co-applicant (JM), have the training and experience standard to therapists working in acute stroke rehabilitation, and will share the task of carrying out the treatment intervention. One therapist (JM) is in the final stages of a MSc in Physiotherapy, has recently completed a research training programme at the University of Dundee and will be involved in data analysis and writing up. The research nurse, who will be employed as the independent rater, has experience of this type of data collection and has carried out this role in many stroke studies. The final member of the research team is a medical statistician (SO), with extensive knowledge and experience of analysis in this type of trial, and who will provide statistical advice.

7. TIMETABLE

Months	Preparation of data collection sheets, training of independent rater	Patient recruitment and implementation of training protocol	Baseline and outcome measurements	Data analysis and writing up
1	[redacted]			
2-27		[redacted]	[redacted]	
28-33			[redacted]	
34-36				[redacted]

8.EXISTING FACILITIES

The research physiotherapists employed on this project will be based within the Department of Physiotherapy at Ninewells Hospital. This department, as well as treatment rooms will provide office space, secretarial support and use of general office equipment. The physiotherapists will work in collaboration with and under supervision of the consultant physician specialising in stroke medicine within the Department of Medicine and Cardiovascular at Ninewells Hospital and Medical School, a department with a strong history of NHS research into stroke and vascular conditions. The department will provide software packages for data entry and analysis.

JUSTIFICATION OF REQUIREMENTS

Our estimates indicate that recruitment of 106 patients will take twenty-seven months and with time for follow up data collection, analysis and writing up, the total project time will be 36 months. This timescale was estimated from records of stroke patients transferred to rehabilitation and home during the last two years, from the small feasibility study we conducted and from the literature. One month will be required to train the independent rater who is a stroke research nurse with extensive experience in this type of data collection. It is necessary to recruit to this position an individual with an understanding of stroke, clinical skills and data collection skills and consequently the grading G reflects this. Physiotherapy treatment of acute stroke patients requires individuals trained and clinically skilled in treating and communicating with these patients. This justifies the grading of Senior 1. Travel costs are required because patients will be spread over two sites and may be discharged home during the participation period. A laptop computer is necessary, with sufficient memory to run SPSS that the independent rater can use when travelling between sites. All other small equipment is required either for treatment or as tools for the outcome measures.

9. RESEARCH OUTCOMES RELATING TO THE NHS IMPLEMENTATION POTENTIAL

We anticipate that findings of this study will establish the effectiveness of an alternative approach to upper limb rehabilitation in acute stroke that addresses tasks often found difficult by stroke patients. Additionally, the study will provide knowledge to contribute to understanding of neural reorganisation during recovery from stroke. Enhanced upper limb recovery for these patients should improve their performance of activities of daily living, increasing the likelihood of these patients returning to independent life in the community. Better arm recovery should improve quality of life and may positively influence post-stroke depression as well as offering patients increased potential for participation in social and vocational activities. Reduced dependency will relieve carer burden, improving quality of life for those required to assist in basic daily activities of living. Better arm recovery and consequent improved performance in activities of daily living early following stroke should reduce time in rehabilitation and therefore rehabilitation costs. Therapists will benefit from evidence of an alternative treatment strategy that is easily carried out, is relevant to functional tasks and that is inexpensive.

11. DISSEMINATION

Results of the study will be disseminated through:

Publication in appropriate peer reviewed medical and therapy journals

Forwarding of results to Acute Stroke Units and appropriate Rehabilitation Centres across Scotland.

Presentation at Scottish, national and international therapy and medical conferences

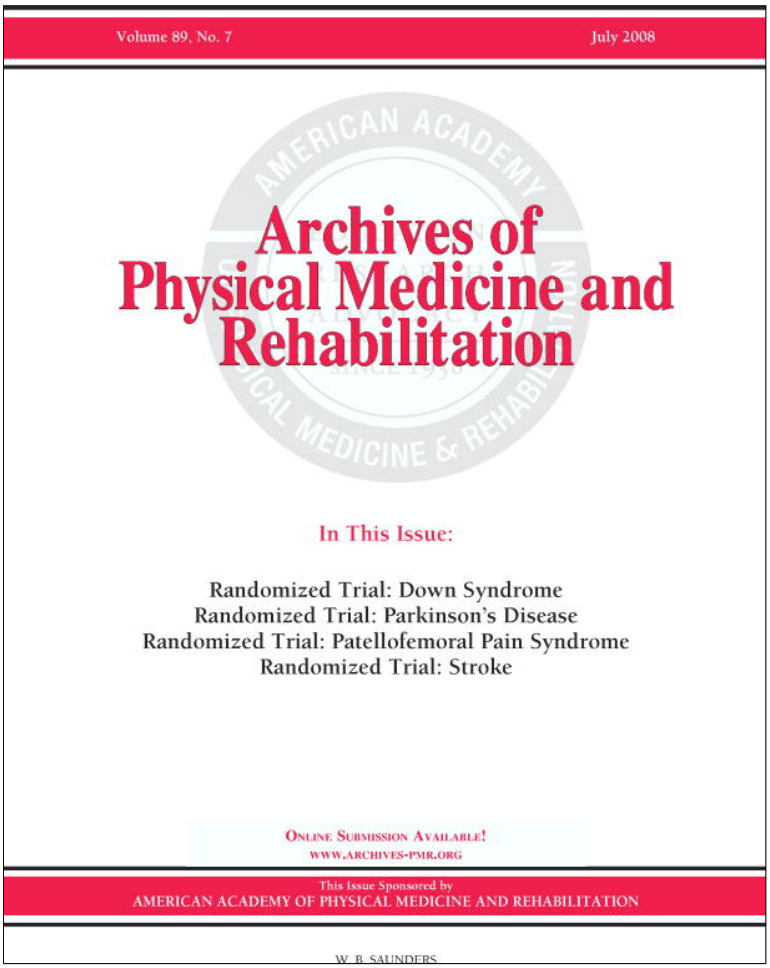
Presentation through lectures at therapy meetings and local and national special interest groups, such as the Association for Physiotherapists Interested in Neurology. We intend to apply separately for CSO funding for this purpose.

REFERENCES

1. **The Scottish Office (1998).** www.show.scot.nhs.uk
2. **Isard. P, Forbes J (1992).** The cost of stroke to the NHS in Scotland. Cerebrovascular Diseases, 2, 47-50.
3. **Caro J J, Huybrechts K F (1999).** Stroke treatment economic model (STEM). Predicting long term costs from functional status. Stroke 30. 2574-2579.
4. **Dobkin B (1995).** The economic impact of stroke. Neurology, 45, (suppl 1) S6-S9.
5. **Herrmann N, Black S, Lawrence R, Szkley C, Szalai (1998).** The Sunnybrooke stroke study. A prospective study of depressive symptoms and functional outcome. Stroke 29, 618-24.
6. **Dennis M, O'Rourke S, Lewis S, Sharpe M, Warlowe C (1998).** A quantitative study of the emotional outcome of people caring for stroke survivors. Stroke 29, 9, 1867-72.
7. **Andersen C S, Linto J, Stewart-Wynne E G (1995).** A population based assessment of the impact and burden of caregiving for long-term stroke survivors. Stroke, 26, 843-849.
8. **Nakayama H, Jorgenson HS, Raaschou HO, Olsen TS (1994).** Recovery of upper extremity function in stroke patients: The Copenhagen Stroke Study. Archives of Physical Medicine and Rehabilitation 75, 394-398.
9. **Crowe JL, Lincoln N, Nouri FM, DeWeet W (1989)** The Effectiveness of biofeedback in the treatment of arm function after stroke. International Disability Studies, 11, 155-160.
10. **Feys HM, DeWeet W, Beat ES, Cox Steck, Spichiger R Vereek L (1998).** Effect of a therapeutic intervention for the hemiplegic upper limb in the acute phase of stroke. Stroke 29, 785-792.
11. **Van derLee JH, Wagenaar, Lankhorst G J, Vogelaar TW, Deville WL, Bouter LM (1999).** Forced Use of the Upper Extremity in Chronic Stroke patients**.** Stroke 30, 2369-2375
12. **Van der Lee JH, Snels IAK, Beckermann H, Lankhorst GJ, Wagenaar RC et al (2001).** Exercise therapy for arm function in stroke patients: a systematic review of randomised controlled trials. Clinical Rehabilitation, 15, 20-30.
13. **Dean CM, Shepherd RB (1997).** Task–related training improves performance of seated reaching tasks after stroke. Stroke 28,722-728.
14. **Mudie HM, Matayas T (1996).** Upper extremity retraining following stroke: effects of bilateral practice. Journal of Neurological Rehabilitation, 10, 167-184.
15. **Mudie HM, Matayas T (2000).** Can simultaneous bilateral movement involve the undamaged hemisphere in reconstruction of neural networks damaged by stroke? Disability and Rehabilitation, 22, 23-37.
16. **Nelles G, Spiekerman G, Jeuptner M, Leonhardt G, Muller S, Gerhard H (1999).** Reorganisation of sensory and motor systems in hemiplegic stroke patients: A positron emission tomography study. Stroke 30, 1510-1516.
17. **Skilbeck CE, Wade DT, Langton Hewer, Wood VA (1983).** Recovery after stroke. Journal of Neurology, Neurosurgery and Psychiatry, 46, 5-8.
18. **Whitall J, Waller S, Silver K, Macko RF (2000).** Repetitive bilateral arm training with auditory cueing improves motor function in chronic hemiparetic stroke. Stroke, 31, 2390-2395.
19. **Powell J, Pdyan D, Granat M, Cameron M, Stott D (1999)** Electrical Stimulation of Wrist Extensors in post-Stroke Hemiplegia. Stroke 30, 1384-1389

