Upper Limb Recovery and Brain Reorganisation Post-stroke

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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
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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.

Chapter 1: Introduction
1.1 Introduction

This thesis generated new knowledge related to brain reorganisation and upper limb (UL) recovery following stroke. It comprises one literature review, three empirical studies and one narrative review.

The first study used review methodology to identify articles reporting findings related to UL recovery and brain activation in a stroke survivor cohort. The findings from this study are reported in Chapter 2.

The second study recruited right-handed patients with first ischaemic stroke who were less than two weeks post-event, and examined associations between changes in UL behavioural outcomes and brain activation as measured by functional magnetic resonance imaging (fMRI). In this study, participants were recruited from recently admitted patients diagnosed with strokes that had affected the sensorimotor function of the UL. Employing a randomised controlled trial (RCT) design, the study's experimental group received more intensive UL task-specific training in addition to standard care, whilst the control group received standard care only. The findings from this study are reported in Chapters 3 and 4. Many researchers have investigated associations between UL function and brain activation [1, 2], but to date, there are no studies that have compared the impact of differing intensities of UL task-specific training in the first month post-stroke. As chapter 2 demonstrates, some studies have investigated differences between patients who experience good recovery and poor recovery, and some studies have reported differences between cortical and subcortical stroke [2-5].

The third study, reported in Chapter 5, compares five commonly used, stroke recovery assessments. Two assessments measure global function, and the other three assessments are specific to UL recovery.

Chapter 6 is a narrative review of the evidence related to UL recovery and task-specific training. This review aimed to translate the evidence into practice-ready strategies that therapists could apply when working with patients affected by stroke.

The final chapter discusses the implications of the evidence generated from this thesis, and again, aims to do this in a format that is practice-ready and useful to therapists working with patients affected by stroke. This opening chapter describes the key issues pertinent to this thesis: ischaemic stroke; the human brain; fMRI; and UL function post-stroke.
1.2 Ischaemic Stroke

In Australia, a stroke occurs once every ten minutes; it is the leading cause of disability in adults and one of the leading causes of death. About one-third of people diagnosed with stroke die within the first year, about one-third return home with minimal residual disability, and one-third to one-half must rely on others to participate in everyday activities [6].

A stroke occurs when there is disruption to the blood flow or vascular supply to the brain and, in turn, disruption to the supply of oxygen and nutrients. Despite the fact that the human brain makes up only 2% of body weight, it accounts for 20% of the body’s total oxygen consumption and receives 11% of its cardiac output [7, 8]. The brain’s energy production relies on an efficient and reliable supply of oxygen and nutrients to the nervous system’s neuron and neuroglial cells. The human brain has an estimated 100 billion neurons, each of which has an average of 10,000 synapses, and “almost one third of this immensely complex system is dedicated to the function of behaviour” [9].

A stroke is a disconnection phenomenon which disrupts communication between the upper and lower neural sub-systems. This disruption can affect many behavioural functions such as mobility, sensation, proprioception, speech, vision and/or cognition and, in turn, the ability to participate independently in everyday activities. An ischaemic stroke results from a “blockage” in the vascular supply to the brain, as opposed to a haemorrhagic stroke which results from a “bleed”. In Australia, ischaemic strokes account for about 80% of all strokes [6, 10]. The term, ischaemia, refers to an area of the brain where the integrity of the cells has been adversely affected by vascular hypoperfusion, resulting in an insufficient supply of oxygen and nutrients [11]. Hypoperfusion can result in the loss of up to 1.9 billion neurons and 14 million synapses per minute, [12] thus rapidly impacting on the connection between the upper and lower neural sub-systems. The most common ischaemic event affecting the UL occurs in the middle cerebral artery [13]. This artery supplies a significant portion of the brain and, more specifically, the frontal and parietal lobes, including the sensorimotor cortices (SM1), the supplementary motor areas (SMA) and the premotor cortices (PMC). Strokes affecting UL function can occur in the cortical or subcortical regions of the human brain [14-16].
1.3 The Human Brain

The human brain or cerebrum is made up of two cerebral hemispheres, divided by its most prominent feature, the inter-hemispheric fissure. Each hemisphere is divided into four lobes – frontal, parietal, occipital and temporal [9] – the distal regions of which are referred to as the cortex (grey matter) and marked by gyri and sulci. A stroke that occurs in these regions is referred to as a cortical stroke. A subcortical stroke occurs in the deeper, proximal regions (white matter) and in or around the internal capsule, a fibrous structure connecting the cortex to other cerebral structures and to the spinal cord. The healthy adult brain is neuroplastic, a term describing its ability to reorganise in response to changes in behavioural demands [17, 18]. Neuroplasticity or brain reorganisation is the foundational mechanism underpinning long-term recovery post-stroke [19]. Evidence indicates differences in the human brain’s neuroplastic responses to cortical and subcortical strokes [20-22].

The brain’s reliance on energy production supported by an efficient delivery of oxygen and nutrients provides a means of measuring neuroplastic changes or changes in brain activation. This is possible using fMRI as it provides “information on the increases in blood flow accompanying neuronal activation” [23]. Its introduction has heralded a global human brain-mapping initiative which is exploring and defining the structure, topography and connectivity of the human brain [24]. Using fMRI to research changes in brain activation has already increased understanding of the way in which different parts of the brain interact and communicate with each another. In addition, it has increased understanding of the reorganisation processes supporting recovery following a stroke event.

Most strokes cause damage in only one cerebral hemisphere which is then referred to as the ipsilesional hemisphere. This damage results in dysfunction in the contralateral side of the body. For example, damage to the sensorimotor area of the left hemisphere can result in a right, stroke-affected UL. However, it is important to bear in mind that only 90% of corticospinal tracts decuss or cross over between the upper and lower neural sub-systems. Moving on from the days when we believed that “right affected left” and “left affected right”, new stroke recovery theory is emerging of inter-hemispheric and intra-hemispheric connectivity which may also contribute to UL dysfunction and recovery [25, 26]. This interconnecting complexity, although not yet fully understood, is driving a growing interest in human brain-mapping, connectivity and tractography [27]. Answers are being sought as to whether or not, following stroke, a damaged, ipsilesional hemisphere is adequately able to inhibit influences from the
contralesional hemisphere, and whether or not there are hierarchies in inter- or intra-hemispheric communication pathways [25]. Evidence related to these issues will contribute towards understanding of the recovery processes post-stroke. Eventually, this knowledge should assist in a neurobiologically-based identification of which behavioural interventions will be effective for which patients and, in turn, provide a more reliable theoretical framework on which to base clinical decision-making [26, 28].

Classifying and mapping regions in the human brain is not a new field of interest [24, 29]. Currently, researchers identify the cytoarchitecture of the human brain using one of a series of available classification systems [24], for example, Brodmann Areas.

Researchers commonly identify regions of interest in the brain based on the available evidence. These regions of interest may be used to conduct hypothesis-based analyses of putative brain regions involved in recovery. Some of the more influential regions of interest related to post-stroke UL recovery are listed in Table 1.1 and shown in Figure 1.1 [2, 31].

Table 1.1: Regions of Interest

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Coding</th>
<th>Brodmann Area</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sensorimotor cortex</td>
<td>M1</td>
<td>BA4</td>
<td>Frontal lobe</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>SMA</td>
<td>BA6, medial surface</td>
<td>Frontal lobe</td>
</tr>
<tr>
<td>Premotor cortex</td>
<td>PMC</td>
<td>BA6, proximal surface</td>
<td>Anterior to M1</td>
</tr>
<tr>
<td>Cingulate area or gyrus</td>
<td>CA</td>
<td>BA23, BA24</td>
<td>Above the corpus colosum</td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td></td>
<td>Overlies the pons and medulla</td>
</tr>
</tbody>
</table>
1.4 Functional Magnetic Resonance Imaging

Innovations in neuroimaging have seen advances in hyperacute interventions post-stroke, for example thrombolysis [32], and they are beginning to influence the interventions used in the subacute phase post-stroke [33]. One such innovation is fMRI, an *in vivo* imaging technique which is safe and non-invasive. Whilst it detects dynamic changes deep within the human brain, it does not measure change in individual neurons, but the activity of populations of neurons. Communication within and between populations is dependent on neurotransmitter-receptor interactions [34]. This excitatory activity is energy-reliant, with increases in demand met by increases in local blood flow. The oxygen and nutrients are taken up at the point of demand, resulting in an output of deoxygenated blood. This oxygenated-to-deoxygenated
gradient is the basis of all blood-oxygen-level-dependent imaging, including fMRI [35]. In fMRI, a magnetic environment is applied and manipulated to produce nucleic reactions. As Mathews [34] explains: “magnetic resonance arises from the interaction of nuclei which have a magnetic moment with an applied magnetic field”. The strength of a magnetic field is measured in units of Tesla (T). A 1.5T machine, such as the one used in these studies, generates a magnetic field that is 25,000 times greater than the Earth’s magnetic field.

The human brain is made up of compounds of different densities. For example, the density of the cortex is different from that of the subcortex [11]. One major contributor to brain density is water, which has molecules made up of one oxygen and two hydrogen atoms (H₂O). The hydrogen atom is important to fMRI capability because it “has one of the strongest of all nuclear moments” [36]. The subatomic particles, neutrons and protons, possess an angular property, referred to as “spin”. The net “neutron + proton” spin constitutes the nuclear moment. Hydrogen also has one of the highest resonant frequencies, as a consequence of its high nucleic moment. A magnetised environment will begin to align nucleic spin and, if manipulated, results in detectable changes in spin gradient and resonant frequencies. Changes in net magnetic moments are measured in voxels or cubes of activation during fMRI. Measured over time, fMRI data provide a unique four-dimensional “window” into changes in brain activation. Although fMRI studies must take into account many potential confounders, for example, the fact that there are “up-to-speed” and relaxation phases with nucleic spin, it has nevertheless demonstrated huge potential in its ability to detect changes in nucleic excitability [37, 38].

In fMRI studies investigating UL recovery, not only is the environment being magnetically manipulated, but the participant is also required to make behavioural changes, for example, finger-tapping. To account for the fact that the human brain is active when a person is supposedly “at rest”, we employed a task-rest blocked study design paradigm, using alternating cycles of both conditions. Analysis of fMRI data often uses active-rest paradigms, with the “rest” component deducted to provide a more adequate measure of excitability related to the active condition, which in our study constituted finger-tapping.

1.5 Upper Limb Function and Recovery

Movement of the arm and hand, or UL, is usually smooth, responsive, accurate and reliable. It is often bilateral, using cooperative movements from the dominant, more
controlling limb and the non-dominant, more supportive limb. Both can work together in free-flowing, exquisite unison, achieving everyday tasks with high levels of accuracy and reliability, time and time again. Consider for a moment, a woman fastening a small necklace clasp at the back of her neck or a man using a mirror to shave the skin folds of his face. Doing up the necklace clasp is achieved with no visual input at all. The finger movements are very fine, requiring accurate texture and force sensorimotor discrimination and high levels of cooperation between both upper limbs. This also applies to shaving, a task achieved using reversed visual feedback provided by the mirror. In both activities, the shoulder joints provide the stability on which the elbow joints can be reliably suspended, releasing the wrists, hands and fingers to manipulate the razor safely across the skin folds or to fasten the clasp of a necklace successfully. To do these actions with fluid, accurate and reliable movements requires extraordinary levels of coordination and cooperation between the two upper limbs, between and within the brain’s hemispheres and between the upper and lower neural sub-systems.

Everyday tasks such as these are achieved on the foundation of many years of practice, beginning with the first, somewhat clumsy hand movements of the small infant exploring its new environment. However, once learned and mastered, these bilateral cooperative movements seem to be done on “auto-pilot”. The person does not have to think about which muscles to contract or relax, or whether or not the UL joints need to be fully extended or otherwise. On the contrary, UL movement just seems to happen. This is fortunate, as tasks are often undertaken in environments where a person is faced with multiple demands. For example, a driver approaching a busy intersection with fast-flowing traffic must rely on accurate, responsive and cooperative bilateral UL movements which must be fully synchronised with bilateral movements of both lower limbs. All movement must be on “auto-pilot” because the driver is also engaging higher cognitive skills to predict, plan and safely navigate the potentially dangerous intersection environment. This “layering-up” of movement, sensation, feedback and executive function makes up what we all take for granted – the ability to participate reliably and repeatedly in everyday tasks.

**Impact of stroke**

A stroke disconnects the pathways that afford access to reliable and accurate UL movement. In the hyperacute phase, the “core” of the stroke lesion is quite rapidly being formed, eventually identifying a region which will be completely ineffective. If this core is positioned in a sensorimotor region or in the structures supporting that region, then UL dysfunction is a likely outcome. The sensori- and motor-related cortices, those
that are primarily responsible for UL function, are positioned in the frontal and parietal lobes of both hemispheres and on either side of the central sulcus. Much like roads linking suburbs to the central business districts in a city’s metropolis, following a stroke the human brain must presumably re-map the networks connecting different regions, shifting connectivity to the routes that are still functioning and working around those that are disconnected and permanently damaged. To do that, evidence demonstrates that the brain recruits undamaged or spared regions on which to learn new ways of achieving everyday tasks [1, 2]. This responsiveness is due to the brain’s ability to reorganise itself. This ability is the foundational basis on which Carr and Shepherd proposed the motor re-learning approach [39]. Their approach uses everyday tasks as a therapeutic medium for post-stroke sensorimotor recovery [40, 41].

A stroke that adversely affects UL function is one of the main causes underlying a survivor’s inability to manage daily tasks without the assistance of others [42]. Up to 75% of stroke patients with UL dysfunction experience persistent difficulties with everyday tasks [43]. This dysfunction affects the ability to participate in everyday activities with ease and, in turn, to reintegrate into the community and experience good quality of life. In Australia, those with a stroke-affected UL are offered rehabilitation, but it is usually limited to the first six weeks post-stroke [44].

To measure UL function and recovery over time, evidence indicates that clinicians are selecting a wide variety of assessments [45]. Chapter 6 compares the performance of five assessments that are often used in the first few months post-event. Stroke rehabilitation is based on a multi-professional team approach and usually involves the expertise of an Occupational Therapist and a Physiotherapist [46-49]. Following discharge from rehabilitation, patients are offered minimal UL training, irrespective of how much ongoing difficulty they are experiencing and despite evidence of continuing recovery months and even years post-stroke [1, 50-53].

**Behavioural intervention**

Evidence concerning effective post-stroke UL behavioural intervention indicates that it should be task-specific and meaningful to the stroke survivor [54, 55], and that higher intensity of training usually results in improved outcomes, especially in the first month post-stroke [47, 56]. At present, most behavioural interventions have a repetitive task-specific component, for example, constraint-induced movement therapy, which has been shown to be very effective post-stroke [51]. Irrespective of which intervention is applied, evidence indicates that for patients with stroke to maximise UL recovery, they
must apply themselves to meaningful, everyday tasks, practising them as often as they can [55]. It is concerning that despite all indications that UL behavioural training can influence recovery months and even years post-stroke [1, 2, 57], Australian data indicate that patients with stroke receive very little rehabilitation [58, 59].

1.6 Conclusion

A stroke is a disconnection phenomenon that causes disruption between the upper and lower neural sub-systems. When stroke affects people’s ability to use their upper limbs, it also affects their ability to participate in everyday activities, with many left dependent on the assistance of others. Post-stroke, the human brain utilises its neuroplastic capacity to reorganise itself in response to behavioural demands, and fMRI has proven useful for investigating these responses. Stroke rehabilitation is the standard care provided to those who have affected ULs, and evidence indicates that UL behavioural intervention post-stroke can influence brain activation patterns. This chapter has introduced the main issues central to this thesis.
1.7 References


Chapter 2: Literature Review
2.1 Abstract

Background: Advanced neuroimaging has provided a “window” into brain reorganisation. This review sought to answer two questions in patients with ischaemic stroke: i) In the first month post-stroke, what brain activation patterns have been shown to correlate with motor recovery of the affected upper limb (UL); and ii) which behavioural interventions have been shown to influence brain activation and improve UL motor recovery?

Methods: Through the PubMed database and secondary searching, articles related to UL recovery and brain activation post-stroke were sourced. This strategy captured 8 eligible studies recruiting participants less than one month post-stroke and one systematic review of studies that recruited participants less than 6 months post-stroke. It also captured 18 studies and 2 systematic reviews that investigated UL interventions and neuroanatomical outcomes.

Results: The current review found that in right-handed patients with ischaemic stroke, changes in cortical activation are detectable in the first month, and as early as the first days, following stroke. In a cohort of almost completely chronic-phase (95.5%) participants, the interventions shown to improve function in the affected UL and influence brain activation included constraint-based and repetitive task-specific interventions. In both early and later stages, changes in activation were found primarily in ipsilesional sensorimotor-related regions.

Conclusion: In patients with ischaemic stroke who are less than one month post-event, early activation in the ipsilesional sensorimotor regions is associated with recovery in the affected UL at 3 months. In the chronic phase, constraint-based and task-based interventions improve sensorimotor function in the affected UL and influence brain activation.
2.2 Introduction

Neuroimaging technologies have made a significant contribution to clinical management following stroke in both the acute [1, 2] and subacute phases [3-6]. In vivo techniques such as position emission tomography (PET) and functional magnetic resonance imaging (fMRI) provide insight into brain haemodynamics and the opportunity to map neural outcomes, for example, changes in brain activation, against behavioural outcomes [7, 8]. Both PET and fMRI can detect change in brain activation over time. Position emission tomography has been identified as one of the most sensitive molecular imaging techniques [9]. It traces gamma rays emitted by a positron-emitting radionuclide contrast injected into the patient prior to scanning. However, fMRI is now the preferred technique because it is non-invasive, non-radioactive and comparatively safe. In fMRI a magnetic environment is applied to manipulate the behaviour of sub-atomic neutron and proton particles [10, 11]. This manipulation, if accompanied by behaviour, for example finger-tapping, provides in vivo data on the location of oxygen-dependent excitatory neural activity (“activation”).

Research using neuroimaging techniques is still establishing the best methods to use when investigating associations between changes in activation and different outcomes [11, 12] in both the healthy brain [13] and the injured brain [8, 14-17]. As the rigour, reliability and validity of experimental studies improve [18-20], this research has the potential to contribute significantly to the scientific evidence that will guide health professionals.

Upper limb function is impaired in up to 75% of those diagnosed with stroke [21]. Even though rehabilitation usually occurs in the first month post-stroke, when most recovery is anticipated [7, 8, 22], to date most stroke studies investigating associations between UL motor recovery and changes in brain activation have recruited participants in the chronic phase [14, 16].

This review critically appraises the evidence related to stroke, brain activation and motor function of the affected upper limb (UL). It aims to answer the following questions, particularly in relation to ischaemic-stroke patients:

1) In the first month post-stroke, what regions of brain activation have been shown to correlate with motor recovery of the affected UL?

2) Which behavioural interventions have been shown to influence brain activation and improve motor recovery of the affected UL?
2.3 Method

To identify the most relevant literature a search was undertaken using the PubMed database. Following that, a secondary (hand) search of related articles was also applied. The PubMed search used the search terms, “stroke”, “brain reorganisation” and “upper”, and limited the search to articles reported in the English language and published between and including 1996 and 2011. This search yielded 70 articles. On the basis of the information in the abstracts, 41 were excluded for the following reasons: non-fMRI/PET (n=18), non-UL (n=8), non-stroke (n=4), narrative literature review (n=6), study methodology (n=2), animal modelling study (n=1), conference proceedings (n=1) and neurosurgery (n=1). A further 3 case studies were excluded because only one participant was recruited for each study. After perusal of the “full text” of the remaining articles, 10 were excluded because their findings were unrelated to the primary aims of the review: non-stroke [23]; white matter integrity [24]; hypertonicity [25, 26]; acupuncture [27, 28]; mirror movements [29]; not reporting imaging results [30]; and non-therapeutic electrical stimulation [23]. To maintain a focus on ischaemic stroke, 5 studies were excluded as ≥25% of participants had haemorrhagic stroke [31-35]; the presence of blood products on MRI leads to significant artefact and confounds fMRI interpretation. One study was excluded because 1 of only 5 participants was diagnosed with traumatic brain injury [36]. The “captured” studies for this review [4, 16, 20, 37-47] included two systematic reviews. Secondary searches using reference lists and associated articles identified another 31 studies [3, 6, 48-76], including one more systematic review [14]. A further systematic review found in the secondary searches, Kokotilo et al [77], was not included because it reviewed modulation of movement only.

2.4 Results

Review question 1

_In the first month (mean <30 days) post-stroke, what activation has been shown to correlate with motor recovery of the affected UL?_

The search captured 8 studies recruiting participants less than one month post-stroke (Table 2.1) and one systematic review (Buma et al) [14]. Studies by Luft et al [40], Lindberg et al [46], Marshall et al [52], Carey LM et al [4] and Loubinoux et al [50] were reviewed in conjunction with associated publications as they referred to the same data as previously published, i.e. Whitall et al [44], Lindberg et al [39], Marshall et al (2009) [53], Carey LM et al [3] and Tombari et al [51] respectively.
In the systematic review, Buma et al [14] reviewed 20 studies recruiting 154 subjects who were less than 6 months post-stroke. Only one of these, Carey LM et al (2006) [3], was eligible for inclusion in the current review because the researchers recruited participants who were less than 1 month post-stroke. Compared with levels of activity normally seen in healthy controls, for the first 6 months post-stroke Buma et al [14] found more activity in motor-related, perilesional and contralesional areas, and associations between good recovery and a return to more normal patterns of activation, and between poor recovery and persistent, contralesional activation. The current review question is focussed on activity in the first month post-stroke only.

