Upper Limb Recovery and Brain Reorganisation Post-stroke

Isobel J. Hubbard, MOT, B ApScOT
Statement of originality

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University’s Digital Repository**, subject to the provisions of the Copyright Act 1968. **Unless an Embargo has been approved for a determined period.

Signed:

Isobel Hubbard
Acknowledgements

This thesis would not have been possible without the support of the following people. I would like to thank:

Professor Mark Parsons
Prof Parsons is a renowned acute stroke researcher with international recognition for his work, particularly in the differential diagnosis of stroke, hyper-acute management and the role of computed tomography in measuring the ischaemic penumbra. Mark has been my primary PhD supervisor and it was his idea to research brain activation patterns in acute stroke using functional magnetic resonance imaging (fMRI). He has been an encourager and mentor.

Professor Leeanne Carey
Prof Carey is a renowned academic researcher with international recognition for her work, particularly in relation to sensory assessment and management post-stroke. Leeanne was one of the first researchers to use position emission tomography and fMRI in stroke recovery research. She has been my PhD supervisor from the outset and an encourager, mentor and professional colleague.

Dr Bill Budd
Dr Budd is a renowned academic researcher with international recognition for his work in human brain mapping in relation to auditory responses. Bill has been my PhD supervisor since 2009, but was involved in most of these studies from early on. He has guided me in the analysis and interpretation of the fMRI data and findings. He has also been an encourager and mentor.

Stroke Survivors
The participants were people who had experienced a recent stroke for the very first time. Despite that, they willingly consented to participating, and to all that this commitment entailed in time and effort. These studies would not have been possible without their goodwill, courage, persistence, patience and generosity.

Ms Kate Day
Kate was involved in the first few years of this thesis journey, contributing in many aspects of the research projects including recruiting, data collection and participant follow-up. She was also the therapy assistant applying the additional upper limb
behavioural training in the randomised controlled trial. Kate has been an invaluable support, encourager and friend.

Ms Glade Vyslysel and Ms Heidi Janssen
Glade and Heidi were the two neurotherapists who were present during the study phase of the thesis journey. They prescribed and supervised most of the upper limb behavioural training in the randomised controlled trial. They were both involved in the acute study alongside Prof Parsons and give integrity to the claim that this research was both multi-professional and practice-driven.

Mr Paul Hubbard
Paul is my life-time partner and friend. He has constantly believed in my ability to complete this PhD, and I have greatly appreciated and valued his support, love and confidence.

Funding Support
This thesis has been undertaken with the support of:

- The National Heart Foundation: http://www.heartfoundation.org.au
- Hunter Medical Research Institute and the Barker family:
- The University of Newcastle: http://newcastle.edu.au/

Publications

*Book chapter*


*Journal publications*


**Published abstracts**


Hubbard IJ, Carey LM, Budd TW, Parsons MW. An RCT of differing intensities of early upper limb training post stroke: Evidence of neuroplastic changes in the ipsilesional SMA. World Congress of NeuroRehabilitation, Melbourne, Victoria, 2012.


## Table of Contents

Statement of originality ............................................................................................................. i
Acknowledgements .................................................................................................................. ii
List of Tables .......................................................................................................................... x
List of Figures ........................................................................................................................ xii
Synopsis .................................................................................................................................. xiii

### Chapter 1: Introduction ................................................................................................. 1
  1.1 Introduction ..................................................................................................................... 2
  1.2 Ischaemic Stroke .............................................................................................................. 3
  1.3 The Human Brain .......................................................................................................... 4
  1.4 Functional Magnetic Resonance Imaging ...................................................................... 6
  1.5 Upper Limb Function and Recovery .............................................................................. 7
  1.6 Conclusion ....................................................................................................................... 10
  1.7 References ...................................................................................................................... 11

### Chapter 2: Literature Review ....................................................................................... 17
  2.1 Abstract .......................................................................................................................... 18
  2.2 Introduction .................................................................................................................... 19
  2.3 Method ........................................................................................................................... 20
  2.4 Results ........................................................................................................................... 20
  2.5 Discussion ....................................................................................................................... 31
  2.6 Limitations and Further Research .................................................................................. 33
  2.7 Conclusion ...................................................................................................................... 34
  2.8 References ...................................................................................................................... 36

### Chapter 3: Comparing Different Intensities of Intervention .................................... 43
  3.1 Abstract .......................................................................................................................... 44
  3.2 Introduction .................................................................................................................... 45
  3.3 Methods .......................................................................................................................... 46
  3.4 Results ............................................................................................................................ 51
  3.5 Discussion ....................................................................................................................... 57
  3.6 Conclusion ....................................................................................................................... 60
  3.7 References ...................................................................................................................... 61
7.6 Anticipating Recovery ................................................................. 141
7.7 Maximising Recovery ............................................................... 144
7.8 Predicting Recovery ................................................................. 147
7.9 Conclusion ................................................................................. 149
7.10 References ................................................................................. 150

APPENDICES ......................................................................................... 157
Appendix for Chapter 2 ........................................................................ 159
Appendices for Chapter 3 .................................................................... 161
Appendices for Chapter 4 .................................................................... 185
# List of Tables

**Table 1.1**: Regions of Interest ................................. 5

**Table 2.1**: Summary of the studies investigating associations between movement of a stroke-affected upper limb and brain activation in the first month post-event ........................................... 22

**Table 2.2**: Brain regions, topography and Brodmann Areas ................. 23

**Table 2.3**: Summary of study findings that compared stroke survivors and healthy controls or patients with good and poor recovery in the first month post-event ........................................... 24