Appendices 16 and 17

Publications from this thesis



ORIGINAL ARTICLE

A Comparison of Bilateral and Unilateral Upper-Limb Task Training in Early Poststroke Rehabilitation: A Randomized Controlled Trial

Jacqui H. Morris, MSc, Frederike van Wijck, PhD, Sara Joice, PhD, Simon A. Ogston, PhD, Ingrid Cole, BSc, Ronald S. MacWalter, MD

ABSTRACT. Morris JH, van Wijck F, Joice S, Ogston SA, Cole I, MacWalter RS. A comparison of bilateral and unilateral upper-limb task training in early poststroke rehabilitation: a randomized controlled trial. Arch Phys Med Rehabil 2008;89: 1237-45.

Objective: To compare the effects of bilateral task training with unilateral task training on upper-limb outcomes in early poststroke rehabilitation.

Design: A single-blinded randomized controlled trial, with outcome assessments at baseline, postintervention (6wk), and follow-up (18wk).

Setting: Inpatient acute and rehabilitation hospitals.

Participants: Patients were randomized to receive bilateral training (n=56) or unilateral training (n=50) at 2 to 4 weeks poststroke onset.

Intervention: Supervised bilateral or unilateral training for 20 minutes on weekdays over 6 weeks using a standardized program.

Main Outcome Measures: Upper-limb outcomes were assessed by Action Research Arm Test (ARAT), Rivermead Motor Assessment upper-limb scale, and Nine-Hole Peg Test (9HPT). Secondary measures included the Modified Barthel Index, Hospital Anxiety and Depression Scale, and Nottingham Health Profile. All assessment was conducted by a blinded assessor.

Results: No significant differences were found in short-term improvement (0−6wk) on any measure ($P>.05$). For overall improvement (0−18wk), the only significant between-group difference was a change in the 9HPT (95% confidence interval [CI], 0.0−0.1; $P=.05$) and ARAT pinch section (95% CI, 0.3−5.6; $P=.03$), which was lower for the bilateral training group. Baseline severity significantly influenced improvement in all upper-limb outcomes ($P<.05$), but this was irrespective of the treatment group.

Conclusions: Bilateral training was no more effective than unilateral training, and in terms of overall improvement in dexterity, the bilateral training group improved significantly less. Intervention timing, task characteristics, dose, and intensity of training may have influenced the results and are therefore areas for future investigation.

Key Words: Cerebrovascular accident; Motor activity; Randomized controlled trial; Rehabilitation; Upper extremity.

ARM RECOVERY AFTER STROKE is typically poor, with 20% to 80% of patients showing incomplete recovery depending on the initial impairment.[1,2] Upper-limb dysfunction in stroke is characterized by paresis, loss of manual dexterity, and movement abnormalities that may impact considerably on the performance of ADLs.[3]

Previous research[4] has typically focused on motor learning approaches involving unilateral training of the hemiplegic arm. Recently, however, bilateral training, in which patients practice identical activities with both upper limbs simultaneously, has been proposed as a strategy to improve hemiplegic upper-limb control and function.[5-9] Control of bilaterally identical synchronous movement appears to occur centrally through bilaterally distributed neural networks linked via the corpus callosum and involving cortical and subcortical areas.[10] These networks indicate a common facilitatory drive to both motor cortices thought to lead to tight temporal and spatial coupling of limb movement observed during bilaterally identical synchronous voluntary movement.[10,11] Beneficial effects of bilateral training in stroke are assumed to arise from this coupling effect in which the nonparetic limb provides a template for the paretic limb in terms of movement characteristics, facilitating restoration of movement.

Indeed, facilitatory effects observed during bilateral compared with unilateral paretic upper-limb movement in patients with chronic stroke have included increased velocity and smoothness of movement.[12,13] Furthermore, several studies[5-9,14] have indicated that therapeutic bilateral training programs may improve short-

List of Abbreviations

ADLs	activities of daily living
ANOVA	analysis of variance
ARAT	Action Research Arm Test
CI	confidence interval
HADS	Hospital Anxiety and Depression Scale
HRQOL	health-related quality of life
9HPT	Nine-Hole Peg Test
MBI	Modified Barthel Index
NHP	Nottingham Health Profile
RMA	Rivermead Motor Assessment
RCT	randomized controlled trial

From the Alliance for Self-Care Research (Morris, Joice), Community Health Sciences, (Ogston), and Department of Medicine and Therapeutics (MacWalter), University of Dundee, Dundee, UK; School of Health Sciences, Queen Margaret University, Edinburgh, UK (van Wijck); and Departments of Physiotherapy, Ninewells Hospital, Dundee, UK (Morris, Cole).

Presented in part to the UK Stroke Forum, December 7, 2006, Harrogate, UK, and the World Confederation of Physical Therapy Congress, June 4, 2007, Vancouver, BC, Canada.

Supported by the Chief Scientist Office, Scottish Executive Health Department (grant no. CHZ/4/80).

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors or upon any organization with which the authors are associated.

Reprint requests to Jacqui H. Morris, MSc, Clinical Research Fellow, Alliance for Self-Care Research, University of Dundee, 11 Airlie Pl, Dundee DD1 4HJ, UK, e-mail: *j.y.morris@dundee.ac.uk*.

0003-9993/08/8907-00557$34.00/0
doi:10.1016/j.apmr.2007.11.039

and long-term unilateral performance of the hemiplegic arm in patients in the chronic poststroke period, suggesting a potential role for bilateral training in influencing poststroke upper-limb recovery of function. Two of those studies were small RCTs,[8,14] whereas others involved case series[5,6,9] or a single-group design[7]; thus, methodologic limitations mean that to date only limited evidence exists to support bilateral training as a rehabilitation strategy. Interventions have been diverse, involving functional tasks,[5,6] simple prefunctional movements,[7,9,14] and electromyographically triggered functional electric stimulation.[8] As a result of this diversity, optimal intervention characteristics remain unclear, and only limited evidence exists to support bilateral training as a rehabilitation strategy.

Little is known about the effectiveness of bilateral training for upper-limb functional outcomes in more acute patients because studies published to date have mainly involved people in the chronic poststroke stage. During the early poststroke period, intensive upper-limb rehabilitation is known to influence short- and long-term outcomes[4]; therefore, the need to determine the effectiveness of bilateral training for patients in this stage is critical. Impairment severity also influences upper-limb recovery[15]; however, the effects of initial severity on responses to bilateral training during early rehabilitation are not known. Furthermore, upper-limb impairment influences poststroke quality of life as a significant predictor of low subjective well-being at 1 year[16] and is associated with poststroke depression.[17] However, the effects of bilateral training on these outcomes have not previously been examined.

The purpose of this study was first to compare effects of bilateral simultaneous upper-limb task training to conventional unilateral upper-limb task training on recovery in acute stroke in terms of upper-limb motor performance and activity and independence in ADLs, HRQOL, and mood. Second, we wanted to determine whether responses in relation to upper-limb recovery were related to the severity of the initial impairment.

METHODS

Design

This was an RCT with blinded assessment at baseline, postintervention assessment at 6 weeks, and follow-up assessment at 18 weeks. Participants were recruited from a cohort of stroke patients sequentially admitted to Ninewells Hospital, Dundee, Scotland, a large teaching hospital with acute rehabilitation facilities. Assessment and intervention were conducted there, in associated rehabilitation hospitals, or in participants' homes depending on their rehabilitation status. The Tayside Committee on Medical Research Ethics provided ethics approval.

Participants

Participants were identified from medical records by the lead researcher (JHM) and were screened between 2 and 4 weeks after stroke onset. Inclusion criteria were as follows: acute unilateral stroke confirmed by a computed tomography scan; persistent upper-limb motor impairment, defined by scores of less than 6 on each of the upper-limb sections of the Motor Assessment Scale[18]; ability to participate in 30-minute physiotherapy sessions; and ability to sit unsupported for 1 minute. Exclusion criteria were severe neglect, aphasia or cognitive impairment that would limit participation, previous stroke resulting in residual disability, premorbid arm impairment, hemiplegic shoulder pain, or inability to provide informed consent.