Table 2.1 reports the studies, captured in the current review, that recruited participants in the first month post-stroke. The 8 studies recruited 99 participants with a mean number per study of 10.6 (range 5–23). All participants were inpatients with first ischaemic stroke who were admitted to hospital. Of these, 98 were right-handed. In all but two studies [74, 78], participants were reported as having received post-stroke rehabilitation. Most participants were diagnosed with subcortical stroke, with 2 studies [51, 74] only recruiting subcortical stroke patients. Marshall et al [53] had the earliest average baseline assessment time point of 47 hours, but they did not have a follow-up assessment. Three studies had a mean baseline assessment time point of less than 1 week post-stroke: Rehme et al [78] at ≤3 days; Puh et al [54] at ≤4 days; and Askim et al [6] at ≤6 days. All studies included healthy controls (mean 8.9,) with the exception of Marshall et al [53]. All studies used a task-rest imaging paradigm, but the tasks varied across studies. For example, Butefisch et al [49] used an alternating finger-to-thumb task.

With the exception of Butefisch et al [49] and Marshall et al [53], all studies investigated change across time points. Using different measures, improvement in the affected UL was detectable in the first two weeks in those with mild strokes [78], in the first 3 months in those with strokes that were not in the primary sensorimotor cortex (SM1) [6] and in the first 6 months in patients who experienced good recovery [3]. Whilst Butefisch et al [49] and Rehme et al [78] found that early activation did not predict recovery in the affected UL, Marshall et al [53] found that UL recovery correlated with more baseline activation in the ipsilesional primary somatosensory cortex (S1) and the posterior cingulate area (CA) than in healthy controls.
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

<table>
<thead>
<tr>
<th>Study (Baseline; Type)</th>
<th>Sn/Hc</th>
<th>Population</th>
<th>Rehabilitation</th>
<th>Activation task</th>
<th>Assessed at:</th>
<th>Affected UL Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Askim et al [6]</td>
<td>12/15</td>
<td>Right-handed</td>
<td>Stroke Unit, early mobilisation and task-specific training</td>
<td>Cued versus self-paced index finger-thumb opposition</td>
<td>5 days 3 months</td>
<td>Significant difference at 3 months when compared with 20 days Measures: UL-MAS and grip strength</td>
</tr>
<tr>
<td>Butefisch et al [49]</td>
<td>5/9</td>
<td>Right-handed</td>
<td>Rehabilitation</td>
<td>Self-paced, alternating finger-thumb opposition</td>
<td>1 month</td>
<td>Reported as good in all patients Measures: Jebsen test and pinch grip</td>
</tr>
<tr>
<td>Tombari et al [51]</td>
<td>8/12</td>
<td>Right-handed</td>
<td>2–3 weeks Bobath</td>
<td>Cued, passive and active, fingers flexed/extended</td>
<td>20 days 4 months 12 months</td>
<td>Significant in first 12 months Measures: Motricity Index and hand grip</td>
</tr>
<tr>
<td>Marshall et al [53]</td>
<td>23</td>
<td>Right-handed</td>
<td>11 patients only: 2–14 hours per week rehabilitation</td>
<td>Cued, opened and closed fist</td>
<td>2 days 3 months</td>
<td>No follow-up</td>
</tr>
<tr>
<td>Nelles et al [74]</td>
<td>5/10</td>
<td>Subcortical</td>
<td>Not reported</td>
<td>Passive and active elbow movement</td>
<td>22 days 2 months</td>
<td>Not reported</td>
</tr>
<tr>
<td>Puh et al. [54]</td>
<td>7</td>
<td>Right-handed</td>
<td>10 days UL training 1.5 hours per day</td>
<td>Self-paced, finger-thumb vs holding block</td>
<td>4 days 2 weeks 3 months (n=3)</td>
<td>Not measured</td>
</tr>
<tr>
<td>Rehme et al [78]</td>
<td>11/11</td>
<td>Right-handed</td>
<td>Not reported</td>
<td>Cued, opened and closed fist</td>
<td>Baseline 1 week 2 weeks</td>
<td>Significant in first 2 weeks Measures: Action Research Arm test</td>
</tr>
</tbody>
</table>

Key: Sn = number of stroke participants, Hc = number of healthy controls, fMRI = functional magnetic resonance imaging, MCA = middle cerebral artery, UL-MAS = upper limb subscale of Motor Assessment Scale, PET = position emission tomography

Table 2.2 lists the brain regions, topography and Brodmann Areas of the human brain reported in studies recruited into this review. Table 2.3 summarises the regions of ipsilesional and contralesional activation associated with movement of a stroke-affected UL in the first month post-event. These results provide two comparisons: those
with good recovery versus those with poor recovery; and stroke patients versus healthy volunteers. Two studies have been excluded from this table: Askim et al [6] because they only compared left versus right hemispheric findings between patients; and Puh et al [54] because they only reported findings on a case-by-case basis.

Table 2.2: Brain regions, topography and Brodmann Areas

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Abbreviation</th>
<th>Topography</th>
<th>Brodmann Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary motor cortex</td>
<td>M1</td>
<td>Precentral gyrus</td>
<td>4</td>
</tr>
<tr>
<td>Primary somatosensory cortex</td>
<td>S1</td>
<td>Postcentral gyrus</td>
<td>3b, 1 and 2</td>
</tr>
<tr>
<td>Secondary somatosensory cortex</td>
<td>S2</td>
<td>Parietal operculum</td>
<td>40 and 43</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Cb</td>
<td>Located within the posterior fossa</td>
<td>1 - IV</td>
</tr>
<tr>
<td>Pre-motor cortex</td>
<td>PMC</td>
<td>Anterior of M1 medial</td>
<td>6</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>SMA</td>
<td>Anterior of M1 lateral</td>
<td>6</td>
</tr>
<tr>
<td>Cingulate area: anterior, posterior</td>
<td>aCA, pCA</td>
<td>Around corpus collosum</td>
<td>24, 32, 23 and 31</td>
</tr>
<tr>
<td>Parietal cortex: inferior, superior</td>
<td>iPC, sPC</td>
<td>Inferior/superior parietal lobule</td>
<td>5, 7 and 40</td>
</tr>
<tr>
<td>Frontal cortex: anterior, superior</td>
<td>aFC, sFC</td>
<td>Anterior frontal lobe</td>
<td>8-11, 45 and 49</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>Insular</td>
<td>Between temporal and frontal lobes</td>
<td>N/A</td>
</tr>
<tr>
<td>Study (Subjects)</td>
<td>Sn/Hc</td>
<td>Comparison</td>
<td>Ipsilesional activation</td>
</tr>
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</tr>
<tr>
<td>Butefisch et al [49] Good recovers</td>
<td>5/9</td>
<td>Stroke vs healthy</td>
<td>At 1 month: SM1</td>
</tr>
<tr>
<td>Carey LM et al [3] MCA strokes</td>
<td>9/10</td>
<td>Good vs poor</td>
<td>At 1 month: SM1, SMA and CA</td>
</tr>
<tr>
<td>Tombari et al [51] Pure motor strokes</td>
<td>8/12</td>
<td>Stroke vs healthy</td>
<td>At 1 month: SMA, PMC, CA and Cb</td>
</tr>
<tr>
<td>Marshall et al [53] Lacuna strokes</td>
<td>23</td>
<td>Affected vs unaffected</td>
<td>At 2 days: Cb</td>
</tr>
<tr>
<td>Nelles et al [74] Severe strokes</td>
<td>5/10</td>
<td>Good vs poor</td>
<td>At 2 days: S1 and CA</td>
</tr>
<tr>
<td>Rehme et al [78] Patients: ≤2 weeks</td>
<td>11/1</td>
<td>Stroke vs healthy</td>
<td>At 5 days: CA</td>
</tr>
</tbody>
</table>

Key: SM1 = primary sensorimotor cortex; M1 = primary motor cortex; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SMA = supplementary motor area; Cb = cerebellum, CA = cingulate area; PMC = premotor cortex; PL = parietal lobe; IPL = inferior parietal lobe; SPL = superior parietal lobe, Sn = number of stroke participants, Hc = number of healthy controls, MCA = middle cerebral artery stroke.

In the first month, patients with good recovery had more ipsilesional SM1, SMA and/or PMC activation and contralesional SMA and PMC activation than those with poor recovery. At the same time, participants had more contralesional PMC activation than healthy controls. Only Rehme et al [78] reported more activation in the healthy control group when compared to those with stroke, reporting higher levels of activation in the ventrolateral nucleus and V5 of the left hemisphere (corresponding with the ipsilesional hemisphere) and in the fusiform gyrus of the right hemisphere. The findings indicate that higher levels of activation in sensorimotor regions such as the SMA and PMC in the first few days post-stroke predicted good recovery.

In summary, this review found that in the first month post-stroke, recovery of the affected UL in right-handed, ischaemic-stroke patients is associated with higher levels of activation in sensorimotor regions such as the SMA and PMC, when compared with healthy controls and those with poor recovery.
Review question 2

*Which behavioural interventions have been shown to influence brain activation and improve motor recovery of the affected UL?*

The search revealed 18 studies and 2 systematic reviews that investigated UL behavioural and sensorimotor interventions (Table 2.4). The review excluded 15 studies that did not apply UL intervention (Appendix 2.1). The included studies recruited 229 patients, with a mean number of participants of 12.7 (range 2–38), all more than a month post-stroke, except for the 12 participants recruited by Askim et al [75]. All studies reported findings as ipsilesional and contralesional activation, but Szarflarski et al [79] only reported their findings on a case-by-case basis. The studies have been grouped according to the intervention, for example, constraint-induced movement therapy (CIMT) and repetitive task-specific training (RTS). The studies by Askim et al [75] and Carey JR et al [62] were allocated to the RTS group because RTS was the primary component of the UL training. Seven studies used randomised controlled trial (RCT) methodology [44, 45, 57-59, 61, 62]. In studies that reported the relevant data, only three studies limited recruitment to right-handed, first-ischaemic-stroke survivors [56, 59, 75]. In relation to stroke sub-type, Lindberg et al [46] only recruited participants with cortical stroke (n=2), and Askim et al [75] and Wittenberg et al [45] only recruited participants with subcortical stroke [45]. Six studies recruited participants with both cortical and subcortical stroke [44, 56, 58, 61, 62, 75].
Table 2.4: Summary of the studies investigating brain activity and behavioural intervention targeting improvement in UL function in patients with stroke

<table>
<thead>
<tr>
<th>Study design</th>
<th>N</th>
<th>Baseline</th>
<th>Included</th>
<th>Task used in imaging</th>
<th>Intervention</th>
<th>Activation</th>
<th>Affected UL function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constraint-induced movement therapy (CIMT)</td>
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<tr>
<td>Dong et al [55]; Pre-post</td>
<td>8</td>
<td>&gt;3 months</td>
<td>Spared M1</td>
<td>Pinch small tube</td>
<td>2 weeks: CIMT (EXCITE protocol)</td>
<td>Contralesional M1 in 3/5 patients</td>
<td>Improved in some participants</td>
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<tr>
<td>Johansen-Berg et al [56]; Pre-post</td>
<td>7</td>
<td>&gt;9 months Mean 37.6 months</td>
<td>First ischaemic stroke, right-handed (6), cortical and subcortical</td>
<td>Fingers flexed and extended</td>
<td>2 weeks: CIMT Training: RTS at home Constraint: 90% wh</td>
<td>Bilateral SM1 and PMC</td>
<td>Improvement correlated with increase in bilateral cerebellar, ipsilesional S2 and PMC</td>
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<tr>
<td>Kim et al [36]; Case study</td>
<td>4</td>
<td>&gt;9 months 21.4 months</td>
<td>Right-handed Non-stroke (1)</td>
<td>Fist and fingers flexed and extended</td>
<td>2 weeks: CIMT Training: 7 hours per day Constraint: 90% wh</td>
<td>Ipsilesional M1 and PMC</td>
<td>Improved in all participants</td>
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<tr>
<td>Lin et al [57]; RCT</td>
<td>13</td>
<td>&gt;9 months &gt;16 months</td>
<td>First stroke Right-handed</td>
<td>Fingers flexed and extended</td>
<td>3 weeks: CIMT Control: Standard care Training: 2 hours per day Constraint: 6 hours per day</td>
<td>CIMT &gt; control: More bilateral PMC and decreasing trends contralesional SM1</td>
<td>CIMT &gt; control: More improvement</td>
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<tr>
<td>Schaechter et al [42]; Case-control</td>
<td>4</td>
<td>3–6 months</td>
<td>First stroke Right-handed</td>
<td>Fingers flexed and extended</td>
<td>2 weeks: CIMT Training: 4 hours per day for 10 days Constraint: 90% wh</td>
<td>CIMT patients: UL recovery may correlate with contralesional motor-related activity</td>
<td>CIMT patients: May correlate with motor-related activity</td>
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<tr>
<td>Szarflarski et al [79]; Pre-post</td>
<td>4</td>
<td>&gt;9 months 72 months</td>
<td>First stroke</td>
<td>Finger-tapping</td>
<td>10 weeks: CIMT Training: 3 days per week for 10 weeks Constraint: 5 hours for 5 days</td>
<td>Increased UL use may increase cortical areas Reported case by case</td>
<td>Improved in 3/4 participants</td>
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<tr>
<td>Wittenberg et al [45]; RCT</td>
<td>16</td>
<td>&gt;9 months 31 months</td>
<td>First ischaemic stroke, subcortical</td>
<td>Fingers flexed and extended</td>
<td>2 weeks: CIMT Training: 6 hours per day (64 hours) Constraint: 90% wh</td>
<td>Intervention &gt; control: decreased with shift towards ipsilesional M1</td>
<td>No between-group difference</td>
</tr>
<tr>
<td>Study design</td>
<td>N</td>
<td>Baseline</td>
<td>Included</td>
<td>Task used in imaging</td>
<td>Intervention</td>
<td>Activation</td>
<td>Affected UL function</td>
</tr>
<tr>
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<tr>
<td>Repetitive task-specific training (RTS)</td>
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<tr>
<td>Askim et al [75]; Cohort</td>
<td>12</td>
<td>&lt;3 months 5.4 days</td>
<td>First ischaemic stroke, spared M1, right-handed, subcortical (10)</td>
<td>Thumb to index finger</td>
<td>Stroke Unit, early mobilisation and RTS</td>
<td>Acute: bilateral SMA and cerebellar, ipsilesional SM1 Chronic: increase in ipsilesional SM1 and contralesional cerebellum</td>
<td>Improved in all participants</td>
</tr>
<tr>
<td>Boyd et al [37]; Pre-post</td>
<td>18</td>
<td>3–9 months</td>
<td>First stroke MCA</td>
<td>Fist on joy stick</td>
<td>5 days: RTS vs general use (control)</td>
<td>Contralesional M1 modified after motor learning</td>
<td>RTS may remediate function</td>
</tr>
<tr>
<td>Carey JR et al [62]; RCT</td>
<td>20</td>
<td>&gt;9 months 39 months</td>
<td>First ischaemic stroke, right-handed (19), cortical and subcortical</td>
<td>Finger-tracking and RTS</td>
<td>2 weeks: Tele-rehabilitation. Track vs move group. Dose: 180 trials per day for 2 weeks</td>
<td>Ipsilesional M1 group and interaction effects, PMC test and interaction effects, and SMA interaction effect</td>
<td>Improved in all participants</td>
</tr>
<tr>
<td>Lindberg et al [39]; Pre-post</td>
<td>7</td>
<td>&gt;9 months 46 months</td>
<td>First ischaemic stroke, cortical MCA</td>
<td>Passive wrist flexed and extended</td>
<td>4 weeks: Repetitive reaching and grasping training, passive/active</td>
<td>Stroke &gt; control: ipsilesional M1 and SM, and contralesional cerebellum</td>
<td>Some improvement trends</td>
</tr>
<tr>
<td>Peripheral Stimulation</td>
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<tr>
<td>Bhatt et al [58]; RCT</td>
<td>20</td>
<td>&gt;9 months 30–35 months</td>
<td>ischaemic stroke, right-handed (19), cortical and subcortical</td>
<td>Finger-tracking</td>
<td>3 weeks: Electrical stimulation Tracking training vs Stimulation plus tracking training Dose: 10 1-hour sessions over 3 weeks</td>
<td>Stimulation plus group only: ipsilesional S1 and SMA correlated with improved function</td>
<td>Improved in 12/20 participants, no between-group differences</td>
</tr>
<tr>
<td>Page et al; Pre-post</td>
<td>8</td>
<td>&gt;9 months 46.5 months</td>
<td>First ischaemic stroke</td>
<td>Wrist flexed and extended</td>
<td>8 weeks: Home-based RTS and stimulation: 30 minutes for 5 days per week over 8 weeks</td>
<td>Post-intervention &gt; pre-intervention: increase in ipsilesional SML and inferior parietal lobe</td>
<td>Improved in all participants</td>
</tr>
<tr>
<td>Transcranial Stimulation</td>
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<tr>
<td>Lindenberg et al [59]; RCT</td>
<td>20</td>
<td>&gt;9 months 30-40 months</td>
<td>First ischaemic stroke, right-handed</td>
<td>Elbow and wrist flexed and extended</td>
<td>1 week: Bilateral transcranial direct current stimulation and OT/PT</td>
<td>Intervention &gt; control: more ipsilesional M1 and PMC and contralesional inferior</td>
<td>Intervention &gt; control: More improvement</td>
</tr>
<tr>
<td>Study design</td>
<td>N</td>
<td>Baseline</td>
<td>Included</td>
<td>Task used in imaging</td>
<td>Intervention</td>
<td>Activation</td>
<td>Affected UL function</td>
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<tr>
<td><strong>Bilateral arm training (BATRAC)</strong></td>
<td></td>
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<td></td>
<td></td>
<td>Control: Sham + OT/PT</td>
<td>frontal gyrus</td>
<td></td>
</tr>
<tr>
<td>Whitall et al [44]; RCT</td>
<td>38</td>
<td>&gt;9 months</td>
<td>First stroke, cortical and subcortical</td>
<td>Elbow flexed and extended</td>
<td>6 weeks: Repetitive bilateral UL training vs standard dose-matched therapy Dose: 1 hour for 3 days per week over 6 weeks</td>
<td>Intervention group: greater ipsilesional SM1, SMA and anterior CA</td>
<td>Improved in all participants, but no between-group difference</td>
</tr>
<tr>
<td><strong>Botulinum toxin A plus UL training</strong></td>
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<tr>
<td>Senkárová et al [43]; Pre-post</td>
<td>4</td>
<td>3–9 months</td>
<td>Ischaemic stroke, mean age 25.5 years</td>
<td>Imagined finger-to-thumb</td>
<td>4 weeks: Botulinum Toxin A Rehabilitation 1 hour per day</td>
<td>Pre-intervention &gt; post-intervention: significant reduction in activation in the posterior CA</td>
<td>Not reported, reduced spasticity</td>
</tr>
<tr>
<td><strong>Mental Practice</strong></td>
<td></td>
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<tr>
<td>Page et al [60]; Pre-post</td>
<td>10</td>
<td>&gt;9 months</td>
<td>First stroke</td>
<td>Wrist flexed and extended</td>
<td>10 weeks: Mental practice plus RTS training: 3 days per week for 10 weeks</td>
<td>Bilateral increase in PMC, M1 and contralesional superior parietal cortex</td>
<td>Improved in all participants</td>
</tr>
<tr>
<td><strong>Mirror therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michielsen et al [61]; RCT</td>
<td>16</td>
<td>&gt;9 months</td>
<td>First stroke, cortical and subcortical</td>
<td>Fist opened and closed</td>
<td>6 weeks: Mirror therapy training: home RTS Dose: 1 hour for 5 days per week</td>
<td>Mirror therapy associated with decrease over time in contralesional M1</td>
<td>Improved in all participants but not sustained at 6 months</td>
</tr>
</tbody>
</table>

Key: RCT = randomised controlled trial, wh = waking hours, S1 = primary sensory cortex, M1 = primary motor cortex, SM1 = primary sensorimotor cortex, PMC = premotor cortex, CA = cingulate area, SMA = supplementary motor area, OT = occupational therapy, PT = physiotherapy, MCA = middle cerebral artery, CIMT = constraint-induced measurement therapy, RTS = repetitive task-specific training
Table 2.4 summarises the studies captured by this review. Seven studies investigated CIMT (with one study including the only non-stroke participant [36]), 4 studies investigated RTS [37, 46, 62, 75], 3 studies investigated peripheral and transcranial stimulation [41, 58, 59] and one study each investigated bilateral arm training with rhythmic auditory cueing [44], botulinum toxin [43], mental practice [60] and mirror therapy [61].