**Table 2.4**: Summary of the studies investigating brain activity and behavioural intervention targeting improvement in UL function in patients with stroke .... 26

**Table 2.5**: Summary of brain activation findings in studies that applied constraint-induced movement therapy and repetitive task-specific training as behavioural interventions targeting improvement in upper limb function in patients with stroke ....................................... 30

**Table 3.1**: Participants’ (n=23) group, stroke sub-type, gender and age ........ 52

**Table 3.2**: Demographic and baseline characteristics of participants ........ 53

**Table 3.3**: Whole-brain activity that was significantly greater in the intensive-training group when compared with the standard-care group ....................... 54

**Table 3.4**: Activity associated with the affected upper limb in the combined regions of interest and following small-volume correction: intensive training greater than standard care corresponding to $t$-values that exceeded the uncorrected $p$ threshold of 0.001 across all time points and at 3 months post-stroke ....................................................... 56

**Table 4.1**: Participants’ characteristics and clinical scores at 1 week, 1 month and 3 months post-stroke ........................................... 71

**Table 4.2**: Demographic and baseline characteristics of all participants and cohorts ........................................... 73
Table 4.3: Whole-brain activity that was significantly greater in the good-recovery cohort compared with the poor-recovery cohort ..............................................................74

Table 4.4: Activity associated with the affected upper limb in the combined ROI and following a small-volume correction: good recovery greater than poor recovery results corresponding to t-values that exceeded the uncorrected p threshold of 0.005 at 3 months post-stroke ..............................................................76

Table 4.5: Percentage of active voxels corresponding to t-values that exceeded the uncorrected p threshold of 0.001 at 1 week post-stroke: differences between the good-recovery and poor-recovery cohorts using the t-test and a 95% confidence interval ........................................................................................................77

Table 4.6: Change in percentage of active voxels at 1 month and at 3 months post-stroke, relative to baseline ..................................................................................78

Table 4.7: Percentage of active voxels corresponding to t-values that exceeded the uncorrected p threshold of 0.001 at 1 week post-stroke: differences between the subcortical and cortical cohorts using the t-test and a 95% confidence interval ........................................................................................................79

Table 4.8: Change relative to baseline (1 week) in the percentage of active voxels corresponding to t-values that exceeded the uncorrected p threshold of 0.001 in the first month and first 3 months post-stroke: differences between the subcortical and cortical cohorts using the Wilcoxon rank-sum and a 95% confidence interval ........................................................................................................80

Table 4.9: Early bilateral activity associated with the affected UL, comparing those who experience good recovery with those who experienced poor recovery ..........81

Table 5.1: Demographic and baseline characteristics of participants ........................................... 98

Table 5.2: Clinical assessments raw scores .................................................................................. 98

Table 5.3: Spearman’s correlations between clinical assessments at each time-point ................................................................................................................................. 100

Table 5.4: Changed scores and responsiveness measures in clinical assessments ...................... 103
List of Figures

Figure 1.1: Regions of interest to sensorimotor function........................................6

Figure 3.1: CONSORT diagram of patients recruited to the study.........................46

Figure 3.2: Sagittal, coronal and axial slices showing clusters of brain activation in the ipsilesional anterior cingulate and supplementary motor areas that are significantly greater in the intensive-training group compared with the standard-care group..........................................................55

Figure 4.1: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation at 3 months that are significantly greater in the good-recovery cohort compared with the poor-recovery cohort........................................75

Figure 4.2: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the good-recovery cohort compared with the poor-recovery cohort at 3 months post-stroke.........................75

Figure 5.1: The mRS, NIHSS, ARAT, UL–MAS and 9HPT box plots..................99

Figure 5.2: NIHSS vs UL–MAS scatter plot.........................................................101

Figure 5.3: ARAT vs UL–MAS scatter plot.........................................................101

Figure 5.4: mRS vs 9HPT scatter plot.........................................................102

Figure 7.1: Graphic depicting a potential hierarchy of restorative approaches in post-stroke rehabilitation that target recovery of an affected upper limb..........147
Synopsis

Stroke represents a disconnection phenomenon that often adversely affects the sensorimotor function of a patient’s upper limb (UL). In adults, the brain’s natural capacity to reorganise in response to changes in behavioural demands provides a foundation for post-stroke recovery. Evidence indicates that UL recovery can be attenuated by an intensive, task-specific, motor training approach.

A review of the relevant literature found that ipsilesional sensorimotor regions are important to early, UL recovery. Results found that, to date, no studies have investigated the association between brain activation patterns and different intensities of early, UL training. Subsequently, a randomised controlled trial compared outcomes in those who received intensive, task-specific, UL training and those who received standard care, and found that early, intensive training was associated with differences in the cerebellar and anterior cingulate regions, indicating that intensive training may increase the effort and attention required when undertaking tasks. A follow-up study that used cohort methods found that ipsilesional sensorimotor regions are also important to good UL recovery. Involvement of areas such as the inferior parietal lobe suggests that recovery may be improved with a multi-modal approach.

In addition, a comparison of five commonly used stroke recovery assessments, three of which were specific to UL recovery, found that the Nine Hole Peg test and the modified Rankin Scale were the most responsive to change. A published review [1] of the literature reporting a task-specific approach to UL recovery identified practice-ready strategies that could be applied in patients with a stroke-affected UL.

The findings from this thesis suggest that in future, if clinicians are seeking to drive brain-based recovery in patients with a stroke-affected UL, they may need to consider brain-based approaches that complement an intensive, task-specific, motor-training approach.