Primary Outcome Measure

Action Research Arm Test. The ARAT is a frequently used, validated, and reliable measure of upper-limb function[19,20] with 4 subsections: grip, grasp, pinch, and gross. Its maximum summed score is 57, indicating best performance. Published guidelines were used.[20] ARAT performances were videotaped and used to assess inter- and intrarater reliability. Single-measure intraclass correlation coefficients were all greater than .95 ($P<.001$), which could be classified as high.[21]

Secondary Outcome Measures

Rivermead Motor Assessment. The RMA upper-limb section was selected as a more impairment-oriented measure of upper-limb performance than the ARAT. Scores range from 0 to 15, with higher scores representing better performance.[22,23]

Nine-Hole Peg Test. The 9HPT assesses fine manual dexterity at upper ranges of ability.[2,24] Scores were calculated as pegs per second.

Modified Barthel Index. The MBI assesses independence in ADLs.[25] Scores range from 0 to 100, and higher scores indicate greater independence in ADLs.

Nottingham Health Profile. The NHP, part 1,[26] assesses HRQOL across 6 domains: energy, pain, emotion, sleep, social isolation, and physical mobility. Weighted scores range from 0 to 600, with lower scores indicating better HRQOL.

Hospital Anxiety and Depression Scale. The HADS assesses mood.[27] The total score ranged between 0 and 42, with subscales of anxiety and depression ranging from 0 to 21. Higher scores indicate greater depression and/or anxiety.

Randomization and Blinding

Participants were randomly assigned to receive bilateral or unilateral training by using concealed web-based randomization, designed by the study statistician (SAO), 2 to 4 weeks after stroke onset and after provision of written informed consent and baseline assessment. Stratifying factors included the side of hemiplegia, stroke classification as determined by the Oxford Community Stroke Project classification,[28] and baseline upper-limb activity measured by the ARAT.[19] Two therapists (an occupational therapist and physiotherapist) trained to use the measures, blinded to treatment allocation and otherwise uninvolved in the trial, collected baseline, postintervention, and follow-up data by using standardized protocols. Participants were instructed not to indicate their group allocation to assessors.

Intervention

Bilateral group. Participants allocated to bilateral training practiced identical tasks with each arm simultaneously. Training lasted 20 minutes a session 5 weekdays a week over 6 weeks in addition to usual therapy. Participants performed as many trials as possible in each session to a maximum of 30 trials of each task, a total of 120 trials per session. The duration and intensity of training reflected other bilateral training studies[5-7] and was pragmatic, given the acute stage of recovery and ongoing usual therapy. Also reflecting the pragmatic nature of the study, participants discharged home before the end of the intervention period continued training at home twice a week through supervised visits of 30 minutes in duration from the same therapists, in line with the usual discharge and follow-up procedures.

Equipment and task protocols were standardized and portable. The program incorporated 4 core tasks typically found difficult by stroke patients; 3 had been used previously in bilateral training studies.[5,6] Participants were asked (1) to move a doweling peg 2cm in diameter by 4cm in height from tabletop to attach to the underside of a shelf placed at eye level; (2) to move a 7-cm^3 block from the table onto a shelf at shoulder

height; (3) to grasp an empty glass, take to the mouth, and return to starting position; and (4) to point to targets raised 30cm from the table and positioned at midline, 40cm to the right, and 40cm to the left of midline.

The fourth task was included because pointing is an important upper-limb function involving proximal and distal control, for which task constraints could be progressed by using targets of varying size.

Participants were assigned to a core protocol if they were able to complete the 4 core tasks at the first training session or to a modified protocol when the core tasks could not be completed. The modified protocol involved tabletop activities incorporating components of the core tasks, including reaching, forearm pronation and supination, wrist extension, and grasp. Training sessions were organized to enhance skill acquisition and retention through block practice in the cognitive stage of learning progressing to random practice in the associative stage of learning.[29] Progressive, standardized graded variations of the core and modified tasks, with specific motor or functional goals and incorporating a range of everyday objects of differing shapes and sizes, were piloted and developed to provide a variation of reaching distances, accuracy, dexterity, and strength requirements. The aim was to encourage active participation matched to the degree of the impairment. Participants allocated to the modified protocol who had very little or no active movement were facilitated in their attempts to achieve goals with assistance from the therapists who withdrew physical assistance as soon as the participant showed active involvement. Goals for these participants, within the modified protocol, involved simple wrist and hand movement and reaching to points marked on the tabletop. Progression for all participants occurred when a participant was successful in 75% of the randomly scheduled trials. To facilitate self-evaluation of performance and maintain participant engagement, knowledge of results was provided after 5 trials using systematic feedback from therapists on goal achievement and movement pattern.[30]

Two senior stroke rehabilitation physiotherapists each with 15 years of experience conducted the intervention.

Control group. Participants in the unilateral training group followed the same program as the bilateral training group but used the paretic upper limb only. The intervention and control sessions occurred away from normal therapy areas so that regular therapists were unaware of group allocation.

Procedure

Participants fulfilling the inclusion and exclusion criteria were provided with study information by the lead researcher (JHM). After this, written informed consent was obtained from those wishing to take part in the study, baseline assessments were conducted, and participants were given an identification number. To randomize participants to bilateral or unilateral training, the lead investigator (JHM) entered participant identification number and stratification factors into the randomization program and then informed the therapists of group allocation.

Power Calculations

Power calculations were based on the suggestion that a difference of 10% of maximum ARAT score, 6 points, represents a minimal clinically significant difference.[31] Fifty-three participants in each group were required for 80% power to detect this difference on the ARAT at P equal to or less than .05.

Statistical Analysis

Data were analyzed using SPSS.[a] Change scores were created by subtraction of baseline from outcome scores at 6 and 18 weeks. Groups were examined for baseline differences and differences in change between baseline and 6 weeks (0−6) and baseline and 18 weeks (0−18) by using chi-square for categorical data, independent samples t tests, and Kruskal-Wallis tests as appropriate.

Additionally, 3 severity subgroups were created according to baseline ARAT and 9HPT scores. The main and interaction effects of subgroup and treatment group were examined by using factorial ANOVA. Change scores between 0 and 6 weeks and between 0 and 18 weeks on the ARAT, RMA, and 9HPT were dependent variables. Subgroup and treatment group allocation were entered as fixed factors, and baseline scores on each measure were entered as covariates.

RESULTS

Data Screening

No deviations from random allocation occurred. Baseline data were complete for all participants. The MBI and NHP baseline scores were skewed and therefore were transformed to approximate normality using square root. The 9HPT baseline score remained skewed after inverse and logarithmic transformation; therefore, nonparametric tests were used for baseline group comparison. Change scores were all normally distributed.

Participants

Between October 2002 and June 2005, 1239 patients were screened for inclusion. One hundred six patients (61 men, 45 women) met criteria and agreed to participate. Ninety-seven (91.5%) participants completed the intervention and postintervention test at 6 weeks. Five participants from the bilateral training group and 4 from the unilateral training group dropped out before 6 weeks for reasons indicated in figure 1. Eighty-five (80%) patients completed follow-up at 18 weeks (see fig 1), with 5 in the bilateral training and 7 in the unilateral training group lost to follow-up. Using t tests and, where appropriate, nonparametric equivalents, no significant differences at baseline in terms of characteristics or baseline scores existed between participants completing the intervention and those who did not ($P>.05$). Reasons for loss to follow-up are provided in figure 1. There were also no significant differences in terms of baseline characteristics or scores on baseline measures between participants who were lost to follow-up and those who were not. Therefore, analysis was conducted using the complete 6-week dataset (n=97) and the complete 18-week dataset (n=85). Blinding was preserved in all cases.