Table 2.5 reports the regions of ipsilesional and contralesional activation resulting from movement of a stroke-affected UL in studies investigating CIMT and RTS only. These two interventions had the highest representation in this review’s results. (The Szarflarski et al [79] study was not included in this table because results were non-randomised, not controlled, or reported as a cohort.) In the 7 CIMT studies, 2 used RCT methodology [45, 57]. Lin et al [57] found that those in the intervention group experienced more improvement in function of the affected UL than those in groups that received standard care. However, Wittenberg et al [45], who applied the highest intensity of daily training over the shortest period of time, found no between-group differences in UL function. In the 4 studies that applied RTS, only Askim et al [75] studied patients in the first few weeks post-stroke. It is worth noting that most studies included some form of repetitive practice in either control [57] or experimental conditions [41, 44, 59-61]; for example, repetitive practice or “shaping” is a standard inclusion in CIMT [56, 79, 80].

Of the 10 studies (Table 2.5), 3 studies compared findings pre- and post-intervention, and 2 studies compared CIMT with standard care. Across all studies, the regions where more ipsilesional activation is seen in the intervention group are the SM1 (n=3 studies), PMC (n=3), SMA (n=2) and cerebellum (n=2), and the regions of more contralesional activation are SMA (n=2) and PMC (n=2).

In studies that applied stimulation, Bhatt et al [58], in a three-way RCT, found that only those who received 3 weeks of both the electrical stimulation and the tracking training showed associations between UL recovery and ipsilesional S1 and SMA activation. However, after applying 8 weeks of unilateral functional electrical stimulation, Page et al [41] reported increased activation in the ipsilesional primary motor cortex. Applying only 1 week of bilateral transcranial direct-current stimulation in combination with occupational therapy and physiotherapy, Lindenberg et al [59] found associations between improvement in the affected UL and ipsilesional changes in M1 and PMC.
This review found inadequate evidence indicating whether botulinum toxin, in conjunction with a behavioural intervention, influences UL function and/or brain activation [43]. Senkárová et al [43] recruited 4 comparatively young participants (mean age 25 years) who received 4 weeks of rehabilitation. Results indicated no change over time in brain activation. Although the researchers claimed to have found UL improvement in their participants, they did not provide behavioural results to substantiate this.

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

<table>
<thead>
<tr>
<th>Study; Design</th>
<th>N</th>
<th>Comparison</th>
<th>Intervention</th>
<th>Ipsilesional</th>
<th>Contralesional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dong et al [55]; Pre-post</td>
<td>8</td>
<td>Post-intervention vs pre-intervention</td>
<td>2 weeks: CIMT</td>
<td>-</td>
<td>M1 in 3/5 participants</td>
</tr>
<tr>
<td>Johansen-Berg et al [56]; Pre-post</td>
<td>7</td>
<td>Post-intervention vs pre-intervention</td>
<td>2 weeks: CIMT</td>
<td>SM1 and PMC</td>
<td>SM1 and PMC</td>
</tr>
<tr>
<td>Kim et al [36]; Case study</td>
<td>4</td>
<td>-</td>
<td>2 weeks: CIMT</td>
<td>M1 and PMC</td>
<td>-</td>
</tr>
<tr>
<td>Lin et al [57]; RCT</td>
<td>13</td>
<td>CIMT vs control</td>
<td>3 weeks: CIMT</td>
<td>PMC</td>
<td>PMC</td>
</tr>
<tr>
<td>Schaechter et al [42]; Case-control</td>
<td>4</td>
<td>Post-intervention vs pre-intervention</td>
<td>2 weeks: CIMT</td>
<td>-</td>
<td>Increases in M1</td>
</tr>
<tr>
<td>Wittenberg et al [45]; RCT</td>
<td>16</td>
<td>CIMT vs control</td>
<td>2 weeks: CIMT</td>
<td>Decrease in M1</td>
<td>Decrease in M1 over time and increase in S2</td>
</tr>
<tr>
<td>Askim et al [75]; Cohort</td>
<td>12</td>
<td>Acute vs chronic</td>
<td>2 weeks: RTS (Stroke Unit)</td>
<td>Acute: SM1, SMA and Cb Chronic: SM1</td>
<td>Acute: SMA and Cb Chronic: Cb</td>
</tr>
<tr>
<td>Boyd et al [37]; Pre-post</td>
<td>18</td>
<td>Post-intervention vs pre-intervention</td>
<td>1 week: RTS</td>
<td>-</td>
<td>M1</td>
</tr>
<tr>
<td>Carey JR et al [62]; RCT</td>
<td>20</td>
<td>Finger-tracking vs moving</td>
<td>2 weeks: RTS (home-based)</td>
<td>Over time, Increase in M1 and decrease in SMA</td>
<td>-</td>
</tr>
<tr>
<td>Lindberg et al [39]; Pre-post</td>
<td>7</td>
<td>Stroke vs control</td>
<td>1 week: RTS</td>
<td>SM1, PMC, SMA and Cb</td>
<td>SMA and Cb</td>
</tr>
</tbody>
</table>

Key: CIMT = constraint-induced movement therapy, RCT = randomised controlled trial, RTS = repetitive task-specific training, M1 = primary motor cortex, SM1 = primary sensorimotor cortex, SMA = supplementary motor area, Cb = cerebellum, PMC = premotor cortex, S2 = secondary somatosensory cortex.
The 2 systematic reviews found an association between interventions targeting motor function of the affected UL and changes in brain activation. Richards et al [16] limited their search to results in the ipsilesional sensorimotor cortex but did not investigate the impact of specific behavioural interventions on patterns of activation. Hodics et al [47] investigated specific interventions and found that CIMT elicited a “treatment-associated increase in activation within the primary motor cortex, dorsal premotor cortex, and supplementary motor area” (p S39). Neither reviews limited recruitment to ischaemic stroke, and both reported on studies published before 2006. This resulted in both reviews only including studies with less than 18 participants.

In summary, the current review found that for patients predominantly in the chronic phase post-stroke, 7 studies investigated CIMT and 4 investigated RTS. These studies provide strong evidence that both interventions influence recovery of the affected UL and result in activation in motor-related regions of the brain. There was also some evidence of changes in brain activation associated with various forms of stimulation, mental practice and mirror therapy.

2.5 Discussion

Brain activation in the first month post-stroke

Based on the findings of this review, most right-handed patients with a first ischaemic stroke experience functionally significant improvement in the motor function of the affected UL and associated changes in brain activation, particularly in motor-related areas. Further, in the first month post-stroke, patients with eventual good recovery had activation in the lesioned hemisphere whilst performing a task with their affected UL in the first week post-stroke. This was particularly in the primary somatosensory area, the ipsilesional SM1, the SMA and the CA. Evidence of activation in motor-related regions of the non-lesioned hemisphere was also found in this review. Whether this pattern of activation is maladaptive or a “normal” response to tasks that, following stroke, have become more complex, is a question raised by Buma et al [14] in their systematic review. In other evidence, Reicker and Groschel [71] found that in patients with good recovery from subcortical stroke, this may be a normal response to more complex UL tasks [71]. In patients with mild strokes, and therefore those with potential for good recovery, Puh et al [54] found early bilateral activation in sensorimotor regions, irrespective of whether a participant was doing a simple or complex task. It is important to achieve a better understanding of this issue of complexity of tasks following stroke, as it has an impact on the understanding of and approaches to stroke recovery, and
also on the significance of the various UL tasks currently being used in the imaging paradigms. This early, bi-hemispheric and neuroplastic response to the damage caused by stroke is consistent with Carey LM and Seitz's [7] theory concerning the different phases of recovery.

The sensorimotor regions of the brain identified as playing a role in early recovery of the affected UL are the SM1, SMA and PMC of both hemispheres. These regions are all located within Brodmann Areas 6 and 4. These areas contribute most of the axons descending the corticospinal tract and, in turn, affect UL motor behaviour [81]. The axons in the SMA and PMC innervate distal and proximal motor units respectively [82]. Therefore, the review findings indicate that patients with a recent stroke and an impaired UL are recruiting secondary sensorimotor areas. This suggests that if the primary sensorimotor regions have been adversely affected by stroke, the brain recruits secondary, or supplementary, regions to support the recovery of arm and hand function post-stroke, particularly those in the ipsilesional hemisphere. In future research, this should be addressed by relating the degree of damage to the SM1 to the degree of secondary motor recruitment. Evidence also indicates that this only occurs in response to behavioural demands. Post-stroke, this is ideally what all interventions should be aiming to elicit if they are targeting arm and hand function.

The findings of involvement of the cerebellum in stroke recovery is consistent with recent research indicating that although traditionally the cerebellum was thought to have been involved in motor coordination and integration, it also contributes towards higher cognitive functions, particularly attention and new learning [83]. The involvement of the cingulate area in the first month post-stroke is also well-aligned with recent research [84-86] demonstrating its importance in motor behaviour, particularly in relation to attention and spatial orientation. The cingulate consists of different subregions, each of which plays a different role. Future research detailing the specific cingulate regions involved would assist in clarifying the nature of its involvement.

Effective behavioural interventions

Almost all sensorimotor interventions captured in this review had a component of RTS. There is an increasing body of evidence pointing to the benefits of a more intensive (or repetitive) and a more task-specific approach to the management of stroke-affected UL [87], resulting in its inclusion in nationally-agreed clinical guidelines [88] and practice recommendations [89]. These findings challenge long-held beliefs concerning “plateaus” in stroke recovery, because they demonstrate that in survivors of even so-
called “mild” ischaemic stroke, as well as in those with more severe stroke, various UL interventions can elicit brain reorganisation months and even years following stroke. Even though the first month post-stroke is the period when most patients are receiving rehabilitation, this review found relatively little research investigating how commonly-used interventions that aim to target sensorimotor recovery of the arm and hand affect brain activation in the early stages following stroke. The regions of the brain that support improvement in UL function in the chronic phase post-stroke are again shown to be primarily in sensorimotor-related areas, including the ipsilesional SM1 and PMC, and the contralesional PMC. The commonalities in brain regions associated with UL recovery in the first month post-stroke (Question 1) and those related to specific behavioural interventions (Question 2) may indicate that the regions recruited to support sensorimotor recovery of a stroke-affected UL may not be as dependent on the type of intervention or time post-stroke as previously believed. Perhaps the evidence indicates that what patients do post-stroke does not matter, as long as they are doing some targeted, sensorimotor intervention.

2.6 Limitations and Further Research

Subacute versus chronic stroke cohorts

The findings from this review provide evidence of an increasing number of studies investigating neuroanatomical outcomes of sensorimotor UL recovery in the first month post-stroke. This review makes an important contribution to knowledge about early UL recovery, as the first month post-stroke is the time when most patients with stroke are receiving rehabilitation and when most recovery is possible [22]. To date, there is only one small (n=12) intervention-related study that recruited in the first month (Askim et al) [75], and this study only investigated UL intervention as a component of the standard care provided by a Comprehensive Stroke Unit. Therefore, further research in the first month after stroke is required to confirm whether or not the time post-stroke that specific behavioural interventions are applied results in significantly different recovery responses and/or brain activation.

Study heterogeneity

Heterogeneity of participants across studies has often been a criticism of stroke recovery research; for example, studies may recruit participants with differing stroke sub-types, lesion locations and/or stroke lesion volumes [8, 14, 22, 90]. Therefore, noteworthy strengths in the very early studies are the across-study recruiting of right-handed survivors of first ischaemic stroke, the selection of the tap-rest blocked design
paradigm, the recruiting of participants with cortical or subcortical lesions, and the reporting of ipsilesional versus contralesional findings. However, increasing the homogeneity of stroke patients must be balanced against the availability of potential participants and the generalisability of results. The participant numbers in this review provide evidence of the challenges that researchers face when recruiting participants for UL-related brain activation studies. Also, limiting recruitment to specific stroke cohorts means that some survivors, e.g. those with multiple strokes and/or significant communication difficulties, are consistently excluded. This leaves gaps in the knowledge generated. Although researchers are beginning to recruit more homogeneous cohorts, as recommended by many researchers [14, 16, 47], there is still capacity to improve between-study consistency, for example, by standardising the task used in the imaging paradigm.

**Future research**

As stated previously, a recommendation from this review is that future research should investigate the impact of specific UL sensorimotor interventions on brain activation in the first month post-stroke. This is primarily because during this time most patients are receiving rehabilitation, and there is the greatest potential for recovery. To strengthen the findings, studies should use a randomised controlled design if possible. However, it is acknowledged that not only is this challenging in the sub-acute phase; it is also not ethically acceptable to recruit participants for non-intervention control groups because that would be in contradiction to standard care as recommended in clinical guidelines.

### 2.7 Conclusion

This review found that in the first month post-stroke, recovery of the affected upper limb is associated with activation in the ipsilesional sensorimotor cortex, supplementary area and premotor cortex in right-handed survivors of first ischaemic stroke. In addition, this review of the literature revealed that in patients with ischaemic stroke who are in the chronic phase, the primary sensorimotor interventions shown to elicit a neuroplastic response were constraint-induced movement therapy and repetitive task-specific training. For the studies investigating various forms of stimulation, mental practice and mirror therapy, this review found that changes in brain activation were again present in sensorimotor regions. It would appear that in the later stages of recovery from stroke, specific rehabilitation approaches may be an important ingredient to achieving clinical improvement and changes in brain activation. The clinical implications of this review are that in the first month post-stroke, most patients with ischaemic stroke resulting in
arm and hand impairment experience some recovery and corresponding changes in brain activation patterns. However, to date there is no evidence indicating whether or not brain activity is influenced by particular training regimes or behavioural interventions in patients less than one month post-stroke.
2.8 References


Chapter 3: Comparing Different Intensities of Intervention

3.1 Abstract

Background: Upper limb dysfunction is experienced by up to 75% of patients post-stroke. The greatest potential for functional improvement is in the first month. Following reperfusion, evidence indicates that neuroplasticity is the mechanism that supports this recovery.

Objective: This study will investigate the effect of increased intensity of task-specific upper limb training in the first month post-stroke on upper limb motor function and brain activation.

Methods: A prospective, single-blinded, longitudinal, randomised controlled trial in patients with acute-ischaemic-stroke patients admitted to two stroke units. Participants were randomised to standard care or standard care plus an additional 30 hours of task-specific upper limb training in the first month post-stroke beginning in week one. Patients were assessed at 1 week, 1 month and 3 months post-stroke. Assessments included functional magnetic resonance imaging and clinical measures.

Results: When compared with the standard care group, the intensive-training group had increased brain activation specifically in the anterior cingulate and ipsilesional supplementary motor areas, and a greater reduction in the extent of activation ($p=0.02$) in the contralesional cerebellum. Although there were no significant differences in mean recovery of upper limb function, intensive therapy was associated with a smaller deviation from mean recovery at one month ($Pr>F_0=0.017$) and three months ($Pr>F=0.006$), indicating more consistent and predictable improvement in motor outcomes.

Conclusion: Early, more intensive, upper limb training was associated with differences in activation in motor-related (supplementary motor area and cerebellum) and attention (anterior cingulate) regions, providing support for the role of these regions and functions in early recovery post-stroke.
3.2 Introduction

A stroke results in permanent damage to the brain, but most patients make some recovery. In the first few hours post-event this relates to early reperfusion, but following this, most of the recovery is related to brain reorganisation (neuroplasticity) [1-3]. Nonetheless, up to one-third of patients need ongoing assistance, with upper limb (UL) dysfunction a major contributor to this disability [4]. Evidence indicates that more intense training can improve functional outcomes [5-8] and influence brain activation, which may be a marker of neuroplasticity [3, 9].

Techniques such as functional magnetic resonance imaging (fMRI) can identify changes in regional cerebral blood flow during a motor task [10]. To date, most fMRI studies investigating UL motor recovery in ischaemic stroke patients have recruited participants at least several months after the event [1, 3, 11, 12]. Buma et al [13] reviewed 19 non-randomised studies that recruited between 2 and 14 participants who were less than 6 months post-stroke. They found a correlation between favourable UL outcomes and changes in activity in motor and non-motor areas in the first few months post-stroke. In the few studies that recruited participants in the first few days post-stroke, researchers reported bilateral reorganisation in the first month [14-17]. For example, Ward et al [18] found bilateral activity after a recent motor stroke. In a recent meta-analysis comparing affected UL movement versus rest, Rehme et al [19] found a convergence of activity in key areas of both hemispheres, including the primary sensorimotor, premotor areas and supplementary motor area, and “that over-activity in contralesional motor areas is a robust phenomenon after stroke”. While increasing evidence supports the association between post-stroke recovery and changes in task-related activation, the cortical mechanisms underlying recovery at different times in the recovery journey and in response to specific interventions require systematic investigation [20].

To date, no studies have used a randomised controlled trial (RCT) design to compare changes in brain activation in response to different intensities of UL motor training in the first month post-stroke [21]. In the current study we therefore investigated the impact of different intensities of task-specific UL training on brain activity and UL recovery in a cohort of adult, first-ischaemic-stroke patients with an affected UL. We hypothesised increased change in activation of motor-related areas, specifically in the primary sensorimotor, premotor, supplementary motor and anterior cingulate areas and in the cerebellum, in those receiving intensive, task-specific UL training, compared with those receiving standard care in the first 3 months post-stroke.
3.3 Methods

This prospective, single-blinded, RCT recruited stroke patients admitted to two acute stroke units. The study received ethical approval from the region’s human research ethics committees, and informed consent was obtained from all participants.

Participants

Participants were recruited within one week of being diagnosed with a first-ever, ischaemic stroke resulting in UL motor impairment (Appendix 3.1). Patients were identified as potential participants by their admitting neurologists. All stroke unit neurologists were informed of the study’s inclusion/exclusion criteria, but a decision to inform the researchers of a potential participant was at the discretion of the treating physician. Therefore, some patients may not have been referred because they were screened as ineligible by the treating physician. Patients were excluded from the study if they were left-handed, scored more than 16 on the UL component of the Motor Assessment Scale (UL-MAS) [22], were unable to correctly respond to a two-step command (NIHSS [23] Item 7a), were fearful of confined spaces and/or had a condition incompatible with MRI. Twenty-four patients who fulfilled the eligibility criteria consented to participate in the study, with one subsequently withdrawing before randomisation because of claustrophobia. All 23 participants remained in the study for the 3-month duration (Figure 3.1).

Study design

Participants were randomised 1:1 to either the standard care group or the intensive-training group, who received an additional 30 hours of UL training that was task-
specific. Randomisation was stratified for hemispheric side of lesion. The randomisation protocol was established prior to the onset of recruitment and was independently administered by an associate researcher not otherwise involved in this study. Before the study started recruiting participants, two sets of envelopes were collated, one for each side of lesion. Each envelope contained a listing of either the standard care or intensive-training group, and all envelopes were then sealed. The two sets remained separate and both were shuffled and placed in two locked containers which remained with the independent administrator throughout the study’s duration. As each participant was recruited into the study, the next envelope was opened by the independent administrator who notified the researchers. All assessors were blinded to randomisation but not to the study’s objectives.

All participants received standard care (Appendix 3.2). On average, this consisted of a mean 6 occasions of service, for a mean 31.5 minutes of occupational therapy and physiotherapy, during a mean 11.5 days as an inpatient of an acute hospital [24]. The intensive-training group received an additional 30 hours of task-specific UL training during the first month post-stroke, applied 2 hours a day, 5 days a week, for 3 weeks. It was prescribed by the “treating” therapist, and applied by the therapists or by a therapy assistant supervised by the prescribing therapists. All participants were discharged during the 3-week intervention period, but for those in the intensive-training group, the additional task-specific UL training continued irrespective of discharge destination.

Clinical and imaging measures were collected at three time points post-stroke: 1 week (baseline); 1 month (post-intervention); and 3 months (follow-up). The baseline assessments were acquired before randomisation. The clinical assessments were conducted by therapists with more than 2 years’ neurological experience. To ensure consistency, therapists were trained in administering the assessments using scripted protocols to maximise reproducibility and consistency. All demographic data were extracted from the patients’ medical records. Infarct volumes were measured using commercial software MiStar (Apollo Medical Imaging Technology, Melbourne, Victoria, Australia) at the baseline imaging time point using an automated threshold-based technique [25]. All data were encoded and either password-protected or stored under lock and key.

**Study procedures and outcomes**

The primary outcome was change in brain activation as measured using fMRI, an *in vivo*, non-invasive, neuroimaging technique that is based on blood-oxygen-level
dependency (BOLD; dependent variable) [20]. Task-related functional imaging sequences were acquired during an alternating finger-tapping and rest paradigm. This was presented in a blocked design comprising 30 seconds of rest followed by 30 seconds of finger-tapping. The rest-tap cycles of 60 seconds acquired over 20 consecutive whole-brain echo-planar images (EPI) were repeated 4 times in alternate order for each UL over two consecutive imaging sequences. Therefore, for each participant, an anatomical image and 160 EPI (80 tap/rest/left; 80 tap/rest/right) were acquired for each of the three post-stroke imaging sessions. The imaging technicians instructed participants via headphones as to when to start and stop tapping their fingers. During the finger-tapping cycles, observational records were kept of the number of finger taps performed per cycle and any extraneous participant movement. During all the imaging sequences, participants lay in a supine position with their eyes open. Both upper limbs were supported in splints designed to limit movement of the wrist and non-tapping fingers and thumb.