Group Characteristics

No statistically significant differences were found at baseline between the bilateral and unilateral training groups (table 1); however, the hospital length of stay was significantly longer for the bilateral training group ($P=.03$) (see table 1), as was the number of intervention sessions ($P=.04$). These differences occurred because 19 (34%) of 56 participants in the bilateral training group compared with 27 (54%) of 50 in the unilateral training group went home during the intervention period. The total number of training trials across the sessions was 1093±711 for the unilateral training group and 1066±413 for the bilateral training

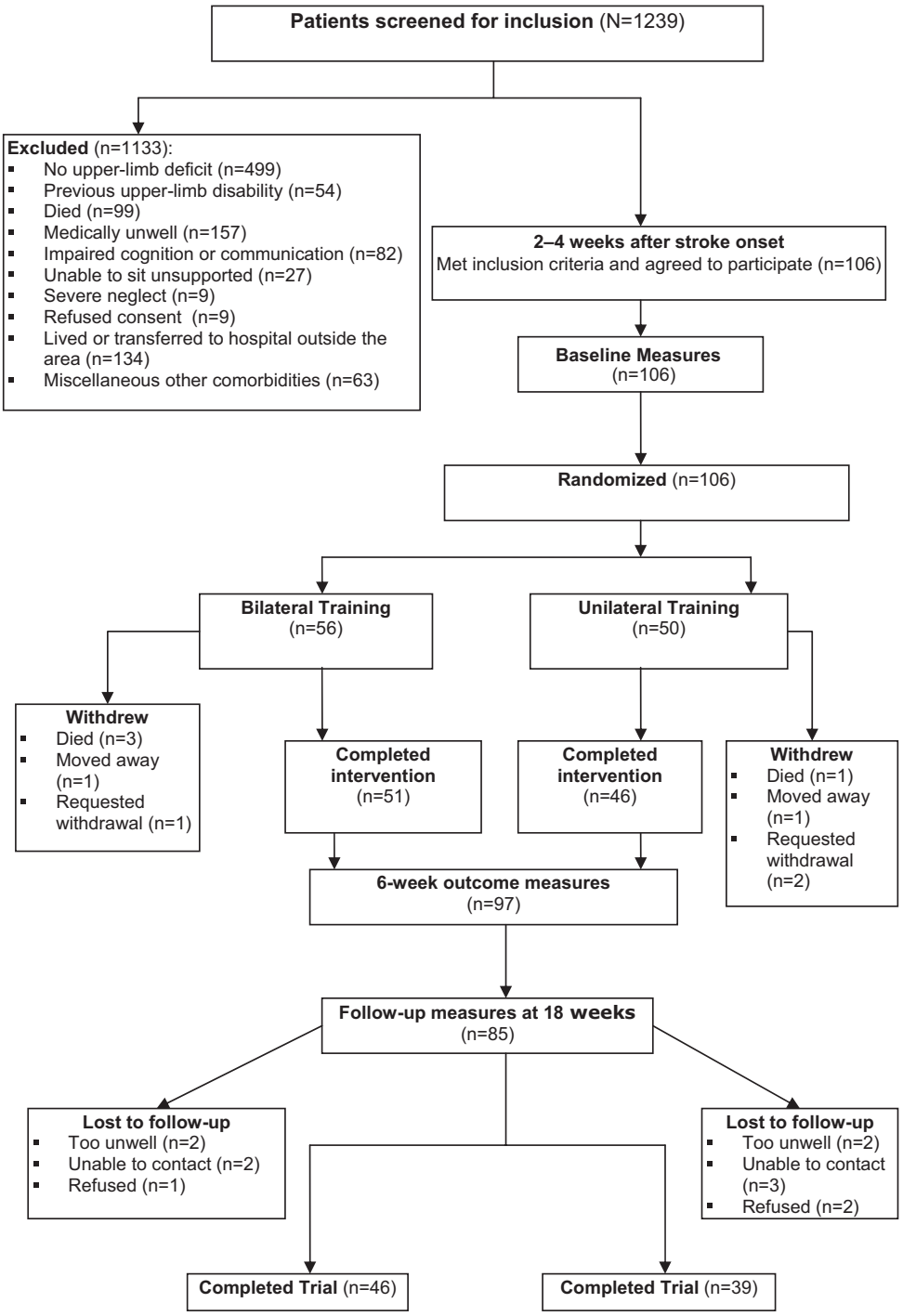


Fig 1. Progress of participants through the trial.

group, which was not significantly different between the groups ($P=.34$); therefore, we can be fairly certain that the dose of therapy was similar for participants in each group. Additionally, there were no significant differences at baseline in terms of any characteristics or outcome measures between participants in the bilateral training group and those in the unilateral training group who were discharged during this period ($P>.05$). At baseline, 39 (69%) patients of 56 in the bilateral training group and 28 (56%) of 50 in the unilateral training group were allocated to the modified task protocol (see table 1), a difference that was not significant ($P=.15$). During the study, 12 patients in the bilateral training group and 13 in the unilateral training group progressed to one or more of the core tasks so that by the end of the study, of the participants who completed the intervention, 27 (52%) of 51 in the bilateral training group and 15 (33%) of 46 in the unilateral training group had undertaken the modified task protocol, again a difference that was not significantly different ($P=.06$). The mean number of sessions before progression occurred was 15.1 ± 6.0 in the bilateral

Table 1: Baseline Characteristics and Outcome Scores

Characteristic	Bilateral Training (n=56)	Unilateral Training (n=50)
Male/Female (n)	34/22	27/23
Age (y)	67.9±13.1	67.8±9.9
Side of deficit (left/right)	27/29	27/23
Ischemic/hemorrhagic stroke	3/53	6/44
Handedness (left/right)	27/29	25/25
Dominant hand affected (yes/no)	49/7	43/7
Nottingham Sensory Assessment upper limb (max, 84)	71.3±14.5	65.2±19.2
Motor Assessment Scale, median (range) (max, 18)	2.0 (0.0–14.0)	5.5 (0.0–12.0)
Oxfordshire Community Stroke Project classification		
Total anterior circulation	3	2
Partial anterior circulation	31	28
Lacunar	21	18
Posterior circulation	1	2
Days to intervention	22.6±5.6	23.2±5.7
Intervention sessions	21.3±5.3	19.0±5.5*
Core task allocation/modified task allocation	17/39	22/28
Hospital stay, median (range)	80 (3–259)	47 (9–284)*
Upper-limb measures, baseline scores		
ARAT total (max, 57)	13.4±15.3	18.5±17.2
Grasp (max, 18)	4.9±6.0	6.7±6.5
Grip (max, 12)	2.7±3.3	4.0±4.0
Pinch (max, 18)	2.2±3.9	3.1±5.4
Gross (max, 9)	3.6±3.2	4.6±3.1
RMA (max, 15)	3.4±3.3	4.3±3.1
9HPT, pegs/s (median, IQR)	0.00 (0.00−0.02)	0.00 (0.00−0.05)
Other measures, baseline scores		
MBI (0−100)	58.5±25.3	65.7±23.5
NHP (0−600)	180±121	174±118
HADS mood: anxiety (0−21)	6.6±4.8	5.9±3.3
HADS mood: depression (0−21)	6.2±3.2	6.6±3.7

NOTE. Values are mean ± SD unless otherwise stated.
*$P \leq .05$.

training group and 14.1±5.4 in the unilateral training group, a difference that was not significant ($P=.68$). Review of the usual therapy records indicated that bilateral training was used by regular therapists in only 1 case.

Change in Upper-Limb Outcomes and ADLs

Both groups improved during the intervention period (table 2); however, no significant differences were found between groups in the mean change between baseline and 6 weeks on the total ARAT score ($P=.68$), ARAT subsections grasp ($P=.43$), grip ($P=.53$), pinch ($P=.41$), and gross ($P=.77$) or in the change in the RMA ($P=.06$), 9HPT ($P=.51$) (see table 2), and the MBI, the measure of ADL independence ($P=.27$) (table 3). For the 85 participants who completed the follow-up assessment at 18 weeks, the difference between groups in the mean change between baseline and 18 weeks on the pinch subsection of the ARAT (95% CI, 0.3−5.6; $P=.03$) and on the 9HPT (95% CI, 0.0−0.1; $P=.05$) reached significance, indicating poorer recovery for the bilateral training group (fig 2). No significant differences were found in the mean change in the total ARAT score ($P=.16$), ARAT grasp ($P=.45$), grip ($P=.21$), or gross ($P=.52$) or on the RMA ($P=.41$) (see table 2) or MBI ($P=.13$) (see table 3) over this period.

Change in HRQOL and Mood

There were no significant differences between bilateral and unilateral training groups between baseline and 6 weeks in change in quality of life (NHP) ($P=.25$), in HADS anxiety ($P=.19$), and HADS depression ($P=.42$) (see table 3). Similarly, no significant differences were found in change between baseline and 18 weeks on the NHP ($P=.34$), HADS anxiety ($P=.43$), and HADS depression ($P=.42$) (see table 3).

The Effects of the Severity of the Impairment on Upper-Limb Outcomes

We were interested in the effects of baseline severity on outcomes; therefore, 3 severity subgroups were created from ARAT and 9HPT baseline scores. Participants in subgroup 1 scored 0 to 3 on the ARAT (n=38), had little or no upper-limb movement, and had no manual dexterity as evidenced by an inability to place any pegs in the 9HPT; participants in subgroup 2 scored between 4 and 28 on the ARAT (n=42) and showed some upper-limb motor control but no fine manual dexterity as evidenced by the inability to place any pegs. Participants in subgroup 3, scoring between 29 and 56 on the ARAT (n=26), could with 4 exceptions place some or all pegs, indicating good manual dexterity.