The secondary outcomes were UL motor function and the impact of stroke. These were measured using the UL component of the Motor Assessment Scale (UL-MAS) and the modified Rankin Scale [26] (mRS) respectively. The UL-MAS [4, 22] is scored 0-18, with a higher score indicating better UL function. The study protocol followed specified instructions [22], and scoring was non-hierarchal, as recommended [27, 28]. If a patient achieves a score of 18, it means they have the dexterity and speed to write legibly and are able to participate in most activities that involve the UL. In respect to severity, Rehme et al [19] define this as mild motor impairment if the UL-MAS score is 14-18 points, moderate if it is 3-13 and severe if the score is 1-2. The UL-MAS has been validated in stroke cohorts and has high inter- and intra-rater reliability [29]. The mRS [30] is scored 0-6, with a higher score indicating a higher degree of disability.

Image data acquisition and processing
Magnetic resonance images were acquired for each participant at 1 week, 1 month and 3 months post-stroke using a 1.5 Tesla Magnetom Siemens Avanto (Erlangen, Germany) MRI scanner. Anatomical images of each participant’s brain were acquired using a high-resolution, T1-weighted, spin-echo imaging sequence. The echo delay time was 4.94ms, the repetition time was 11ms, the flip angle was 15°, the matrix = 256 x 256 and the field of view was 256mm. This provided 176 sagittal slices at 1mm³ resolution. Images were acquired using an EPI sequence. The echo delay time was 50ms, the repetition time was 3080ms, the matrix = 64 × 64 and the field of view was
220mm. This provided 36 axial images at a resolution of 3.4 × 3.4 × 3mm, with a 0.8mm inter-slice gap.

All imaging data were pre-processed and analysed using Statistical Parametric Mapping (SPM) version 5 [31] and Matlab [32] version R2011b software packages. For each of the three sessions, one T1 and 160 EPI were acquired in Dicom format and later converted to Analyse format for processing in SPM5. For each session, the EPI were acquired in two imaging blocks of 80 images where the participants undertook either left or right hand rest-tap cycles of 30 seconds, and where the order of left versus right finger-tapping was counterbalanced across participants.

In order to standardise EPI data across participants, images for participants with right hemispheric lesions (n=12) were reversed so that, for all participants, the “left” hemisphere represented the lesioned hemisphere and the “right” hemisphere represented the contralesional hemisphere. To facilitate analyses across participants, all the T1 images and EPI for each participant were transformed into standardised Montreal Neurological Institute (MNI) stereotaxic space. To achieve this, the three T1 images for each imaging session were realigned and co-registered and a mean T1 image derived and transformed into MNI space using a symmetrically modified version of the original SPM/MNI 305 MRI template (“avg305T1.nii”) created using left-right symmetrical tissue classification priors according to the procedure used by Didelot et al [33].

The EPI were then realigned and co-registered to the first functional image acquired in the first session (1 week), and an across-sessions mean-EPI was derived. This individual across-sessions mean-EPI was then co-registered and normalised to the symmetrical mean-T1 image, and the resulting normalisation parameters applied to each individual’s EPI data over all three imaging sessions. The integrity of the EPI data was then assessed using the TSDiffAna [34] procedure to identify any within-session changes in mean EPI intensity between successive EPI greater than 1 standard deviation. No such artefacts were identified, nor was any within-session movement identified that was greater than 3mm for both shifts and rotations in the three image planes (x, y and z) (Appendix 3.3). To account for the variance or artefact associated with the realignment of EPI within and across sessions, the realignment parameters (x, y and z shifts and rotations) for each session were included as regressors in the subsequent SPM5 first-level general linear model analyses, as described below.
Image data analysis

A within-subject or first-level analysis was carried out for each individual participant’s normalised EPI using canonical haemodynamic response function in SPM to convolve the EPI series data to the intensive-training study design. For each participant, three SPM \( t \)-contrast images were created to compare ipsilesional-hand tap versus rest, contralesional-hand tap versus rest and both-hand tap versus rest, for each of the 3 sessions for which imaging data were collected. An additional 3 equivalent contrasts were also created across all 3 sessions (Appendix 3.4). This resulted in 12 SPM \( t \)-contrasts per participant.

Data analysis: Differences in brain activation

To investigate between-group results, the 12 SPM \( t \)-contrast images for each participant’s first-level, fixed-effects contrast images (threshold \( p < 0.001 \) uncorrected) were submitted to second-level, random-effects analyses using only the stroke-affected UL contrasts for the conditions of intensive-training versus standard care. The \textit{a priori} \( p \)-value was set at <0.001 (uncorrected), and a correction was applied using a family-wise error cluster threshold set at \( p<0.05 \). Full factorial analysis identified the clusters of voxel-based activity combined across all imaging sessions (effect of group) and at each of the 3 time points (effect of time). Flexible factorial analysis identified the interaction effect of group by time. The voxel size was set at 3 x 3 x 3mm. Locations of significant activation were interpreted using the Anatomy Toolbox in SPM 2005 [35]. To correct for participant heterogeneity, a small-volume correction was applied using a template created using Eickhoff et al [35] and the MarsBaR software packages. The template included the bilateral Brodmann Areas 1, 2, 3, 4 and 6 (includes the pre-motor cortex, the supplementary motor area and primary sensorimotor cortex) and the cingulate area and cerebellum.

To investigate region-based activity, \textit{post hoc} analysis was conducted to identify changes at specific time points. The \textit{a priori} selection of regions was based on the sensorimotor areas identified in previous research [3, 13, 21]. Extent of activation data was used to analyse the percentage of active voxels at 1 week (baseline), and over time in the 1 month and 3 months post-stroke time periods. Regions were defined using the cytoarchitectural probability atlas from the Anatomy Toolbox in SPM (version 17) [35]. The STATA [36] version 11.0 software package was used to investigate differences at baseline, and the change relative to baseline in the first month and in the first 3 months.
**Data analysis: Differences in upper limb function**

Between-group differences were investigated using the UL-MAS and mRS data and the STATA [36] version 11.0 software package. The \( t \)-test (CI=95%) was used to investigate between-group differences in the mean age, disability (mRS) and frequency of finger-tapping at 1 week. General linear mixed models, with a random effect for each participant, were used to determine if there were differences between the standard-care and intensive-training groups at 1 week and 3 months post-stroke. The models included the independent variables of time, group and an interaction term between time and group. The \( p \)-value of the interaction term was used to determine significance. The interaction term was dropped from the models to investigate change across time points within the whole cohort. Differences in the variation between groups were investigated using the UL-MAS data and Levene’s [37] robust test to compare the standard deviations in the standard care group and the intensive-training group (Appendix 3.5).

**3.4 Results**

The study recruited 23 participants. Of these, 12 were randomised to the standard-care group and had a mean age of 69.3 years, and 11 were randomised to the intensive-training group and had a mean age of 61.7 years (Table 3.1). At one week post-stroke, there were no significant between-group differences in age (\( t=1.57; \ p=0.13; \ CI=95% \)), disability (mRS; \( t=0.07; \ p=0.93; \ CI=95% \)) or frequency of finger-tapping (\( t=0.56; \ p=0.58; \ CI=95% \)) (Table 3.2). All participants were admitted to a Stroke Unit and remained in the hospital for a mean 8.3 days. Seven participants (30.4%) were discharged directly home, 15 (65.2%) received inpatient rehabilitation and 15 received outpatient rehabilitation.
Table 3.1: Participants’ (n=23) group, stroke subtype, gender and age

<table>
<thead>
<tr>
<th>Group</th>
<th>Subtype</th>
<th>Side of lesion</th>
<th>Volume (mL)</th>
<th>OCS</th>
<th>Lesion location</th>
<th>Sex</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard-care</td>
<td>Cortical</td>
<td>Left</td>
<td>2</td>
<td>PAC</td>
<td>Posterior frontal</td>
<td>F</td>
<td>72</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Cortical</td>
<td>Right</td>
<td>25</td>
<td>PAC</td>
<td>Posterior division MCA; temporal parietal</td>
<td>M</td>
<td>63</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Cortical</td>
<td>Right</td>
<td>2</td>
<td>PAC</td>
<td>Anterior frontal lobe</td>
<td>M</td>
<td>83</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Cortical</td>
<td>Right</td>
<td>12</td>
<td>PAC</td>
<td>Striatocapsular</td>
<td>F</td>
<td>69</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Subcortical</td>
<td>Left</td>
<td>3</td>
<td>PAC</td>
<td>Anterior parietal; postcentral gyrus</td>
<td>M</td>
<td>82</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Subcortical</td>
<td>Left</td>
<td>2</td>
<td>LAC</td>
<td>Posterior limb; internal capsule</td>
<td>F</td>
<td>69</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Subcortical</td>
<td>Left</td>
<td>8</td>
<td>PAC</td>
<td>Striatocapsular</td>
<td>M</td>
<td>66</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Subcortical</td>
<td>Right</td>
<td>1</td>
<td>LAC</td>
<td>Posterior limb; internal capsule</td>
<td>M</td>
<td>69</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Subcortical</td>
<td>Right</td>
<td>3</td>
<td>LAC</td>
<td>Striatocapsular</td>
<td>M</td>
<td>65</td>
</tr>
<tr>
<td>Standard-care</td>
<td>Subcortical</td>
<td>Right</td>
<td>4</td>
<td>LAC</td>
<td>Striatocapsular</td>
<td>M</td>
<td>47</td>
</tr>
<tr>
<td>Intensive-training</td>
<td>Cortical</td>
<td>Right</td>
<td>5</td>
<td>PAC</td>
<td>Posterior frontal; precentral gyrus</td>
<td>F</td>
<td>48</td>
</tr>
<tr>
<td>Intensive-training</td>
<td>Cortical</td>
<td>Left</td>
<td>3</td>
<td>PAC</td>
<td>Anterior parietal; postcentral gyrus</td>
<td>M</td>
<td>73</td>
</tr>
<tr>
<td>Intensive-training</td>
<td>Cortical</td>
<td>Right</td>
<td>14</td>
<td>PAC</td>
<td>Posterior division MCA; temporal parietal</td>
<td>F</td>
<td>47</td>
</tr>
<tr>
<td>Intensive-training</td>
<td>Cortical</td>
<td>Left</td>
<td>5</td>
<td>PAC</td>
<td>Anterior frontal</td>
<td>M</td>
<td>72</td>
</tr>
<tr>
<td>Intensive-training</td>
<td>Cortical</td>
<td>Right</td>
<td>2</td>
<td>LAC</td>
<td>Striatocapsular</td>
<td>F</td>
<td>81</td>
</tr>
<tr>
<td>Intensive-training</td>
<td>Subcortical</td>
<td>Left</td>
<td>2</td>
<td>LAC</td>
<td>Posterior limb; internal capsule</td>
<td>F</td>
<td>37</td>
</tr>
</tbody>
</table>
Table 3.2: Demographic and baseline characteristics of participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistic</th>
<th>Standard care (n=12)</th>
<th>Intensive-training (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Female</td>
<td>Frequency (%)</td>
<td>4 (33)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>Frequency (%)</td>
<td>8 (67)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Handedness: Right</td>
<td>Frequency (%)</td>
<td>12 (100)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Affected UL: Left</td>
<td>Frequency (%)</td>
<td>7 (58)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Affected UL: Right</td>
<td>Frequency (%)</td>
<td>5 (42)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Stroke sub-type: Cortical</td>
<td>Frequency (%)</td>
<td>5 (42)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Sub-type: Subcortical</td>
<td>Frequency (%)</td>
<td>7 (58)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (sd)</td>
<td>69.3 (9.4)</td>
<td>61.7 (13.4)</td>
</tr>
<tr>
<td></td>
<td>Median (min, max)</td>
<td>69.0 (47.0, 83.0)</td>
<td>63.0 (37.0, 81.0)</td>
</tr>
<tr>
<td>Stroke severity (mRS)</td>
<td>Mean (sd)</td>
<td>3.8 (0.9)</td>
<td>3.7 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Median (min, max)</td>
<td>4.0 (2.0, 5.0)</td>
<td>4.0 (3.0, 4.0)</td>
</tr>
<tr>
<td>UL function (UL-MAS)</td>
<td>Mean (sd)</td>
<td>8.7 (4.7)</td>
<td>10.4 (3.4)</td>
</tr>
<tr>
<td></td>
<td>Median (min, max)</td>
<td>10.0 (1.0, 15.0)</td>
<td>11.0 (5.0, 16.0)</td>
</tr>
<tr>
<td>Finger-tapping counts</td>
<td>Mean (sd)</td>
<td>18.6 (10.9)</td>
<td>20.6 (5.8)</td>
</tr>
<tr>
<td></td>
<td>Median (min, max)</td>
<td>18 (0.43)</td>
<td>22 (10.8, 29.3)</td>
</tr>
</tbody>
</table>

Key: mRS=modified Rankin scale; UL–MAS=UL component of the Motor Assessment Scale; sd=standard deviation, min=minimum, max=maximum

Differences in brain activation

Clusters of brain activation were associated with the affected UL in the ipsilesional hemisphere across all 3 time points. When compared with the standard care group, the intensive-training group had significant clusters of greater activity in the ipsilesional anterior cingulate and supplementary motor areas. Figure 3.2 reports results from the affected UL, hand-tapping versus rest, across all three time points combined. The voxel-wise cluster-forming significance threshold is $p<0.001$, and the family-wise error cluster threshold is $p<0.05$. This showed a positive effect of group, but no significant result was found associated with either time or group by time. At 3 months post-stroke, the intensive-training group demonstrated trends towards greater activity in the ipsilesional anterior cingulate and supplementary motor areas (Table 3.3).
Table 3.3: Brain activation associated with the affected upper limb following a 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. Voxel-wise significance was set at $p<0.01$ and the family-wise error cluster threshold was set at $p<0.05$.

<table>
<thead>
<tr>
<th>Cluster level</th>
<th>Voxel level</th>
<th>Across all time points</th>
<th>At 3 months post-stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$ FWE corrected</td>
<td>$k$</td>
<td>$p$ uncorr</td>
<td>$p$FWE</td>
</tr>
<tr>
<td>0.020</td>
<td>286</td>
<td>0.004</td>
<td>0.086</td>
</tr>
<tr>
<td>0.088</td>
<td>0.037</td>
<td>4.92</td>
<td>-0, 24, 30</td>
</tr>
<tr>
<td>0.099</td>
<td>0.037</td>
<td>4.85</td>
<td>-3, 18, 57</td>
</tr>
<tr>
<td>0.105</td>
<td>0.037</td>
<td>4.82</td>
<td>3, 21, 36</td>
</tr>
<tr>
<td>0.176</td>
<td>0.037</td>
<td>4.52</td>
<td>6, 12, 48</td>
</tr>
<tr>
<td>0.150</td>
<td>138</td>
<td>0.030</td>
<td>0.656</td>
</tr>
</tbody>
</table>

Key: FWE=family wise error; FDR=false discovery rate; uncorr=uncorrected; MNI= Montreal Neurological Institute; SMA=supplementary motor area; CA=cingulate area.
### Cluster level

<table>
<thead>
<tr>
<th>$p$ <strong>FWE-corr</strong></th>
<th>$k$</th>
<th>$p$ <strong>uncorr</strong></th>
<th>$p$ <strong>FWE</strong></th>
<th>(Z)</th>
<th>MNI coordinates</th>
<th>Probable region</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.007</td>
<td>13</td>
<td>0.001</td>
<td>0.425</td>
<td>3.97</td>
<td>-0.33, 27</td>
<td>Ipsilesional anterior cingulate area</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td>0.432</td>
<td>3.97</td>
<td>-0.24, 30</td>
<td>Ipsilesional anterior cingulate area</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.471</td>
<td>3.93</td>
<td>-3, 18, 57</td>
<td>Ipsilesional supplementary motor area</td>
</tr>
</tbody>
</table>

Key: FWE=family wise error; k=number of voxels in the cluster; uncorr=uncorrected; MNI= Montreal Neurological Institute.

**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. The contrasts analysed were those reporting the affected hand-tapping versus rest, across all three sessions. The SPM t-image is displayed at a voxel-wise significance threshold of $p<0.001$ uncorrected and a family wise error cluster threshold at $p<0.05$. The data have not been smoothed.

### Region-based activity

No differences were found at baseline when comparing the extent of activation between the intensive-training and the standard-care group in the bilateral supplementary motor area, the primary sensorimotor area, the cingulate area or the cerebellum. When investigating change-over-time relative to baseline, the extent of activation in the intensive-training group reduced significantly more in the contralesional cerebellum (rank sum $p=0.02$) in the first 3 months post-stroke (Table 3.4) when compared with the standard care group.
Table 3.4: Change in percentage of active voxels in defined regions of interest at 1 month and 3 months post-stroke relative to baseline: differences between the standard-care and intensive-training groups. Change corresponds 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 standard care and intensive-training groups using the Wilcoxon rank-sum and a 95% confidence interval.

<table>
<thead>
<tr>
<th>Percentage of active voxels</th>
<th>In the first month</th>
<th>In the first 3 months</th>
<th>Rank sum</th>
<th>p-value</th>
<th>Rank sum</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilesional SMA</td>
<td>-1.08 (9.53)</td>
<td>-1.05 (15.94)</td>
<td>0.90</td>
<td></td>
<td>-1.56 (8.11)</td>
<td>-4.75 (11.31)</td>
</tr>
<tr>
<td>Contralesional SMA</td>
<td>-1.72 (13.16)</td>
<td>-6.13 (12.48)</td>
<td>0.42</td>
<td></td>
<td>-5.39 (12.90)</td>
<td>-10.64 (21.30)</td>
</tr>
<tr>
<td>Ipsilesional SM1</td>
<td>1.27 (5.94)</td>
<td>3.80 (13.33)</td>
<td>0.19</td>
<td></td>
<td>5.35 (13.10)</td>
<td>-0.43 (12.18)</td>
</tr>
<tr>
<td>Contralesional SM1</td>
<td>-2.20 (14.24)</td>
<td>-1.85 (11.87)</td>
<td>0.71</td>
<td></td>
<td>-2.90 (19.12)</td>
<td>-0.10 (12.36)</td>
</tr>
<tr>
<td>Ipsilesional Cb</td>
<td>-1.90 (4.45)</td>
<td>-2.47 (14.78)</td>
<td>0.32</td>
<td></td>
<td>-2.39 (12.64)</td>
<td>-4.14 (15.23)</td>
</tr>
<tr>
<td>Contralesional Cb</td>
<td>1.64 (3.74)</td>
<td>-2.68 (7.40)</td>
<td>0.27</td>
<td></td>
<td>-0.23 (1.95)</td>
<td>-2.89 (9.23)</td>
</tr>
<tr>
<td>Ipsilesional CA</td>
<td>-0.44 (1.48)</td>
<td>2.16 (7.31)</td>
<td>0.88</td>
<td></td>
<td>0.25 (1.90)</td>
<td>-0.32 (0.80)</td>
</tr>
<tr>
<td>Contralesional CA</td>
<td>0.57 (2.35)</td>
<td>2.15 (5.87)</td>
<td>0.80</td>
<td></td>
<td>0.88 (2.48)</td>
<td>-0.01 (1.13)</td>
</tr>
</tbody>
</table>

Key: sd=standard deviation; MA=supplementary motor area; SMI=primary sensory motor cortex; Cb=cerebellum; CA=cingulate area

In summary, the intensive-training group had greater activation in the ipsilesional anterior cingulate and supplementary motor areas and a greater reduction in the extent of activation in the contralesional cerebellum in the first 3 months post-stroke when compared with the standard care group.

Differences in upper limb function

In the first three months, all participants showed significant improvement in the motor function of their affected UL and in their degree of disability: UL-MAS, p<0.0001; mRS, p=0.0002 (Appendix 3.6). Additionally, the level of recovery achieved at 1 month post-stroke was maintained at 3 months. There were no significant between-group differences in change over time in the clinical outcome scores. Although there were no significant differences in mean recovery of UL function between the two groups, the
intensive-training group had a smaller deviation from mean recovery at one month (Pr>F0=0.017) and three months (Pr>F=0.006), indicating more consistent and predictable improvement in motor outcomes.

Across the first 3 months post-stroke, when compared with those in the standard care group, the intensive-training group had more activity in the ipsilesional anterior cingulate and supplementary motor areas, and they experienced a greater reduction in the percentage of active voxels in the contralesional cerebellum. All participants experienced significant improvement in their degree of disability and in the motor function of their affected UL, but the UL improvement in those recruited to the intensive-training group was more consistent.

3.5 Discussion

This is the first study to show that more intensive rehabilitation (task-specific UL training) in the first month post-stroke is associated with increased brain activation in motor-related and attention areas. Intensive UL rehabilitation training also led to more consistent recovery of clinical UL function. This is the first RCT to demonstrate that the ipsilesional supplementary motor and anterior cingulate areas may make a functionally significant contribution to the recovery of the affected UL after stroke, and the first to do so in the first three months post-event [3, 13]. This study is also the first to show a potential association between more intensive UL training in the first month post-stroke and more predictable and consistent motor recovery. It also demonstrated that this UL training regimen is effective, safe and clinically feasible. Furthermore, this study found that changes in brain activation persist until the end of the 3 month, follow-up period post-stroke. These findings are consistent with current views that increased brain activation may be a marker of cortical reorganisation (“plasticity”), and further, this plasticity may be associated with improvement in UL function [19, 20, 38]. The findings from this study have important translational relevance to clinical practice.