Using the factorial ANOVA, from baseline to 6 weeks, no significant interaction effect between the ARAT subgroup and group allocation was found for change in the upper-limb variables ($P>.05$) (table 4). However, there were 3 significant main effects in which baseline severity predicted recovery on the ARAT ($P<.01$), RMA ($P=.02$), and 9HPT ($P<.01$) (see table 4). From baseline to 18 weeks, no significant interaction effect between the ARAT subgroup and group allocation was found for change on the upper-limb variables ($P>.05$) (see table 4). Again, 3 significant main effects existed in which baseline severity on the ARAT predicted recovery over this period on the ARAT ($P=.01$), RMA ($P=.04$), and 9HPT ($P<.01$).

DISCUSSION

This study compared the effects of bilateral and unilateral upper-limb task training on upper-limb outcomes, ADLs, HRQOL, and mood during early poststroke rehabilitation. It also examined whether responses to upper-limb training were related to the severity of the initial impairment. To our knowledge, this is the largest RCT to date to investigate bilateral upper-limb training in participants with acute stroke. Although both groups improved, we found no beneficial effects of bilateral over unilateral training in terms of upper-limb recovery over 6 weeks of intervention or at the 18-week follow-up, regardless of the initial severity. In fact, recovery of dexterity, measured by the ARAT pinch subscale and 9HPT between baseline and 18 weeks, was significantly poorer for participants receiving bilateral training. Furthermore, there were no beneficial effects of bilateral training over unilateral training in terms of performance in ADLs, HRQOL, or mood.

Although direct comparisons with other bilateral training studies are difficult because of diverse methodologies and outcomes, our findings do not support previous studies in which participants with predominantly chronic stroke exhibited improved motor and functional outcomes with bilateral training.[5-9] Our findings may differ from those studies for 2 possible

Table 2: Change Scores on ARAT Total, Grasp, Grip, and Gross Subsections and RMA (upper-limb section) for Bilateral and Unilateral Training Groups

Upper-Limb Measures 6-Week Scores and Change 0 to 6 Weeks	Bilateral Training (n=51)	Unilateral Training (n=46)	*P* (95% CI for difference in mean change between groups)	Upper-Limb Measures 18-Week Scores and Change 0 to 18 Weeks	Bilateral Training (n=46)	Unilateral Training (n=39)	*P* (95% CI for difference in mean change between groups)
ARAT total (max, 57)	27.9±19.5	34.3±19.8		ARAT total (max, 57)	29.0±21.9	37.6±21.2	
Change	14.3±13.2	15.4±12.6	0.68 (−4.1 to 6.3)	Change	14.3±13.2	18.6±13.6	0.16 (−1.7 to 1.3)
Grasp (max, 18)	9.5±6.6	11.6±6.8		Grasp (max, 18)	9.8±7.5	12.2±7.0	
Change	4.2±4.4	4.9±5.1	0.43 (−1.2 to 2.7)	Change	4.3±5.3	5.1±4.8	0.45 (−1.4 to 3.0)
Grip (max, 12)	6.0±4.3	7.6±4.3		Grip (max, 12)	5.9±4.7	8.2±4.6	
Change	3.2±2.9	3.6±3.3	0.53 (−0.9 to 1.7)	Change	3.0±3.3	3.8±3.0	0.21 (−0.5 to 2.2)
Gross (max, 9)	5.3±3.2	6.3±3.1		Gross (max, 9)	5.6±3.5	6.2±3.4	
Change	1.7±2.4	1.8±1.8	0.77 (−0.7 to 1.0)	Change	1.8±2.6	1.5±1.6	0.52 (−1.3 to 0.6)
RMA (max, 15)	5.5±3.5	7.1±3.8		RMA (max, 15)	6.0±4.1	7.3±4.0	
Change	1.9±2.3	2.8±2.7	0.06 (−0.1 to 2.0)	Change	2.3±3.1	2.8±3.0	0.41 (−0.8 to 1.9)

NOTE. Values are mean ± SD.

reasons: the nature of the intervention tasks and the timing of the intervention.

In our study, participants were trained in complex multijoint functionally relevant tasks, whereas other bilateral training studies have involved protocols using simple repetitive movements with electric stimulation[8] or auditory cueing.[7,14] Such augmentation of bilateral movement may provide more effective upper-limb coupling and consequent facilitation of the paretic arm than was possible with the free movements practiced in our study, suggesting that the effects of bilateral training may be influenced by task constraints. Furthermore, visualizing and processing information from the nonparetic limb, while simultaneously attempting to perform new, progressively changing, relatively complex precise motor goals with both arms may have provided a dual-task challenge greater than in other studies. Evidence suggests that stroke participants find tasks requiring divided attention difficult,[32] and aimed movements of the hemiplegic arm require greater attentional resources than aimed movements in healthy subjects.[33] Anecdotally, participants receiving bilateral training in our study reported difficulty in attending to both limbs during practice, suggesting that attentional demands and task complexity may have influenced outcomes.

Intervention timing may also have influenced outcomes. We found no effects of bilateral training with acute stroke participants, whereas studies showing positive effects were conducted mainly with participants with chronic stroke.[7,8,14] Stroke appears to alter normal transcallosal inhibition, resulting in increased intact hemisphere excitability during hemiparetic arm movement that may be inhibitory in nature, thus suppressing output from the damaged hemisphere.[34] Depending on the lesion site and size, this overactivation appears transient, and more normal contralateral activation patterns resume over time.[35] Identical motor commands generated in each hemisphere during bilateral movement may modulate transcallosal inhibition, balancing stroke-related interhemispheric overactivity and facilitating output from the damaged hemisphere as well as from normally inhibited ipsilateral pathways of the undamaged hemisphere to augment movement of the paretic arm.[9,36] The extensive disruption of normal transcallosal inhibition soon after stroke may, however, render bilateral training less effective than in chronic stages when interhemispheric interactions have resumed a more normal balance; therefore, the effects of bilateral training may be time dependent. Therefore, future studies should investigate cortical activation patterns during bilateral training in the early poststroke period.

We found no significant between-group differences in the change in dexterity between baseline and 6 weeks; however, participants receiving unilateral training showed significantly better longer-term improvement in dexterity, suggesting that this group showed accelerated dexterity gains in the posttreatment phase. Given that training specificity is thought to be critical to training effect,[4] bilateral practice of dexterity tasks in which both arms perform identical movement may be somewhat artificial and probably insufficiently related to everyday life dexterity requirements to provide a training effect. Tasks involving fine finger control are most commonly performed unilaterally or with hands performing bimanually different but coordinated tasks (eg, when tying shoelaces or typing). A mismatch between practice mode and performance requirements for dexterity tasks in everyday life may thus have led to the lower transfer of training effects to recovery of long-term dexterity in the bilateral training group.

Furthermore, anatomically, distal upper-limb muscles involved in dexterity show predominantly contralateral corticospinal control, and contributions of ipsilateral and bilateral control mechanisms to dexterity performance are limited.[37] Ipsilateral pathways from the undamaged hemisphere thought to become accessible for hemiparetic arm motor control during bilateral training[9] are therefore unlikely to be involved in dexterity, which may explain poorer dexterity recovery of the bilateral training group. However, results must be interpreted carefully because many participants could not perform the dexterity tests (38% at 6wk, 26% at 18wk) because of poor finger control, reflecting floor effects of the tests.

Independence in ADLs improved for both groups but did not differ between groups during the study, despite greater unilateral training group recovery in dexterity. The MBI is probably too insensitive to detect dexterity changes, and participants may also have compensated with the unaffected upper limb to achieve independence in ADLs, a recognized phenomenon.[20]

The change in HRQOL and mood did not differ between groups despite greater unilateral training group recovery in dexterity, suggesting that change in dexterity was not sufficiently clinically significant to influence these outcomes. Although upper-limb outcomes are known to influence HRQOL and well-being a year poststroke,[16] they may have little impact on HRQOL and mood in acute stroke when ambulation may be a greater concern to the patient.[25]

Table 3: Change Scores on the MBI, NHP, and HADS for Bilateral and Unilateral Training Groups

Measure 6-Week Scores and Change 0 to 6 Weeks	Bilateral Training (n=51)	Unilateral Training (n=46)	*P* (95% CI for difference in mean change)	Measure 18-Week Scores and Change 0 to 18 Weeks	Bilateral Training (n=46)	Unilateral Training (n=39)	*P* (95% CI for difference in mean change)
MBI (0–100)	83.0±16.2	85.1±19.2		MBI (0–100)	86±16.9	86.3±18.4	
Change	23.4±17.0	19.6±17.1	0.27 (−10.7 to 3.1)	Change	24.9±23.5	18.1±15.7	0.13 (−15.6 to 2.0)
NHP (0–600)	126.0±101.0	104.0±85.0		NHP (0–600)	122.0±110.0	92.0±92.0	
Change	−50.8±99.0	−73.7±95.3	0.25 (−62.3 to 16.3)	Change	−54.5±15.0	−77.5±105.1	0.34 (−70.8 to 4.7)
HADS anxiety (0–21)	5.2±4.1	5.7±3.9		HADS anxiety (0–21)	5.6±4.5	4.6±3.6	
Change	−1.4±3.5	−0.4±3.5	0.19 (−0.5 to 2.3)	Change	−1.1±3.6	−0.5±3.1	0.43 (−0.9 to 2.1)
HADS depression (0–21)	5.8±3.3	5.7±3.5		HADS depression (0–21)	5.4±4.5	4.5±3.2	
Change	−0.3±3.2	−0.8±2.9	0.42 (−1.8 to 0.7)	Change	−0.9±3.8	−1.4±2.1	0.42 (−1.9 to 0.8)

NOTE. Values are mean ± SD.

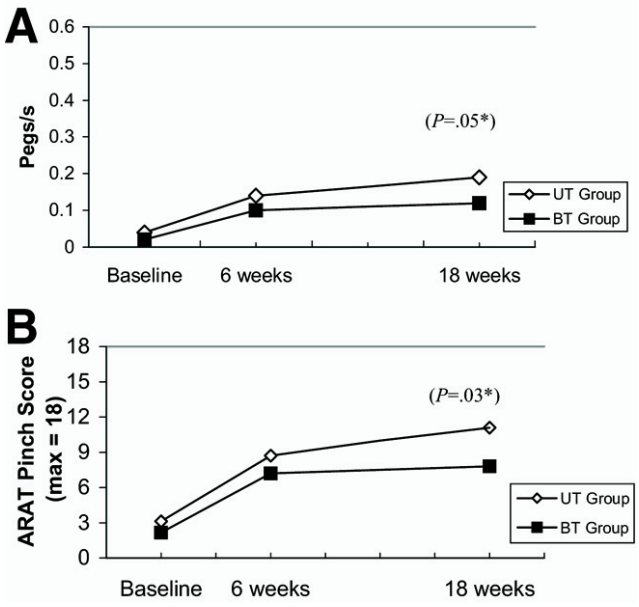


Fig 2. Change in dexterity in (A) 9HPT and (B) ARAT pinch between baseline, 6 weeks, and 18 weeks for bilateral (BT) and unilateral training (UT) groups. *Significant at $P \leq .05$.

Study Limitations

In terms of study limitations, participants presented with various sites, types of lesion, and severity of motor deficits, leading to high variability in upper-limb scores that may have masked significant results. To account for influences of severity on responses to training, we created severity subgroups. Results suggest no benefits for bilateral over unilateral training for the subgroups, but baseline severity did influence recovery, supporting previous evidence.[38] Participant numbers in each subgroup may have been too small to detect significant differences in relation to the effects of training group allocation.

The bilateral training group showed lower baseline scores on all physical measures, which may have contributed to the findings. Although not statistically different, the difference in total ARAT scores was probably clinically significant.[31] Patients were allocated to modified or core tasks depending on their performance at the first training session. Each protocol involved standardized tasks and progression and either unilateral or bilateral practice. The main difference between protocols was that in the modified protocol, when participants could not achieve a task, physical assistance was provided by the therapist until the patient was able to perform the task independently, thus adding additional variables that may have influenced results to the otherwise carefully standardized therapeutic program. The difference between groups in the proportion of participants allocated to or completing the core and modified protocols did not reach statistical significance, and there was no significant difference in the number of sessions taken to progress to the core protocol on one or more tasks. Nonetheless, a greater proportion of patients in the bilateral training group received modified training throughout, probably reflecting the baseline clinical characteristics of that group.

In line with other upper-limb studies in stroke,[4] change scores were the variable of interest in the study because they account for heterogeneity within the sample at baseline. The use of change scores for subgroup analysis may be a less than optimal approach because it eliminates the variable of time as

Table 4: Change Scores and Main and Interaction Effects for Severity Subgroups

		Bilateral Training		Unilateral Training		ANOVA			
	Subgroup	n	Change	n	Change	Source of Variance	*df*	F	*P*
Change 0 to 6 weeks									
ARAT (max, 57)	1	12	10.7±15.3	23	8.4±12.0	Main effects: treatment group	1,89	0.04	.85
	2	22	20.1±11.2	17	20.4±13.1	subgroup	2,89	7.94	.00*
	3	12	13.5±8.3	11	13.4±8.3	Treatment group by subgroup	2,89	0.13	.87
RMA (max, 15)	1	12	2.0±2.8	23	1.7±3.0	Main effects: treatment group	1,89	2.48	.12
	2	22	1.9±1.8	17	3.6±2.6	subgroup	2,89	4.12	.02*
	3	12	1.4±1.9	11	2.6±2.4	Treatment group by subgroup	2,89	1.30	.28
9HPT (pegs/s)	1	12	0.01±0.04	23	0.01±0.01	Main effects: treatment group	1,89	0.10	.75
	2	22	0.08±0.12	17	0.11±0.12	subgroup	2,89	18.16	.00*
	3	12	0.19±0.19	11	0.17±0.11	Treatment group by subgroup	2,89	0.84	.43
Change 0 to 18 weeks									
ARAT (max, 57)	1	10	11.0±17.2	20	10.9±15.1	Main effects: treatment group	1,78	0.68	.41
	2	18	17.8±13.7	15	24.9±13.4	subgroup	2,78	5.41	.01*
	3	11	15.7±5.5	11	15.3±7.0	Treatment group by subgroup	2,78	0.74	.48
RMA (max, 15)	1	10	2.3±3.9	20	2.5±3.9	Main effects: treatment group	1,78	0.38	.54
	2	18	2.1±2.6	15	3.4±2.8	subgroup	2,78	3.27	.04*
	3	11	2.6±1.6	11	2.3±2.4	Treatment group by subgroup	2,78	0.47	.63
9HPT (pegs/s)	1	10	0.02±0.06	20	0.04±0.06	Main effects: treatment group	1,78	2.48	.12
	2	18	0.09±0.13	15	0.15±0.15	subgroup	2,78	17.91	.00*
	3	11	0.21±0.12	11	0.24±0.15	Treatment group by subgroup	2,78	0.48	.62

NOTE. Values are mean ± SD. Subgroup 1 is patients scoring 0 to 3 on the ARAT at baseline. Subgroup 2 is patients scoring 4 to 28 on the ARAT at baseline. Subgroup 3 is patients scoring 29 to 57 on the ARAT at baseline.
*Significant at $P \leq .05$.

a factor in the analysis. We elected to conduct subgroup analysis in this way to provide consistency with the main analysis, which addressed change. We can be fairly certain that results of the ANOVA using change scores was robust given that we additionally conducted the same analysis of subgroups on outcome scores at 6 and 18 weeks and found the same pattern of results, which we have not presented here.

Of the patients who completed the intervention, there were no deviations from randomized allocation leading to change of group; therefore, intention-to-treat analysis for protocol violation was not required. We had no follow-up data for participants who did not complete the intervention; therefore, their data were classified as missing. Missing data caused by dropouts and losses to follow-up may therefore have influenced our findings. Given that we found no baseline differences between those who did not complete the study and the rest of the sample and we can explain dropout and loss to follow-up (see fig 1), we can be fairly certain that there were no particular characteristics that predisposed patients to dropout or not to complete the follow-up tests. We therefore elected to present an analysis of the complete cases only. To ensure that this was a robust representation of the findings, we performed analysis using 3 different methods of imputation for the missing data. After testing that the missing data were randomly distributed, analysis of datasets with substitution of the unilateral and bilateral training group mean values for the missing data on each measure in each of those groups, carry forward of the last known value, and expectation maximization using SPSS to generate missing values[39] were all conducted. None of these methods produced findings that were different from the results in which no method of imputation was used and provides us with a reasonable degree of certainty that results from the complete data were not biased by the missing cases.

Measurements were conducted at 2 endpoints using functional measures selected for clinical relevance but were relatively crude. Other studies, performed by using kinematic analysis, have shown immediate improvements in the quality and timing of upper-limb movement during bilateral conditions in chronic stroke[12] and in some cases during subsequent unilateral performance.[5,6,8] Immediate and subtle effects of bilateral training on movement parameters may have therefore been missed in our study.

Although the training dose was in line with other bilateral training studies,[5,7] compared with some recent studies of other upper-limb intervention,[40] the dose of therapy in this study was low. Given the additional attentional demands faced by the bilateral training group, the therapy dose may have been insufficient to provide an effect of bilateral training.