Differences in brain activation patterns

Previous studies have shown an association between improved clinical recovery and brain activation but not in a randomised trial [3, 13]. This is the first RCT of more intensive, early UL therapy in stroke patients that used fMRI measures of brain activation as an outcome, in addition to clinical measures. The finding that increased brain activation in motor-related and attention areas was associated with recovery of UL function in those that received increased intensity of training is clinically relevant. There is increasing agreement that the intensity of intervention in the first month post-
stroke influences outcomes [2, 39], and this is the time when most stroke patients are engaged in rehabilitation. We have shown that more intensive therapy in the first month after stroke leads to changes in brain activation that likely reflect plasticity [19, 20, 38], and this may provide a potential explanation as to why early intervention is effective.

The significance of region-based activation

Evidence increasingly identifies the ipsilesional supplementary motor area as important to UL recovery in the first 3 months post-stroke [19], and, to a lesser degree, the ipsilesional anterior cingulate area [9, 40, 41]. The current study’s findings support the theory that stroke recovery may be associated with the recruitment of spared, sensorimotor [3, 13, 42] and attention [43-45] regions. However, the authors acknowledge that other areas of the brain may also be making a functionally significant contribution, but that this activation may be sub-threshold and not seen. No single pattern of neuroplastic change is observed during recovery; rather, they are distinctly different in different regions and seem to depend on deficits caused by an initial lesion, as well as training interventions [20, 46].

The finding of an association between activation of the ipsilesional anterior cingulate area and more intensive, task-specific UL training is clinically significant. It suggests this rehabilitation paradigm may require patients to pay more attention to the task [44, 47]. The anterior cingulate area has been shown to be associated with effortful tasks, error detection, attention and learning [43]. The potential involvement of the cerebellum may highlight the interconnectedness between the cortex and cerebellum, a phenomenon yet to be fully understood [44, 48]. Evidence indicates an increased reliance on the cerebellum with transfer of motor learning [49, 50]. The fact that no significant differences were found in areas where differences were anticipated, for example, the primary sensorimotor cortex, is noteworthy, because the location of most of the lesions in this study were in a sensorimotor region, or in directly connected subcortical regions. To find that the only between-group differences were in the ipsilesional supplementary motor area and the ipsilesional anterior cingulate area, a region linked with effortful tasks and early learning [49, 50] is important, and needs further investigation. To find that activity in the cerebellar and anterior cingulate regions are significant provides a basis for alternative hypotheses related to stroke recovery: that is, that the differences between the intensive-training and standard care groups may reflect differences in the effort and attention that patients may need to apply when undertaking motor tasks; and/or that these regions are differentially accessed during the process of intensive motor training.
Intensive upper limb training in the first month

This study found that all participants experienced improvement in the first month post-stroke, which was maintained at three months. It also demonstrated that patients in the first month tolerated an additional 30 hours of UL training, and that this dose was effective, safe, clinically feasible and associated with more consistent improvement in motor function. Thus, this study provides evidence to support current recommendations in clinical practice.[51, 52]. Because this study was undertaken in the first month post-stroke, it was anticipated that both groups would experience recovery due to the combination of natural history and post-stroke rehabilitation [2]. However, the finding that more intensive, task-specific UL training resulted in more consistent, and predictable, improvement in UL function is novel and clinically important. Theories of learning indicate that performance becomes more consistent and predictable when well-learnt [53, 54]. It is possible that the additional training provided to those in the experimental group led to more stable improved performance, not only in individuals but in the group as a whole. Even though there is consensus that patients with stroke should receive early, more intensive training [7, 8, 55, 56], questions remain about how much additional intervention is required to ensure more consistent outcomes; for example, Horn et al [6] found an association between more intensive, early UL intervention and higher scores in functional independence, whilst Rodgers et al [7] found no differences. However, the current study was unable to show that increasing intensity improved the overall magnitude of motor recovery. This is most likely because of low participant numbers and a known ceiling effect in the UL-MAS [28]. To find an association between more predictable recovery and intensive UL training suggests that testing for between-group variance may be a more sensitive outcome than only measuring mean between-group changes.

Neurobiological change is evident after physical recovery

The finding of persistent increases in brain activation in the intensive-training group at 3 months, beyond the first period when most of the clinical recovery occurred, is noteworthy. Although increased activation at one month paralleled clinical recovery, the persistence of increased activation is highly likely to reflect cortical reorganisation. Additionally, it appears that such plasticity may have contributed towards improved clinical UL function. These findings suggest that it may be possible to use fMRI as a measure of “effective” plasticity following stroke, and, if this was the case, it may be a useful biologic measure of rehabilitation interventions.
**Strengths and limitations**

This study’s strengths lie in its RCT design, its recruitment of patients during their acute admission post-stroke and, when compared with other fMRI studies, the relatively high (n=23) participant numbers. It also recruited similar numbers of participants with left and right hemispheric stroke, and cortical and subcortical stroke. However, the sample size is still limited and likely hindered our ability to find between-group differences with the traditional standard clinical outcomes. This was further challenged by the ceiling effect in the UL-MAS. Both issues should be taken into consideration in future UL research that recruits participants with mild to moderate stroke. Also, because the tapping task was not controlled for, it was not possible to identify whether the increased activity observed in the anterior cingulate area was a by-product that arose from finger-tapping performance or an increased effort during the motor task in the scanner. It was also not possible to test for possible between-group differences in the way finger-tapping was performed by patients. Nonetheless, the increased activity was differentially observed in the group receiving increased intensity of UL training, despite similar levels of impairment and recovery across groups. As most participants will demonstrate early recovery, more sensitive measures of between-group variances in improvement, as used in the current study, may need to be considered as outcomes.

### 3.6 Conclusion

This is the first RCT of first-ischaemic-stroke patients with an affected UL that compared early, intensive, task-specific UL training with standard care. The study found that those who received intensive-training had more activation in the anterior cingulate and the supplementary motor areas, and experienced more predictable and consistent UL recovery. Increasing the dose of UL training by an additional 30 hours in the first month post-stroke was clinically safe and feasible. These findings have considerable translational value as they contribute to the knowledge supporting an evidence-based approach to UL recovery post-stroke, and provide direct evidence that more intensive rehabilitation contributes to neuroplasticity.
3.7 References


Chapter 4: Comparing Different Cohorts
4.1 Abstract

**Introduction:** Understanding the differences in neuroanatomical recovery in patients who experience good versus poor recovery, and in those with subcortical versus cortical stroke, will help provide a scientific basis to the therapeutic approaches targeting recovery of the stroke-affected upper limb (UL).

**Objective:** To investigate and characterise differences in brain activation in patients who experienced good versus poor recovery, and in those with cortical versus subcortical stroke in the first three months post-stroke.

**Methods:** This is a cohort, longitudinal study. Participants (n=23) with ischaemic stroke were assessed at 1 week, 1 month and 3 months post-stroke. The primary outcome was changes in brain activation patterns as measured by functional magnetic resonance imaging.

**Results:** At 3 months post-stroke, those with good UL recovery had greater ipsilesional activation in the inferior parietal lobe when compared with those who experienced poor UL recovery. The only difference found between those with subcortical and cortical stroke was that those with subcortical stroke experienced better recovery overall.

**Conclusions:** The ipsilesional sensorimotor is important to good UL recovery. The involvement of areas such as the inferior parietal lobe suggest that recovery post-stroke may be improved with a multi-modal approach that applies strategies which aim to actively recruit regions responsible for increasing attention to a task and for overriding prior learning.
4.2 Introduction

The World Health Organization [1] reports that each year 15 million people world-wide experience stroke, and 5 million of them are left permanently disabled. Stroke has been aptly described as “disconnection phenomena” [2], with the outcome greatly dependent on which brain region, or regions, are affected by the disruption. Permanent disability often results from a stroke that has disrupted connections along the corticospinal tracts, and/or to and from the brain’s sensorimotor regions [3]. In up to 75% of people, the stroke will adversely affect sensorimotor function of the upper limb (UL) [4]. The most likely cause of UL dysfunction is a disruption to blood flow in the middle cerebral artery, which supplies oxygen and nutrients to the human brain’s sensorimotor regions and to the associated corticospinal tracts [5, 6]. Rehabilitation is the primary approach to maximising UL recovery following stroke, but, with growing pressure on limited health resources, it is increasingly important that clinicians can identify those who are most likely to benefit and, in turn, experience “good” recovery [7-10]. One contributing factor may be whether a person has had subcortical or cortical stroke.

Both subcortical and cortical strokes involving motor regions can adversely impact sensorimotor function of the UL. Whereas cortical strokes disrupt brain activity in sensorimotor cortico-regions [11, 12], subcortical strokes disrupt the supporting structures and connections to and from the cortex [13-15]. In studies that compared outcomes between subcortical and cortical strokes [16, 17], Oh et al [18] found that applying transcranial magnetic stimulation to the contralesional hemisphere induced intracortical inhibition in those with subcortical stroke, and disinhibition in those with cortical stroke. There is a general assumption in clinical practice that people are more likely to experience good recovery following subcortical stroke; however, this is not well-established [19].

This study will investigate the differences in brain activation between those who experienced good recovery and those who experienced poor recovery, and between those diagnosed with subcortical stroke and those diagnosed with cortical stroke. This study used data from a randomised controlled trial which recruited 23 right-handed patients with first ischaemic stroke. The original study investigated differences between those receiving standard care, and those receiving standard care and an additional 30 hours of task-specific UL training in the first month post-stroke [20].
4.3 Methods

This study re-analysed data from a randomised controlled trial. The original study received ethical approval from the region’s health and academic committees for research involving humans. The following is a summary only, as the methods have been previously reported (Chapter 3).

Participants

Participants included adult, right-handed patients who were diagnosed with a recent, first ischaemic stroke which resulted in an adversely affected UL. Potential participants were recruited from two regional Acute Stroke Units. Patients were excluded if they were unable to respond correctly to a two-step command, were fearful of confined spaces and/or had a condition which was incompatible with the magnetic resonance imaging (MRI) environment. All participants (n=23) received standard care, and 11 received an additional 30 hours of task-specific UL training in the first month post-stroke. However, the analysis for this study was irrespective of the upper-limb retraining that a patient received.

Study outcomes

As previously reported [20], imaging and clinical measures were collected at three time points post-stroke: 1 week (baseline), 1 month and 3 months. The primary outcome was changes in brain activation, which was measured using functional magnetic resonance imaging (fMRI). Images were acquired for each participant at 1 week, 1 month and 3 months, using a 1.5 Telsa Magnetom Siemens Avanto (Erlangen, Germany) magnetic resonance imaging scanner. The fMRI sequence consisted of alternate 35-second blocks of scanning between rest and active finger-tapping. This was applied across 4 cycles per session, and to both hands separately. All imaging data were analysed using the Statistical Parametric Mapping (SPM5) [21] version 5 and Matlab [22] software packages. The modified Rankin Scale (mRS) [23] measured the global impact of stroke, and the UL component of the Motor Assessment Scale (UL–MAS) [4, 24] measured function of the UL. The UL–MAS scores were used to identify those who experienced good sensorimotor recovery of the UL and those who experienced poor recovery.

Cohort identification

The allocation of participants to either the “good recovery” or “poor recovery” groups was based on the change-over-time results in the UL–MAS data. Minimal, clinically important differences in UL function have been defined as a shift of between 5% and
10% of an instrument’s range [25, 26]. In relation to the UL–MAS, a ≥2 point positive shift (11%) has been found to be clinically significant in a cohort of participants in the chronic phase post-stroke [27]. In this study we applied a more conservative threshold on the basis of the fact that in the first month post-stroke, more functional improvement in the affected UL is anticipated as a result of the combined influence of natural history and standard care [28]. For the purposes of this study, participants who achieved a ≥6 point, positive shift (33%) in the UL–MAS score were classified as having experienced “good recovery”. As the UL–MAS is known to have a ceiling effect [29, 30], an additional participant was allocated to the good recovery cohort because, although he only achieved a 4-point positive shift, he reached the maximum score of 18 during the 3-month study period. As a result, 12 participants were allocated to the “good recovery” cohort, and 11 were allocated to the “poor recovery” cohort (Table 4.1).

The identification of participants as diagnosed with subcortical or cortical stroke was determined by one of the study’s investigators (MP), who is a neurologist with many years’ experience in assessing imaging data [31]. The process was based on each participant’s neuroimaging [32, 33] (See Appendix 3.1) and resulted in 13 participants being diagnosed with subcortical stroke and 11 diagnosed with cortical stroke (Table 4.1).
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Sub-type</th>
<th>Gender</th>
<th>Lesioned hemisphere</th>
<th>At 1 week post-stroke</th>
<th>At 1 month post-stroke</th>
<th>Positive shift in UL–MAS in the first month</th>
<th>At 3 months post-stroke</th>
<th>Positive shift in UL–MAS in first 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Subcortical</td>
<td>M</td>
<td>R</td>
<td>3</td>
<td>11</td>
<td>2</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Good</td>
<td>Subcortical</td>
<td>M</td>
<td>L</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>16</td>
<td>9</td>
</tr>
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<td>M</td>
<td>R</td>
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</tr>
<tr>
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<td>L</td>
<td>4</td>
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<td>R</td>
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<td>L</td>
<td>4</td>
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<td>2</td>
<td>16</td>
<td>2</td>
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<tr>
<td>Good</td>
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<td>R</td>
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<td>9</td>
</tr>
<tr>
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<td>Cortical</td>
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<td>R</td>
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<td>3</td>
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<td>7</td>
</tr>
<tr>
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<td>Cortical</td>
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<td>L</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Poor</td>
<td>Subcortical</td>
<td>M</td>
<td>R</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Poor</td>
<td>Subcortical</td>
<td>M</td>
<td>L</td>
<td>3</td>
<td>16</td>
<td>2</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Poor</td>
<td>Subcortical</td>
<td>M</td>
<td>R</td>
<td>4</td>
<td>13</td>
<td>2</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Poor</td>
<td>Subcortical</td>
<td>M</td>
<td>L</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Poor</td>
<td>Subcortical</td>
<td>F</td>
<td>L</td>
<td>3</td>
<td>12</td>
<td>2</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Poor</td>
<td>Subcortical</td>
<td>F</td>
<td>L</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>16</td>
<td>4</td>
</tr>
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<td>Subcortical</td>
<td>F</td>
<td>R</td>
<td>3</td>
<td>15</td>
<td>2</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Poor</td>
<td>Cortical</td>
<td>M</td>
<td>R</td>
<td>4</td>
<td>9</td>
<td>3</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Poor</td>
<td>Cortical</td>
<td>M</td>
<td>R</td>
<td>2</td>
<td>14</td>
<td>2</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Poor</td>
<td>Cortical</td>
<td>F</td>
<td>R</td>
<td>3</td>
<td>11</td>
<td>2</td>
<td>16</td>
<td>5</td>
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<tr>
<td>Poor</td>
<td>Cortical</td>
<td>F</td>
<td>R</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

Key: mRS=modified Rankin score; UL–MAS=upper limb component of the Motor Assessment Scale
Investigating between-cohort differences

The same method was used to investigate differences between participants with good and poor UL recovery, and between participants with subcortical and cortical stroke. The methods used to acquire, process and analyse the imaging data are reported in Chapter 3. In order to be able to compare ipsilesional and contralesional data, the MRI images for participants with right hemispheric stroke were left-right reversed or “flipped”. This resulted in the “left” hemisphere results representing those of the lesioned hemisphere and the “right” hemisphere results representing those of the contralesional hemisphere. All reported results are from outcomes associated with the affected UL only, and all were registered to the standardised Montreal Neurological Institute (MNI) stereotaxic space. The imaging data were analysed in two phases. The first investigated whole-brain activity, and the second investigated activity in defined regions of interest (ROI). Whole-brain activity was tested to identify the clusters of voxel-based activity across all 3 time points and at each of the 3 time points. The voxel size was set at 3 x 3 x 3mm. Using SPM Version 5 [34], supra-threshold voxels were identified and mapped to reveal the regions of activity for both conditions: good versus poor recovery; and subcortical versus cortical stroke.

To reduce the influence of individual variations whilst testing for between-group differences, a combined ROI, made up of the bilateral cingulate area, inferior parietal lobe, primary motor cortex and Brodmann area (BA) 6, was used to apply a small-volume correction across anatomical regions. The selection of regions was based on the evidence to date [7, 35-37]. The combined ROI template was created using the Eickhoff et al [34] atlas and the MarsBaR [38] software package. In addition, the extent of activity in the ROI was investigated using the data related to the percentage of active voxels and the STATA Version 11.0 [39] software package. The extent of activity was compared at 1 week (baseline), and over time in the 1 month and 3 months post-stroke time periods for both conditions: good versus poor recovery; and subcortical versus cortical stroke.

To test for differences in functional recovery between those with subcortical stroke and those with cortical stroke, the UL–MAS scores and the mRS scores were compared using the STATA [39] Version 10 software package. The distribution of data was tested across all participants for basic properties and normality. Generalised linear mixed models with a random effect for each participant were used to determine if there were significant
between-group differences. The models included the independent variables of time, and an interaction term between time and group. The \( p \)-value of the interaction term was only used to determine if there was a significant between-group difference for the subcortical greater than the cortical condition, and for the cortical greater than the subcortical condition.

### 4.4 Results

The study recruited 23 right-handed patients with a first ischaemic stroke (Table 4.2). The mean age of the participants was 65.6 years, and 13 (57\%) were men. The results reported in this paper are for the stroke-affected (right) upper limb only.

**Table 4.2: Demographic and baseline characteristics of all participants and cohorts**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistic</th>
<th>Good recovery (n=12)</th>
<th>Poor recovery (n=11)</th>
<th>Subcortical (n=13)</th>
<th>Cortical (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: female</td>
<td>Frequency (%)</td>
<td>5 (50)</td>
<td>5 (33)</td>
<td>5 (33)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Gender: male</td>
<td>Frequency (%)</td>
<td>7 (70)</td>
<td>6 (46)</td>
<td>5 (45)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Handedness: right</td>
<td>Frequency (%)</td>
<td>12 (100)</td>
<td>11 (100)</td>
<td>13 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Affected UL: left</td>
<td>Frequency (%)</td>
<td>5 (50)</td>
<td>7 (53)</td>
<td>6 (46)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Affected UL: right</td>
<td>Frequency (%)</td>
<td>7 (70)</td>
<td>4 (36)</td>
<td>7 (53)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (sd)</td>
<td>62.4 (13.1)</td>
<td>69.2 (9.7)</td>
<td>63.1 (10.8)</td>
<td>69 (12.9)</td>
</tr>
<tr>
<td>UL–MAS</td>
<td>Mean (sd)</td>
<td>8.5 (2.3)</td>
<td>10.5 (5.1)</td>
<td>9 (5.0)</td>
<td>10.1 (2.9)</td>
</tr>
</tbody>
</table>

Key: UL=upper limb; sd=standard deviation; UL–MAS=upper limb component of the Motor Assessment scale.

### Comparing good recovery versus poor recovery

The results showed no between-group differences when whole-brain results from all three sessions were combined, and no differences at 1 week and 1 month post-stroke (Appendix 4.1). However, at 3 months post-stroke (Table 4.3; Figures 4.1 and 4.2), when compared to those who experienced poor recovery, those with good recovery had significantly more activity associated with finger-tapping of the affected UL, in a central region that could not
be defined using MNI coordinates, and trends towards more activity in the ipsilesional inferior parietal lobe, supplementary motor area and Brodmann Area (BA) 44.

Table 4.3: Whole-brain activity that was significantly greater in the good-recovery cohort compared with the poor-recovery cohort. The contrasts analysed were those reporting the affected finger-tapping versus rest at 3 months post-stroke. The voxel-wise significance threshold was \( p < 0.001 \), and the family-wise error cluster threshold was \( p < 0.05 \).

<table>
<thead>
<tr>
<th>Cluster level</th>
<th>Voxel level</th>
<th>p FWE-corrected</th>
<th>k</th>
<th>p uncor</th>
<th>pFWE</th>
<th>pFDR</th>
<th>T</th>
<th>(Z)</th>
<th>MNI coordinates</th>
<th>Probable region</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000</td>
<td>219</td>
<td>0.000</td>
<td></td>
<td></td>
<td>0.026</td>
<td>0.022</td>
<td>6.66</td>
<td>4.83</td>
<td>3, -6, 27</td>
<td>Not identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.235</td>
<td>0.039</td>
<td>5.35</td>
<td>4.20</td>
<td>-57, -39, 36</td>
<td>Ipsilesional inferior parietal lobe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.236</td>
<td>0.039</td>
<td>5.35</td>
<td>4.20</td>
<td>-3, 3, 57</td>
<td>Ipsilesional supplementary motor area</td>
</tr>
<tr>
<td>0.000</td>
<td>236</td>
<td>0.000</td>
<td></td>
<td></td>
<td>0.303</td>
<td>0.039</td>
<td>5.18</td>
<td>4.11</td>
<td>-51, 3, 12</td>
<td>Ipsilesional BA44 and 45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.719</td>
<td>0.045</td>
<td>4.48</td>
<td>3.71</td>
<td>-48, 9, 21</td>
<td>Ipsilesional BA44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.761</td>
<td>0.047</td>
<td>4.41</td>
<td>3.67</td>
<td>-36, 12, 6</td>
<td>Ipsilesional Insular lobe</td>
</tr>
</tbody>
</table>

Key: uncor=uncorrected, FWE=Family-wise error; FDR=False discovery rate; MNI=Montreal Neurological Institute; BA=Brodmann area
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. Clusters include the ipsilesional inferior parietal lobe and supplementary motor area. SPM $t$-image is displayed at a voxel-wise significance threshold of $p<0.001$ uncorrected, and a family-wise error cluster threshold at $p<0.05$. The data have not been smoothed.