Future work should examine optimal timing, dose and training characteristics for bilateral training, and its effects on patients at different stages of recovery using sensitive measures of impairment and function. Relationships between tasks practiced, test tasks, and functional outcomes also need further investigation, along with the effects of lesion location and the severity of impairment.

CONCLUSIONS

This study suggests that 20 minutes a day of bilateral training of functionally related tasks is no more effective than unilateral training for upper-limb recovery in acute stroke patients, regardless of the initial severity of the impairment. Furthermore, for recovery of dexterity, bilateral training actually appears less beneficial. Independence in ADLs, HRQOL, and mood were not influenced by bilateral training. Several other studies have found benefits of bilateral training; therefore, this approach cannot be rejected altogether as an upper-limb intervention in stroke on the basis of our study findings. The study does suggest that training characteristics, such as the nature of the tasks trained and the strength of interlimb coupling required for effects, may influence outcomes; therefore, future work should examine the optimal timing, dose, and

training tasks that might optimize the already known facilitatory effects of interlimb coupling.

Acknowledgments: We thank the research physiotherapists and occupational therapist who executed the treatment and assessment protocols and physiotherapists in hospitals across Dundee and Angus for their assistance throughout the trial.

References

1. Nakayama H, Jorgenson HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen stroke study. Arch Phys Med Rehabil 1994;75:394-8.
2. Parker VM, Wade DT, Langton Hewer R. Loss of arm function after stroke: measurement, frequency, and recovery. Int Rehabil Med 1986;8:69-73.
3. Sveen U, Bautz-Holter E, Sødring KM, Wyller TB, Laake K. Association between impairments, self-care ability and social activities 1 year after stroke. Disabil Rehabil 1999;21:372-7.
4. Winstein CJ, Rose DK, Tan SM, Lewthwaite R, Chui HC, Azen SP. A randomized controlled comparison of upper-extremity rehabilitation strategies in acute stroke: a pilot study of immediate and long-term outcomes. Arch Phys Med Rehabil 2004;85:620-8.
5. Mudie MH, Matyas TA. Upper extremity retraining following stroke: effects of bilateral practice. J Neurol Rehabil 1996;10:167-84.
6. Mudie MH, Matyas TA. Can simultaneous bilateral movement involve the undamaged hemisphere in reconstruction of neural networks damaged by stroke? Disabil Rehabil 2000;22:23-37.
7. Whitall J, McCombe Waller S, Silver KH, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke [published erratum in: Stroke 2007;38:e22]. Stroke 2000;10:2390-5.
8. Cauraugh JH, Kim S. Two coupled motor recovery protocols are better than one: electromyogram-triggered neuromuscular stimulation and bilateral movements. Stroke 2002;33:1589-94.
9. Stinear JW, Byblow WD. Rhythmic bilateral movement training modulates corticomotor excitability and enhances upper limb motricity poststroke: a pilot study. J Clin Neurophysiol 2004;21:124-31.
10. Swinnen SP. Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci 2002;3:348-59.
11. Kelso JA, Southard DL, Goodman D. On the nature of human interlimb coordination. Science 1979;203:1029-31.
12. Cunningham CL, Stoykov ME, Walter CB. Bilateral facilitation of motor control in chronic hemiplegia. Acta Psychol (Amst) 2002; 110:321-37.
13. Harris-Love ML, McCombe Waller S, Whitall J. Exploiting interlimb coupling to improve paretic arm reaching performance in people with chronic stroke. Arch Phys Med Rehabil 2005;86:2131-7.
14. Luft AR, McCombe Waller S, Whitall J, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial [published erratum in: JAMA 2004; 292:2470]. JAMA 2004;292:1853-61.
15. Parry RH, Lincoln NB, Vass CD. Effect of severity of arm impairment on response to additional physiotherapy early after stroke. Clin Rehabil 1999;13:187-98.
16. Wyller TB, Holmen J, Laake P, Laake K. Correlates of subjective well-being in stroke patients. Stroke 1998;29:363-7.
17. Penta M, Tesio L, Arnould C, Zancan A, Thonnard J. The ABILHAND questionnaire as a measure of manual ability in chronic stroke patients: Rasch-based validation and relationship to upper limb impairment. Stroke 2001;32:1627-34.
18. Carr JH, Shepherd RB, Nordholm L, Lynne D. Investigation of a new motor assessment scale for stroke patients. Phys Ther 1985; 65:175-80.
19. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res 1981;4:483-92.
20. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. Clin Rehabil 2005;19:404-11.
21. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86:420-8.
22. Lincoln N, Leadbitter D. Assessment of motor function in stroke patients. Physiotherapy 1979;65:48-51.
23. Adams SA, Ashburn A, Pickering RM, Taylor D. The scalability of the Rivermead Motor Assessment in acute stroke patients. Clin Rehabil 1997;11:42-51.
24. Heller A, Wade DT, Wood VA, Sunderland A, Hewer RL, Ward E. Arm function after stroke: measurement and recovery over the first three months. J Neurol Neurosurg Psychiatry 1987;50:714-9.
25. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol 1989;42:703-9.
26. Hunt SM, McEwen J. The development of a subjective health indicator. Sociol Health Illn 1980;2:231-46.
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
28. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337:1521-6.
29. Hanlon RE. Motor learning following unilateral stroke. Arch Phys Med Rehabil 1996;77:811-5.
30. Winstein C. Motor learning considerations in stroke rehabilitation. In: Duncan P, Badke M, editors. Stroke rehabilitation: the recovery of motor control. Chicago: Year Book Medical; 1987. p 109-34.
31. Van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Devillé WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. Stroke 1999;30:2369-75.
32. McDowd JM, Filion DL, Pohl PS, Richards LG, Stiers W. Attentional abilities and functional outcomes following stroke. J Gerontol B Psychol Sci Soc Sci 2003;58:P45-53.
33. Platz T, Bock S, Prass K. Reduced skilfulness of arm motor behaviour among motor stroke patients with good clinical recovery: does it indicate reduced automaticity? Can it be improved by unilateral or bilateral training? A kinematic motion analysis study. Neuropsychologia 2001;39:687-98.
34. Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. Stroke 2000;31:1210-6.
35. Feydy A, Carlier R, Roby-Brami A, et al. Longitudinal study of motor recovery after stroke: recruitment and focusing of brain activation. Stroke 2002;33:1610-7.
36. Cauraugh JH, Summers JJ. Neural plasticity and bilateral movements: a rehabilitation approach for chronic stroke. Prog Neurobiol 2005;75:309-20.
37. Tanji J, Okano K, Sato KC. Neuronal activity in cortical motor areas related to ipsilateral, contralateral, and bilateral digit movements of the monkey. J Neurophysiol 1988;60:325-43.
38. Feys H, Weerdt W, Nuyens G, van de Winckel A, Selz B, Kiekens C. Predicting motor recovery of the upper limb after stroke rehabilitation: value of a clinical examination. Physiother Res Int 2000;5:1-18.
39. Tabachnick BG, Fidell LS. Using multivariate statistics. 4th ed. Boston: Allyn & Bacon; 2001.
40. Taub E, Uswatte G, King DK, Morris D, Crago JE, Chatterjee A. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. Stroke 2006;37:1045-9.

Supplier

a. Version 11; SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

Appendix 17

Conference Abstracts

RESPONSES TO BILATERAL SIMULTANEOUS UPPER LIMB TASK TRAINING COMPARED TO UNILATERAL TASK TRAINING IN ACUTE STROKE: A RANDOMISED CONTROLLED TRIAL.

Morris, J. H., Van Wijck, F, Joice S, Ogston S, Cole, I, MacWalter RS 2006. **Responses to Bilateral Simultaneous Upper Limb Task Training Compared to Unilateral Task Training in Acute Stroke: A Randomised Controlled Trial.** UK Stroke Forum, Harrogate 8th December 2006. The abstract was awarded a top five plenary oral presentation slot at the conference.

Introduction: Studies of individuals with chronic stroke suggest that bilateral training may improve upper limb (UL) recovery. Effectiveness of this intervention for individuals soon after stroke is unclear however. The purpose of this study was to compare effects on UL recovery of bilateral task training (BTT) with unilateral task (UTT) training in the acute post-stroke period.

Methods: Patients diagnosed with stroke demonstrating a new UL deficit (n=106) were randomised to receive BTT (n=56) or UTT (n=50) 2-4 weeks post onset. Both groups undertook standardised UL retraining (20 minutes, 5 days/week, for 6 weeks) in addition to normal rehabilitation. The BTT group practised with both arms simultaneously but independently whereas the UTT group practised with the affected arm only. Outcome measures included: Action Research Arm Test (ARAT), Rivermead Motor Assessment Upper Limb Scale (RMA) and Nine Hole Peg Test (NHPT), recorded at baseline, 6 weeks and 18 weeks by a blinded assessor.