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. Clusters include the ipsilesional inferior parietal lobe and supplementary motor area. SPM $t$-image is displayed at a voxel-wise significance threshold of $p<0.001$ uncorrected, and a family-wise error cluster threshold at $p<0.05$. 

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When investigating activity in the combined ROI, there were no differences detected at 1 week and 1 month post-stroke when the results of those who experienced good recovery were compared with the results of those who experienced poor recovery. However, at 3 months post-stroke, differences were detectable in two medial regions not found on current probability maps and in the ipsilesional inferior parietal lobe (Table 4.4; Appendix 4.2).

**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. Voxel-wise significance was set at p<0.05, and the family-wise error cluster threshold was set at p<0.05.**

<table>
<thead>
<tr>
<th>Cluster level</th>
<th>Voxel level</th>
</tr>
</thead>
<tbody>
<tr>
<td>p FWE-corrected</td>
<td>k</td>
</tr>
<tr>
<td>0.042</td>
<td>1736</td>
</tr>
<tr>
<td>0.078</td>
<td>0.012</td>
</tr>
<tr>
<td>0.011</td>
<td>211</td>
</tr>
</tbody>
</table>

Key: uncor=uncorrected, FWE=Family-wise error; FDR=False discovery rate; MNI= Montreal Neurological Institute.

When investigating the extent of activation (Table 4.5), at 1 week post-stroke, those with good recovery had greater activation in the contralesional primary sensorimotor cortex (p=0.01) and supplementary motor area (p=0.04), and there was evidence of trends towards greater activity in the ipsilesional supplementary motor and cingulate areas.
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. Clusters include the contralesional primary motor cortex and supplementary motor area.

<table>
<thead>
<tr>
<th>Regions of activity at 1 week post-stroke</th>
<th>Cohort</th>
<th>CI=95%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Good</td>
</tr>
<tr>
<td>Ipsilesional supplementary motor area</td>
<td>Mean (sd)</td>
<td>13.6 (14.6)</td>
</tr>
<tr>
<td>Contralesional supplementary motor area</td>
<td>Mean (sd)</td>
<td>21.52 (20.25)</td>
</tr>
<tr>
<td>Ipsilesional primary sensorimotor cortex</td>
<td>Mean (sd)</td>
<td>3.03 (6.95)</td>
</tr>
<tr>
<td>Contralesional primary sensorimotor cortex</td>
<td>Mean (sd)</td>
<td>14.40 (13.62)</td>
</tr>
<tr>
<td>Ipsilesional cerebellum</td>
<td>Mean (sd)</td>
<td>9.43 (17.26)</td>
</tr>
<tr>
<td>Contralesional cerebellum</td>
<td>Mean (sd)</td>
<td>3.18 (3.63)</td>
</tr>
<tr>
<td>Ipsilesional cingulate area</td>
<td>Mean (sd)</td>
<td>1.06 (1.82)</td>
</tr>
<tr>
<td>Contralesional cingulate area</td>
<td>Mean (sd)</td>
<td>0.51 (0.81)</td>
</tr>
</tbody>
</table>

Key: CI=confidence interval; sd=standard deviation; *= statistically significance <0.05.

When investigating changes in brain activity over time (Table 4.6), results indicated that, when compared with those with poor recovery, those with good recovery had significantly greater reduction in activity in the contralesional primary sensorimotor cortex (\( p=0.008 \)) in the first month and first 3 months post-stroke. In the first 3 months, there was also a greater reduction in activity in the ipsilesional cingulate area (\( p=0.04 \)).
Table 4.6: Change in percentage of active voxels at 1 month and at 3 months post-stroke, relative to baseline. Activity associated with the affected upper limb with t-values that exceeded the uncorrected p threshold of 0.001, comparing those with good recovery and poor recovery using the Wilcoxon rank-sum and a 95% confidence interval

<table>
<thead>
<tr>
<th>Percentage of active voxels</th>
<th>Change in the first month</th>
<th>Change in the first 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good recovery</td>
<td>Poor recovery</td>
</tr>
<tr>
<td>Ipsilesional SMA</td>
<td>-0.68 (14.22)</td>
<td>-1.50 (11.44)</td>
</tr>
<tr>
<td>Contralesional SMA</td>
<td>-9.34 (13.75)</td>
<td>2.22 (8.51)</td>
</tr>
<tr>
<td>Ipsilesional SM1</td>
<td>3.98 (7.91)</td>
<td>0.85 (12.07)</td>
</tr>
<tr>
<td>Contralesional SM1</td>
<td>-8.27 (11.73)</td>
<td>4.77 (10.71)</td>
</tr>
<tr>
<td>Ipsilesional cerebellum</td>
<td>-4.14 (13.85)</td>
<td>-0.02 (4.45)</td>
</tr>
<tr>
<td>Contralesional cerebellum</td>
<td>0.44 (5.47)</td>
<td>-1.36 (6.78)</td>
</tr>
<tr>
<td>Ipsilesional cingulate area</td>
<td>-0.49 (2.12)</td>
<td>2.21 (7.11)</td>
</tr>
<tr>
<td>Contralesional cingulate area</td>
<td>-0.02 (1.59)</td>
<td>2.80 (5.88)</td>
</tr>
</tbody>
</table>

Key: SMA=supplementary motor area; SM1=primary sensorimotor area; *= statistically significance >0.05.

Comparing subcortical stroke versus cortical stroke

There were no between-cohort differences in either the whole-brain activity or the activity in the ROI when results were investigated as subcortical stroke greater than cortical stroke (Appendix 4.3) or when results were investigated as cortical stroke greater than subcortical stroke (Appendix 4.4). There was no significant effect from time, group or group by time.

Differences in the extent of activation were detected at levels indicating a trend only. At 1 week post-stroke, those with subcortical stroke showed trends ($p=0.06$) towards more activity in the contralesional supplementary motor area (Table 4.7).
### 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

<table>
<thead>
<tr>
<th>Extent of activity at 1 week post-stroke</th>
<th>Cohort</th>
<th>CI=95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of active voxels</td>
<td>Statistic</td>
<td>Subcortical stroke</td>
</tr>
<tr>
<td>Ipsilesional supplementary motor area</td>
<td>Mean (sd)</td>
<td>10.33 (12.01)</td>
</tr>
<tr>
<td>Contralesional supplementary motor area</td>
<td>Mean (sd)</td>
<td>11.05 (11.16)</td>
</tr>
<tr>
<td>Ipsilesional primary sensorimotor cortex</td>
<td>Mean (sd)</td>
<td>4.55 (8.91)</td>
</tr>
<tr>
<td>Contralesional primary sensorimotor cortex</td>
<td>Mean (sd)</td>
<td>6.93 (6.77)</td>
</tr>
<tr>
<td>Ipsilesional cerebellum</td>
<td>Mean (sd)</td>
<td>5.42 (13.41)</td>
</tr>
<tr>
<td>Contralesional cerebellum</td>
<td>Mean (sd)</td>
<td>2.73 (5.87)</td>
</tr>
<tr>
<td>Ipsilesional cingulate area</td>
<td>Mean (sd)</td>
<td>0.64 (1.28)</td>
</tr>
<tr>
<td>Contralesional cingulate area</td>
<td>Mean (sd)</td>
<td>0.42 (0.78)</td>
</tr>
</tbody>
</table>

Key: CI=confidence interval; sd=standard deviation.

When investigating changes in the extent of activity over time that were associated with movement of the affected UL (Table 4.8), results indicated no significant differences between the two cohorts in the first month and first 3 months post-stroke.
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.

<table>
<thead>
<tr>
<th>Percentage of active voxels</th>
<th>Change in the first month</th>
<th>Change in the first 3 months</th>
<th>Rank sum</th>
<th>Rank sum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subcortical Mean (sd)</td>
<td>Cortical Mean (sd)</td>
<td>Subcortical Mean (sd)</td>
<td>Cortical Mean (sd)</td>
</tr>
</tbody>
</table>
| Ipsilesional SMA           | -0.74 (11.48)             | -1.50 (14.73)               | -3.41 (11.65)        | -2.71 (6.89)        | 0.95    
| Contralesional SMA         | -0.22 (7.28)              | -8.51 (16.82)               | -4.68 (10.35)        | -12.09 (23.40)      | 0.58    
| Ipsilesional SM1           | 4.5 (12.97)               | -0.27 (2.36)                | 2.50 (17.03)         | 2.67 (3.06)         | 0.08    
| Contralesional SM1         | 2.75 (11.46)              | -8.25 (12.38)               | 1.49 (13.38)         | -5.22 (18.76)       | 0.26    
| Ipsilesional cerebellum    | -2.08 (13.36)             | -2.29 (5.40)                | -2.64 (15.17)        | -3.99 (12.11)       | 0.42    
| Contralesional cerebellum  | -0.53 (6.94)              | -0.28 (5.06)                | -1.86 (5.61)         | -1.04 (7.85)        | 0.51    
| Ipsilesional cingulate area| 1.78 (6.73)               | -0.47 (1.65)                | 0.06 (1.64)          | -0.13 (1.31)        | 0.38    
| Contralesional cingulate area| 2.23 (5.60)             | 0.16 (1.42)                 | 0.64 (2.30)          | 0.21 (1.42)         | 0.30    

Key: CI=confidence interval; sd=standard deviation; SMA=supplementary motor area; SM1=primary sensorimotor area.

When comparing change in clinical outcomes in the first 3 months post-stroke, results indicated that those with subcortical stroke (-0.63) tended (p=0.06) to experience better global recovery (mRS) than those with cortical stroke (-0.38). However, this did not reach statistical significance. There were no between-cohort differences (p=0.44) in recovery of function in the affected UL (UL─MAS) in subcortical stroke (1.36) versus cortical stroke (1.81).

4.5 Discussion

In a cohort of patients with first ischaemic stroke that had adversely affected the UL, this study found differences in brain activation patterns in the first 3 months between those who experienced good recovery and those who experienced poor recovery. In comparison, there were no differences between those diagnosed with subcortical stroke and those diagnosed with cortical stroke.
Good recovery versus poor recovery

This study found that good recovery of an affected UL was associated with very early activity in the contralesional primary sensorimotor cortex and supplementary motor area, and a reduction in activity in these areas in the first 3 months. Good UL recovery was also associated with greater levels of activity in ipsilesional regions such as the inferior parietal lobe and supplementary motor area. This bilateral involvement associated with good, early UL motor recovery was also demonstrated by Carey et al [35], Nelles et al [37] and Rehme et al [36] (Table 4.9), but between-study differences need further investigation.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Sn/Hc</th>
<th>Stroke cohort</th>
<th>Ipsilesional activation</th>
<th>Contralesional activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carey et al [35]</td>
<td>9/10</td>
<td>Middle cerebral artery</td>
<td>At 1 month post-stroke: Primary sensorimotor cortex, supplementary motor area and cingulate area</td>
<td>At 1 month post-stroke: Supplementary motor area and premotor cortex</td>
</tr>
<tr>
<td>Nelles et al [37]</td>
<td>10/5</td>
<td>Severe strokes</td>
<td>At 7 days post-stroke: Primary sensory cortex and parietal lobe</td>
<td>At 7 days post-stroke: Inferior parietal lobe</td>
</tr>
<tr>
<td>Rehme et al [36]</td>
<td>11/11</td>
<td>Mild strokes</td>
<td>At 10 days post-stroke: Primary motor cortex, supplementary motor area, premotor cortex, superior parietal lobe and secondary somatosensory cortex</td>
<td>At 10 days post-stroke: Primary motor cortex, supplementary motor area, premotor cortex, superior parietal lobe and secondary somatosensory cortex</td>
</tr>
</tbody>
</table>

Key: Sn=Number of participants with stroke; Hc=number of healthy participants

The involvement of ipsilesional regions such as the inferior parietal cortex and BA44 in good UL recovery suggests that in the first month post-stroke, sensorimotor recovery may require patients to pay extra attention to everyday tasks and/or to learn to over-ride pre-learnt and pre-mastered skills [40-42]. If this activity is generated in a speech production area, such as the Brocas, then perhaps this reflects a possible influence of strategies such as “self talk”. However, as this activation was bilateral, it may reflect greater activation in regions in the dorsolateral, prefrontal cortex involved in inhibitory brain activation, indicating that inhibition may provide better motor control in stroke patients performing the finger-tapping task. Interestingly, Caspers et al [42] found similarities between the structure and function of the inferior parietal lobe and BA44, commenting that both have been shown to support task organisation and communication. They suggested that the
inferior parietal lobe may bridge activity between parietal and visual regions. These findings imply that the parietal lobe and BA44 may play a supportive role post-stroke, even though these regions were not previously recognised for their association with sensorimotor recovery [43-45]. As Johansson [46] states: “Action, gestures, and language are closely related in the human brain.” She suggests that evidence is increasingly directing health professionals to apply a multisensory or multimodal approach to maximising recovery after stroke. To achieve a multimodal approach, strategies should aim to actively recruit cortical regions that prior to the stroke were only recruited when participating in more complex tasks [47, 48], and they should take into account a person’s ability to attend to a task [49]. Future research may ratify whether or not those strategies should include those that purposefully apply an additional communication component, such as self-talk and verbal rehearsal, during task-specific training.

This study found that, in the first week post-stroke, those who experienced good recovery had higher levels of contralesional activity in sensorimotor-related regions, when compared with those who experienced poor recovery; and this is consistent with the majority of other studies [35, 50]. Measuring the level of contralesional activity in the first few days post-stroke, in regions that have a secondary role in sensorimotor function, such as the supplementary motor area, may provide a biomarker that could predict those who are most likely to experience good UL recovery post-stroke [51]. Loubinoux et al [52] also found that recovery could be predicted on the basis of differences in brain activation as measured by fMRI, but only in those with subcortical stroke. Therefore, more research is required before this evidence can be translated across into clinical practice.

**Subcortical stroke versus cortical stroke**

This study found no differences in brain activation between those with subcortical stroke and those with cortical stroke [16, 53]. There was evidence of potential differences in the contralesional supplementary motor area in the first month, and in ipsilesional primary sensorimotor area in the first 3 months, but they did not reach significance. Renner et al [17] recruited similar numbers of participants with cortical and subcortical stroke to the current study and found differences in intracortical facilitation, but only in those with subcortical stroke. They suggested that this may indicate a difference in the mechanisms supporting post-stroke recovery following subcortical and cortical strokes. It is unclear why
the current study did not demonstrate differences in brain activation patterns between these two cohorts. Further research is required into whether this was because recruitment was very soon after the stroke event, as previous studies have been in the chronic phase post-stroke [50, 54]. The presumption that those with subcortical stroke experience better recovery than those with cortical stroke is not ratified by the results of this study [19].

Strengths and limitations

Although this study has relatively large numbers in comparison with other studies in this field [50, 54, 55], its low numbers have nevertheless limited the ability to obtain statistically significant results, particularly in relation to the UL behavioural findings. Obviously, larger participant numbers should be considered in future studies, but in light of the fact that recruiting into clinically-based, post-stroke fMRI trials is so very challenging, the collective value of a meta-analysis would be a useful addition to this field of research [56]. This study is limited by the fact that it does not account for variables such as stroke severity, lesion location and volume, and the speed and intensity of finger-tapping. Another potential limitation is that the study’s cohort is also about 10 years younger than the national mean for first-ever stroke. This study’s strength lies in the fact that it recruited during the first few days post-stroke and that the study period included the period of time when the highest levels of recovery are anticipated and when patients would be receiving the highest intensities of health care. There are very few studies that have achieved this during patients’ acute admission [7, 35, 36, 48, 50, 57]. A further strength is in the fact that the UL intervention that all participants received is aligned with the standard care that is increasingly being offered to patients in the first month post-stroke.

4.6 Conclusion

Advances in our understanding of brain reorganisation have given new impetus to stroke recovery practice [28, 58-62], and it is now firmly understood that the brain’s natural ability to reorganise is foundational to recovery following stroke. Evidence is increasingly indicating that over time, upper limb recovery is associated with a reduction [48] in contralesional activation [63] and recruitment of ipsilesional, motor-related areas [50, 54]. However, as Pascual-Leone et al [64] state: “The challenge we face is to learn enough
about the mechanisms of plasticity to modulate them to achieve the best behavioural outcome for a given subject.”
4.7 References


Chapter 5: Correlation between Assessments
5.1 Abstract

**Background:** Five stroke recovery assessments often selected by clinicians and researchers are the modified Rankin Score (mRS), National Institute of Health Stroke Scale (NIHSS), Action Research Arm test (ARAT), upper limb (UL) component of the Motor Assessment Scale (UL–MAS) and Nine Hole Peg test (9HPT). To date there is no evidence reporting the associations between these UL-specific assessments and global outcome measures in the first three months post-stroke.

**Methods:** This study used data collected from a randomised controlled trial of motor function in right-handed patients with a stroke and an affected UL (n=23). All participants were assessed at 1 week post-stroke and again at 1 month and 3 months. Correlational analysis examined the relationship between assessments and Wilcoxon signed-rank-tested responsiveness to change.

**Results:** There was moderate to strong correlation between assessments, varying over time. Correlation between the UL-specific assessments was moderately high (>0.6) between assessments and across time points. Between the two global measures, the mRS and NIHSS, it varied across time points; at baseline it was 0.48, and at 3 months it was 0.73. In this cohort and in the first three months, the mRS and 9HPT were most responsive to change.

**Conclusions:** The findings showed that in the first three months post-stroke and in an early-stroke-survivor cohort with an affected UL, a weak to moderate correlation was observed between the five assessments, and a moderately strong correlation was observed between the UL-specific assessments. The 9HPT and mRS were the most responsive to change.
5.2 Introduction

There are many and varied assessments currently being used in stroke rehabilitation, with little consistency across Rehabilitation Units [1-4]. Rehabilitation has been defined as “an educational, problem-solving process that focuses on activity limitations and aims to optimize patient social participation and well-being…” [5]. Australia’s Clinical Guidelines for Stroke Management [6] recommend that clinicians select standardised, valid and reliable assessments to measure change during the recovery phase. The assessments of interest to this study are two that measure global outcomes (the modified Rankin Scale (mRS) and National Institute of Health Stroke Scale (NIHSS)) and three that measure upper limb (UL) function (the Action Research Arm test (ARAT) [7], the UL component of the Motor Assessment Scale (UL–MAS) [8-10] and the Nine Hole Peg test (9HPT)) [11]. All five assessments are standardised and are often used by researchers to measure recovery outcomes post-stroke [2, 12-15]. However, the relationship between these assessments has not been systematically investigated. Further, varying assessments across studies make it difficult to compare findings and critically appraise stroke recovery evidence [16-23].

In studies investigating UL assessments only, Beebe and Lang [24] compared six assessments and found strong correlation between the ARAT and the 9HPT at 1 and 3 months post-stroke. Hsueh and Hsieh [25] compared the ARAT and the UL–MAS and found similarities in their responsiveness to change. Even though authors have compared up to 11 motor assessment scales at the one time [26], to date there is no evidence comparing the relationship between UL-specific assessments and global outcome measures, and minimal evidence related to clinical sensitivity in the first 3 months post-stroke [24]. An improved understanding of the relationship between and sensitivity of assessments will assist researchers and clinicians to more adequately appraise the evidence related to activity limitation, stroke rehabilitation and UL outcomes [9, 25, 27-31]. We propose that because a person with a stroke-affected UL experiences difficulty participating in everyday activities, there should be some correlation between UL-specific assessments and global outcome measures.

This study sought to ratify the following hypotheses. In the first three months post-stroke and in a cohort of right-handed patients with a first ischaemic stroke:
1. There is a moderate relationship between the global measures (the mRS and NIHSS) and the UL-specific measures (the ARAT, UL–MAS and 9HPT).

2. There is a moderate to strong relationship between the UL-specific assessments (the ARAT, UL–MAS and 9HPT).

3. Changed scores on global and UL-specific measures will demonstrate moderate to strong association and responsiveness to change.

5.3 Clinical Assessments

Modified Rankin Scale (mRS)

The Rankin Scale was created in 1957 [32] to measure global dependence post-stroke. In 1988 it was refined to become the modified Rankin Scale (mRS) [33]. The modified version is a 7-point scale where a higher score indicates greater dependence. A zero score indicates that a stroke survivor is able to participate independently in everyday activities. A score of 3 indicates moderate dependence and disability, a score of 5 indicates severe disability, and a score of 6 indicates the patient has died. The mRS is often used in stroke studies [15, 21, 34-36].

National Institute of Stroke Scale (NIHSS)

This assessment is the most widely used, mainly because it is commonly selected for clinical stroke trials, often in conjunction with the mRS [37-41]. The NIHSS is designed to measure neurological capacity across 15 different domains. These include UL function, lower limb function, coordination, communication, cognition, sensation and vision. A higher score indicates a poorer outcome.

Action Research Arm Test (ARAT)

This is a 57-point scale where a higher score indicates better UL performance. The ARAT is designed to measure unilateral UL function and uses an hierarchal structure. It has four subsets – Grasp, Grip, Pinch and Gross Movement – and good inter-rater and intra-rater reliability [27, 42, 43]. However, there is some unresolved controversy over its hierarchal properties [44, 45]. The ARAT has often been selected in studies investigating UL recovery following stroke [19, 20, 29, 46-49].
Upper Limb Component of the Motor Assessment Scale (UL–MAS)

This is an 18-point scale where a higher score indicates better UL performance. It comprises three UL subsets from the Motor Assessment scale [8], and these have been independently validated as the UL–MAS [9]. It has good inter-rater and test-retest reliability [27, 50] and good validity in a stroke population [10, 25, 51, 52]. There has been controversy surrounding its hierarchal scoring properties, with recent evidence indicating that each individual item should be scored irrespective of its position in the subset [10, 53]. This UL assessment is often selected in studies investigating post-stroke UL recovery [9, 21, 54] and by therapists in clinical practice [3].

Nine Hole Peg Test (9HPT)

This is a timed assessment of UL dexterity and, as the name implies, requires a person to place 9 pegs in 9 holes and then remove them as quickly as possible. It is designed to measure unilateral UL performance, particularly the pinch grip, reach and release movements. Croarkin et al [27] found the 9HPT to have the highest levels of reliability and validity when compared with 8 other UL-specific assessments, including the UL-MAS and ARAT. There are aged-matched normative data available for this assessment, providing additional comparative analysis potential [11, 55]. Again, the assessment has also been frequently used in stroke recovery studies [21, 31, 56, 57].

5.4 Methods

This study analysed data collected for a randomised controlled study of right-handed patients with a first ischaemic stroke (n=23). The original study received ethical approval from the region’s health and academic committees for human research. A summary of the methodology relevant to the present analysis is provided below.

Participants

Participants were recruited from two regional Acute Stroke Units. The study recruited adult patients with cortical and/or subcortical lesions resulting in an impaired UL. Patients were identified as potential participants by the admitting Neurologist who was informed about the study’s inclusion/exclusion criteria. The decision to inform the researchers about a potential participant was at the Neurologist’s discretion. Patients were excluded from the
study if they scored ≥16 on the UL–MAS (i.e. very mild UL dysfunction), and/or were unable to respond to a two-step command (NIHSS, item 7a), and/or were fearful of confined spaces or incompatible with the imaging environment. All referred participants (n=24) consented to participate in the study, with one withdrawing at baseline. The remaining 23 stayed in the study for its 3-month duration.

**Upper limb behavioural intervention**

All participants received standard care, with all UL behavioural intervention prescribed by therapists with more than two years’ neurological experience. Most of the UL behavioural intervention was applied by a therapy assistant who was guided by the prescribing therapists, and the rest was applied by therapists. Within the first month post-stroke, half the participants received an additional 30 hours of UL intervention over a 3-week period as part of the randomised controlled trial design, but for the purposes of this study, data from all 23 participants were analysed as a single cohort.

**Outcome measures**

Participants were assessed within 10 days of their stroke events (baseline) and then again at 1 month and 3 months. In each session, participants were assessed using the NIHSS, ARAT, UL–MAS, 9HPT and mRS, and the assessments were applied in that order. Participants and, where relevant, their family or carers, were also asked to self-report the pre-stroke level of disability as measured by the mRS. Non-hierarchical scoring with the UL–MAS was used as recommended [10]. There were three assessors, one Physiotherapist and two Occupational Therapists, all with more than two years’ experience in neurology. One assessor was involved in each session, but assessors varied across sessions and between participants. To increase consistency and inter-rater reliability, prior to recruitment therapists undertook training in using the assessments, and reviewed and if necessary edited the assessment scripts that were then used by all assessors with prior agreement on scoring definitions. Assessors were not blinded to the study’s objectives or design, but were always blinded to the participant’s group allocation.

**Data analysis**

For data analysis, SPSS version 11 (SPSS Inc. Chicago, IL) was used. Outcome measures were analysed at baseline, 1 month and 3 months. Descriptive analysis was
used to examine distribution of scores across measures. Correlations between assessments at the 3 time points were tested using the Spearman's coefficient. Magnitude of the correlation coefficients (r) was interpreted as follows: r<0.25 indicated little or no relationship; 0.25–0.60 indicated a fair degree of relationship; r>0.60–0.75 indicated a moderate relationship; and r>0.75–90 indicated a strong to very strong relationship [24, 30, 58]. Because this was a small sample and performance scores were not normally distributed, responsiveness to change was calculated using the non-parametric Wilcoxon signed-rank test. The responsiveness of assessments was examined between 1 week (baseline) and 1 month, and between baseline and 3 months. The latter two time points are of clinical significance in the stroke recovery process. In the first month post-stroke most patients are experiencing their greatest gains, and after 3 months most of them have been discharged from rehabilitation. As with other studies, a higher effect size was interpreted as indicative of a higher responsiveness to change [24, 25, 30]. Following a review of the results, we identified relationships “of interest”, which were then examined in more detail by generating scatter plots.

5.5 Results

The 23 participants had a mean age of 65.7 years (Table 1), and 13 (56.5%) participants were men. Most participants experienced no difficulties undertaking everyday activities prior to their stroke, as evidenced by a very low mean pre-admission mRS of 0.3 (Table 5.1). Ten were diagnosed with cortical stroke, and 11 had strokes which affected the dominant (right) UL.
Findings indicated that patients with a first ischaemic stroke experience most of their improvement in the first month, (Table 5.2; Figure 5.1), with mRS scores indicating that stroke impact in the first week was moderately severe.

Table 5.2: Clinical assessments raw scores

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD); range</th>
<th>1 month Mean (SD); range</th>
<th>3 months Mean (SD); range</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS</td>
<td>3.73 (.69); 2–5</td>
<td>2.57 (0.73); 2–4</td>
<td>2.13 (0.87); 1–4</td>
</tr>
<tr>
<td>NIHSS</td>
<td>4.96 (2.16); 2–10</td>
<td>1.87 (1.66); 0–6</td>
<td>1.39 (1.90); 0–6</td>
</tr>
<tr>
<td>ARAT</td>
<td>29.30 (17.11); 0–56</td>
<td>48.91 (16.20); 0–57</td>
<td>49.65 (16.03;0–57</td>
</tr>
<tr>
<td>UL–MAS</td>
<td>9.48 (4.15); 1–16</td>
<td>14.26 (4.21); 1–18</td>
<td>14.52 (4.76); 0–18</td>
</tr>
<tr>
<td>9HPT</td>
<td>109.83 (27.03); 60.56–130</td>
<td>54.20 (36.61); 21.83–130</td>
<td>45.54 (34.07); 21.58–130</td>
</tr>
</tbody>
</table>
Correlation across assessments

As hypothesised, the correlation coefficients were positive across the five assessments, but there was variation between measures and time points (Table 5.3).
Table 5.3: Spearman’s correlations between clinical assessments at each time-point

<table>
<thead>
<tr>
<th>Performance scores at each corresponding time-point</th>
<th>mRS</th>
<th>NIHSS</th>
<th>UL–MAS</th>
<th>ARAT</th>
<th>9HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS</td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.48 (0.02)</td>
<td>na</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL–MAS</td>
<td>-0.67 (0.0004)</td>
<td>-0.71 (0.0002)</td>
<td>na</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAT</td>
<td>-0.60 (0.0024)</td>
<td>-0.69 (0.0003)</td>
<td>0.93 (&lt;0.0000)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>9HPT</td>
<td>0.31 (0.17)</td>
<td>0.49 (0.030)</td>
<td>-0.72 (0.0004)</td>
<td>-0.66 (0.0017)</td>
<td>na</td>
</tr>
<tr>
<td><strong>1 month</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS</td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.62 (0.0013)</td>
<td>na</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL–MAS</td>
<td>-0.49 (0.019)</td>
<td>-0.54 (0.0079)</td>
<td>na</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAT</td>
<td>-0.44 (0.035)</td>
<td>-0.59 (0.0029)</td>
<td>0.74 (&lt;0.0001)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>9HPT</td>
<td>0.35 (0.137)</td>
<td>0.74 (0.0002)</td>
<td>-0.64 (0.0023)</td>
<td>-0.68 (0.0010)</td>
<td>na</td>
</tr>
<tr>
<td><strong>3 month</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS</td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.73 (0.0001)</td>
<td>na</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL–MAS</td>
<td>-0.36 (0.076)</td>
<td>-0.45 (0.033)</td>
<td>na</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARAT</td>
<td>-0.63 (0.0013)</td>
<td>-0.84 (0.0000)</td>
<td>0.64 (0.0011)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>9HPT</td>
<td>0.61 (0.0041)</td>
<td>0.64 (0.0024)</td>
<td>-0.61 (0.0046)</td>
<td>-0.63 (0.0028)</td>
<td>na</td>
</tr>
</tbody>
</table>

Correlations across time points were evident between the UL-specific assessments and the global measures, but there was variation between assessments and/or time points. For example, between the NIHSS and UL–MAS (Figure 5.2) correlation was strong at baseline (0.71), moderate at 1 month (-0.54) and weak at 3 months (-0.45). There was more variation between the NIHSS and 9HPT and the NIHSS and ARAT, with results ranging between 0.49 (9HPT at baseline) and 0.84 (ARAT at 3 months). Correlation between the three UL-specific assessments was moderately high (>0.6) between assessments and across time points. Between the two global measures, the mRS and NIHSS varied across time points; it was 0.48 at baseline and 0.73 at 3 months.
In relation to \textit{time post-stroke}, at baseline the strongest correlation was between the ARAT and UL–MAS (0.93) (Table 5.3; Figure 5.), with strong correlation between the NIHSS and UL–MAS (-0.71) and the UL–MAS and 9HPT (-0.72). The weakest correlation was between the mRS and 9HPT (0.31) (Table 5.3; Figure 5.4). At 1 month the strongest correlation was between the NIHSS and 9HPT (0.74) and between the UL–MAS and ARAT (0.74). The weakest correlation was again between the mRS and 9HPT (0.35). At 3 months, the strongest correlation was between the NIHSS and ARAT (-0.84) and the weakest between the mRS and UL–MAS (-0.36). The relationship between the mRS and 9HPT was moderate at 3 months (Table 5.3).
Figure 5.4: mRS vs 9HPT scatter plot

Responsiveness to change

All assessments were strongly and significantly responsive, ranging from 1.15 to 2.38 (Table 5.4). The three UL-specific assessments and the two global measures were all strongly responsive to change between baseline and 1 month, and between baseline and 3 months. The 9HPT was the most responsive overall, with results indicating an effect size (ES) of 2.06 in the first month and 2.38 in the first 3 months, followed by the mRS with an ES of 1.7 in the first month and 2.34 in the first 3 months.
Table 5.4: Changed scores and responsiveness measures in clinical assessments

<table>
<thead>
<tr>
<th>Baseline to 1 month</th>
<th>Changed mean score Mean (SD)</th>
<th>Effect size</th>
<th>Wilcoxon signed-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>z-value</td>
</tr>
<tr>
<td>mRS</td>
<td>-1.174 (0.650)</td>
<td>-1.705</td>
<td>-4.217</td>
</tr>
<tr>
<td>NIHSS</td>
<td>-3.087 (1.411)</td>
<td>-1.427</td>
<td>-4.233</td>
</tr>
<tr>
<td>UL–MAS</td>
<td>4.783 (3.477)</td>
<td>1.151</td>
<td>4.159</td>
</tr>
<tr>
<td>ARAT</td>
<td>19.609 (15.538)</td>
<td>1.147</td>
<td>4.062</td>
</tr>
<tr>
<td>9HPT</td>
<td>-55.638 (36.104)</td>
<td>-2.058</td>
<td>-3.817</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline to 3 months</th>
<th>Changed mean score Mean (SD)</th>
<th>Effect size</th>
<th>Wilcoxon signed-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>z-value</td>
</tr>
<tr>
<td>mRS</td>
<td>-1.609 (0.941)</td>
<td>-2.336</td>
<td>-4.208</td>
</tr>
<tr>
<td>NIHSS</td>
<td>-3.565 (1.779)</td>
<td>-1.648</td>
<td>-4.191</td>
</tr>
<tr>
<td>UL–MAS</td>
<td>5.043 (3.574)</td>
<td>1.214</td>
<td>4.082</td>
</tr>
<tr>
<td>ARAT</td>
<td>20.348 (16.447)</td>
<td>1.190</td>
<td>4.155</td>
</tr>
<tr>
<td>9HPT</td>
<td>-64.292 (34.589)</td>
<td>-2.379</td>
<td>-3.867</td>
</tr>
</tbody>
</table>

5.6 Discussion

Correlation across assessments

The findings showed that, as hypothesised, there was correlation between all five assessments, and this included correlation between UL-specific assessments and global measures. However, the magnitude of the correlation varied across assessments and time post-stroke. Correlation between the two global measures, the mRS and NIHSS, increased from moderate to strong over 3 months. This is an important finding as both are often used in tandem in stroke recovery and epidemiological studies [34, 36, 37, 39, 40].

Correlation between the three UL-specific assessments, the ARAT, UL–MAS and 9HPT, remained above 0.6 in the first three months post-stroke. It was strongest in the first ten days and strongest between the ARAT and UL-MAS. This is reassuring, as this time period is when most patients with an affected UL are receiving rehabilitation [59] and when most UL recovery is anticipated [4, 60]. As the scatter plot demonstrates (Figure 5.4), the ARAT and UL–MAS are well-aligned when it comes to measuring upper limb outcomes at all 3 time points, but both show floor and ceiling effects. What are the similarities and
differences among the three UL assessments? All three measure unilateral function, with the exception of one bilateral item in the UL–MAS. All three are completed entirely in a sitting position, again, with the exception of the UL–MAS, which has three of its 18 items assessed in a lying position and one in a standing position [8, 10]. However, in contrast to the UL–MAS and ARAT, the 9HPT is a repetition of the same tasks and is timed overall. The only other timed components are three individual items in the UL–MAS. These differences and similarities may underpin the variability in the correlation findings between the UL-specific assessments.

The stronger and more consistent correlation between the ARAT and UL–MAS is supportive of Hsueh and Hsieh’s [25] findings. They compared the two assessments in a very similar cohort (n=43), having excluded those with more than one stroke and those more than 2 months post-stroke, but they included those with intracerebral haemorrhagic stroke. However, our correlation coefficients were lower than those of Beebe and Lang [24] who found strong levels of correlation (>0.85) between the ARAT and 9HPT at 1 month and 3 months. They also compared assessments in another very similar cohort (n=33), recruiting participants using similar inclusion/exclusion criteria to Hsueh and Hsieh. The average baseline time post-stroke in Beebe and Lang’s study was 18.6 days (SD 5.6). One major difference was that they recruited 14 (42%) left-handed participants. Their 1-month mean scores were ARAT=26.4 (SD 23.9) and 9HPT=88.8 (SD 40.2), whereas the scores in this study were 48.91 (SD 16.20) and 54.20 (SD 36.61) respectively. The better performance scores in our cohort raise questions about between-cohort differences and may reflect the fact that half the participants in our study received more intensive intervention in the first month [61]. Even though research is required to investigate these relationships further, our study supported the hypothesis that in right-handed patients with a first ischaemic stroke, there was a moderate to strong (>0.6) relationship between the ARAT, UL–MAS and 9HPT at 1 week, 1 month and 3 months.

In respect to findings between UL-specific assessments and global measures, there was strong correlation between the NIHSS and UL–MAS at baseline through to 3 months, although it reduced across time points. As the scatter plot shows (Figure 5.2), there appears to be polarisation at 1 month, indicating that although many participants improved during this time, a few experienced persistent stroke-related difficulties in the first 3
months. Such correlation was not as evident between the NIHSS and the ARAT or 9HPT, or between the mRS and the UL-specific assessments. Even though the NIHSS is a global measure, it includes three UL-specific domains, and this may explain some of the between-assessment correlation. However, it does not explain the higher and more consistent correlation specific to the UL–MAS. Glymore et al [62] found that the NIHSS score at a mean of 13 days post-stroke could predict scores on a physical performance test and an expanded Barthel Index [63] (measuring activities of daily living) 3 and 6 months post-stroke, particularly in those with subcortical strokes. They recruited participants (n=291) with ischaemic stroke irrespective of UL involvement, and included 20% with recurrent strokes. Even though this evidence relates to a different cohort and does not relate to UL function or assessment correlation, it provides evidence of relationships between functional assessments and global measures.

The 9HPT varied the most in its correlation with all other assessments, ranging from a weak correlation with the mRS at baseline, to a moderately strong correlation with the NIHSS at 1 month. From the 9HPT and mRS scatter plots (Figure 5.4), it is difficult to identify any obvious patterns in this between-assessment relationship. As previously stated, the 9HPT is essentially a repetition of a single grasp-and-release task, in stark contrast to the mRS, which is a broad measure of dependence post-stroke [64]. The 9HPT also has a timed component which may be reflective of other underlying abilities [11]. The mRS showed more variation with all the other assessments. For example, at baseline it had weak correlation with the 9HPT and NIHSS and moderate correlation with the ARAT and UL–MAS. This suggests that the mRS is the assessment that is best able to be used on its own.

The hypothesis was that because UL function is essential to participation in everyday activities, there would be some correlation between all five assessments. Our study supported the hypothesis that in a cohort of right-handed patients with a first ischaemic stroke there would be relationship between all five assessments post-stroke. These correlations ranged from 0.3 to 0.8, depending on assessment type and time points. As the data were drawn from a randomised controlled trial, group assignment could be an explanatory variable in the multiple regression. Group assignment as a potential variable of influence could be further investigated in a future study.
Responsiveness to change

The results showed that between baseline and 1 month, and between baseline and 3 months, all five assessments were strongly responsive to change post-stroke. In relation to the UL-specific assessments, there were similarities between the responsiveness of the UL–MAS and the ARAT (Figure 5.4), supporting the findings of Hsueh and Hsieh [25]. However, the most responsive UL assessment in our study over both periods of time was the 9HPT. These findings are in contrast to those of Beebe and Lang [24] who found lower levels of responsiveness in the 9HPT and ARAT between 1 and 3 months post-stroke. These differences in findings may relate to the fact that the changes in our study were measured from 10 days post-stroke and therefore included more of the UL recovery that occurs in the first month post-stroke [4]. The second most responsive assessment was the mRS, but only from baseline to 3 months. When comparing the mRS with ADL assessments, Dromerick et al [64] found the mRS was responsive to change, but less responsive than the Barthel Index. Even though our findings show the mRS and 9HPT are the more responsive to change, they also show that they are quite different from one another (Figure 5.4). Overall, our findings support the hypothesis that in a cohort of right-handed patients with a first ischaemic stroke, all assessments showed a strong responsiveness to change from baseline to 1 month and to 3 months.

As the three hypotheses indicate, these findings were only tested in right-handed patients with a first ischaemic stroke resulting in an impaired UL. Therefore, they do not necessarily apply to a broader stroke cohort or to those with haemorrhagic stroke. This is particularly pertinent to the global measures as they are often used in studies recruiting participants with stroke irrespective of whether or not they have an affected UL [2, 35, 37, 39].

The most important finding of this study is that all five assessments were responsive to change in the first month and in the first 3 months post-stroke. Our findings show correlation between UL-specific assessments and global outcome measures in a cohort of patients with a stroke-affected UL and, in turn, those experiencing difficulty participating in everyday activities. However, the relationship between UL-specific assessments and global outcome measures needs to be studied in more detail and in a broader cohort to increase the generalisability of findings. The present study indicates that the most responsive measures at 3 months are the 9HPT and the mRS. If clinicians or researchers
require measures that are responsive to early UL changes in right-handed patients with a first ischaemic stroke, they could confidently select all or any of the five assessments, but it may not be necessary to use the ARAT and the UL–MAS.

5.7 Conclusions

These findings demonstrate that among patients in the first three months post-stroke, if clinicians or researchers want to measure change in a cohort of right-handed patients with a first ischaemic stroke that has resulted in an impaired UL, they can confidently select the modified Rankin Scale, the National Institute of Health Stroke Scale, the Action Research Arm test, the UL component of the Motor Assessment Scale and/or the Nine Hole Peg test. The findings showed that in the first three months post-stroke, a weak to moderate correlation may be observed between UL-specific assessments and global outcome measures, a moderately strong correlation may be observed between the Action Research Arm test, the UL component of the Motor Assessment Scale and the Nine Hole Peg test, and the mRS and 9HPT may be the most responsive to change.
5.8 References


Chapter 6: Task-specific Training

This is the accepted version of the following article: Hubbard IJ, Parsons MW, Neilson C and Carey LM. Task-specific training: Evidence for and translation to clinical practice. Occupational Therapy International, 2009. 16(3-4): p. 175-189, which has been published in final form at http://onlinelibrary.wiley.com/doi/10.1002/oti.275/abstract.
6.1 Abstract

There is mounting evidence of the value of task-specific training as a neuromotor intervention in neurological rehabilitation. The evidence is founded in the psychology of motor skill learning and in the neuroscience of experience-dependent and learning-dependent neural plastic changes in the brain in animals and humans. Further, there is growing empirical evidence for the effectiveness of task-specific training in rehabilitation and for neural plastic changes following task-oriented training. In this paper we will position the evidence for task-specific training in the context of rehabilitation, review its relevance for occupation-based neurological rehabilitation, particularly in relation to upper limb function and everyday activities, and recommend evidence-driven strategies for its application. We recommend that task-specific training be routinely applied by occupational therapists as a component of their neuromotor interventions, particularly in management related to post-stroke upper limb recovery. Specifically, we propose five implementation strategies based on review of the evidence. Task-specific training should be relevant to the patient/client and to the context, be randomly assigned, be repetitive and involve massed practice, aim towards reconstruction of the whole task, and be reinforced with positive and timely feedback.