Results: No significant baseline differences existed ($p>0.05$). For short-term change (0-6 weeks) the difference between groups in mean RMA change approached significance in favour of the UTT group (95%CI = -0.05, 1.98; $p=0.06$), but no significant differences existed in mean change in total ARAT (95%CI = -4.15, 6.34; $p=0.68$), ARAT sub-sections ($p>0.06$), or NHPT (95%CI = -0.03, 0.07; $p=0.51$). The only significant differences between groups at 0 -18 weeks were in mean change in the NHPT (95%CI = 0.00, 0.12; $p=0.05$) and in the ARAT sub-group section pinch (95%CI = 0.35, 5.60; $p=0.03$), where improvement was greatest for the UTT group.

Conclusions: BTT appears no more effective than UTT for UL recovery in individuals with acute stroke, but for recovery of dexterity, UTT appears advantageous. The data from this study suggest that there is as yet no evidence to replace UTT with BTT in acute stroke.

RESPONSES TO BILATERAL UPPER LIMB TRAINING IN ACUTE STROKE AND EFFECTS OF SEVERITY OF INITIAL UPPER LIMB IMPAIRMENT

Morris J. H., Van Wijck F, Joice S, Ogston S., Cole, I, MacWalter R.S. 2007. **Bilateral Upper Limb Therapeutic Exercise in Acute Stroke and Effects of Severity of Initial Upper Limb Impairment**. World Congress of Physical Therapists, Vancouver, 4th June 2007.

Purpose: Upper limb (UL) deficits contribute to limitations in activity and participation for individuals with stroke. Studies conducted in the chronic post-stroke stage suggest that bilateral training may improve UL recovery, however effectiveness of this intervention in acute stroke and responses related to severity of impairment have not been fully explored. The purpose of this study was to compare effects on UL outcomes of bilateral training with unilateral training in the acute post-stroke period and to determine if severity of initial impairment influences responses.

Relevance: Novel training approaches for stroke are emerging from developments in neuroscience and behavioural science. Physiotherapy research needs to determine when and for whom these approaches are most effective. This study investigates effectiveness for acute patients of a training approach previously studied in chronic stroke.

Design: Randomised controlled trial

Participants: 106 individuals with acute unilateral stroke and new UL impairment provided consent and were randomised to receive bilateral or unilateral training.
Intervention: Training commenced 2-4 weeks following stroke onset. Both groups participated in standardised UL retraining (20 minutes, 5 days/week, for 6 weeks) additional to normal rehabilitation. The bilateral group trained both arms simultaneously but independently; the unilateral group trained the affected arm only.

Measures: Outcome measures included: Action Research Arm Test (ARAT), Rivermead Motor Assessment Upper Limb Scale (RMA) and Nine Hole Peg Test (NHPT), recorded at baseline, 6 weeks and 18 weeks by a blinded assessor.
Analysis:Change scores (between 0-6 weeks, and 0-18 weeks) were examined using t-tests and non-parametric equivalents. Three severity sub-groups were defined from ARAT and NHPT baseline data. Main and interaction effects of ARAT Level sub-groups and treatment allocation were examined using factorial ANOVA with change on ARAT, RMA and NHPT scores as dependent variables.

Results: No significant baseline differences existed ($p>0.05$). Groups did not differ significantly in mean change between 0-6 weeks in ARAT ($p=0.68$), RMA ($p=0.06$), or NHPT ($p=0.51$) scores. Between 0-18 weeks only the difference in mean NHPT change was significant ($p=0.05$), with greater improvement for the unilateral group than the bilateral group (0.15 pegs/sec + 0.15; 0.10 pegs/sec + 0.03 respectively). Baseline severity significantly influenced change on all measures between 0-6 weeks and 0-18 weeks ($p<0.05$) however this was not related to treatment allocation. No other interaction effects existed.

Conclusions: Bilateral training appears no more effective than unilateral training for UL recovery in individuals with acute stroke even after controlling for initial impairment severity. However in the long-term, unilateral training appears most beneficial for dexterity. This data suggests that there is as yet no evidence supporting replacement of conventional unilateral training with bilateral training in acute stroke for improvement of unilateral UL performance. Some of the selected outcome measures have been criticised for limited sensitivity, therefore future research should determine optimal intervention and patient characteristics for bilateral training utilising measures sensitive to improvements.

DETERMINANTS OF UPPER LIMB RECOVERY FOLLOWING STROKE

Morris J. H, Van Wijck, F 2007. **Determinants of Upper Limb Recovery Following Stroke** UK Stroke Forum, Harrogate, 4-6th December 2007

Background: Upper limb (UL) hemiparesis is a common consequence of stroke, often leading to impairment and activity limitation. Prediction of UL recovery following stroke enables clinicians to deliver optimal interventions and to inform patients of likely recovery. This descriptive literature review examined factors that predict recovery and responses to UL rehabilitation.
Method: Searches were conducted in CINAHL, MEDLINE, EMBASE and PSYCHINFO to identify studies examining predictors or determinants of UL recovery and responses to UL rehabilitation.

Results: 33 studies identified predictors. The body of evidence yielded the following factors:
Motor impairment and activity limitation consistently predicted outcome impairment or activity limitation (12 studies) and responses to UL rehabilitation (seven trials). Direction of prediction depended on the intervention.
Grip and arm strength predicted impairment and activity limitation (four studies).
Side of lesion and hand dominance: impact on impairment and activity limitation was equivocal across six studies; two studies suggested that right hand dominant hemiparesis improves training responses.
Proprioceptive and sensory loss: equivocal results were found for impact of proprioception on impairment and activity limitation (six studies). There were similar findings for cutaneous sensation (four studies).
Age did not influence impairment or activity limitation but older patients had poorer activity outcomes following training (one study).
Gender: men had lowest UL impairment until one year (one study).
Sub-cortical lesions predicted greater UL impairment (two studies)
Muscle tone did not influence UL outcomes (two studies)

Conclusions: This descriptive review indicated that understanding of predictors of UL recovery and response to treatment is in its infancy. Motor impairment and strength are the most important determinants of UL outcomes and responses to rehabilitation, but the impact of many other factors, such as cutaneous sensation, proprioception, and side of lesion on recovery and training responses are unclear and require further investigation to determine their importance.

HEALTH RELATED QUALITY OF LIFE IS INFLUENCED BY UPPER LIMB IMPAIRMENT SIX MONTHS AFTER STROKE ONSET

Morris J. H, Van Wijck, F 2008. **Health related quality of life is influenced by upper limb impairment six months after stroke onset**. Oral presentation Enhancing Self-care Conference, University of St Andrews, September 15-17, 2008.

Background
Health related quality of life (HRQOL) is an important index of stroke recovery influenced by functional, psychological and social factors. Following stroke, upper limb (UL) function is typically poor, which may impact significantly on self-care independence. However little is known about whether UL impairment influences HRQOL, or its relative importance in predicting HRQOL compared to other physical and psychological factors.
Aims: To examine the relative importance of UL impairment in predicting HRQOL measured on the Nottingham Health Profile (NHP) 5 to 6 months after stroke onset.
Methods: Data was gathered as part of a single site clinical study of stroke UL recovery. Patients with stroke demonstrating UL impairment (n=106) were assessed 20-22 weeks after stroke onset. Scores for UL impairment [Rivermead Motor Assessment(RMA)], Activities of Daily Living (Modified Barthel Index), Mood (Hospital Anxiety and Depression Scale) and key patient characteristics significantly associated with NHP scores were entered simultaneously into multiple linear regression equations with total NHP and NHP subsection scores as dependent variables.
Findings: RMA scores, Anxiety and Depression significantly predicted the variance in total NHP (r^2 =0.48, $p<0.05$). RMA score, age and gender together significantly predicted the variance in Physical Activities (r^2=0.37,$p\leq0.05$). Anxiety alone significantly predicted the variance in NHP subsections Pain (r^2=0.12, p=0.01), Emotional Reactions (r^2=0.41,p=0.00), Sleep (r^2=0.09,p=0.02) and Social Isolation (r^2=0.22,p=0.01). Anxiety and depression significantly predicted Energy Levels (r^2=0.30, $p<0.05$).
Discussion: Having less UL impairment contributed in part to better overall HRQOL and perceived physical activity levels along with lower age and being male. However overall, anxiety and depression were the most important predictors of HRQOL in this cohort. Effective rehabilitation efforts targeting UL functional ability whilst accounting for age and gender should contribute to better overall HRQOL and self-care independence for individuals recovering from stroke. Adequate assessment and treatment of anxiety and depression is required.