6.2 Introduction: Task-specific Training

There is mounting evidence that therapists treating people affected by neurological disorders should prescribe task-specific training in their therapy [1-3]. Task-specific training is a term that has evolved from the movement science and motor skill learning literature [4] and is defined as training or therapy where patients “practice context-specific motor tasks and receive some form of feedback” [5]( p.576). In the field of skill learning it may be associated with different practice conditions, feedback and conditions of transfer [3, 4]. Task-specific training in rehabilitation focuses on improvement of performance in functional tasks through goal-directed practice and repetition. The focus is on training of functional tasks rather than on impairment, such as with muscle strengthening. Other terms used that reflect these elements are “repetitive functional task practice”, “repetitive task practice” [1], “task-related training” [6] and “task-orientated therapy” [7].
A strength of the task-specific training approach lies in its scientific origins. The evidence informing task-specific training is based on animal (basic science) research [8-10], has been developed within the psychology literature of motor control and learning [4], and has since been applied in human studies with “healthy” participants [4] and following injury [11-13]. Further, there is increasing evidence of neural plastic changes associated with training [14]. Learning is reported to be maximal for the specific task trained [15, 16]. Importantly, repetitive use alone may not be sufficient to effect changes in cortical representation. Rather, changes are associated with specific skill learning, consistent with a learning-dependent model of neural plasticity [17, 18]. Neurophysiological evidence also supports the value of the object used or task undertaken in the organisation of movement [19, 20]. The evidence indicates that cortico-motor neuron pools are organised relative to specific tasks, rather than specific muscles. Importantly, evidence suggests that motor skill learning capability may be retained in stroke survivors under similar conditions to healthy volunteers [21][3].

6.3 Neural Plasticity and Task-specific Training

A major contributor to the theoretical framework informing neuromotor rehabilitation is the evidence concerning brain plasticity. Neuroplasticity refers to the brain’s ability to reorganise itself in response to changes in behavioural demands [22]. It is important to remember that this is a capacity of both the healthy and injured brain, and is therefore always active. Non-invasive technology, such as functional magnetic resonance imaging (fMRI), provides an opportunity to better understand how the brain's circuits interact with one another, and to explore the reorganisation that occurs when one or more areas of the brain are either partially or completely “shut down” following injury. Researchers have suggested that in time, therapists should be able to decide on the most optimal intervention for an individual, based on evidence of residual brain circuits [23-30].

Animal studies have demonstrated that task-specific training, e.g. skilled reaching task, can restore function by using spared (non-affected) parts of the brain which are generally adjacent to the lesion [10] and/or recruiting supplementary parts of the brain [31]. Many authors have detailed the neurobiological changes underlying the brain’s reorganisation in response to task-specific training. Rossi et al (2007) conclude: “Regardless of concomitant interventions, the extent of functional improvement is strongly dependent on the specific
external stimulation that the rewiring circuits experience. Adaptive cortical reorganization in both intact and injured CNS is not induced by generic use or activation, but requires the application of task-specific training protocols” (p.19).

Neural plastic changes have also been demonstrated in the human brain [14, 24, 32] following an ischaemic stroke and neuromotor interventions. For example, the effect of task-oriented arm training on motor function and brain reorganization has been investigated in randomized controlled trials with a small number of patients [33, 34]. Using a task-oriented training regime of intensive finger movement tracking, improvement in finger control was found in association with evidence of brain reorganization in chronic stroke patients [33]. There are now an increasing number of such studies measuring changes in brain activation patterns following task-specific training; although still relatively small in participant numbers, they have provided enough data for meta-analysis [14]. Findings from this analysis suggest that task-specific training can influence functional outcomes and brain activation patterns.

As summarized by Bayona et al [7]: “Task-oriented therapy is important. It makes intuitive sense that the best way to relearn a given task is to train specifically for that task. In animals, functional reorganization is greater for tasks that are meaningful to the animal. Repetition alone, without usefulness or meaning in terms of function, is not enough to produce increased motor cortical representations. In humans, less intense but task-specific training regimens with the more affected limb can produce cortical reorganization and associated, meaningful functional improvements” (p.58).

### 6.4 Evidence for Task-specific Training in Rehabilitation

Evidence indicates that task-specific training could have relevance for people affected by traumatic brain injury [35, 36], Parkinson’s disease [37], total hip replacement [38], work-related injury [39] and/or spinal cord injury [40, 41]. However, most of the task-specific training evidence relates to post-stroke recovery. It has been found to be effective in cognitive neurorehabilitation [42], sensory retraining [43], gait retraining [44-46] sit-to-stand retraining [35] and motor training of the upper limb [12, 47-54].

Task-specific training is a core element of a number of interventions, as discussed below. It may be augmented by strategies to enhance learning, as used in the motor relearning or
movement sciences approaches, or to force use of the limb in daily activities, as in the constraint-induced movement therapy (CIMT) approaches [3]. Equipment or virtual environments may also be used to facilitate the movement or learning environment. A recent systematic review of repetitive functional task practice in stroke rehabilitation included 31 trials with 1078 participants [1]. Overall, it was found that some form of task-specific training resulted in improvement in global motor function, and in both arm and lower limb function, although the evidence for upper limb interventions was less clear due to insufficient good-quality evidence. Nineteen trials, with 634 participants, measured arm or hand function. The pooled effects for the impact of repetitive functional task training across all trials showed small effect sizes, which were statistically significant for arm function and marginally non-significant for hand function. There was little or no evidence for modification of treatment effects due to time post-stroke or dosage of task practice. However, for the upper limb, the type of intervention did impact on treatment effects, with findings from the CIMT studies showing a large, statistically significant effect. Improvement in activities of daily living was also reported, and it was recommended that adverse effects should be monitored with this therapy. Retention effects persisted for up to 6 months, with retention beyond this time unclear. Economic modelling suggested that task-specific training was cost-effective.

Post-stroke, there is evidence that task-specific, upper limb training not only impacts functional recovery but also brain activation patterns. This evidence includes a meta-analysis by Richards et al [14] and a review by Carey and Seitz [24]. Examples of upper limb, task-specific training used include task-oriented motor training [34]; CIMT and household tasks such as “eating, opening and closing jars and spring-loaded clothespins” [55](p.712); CIMT and “gross and fine motor skills, such as grasping and using a spoon and picking up an object with a specified grasp” [56](p.328); and CIMT and “gross motor activities such as throwing a ball and simulating hockey, and fine motor activities using pegs and putty, and general activities related to daily living (ADL)” [57](p.242). It is worth noting that much of this task-specific training was supervised by physiotherapists; the rationale for this is not discussed.
6.5 Task-specific Training: How Does It Relate to Current Interventions?

It will be increasingly obvious to the reader that firstly, the term, “task-specific training”, is part of a broad range of interventions, and secondly, it is difficult to differentiate it from routinely used neuromotor interventions in current occupational therapy practice. For occupational therapists, neuromotor interventions have been historically driven by three primary approaches: neurodevelopmental, sensorimotor and motor relearning approaches [58, 59].

The Bobath approach [60], sometimes referred to as neuro-developmental therapy (NDT), is based on the concept of abnormal patterns of movement and stresses the importance of “breaking-down” the abnormal or maladaptive patterns with the use of limb and trunk positioning and/or weight-bearing and is still very much in use today [61]. Walker et al [62] surveyed therapists in the United Kingdom and found that most reported they used a Bobath approach when treating stroke patients. Whilst the approach focuses on patterns of movement, it also includes incorporation of these movement strategies in daily activities, once improvements in patterns of movement have been achieved [63], and thus has an element of task-specific practice. It does not, however, recognise that movement is organised according to the object used or the environment.

The sensorimotor approach, originating from the research of Ayres [64] and further developed by others, e.g. Case-Smith [65], is based on theories of a child’s healthy development through a series of motor skills “milestones”. Ayres’ approach, although primarily aimed at paediatric neurorehabilitation, has also been used in adult neurorehabilitation [66]. In the sensorimotor approach, therapists selected tasks and activities which enabled them to modulate the amount of stimulation and were “of interest” to the patient. The sensorimotor approach has some similarities, therefore, with task-specific training in that it is task-oriented, uses tasks which are meaningful to the patient, and involves repetition and practice. It does not, however, incorporate motor learning principles.

The motor relearning approach, as described by Carr and Shepherd [6, 67], is derived from the movement science literature and incorporates principles closely aligned with task-
specific training. It includes isolated training practice of impaired essential movements and then immediate practice within the relevant, specific functional task. As such, it emphasises specific training of motor control in everyday activities and represents a shift away from facilitation of movement and exercise therapy. This approach formally identifies the task as integral to effective motor relearning. The repetitive task training is combined with techniques to enhance cognitive involvement, e.g. through functional relevance of tasks used and knowledge of performance. Task-specific training is most closely related to the motor relearning approach, but the two are not synonymous.

An approach that has gained interest more recently and is supported by evidence from animal studies [10, 68, 69] and systematic review [50] is CIMT, which is primarily designed to reverse the conditioning that leads to "learned non-use" and aims to promote spontaneous use of the hand through using “shaping” procedures [69, 70]. The approach involves a constraint applied to the less affected limb and intensive upper limb training of the more affected limb. The “shaping” procedure is based on operant conditioning, with the aim of eliciting a behaviour (task goal) and reinforcing it (positive feedback). This involves intensive periods of task practice using shaping and progressive increments in task difficulty, feedback and encouragement [71]. Although the approach is task-based and involves practice of graded activities, the focus is not on the acquisition of a voluntary skill or the optimisation of motor skill learning [3].

6.6 Task-specific Training and Use of Everyday Activities

It is recognised that “movement emerges from an interaction between the individual, the task, and the environment in which the task is being carried out” [72]. This model is consistent with the task-oriented, occupation focus of occupational therapy. It has been suggested that the organization of movement of the upper limb for reaching is positively influenced by the conditions in which it is undertaken [73]. Further, movement kinematics of the upper limb are different under different conditions, from real life action to simulated conditions, in healthy volunteers [74]. Similarly, van Vliet et al [75] found that there was a difference in movement kinematics of the upper limb when undertaking a more functional goal of drinking from a glass, compared with only moving a glass of water, further highlighting the goal of the task. Wu et al [76] concluded that the use of real and functional
objects might be an effective way of facilitating efficient, smooth and coordinated movement with the impaired arm after stroke.

Task-specific training often uses “real world” or everyday tasks as the therapeutic medium in functional recovery. In combination with high levels of massed practice, it aims to achieve optimal function, which, in turn, allows the patient/client to adequately undertake everyday activities [25]. To review the importance of tasks and everyday activities in neurorehabilitation and, further, to report this to occupational therapists could well be “preaching to the converted”. However, the present authors suggest that this body of evidence serves to validate the focus of occupations, tasks and activities in neuromotor interventions. Suffice to say that researchers and opinion leaders are in agreement that there is ample evidence to support neuromotor interventions which are task-specific and based in and around everyday activities [7, 25, 30, 47, 77, 78]. In this context we may define task specific training as training or intervention which utilises as its principal therapeutic medium, ordinary everyday activities which are intrinsically and/or extrinsically meaningful to the patient or client.

6.7 Recommendations for Application of Task-specific Training in Clinical Practice

Taking into consideration the limitations and strengths of the evidence available, the authors recommend that task-specific training be routinely applied by occupational therapists as a component of their neuromotor interventions, particularly in post-stroke upper limb management. Further, authors and researchers should consider using “task-specific” terminology if reporting on outcomes related to neuromotor interventions, particularly those based in and around everyday tasks, occupations and/or activities.

Following a review of the task-specific evidence, it is also possible to recommend five strategies to guide application of task-specific training in clinical practice. These are consistent with guidelines put forward by others (e.g. Bayona et al [7]; Byl et al[48]; Carey [79]; Davis [80]; Dobkin & Carmichael [25]; Krakauer [81]; Mathiowetz [78]). The strategies are presented in “practice-ready” dialogue, with the aim of assisting therapists in translating them into clinical practice. To facilitate recall, they have been formulated as the
five “Rs”, i.e. task-specific training should be *Relevant, Randomly ordered and Repetitive*, aim towards *Reconstruction* of the whole task and be positively *Reinforced*.

**Strategy 1**

*Task-specific training should be Relevant to the patient and to the context*: Firstly, it should involve activities which are intrinsically and/or extrinsically meaningful to the patient [7, 48, 80]. A patient-generated index such as the Canadian Occupational Performance Measure [82] can be used to formally identify these tasks and this, in turn, can serve as an outcome measure for later re-assessment. The evidence infers that to spend large amounts of time and effort on tasks and activities which, although appearing important to the therapist and/or institution, have no such value for the patient, could be counterproductive.

Secondly, evidence indicates that where possible, the task trained should be “real world” or context-specific [72]. For example, if a patient/client is relearning to use a knife and fork, then they should be doing this in a sitting position and, if possible, with “real” food and using ordinary cutlery and crockery. This evidence supports the move in many neurorehabilitation settings to set up the treatment environment to reflect the usual home and/or community environment. Some may also refer to this as enriching the environment [28, 80].

**Strategy 2**

*Task-specific training practice sequences should be Randomly ordered*: Task variability has been identified as important to increasing “generalisation of learning to new tasks” [81](p.85). Further, evidence indicates that utilizing randomly ordered practice facilitates retention and transfer, thus increasing the task’s generalizability [4]. Task-specific therapy, therefore, should be random in its application, using differing contexts and settings and differing occupational demands and sequences [7, 25, 30, 80]. If task-specific training is too task- or movement-specific and applied in only one context or sequence, then potentially the skills re-learnt or learnt are not as readily applied across similar tasks and alternative settings. Clearly, there are times when this is neither practical nor feasible, e.g. showering, but for the most part, where possible, therapists should randomly schedule therapy routines and task selection.
Strategy 3

Task-specific training should be Repetitive: Task-specific training should be repetitive and involve massed practice [3, 4]. The old adage of “practice makes perfect” applies in this context, as it is practice which assists the healthy and injured brain alike to master skills and to reorganise to accommodate the new learning. Most researchers [47] and commentators [7, 78] recommend that the more a task is practiced, the better the overall performance. However, Page [83] suggests that task specificity is clinically more significant than intensity, and recommends that task-specific training is still worth considering even if patients are not able to manage high-intensity treatment regimes.

Bearing in mind that for much of the day, patients in hospital are frequently doing very little [84, 85], therapists should assume that more is better and that most patients are not practicing enough. It is recommended that the maximum amount of repetition feasible should be prescribed in task-specific, neuromotor interventions and that the task-specific environment should be as occupationally demanding as possible [28], with every opportunity afforded to patients to practice real-world tasks [30].

Strategy 4

Task-specific training should aim towards Reconstruction of the whole task: When formulating a treatment plan, a therapist will:

1. Deconstruct a task into its component parts
2. Assess the patient’s performance of the whole task and of its component parts
3. Identify which skills and/or component parts are adversely affected and why
4. Formulate a treatment plan targeted at the mismatch between “can do” and “need/want to do”.

Task-specific training should start with skill acquisition and massed practice of the individual component parts (shaping) [52], moving towards the re-grouping and normal sequencing of some, most and, if feasible, eventually all of the component parts. However, in the midst of all the planning, prescribing, goal-setting, documenting and discharge planning, the achieving of whole tasks may become lost in the day-to-day activity of the
neurorehabilitation setting. Nevertheless, the overriding goal should be the reconstruction of the whole task to maintain focus and motivation.

The evidence suggests that it is unwise to simply prescribe a series of self-directed upper limb exercises, with an increasing dose of practice which, although seemingly advantageous, bears no relationship to the mastering of a task that is important to the patient. If the patient’s interest and motivation are to be maintained, task-specific interventions should be in the context of eventual mastery of a whole task that has been identified as relevant. Further, interventions should include complex tasks as a means of involving more regions of the brain in the reorganization response [77, 78, 80, 81].

**Strategy 5**

*Task-specific training should be positively Reinforced:* The evidence indicates that task-specific therapy should include timely and positive feedback, but that all rewards should fade over time to prevent unnecessary dependency [25, 78, 80, 86]. Therapists can enhance the feedback environment by using commentary and positive encouragement. However, this augmented reinforcement or artificial feedback should “fade” over the duration of a task, session and admission as it is potentially maladaptive. Dobkin and Carmichael [25] recommend that this feedback is always positive.

The five strategies arise out of the task-specific evidence and expert commentary. Again, much of this may not be new to readers, but may provide evidence to support practices already applied. However, there is some evidence that the inpatient setting in particular can raise competing agendas for therapists [87], and these strategies may serve to refocus the efforts of therapists in their prescription of neuromotor interventions.

### 6.8 Implications

The evidence related to task-specific training has direct application to occupational therapy practice and resonates with the theory and ideology associated with occupational science [88] and occupational therapy. The strategies are steeped in long-held, professional values concerning client-centred practice and the importance of involving the patient/client in goal setting and rehabilitation agendas [89]. However, whilst the premise of occupation and our approach to learning new motor skills is highly consistent with task-specific training, it is
not a term that is commonly used by occupational therapists. Further, despite the growing evidence for task-specific training, rehabilitation is commonly based instead on accepted practice or custom. The theoretical and empirical foundations for task-specific training, derived from research on brain plasticity and motor learning, provide a strong, evidence-based platform for occupational therapists to confidently select neuromotor interventions which involve task-specific training and everyday tasks and activities.
6.9 References


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Chapter 7: Generating New Knowledge
7.1 Summary of Thesis Findings

This thesis comprises four studies that have generated new knowledge that is specific to right-handed patients who have been diagnosed with an acute, first ischaemic stroke which has left them with an adversely affected upper limb (UL). This knowledge is relevant to clinicians assessing UL recovery and prescribing UL interventions.

The literature review (Chapter 2) demonstrated that changes in brain activation associated with UL recovery are detectable even in the first few days post-stroke. They are primarily in ipsilesional sensorimotor-related regions such as the supplementary motor area. This review also found that, when compared with those who experienced poor UL recovery, those who experienced good recovery had greater brain activation in the ipsilesional primary sensorimotor, supplementary motor and cingulate areas. However, more than 95% of the studies investigating associations between changes in brain activation, UL function and UL interventions recruited participants in the chronic phase post-stroke. The interventions shown to improve UL function and influence brain activation included repetitive task-specific training and constraint-based therapy.

The review established the rationale for the first study, which was a randomised controlled trial (Chapter 3) investigating the impact of intensive, task-specific UL training in the first month post-stroke. This study is the first to provide high-level evidence of an association between intensive, task-specific UL training and greater brain activation over time in the ipsilesional anterior cingulate and supplementary motor areas, and a reduction in activation over time in the contralesional cerebellum. This study also demonstrated an association between more intensive UL training and more consistent UL recovery. The primary significance of the new knowledge that this study generated is that it applies to a cohort of patients who are less than 3 months post-stroke. A future direction for this research would be to analyse the investigation’s structural data acquired during the investigation. This is very important for clinical practice, as this is the time when most recovery is anticipated, and the time when most patients are receiving UL rehabilitation.

The second study (Chapter 4) in this thesis investigated the differences between subgroups of participants recruited into the randomised controlled trial. The two sets of cohorts investigated were those who experienced good and poor UL recovery, and those
diagnosed with subcortical and cortical stroke. Although the study showed no differences between those diagnosed with subcortical and cortical stroke, it demonstrated that in the first 3 months post-event, when compared with those who experienced poor recovery, those with good UL recovery had more activation in the ipsilesional inferior parietal lobe, supplementary motor area and Brodmann Area (BA) 44, and reduced activation in the contralesional primary sensorimotor area. This is the first study to demonstrate an association between good UL recovery and the ipsilesional BA44. To find that regions like BA44 and the inferior parietal lobe are associated with improved UL recovery suggests that, in the first few weeks post-stroke, the brain utilises regions known to support communication, attention and problem-solving. This provides theoretical evidence that a multi-sensory [1] or multi-modal approach may be more effective in maximising UL recovery post-stroke than the current recommended, task-specific approach.

Understanding the contribution of different regions of the brain will potentially guide and direct clinicians prescribing and applying interventions to patients with recent stroke.

The third study in this thesis (Chapter 5) compared five assessments that are often used to measure recovery in patients with a stroke-affected UL. Two were global measures, and three were UL-specific measures. This is the first study to demonstrate a correlation between global and UL-specific assessments. In relation to the latter, the high correlation found in the first 3 months post-stroke between the Action Research Arm test and the UL component of the Motor Assessment Scale indicates that there is no reason to use both assessments when measuring recovery in patients with a recent stroke. It is recommended that clinicians use standardised assessments to accurately measure recovery [2]. All five measures are standardised and can be used to assess outcomes in patients with an adversely affected UL.

Currently, it is recommended that clinicians apply a task-specific approach to UL recovery in nationally-agreed, clinical guidelines [2]. As part of this thesis, a review of the evidence related to UL intervention was published in 2009 [3] (Chapter 6). This publication, which has been cited by many, included practice-driven strategies. However, as a result of the new knowledge generated by this thesis, the authors recommend that clinicians consider approaches that place a greater focus on the brain and, in turn, a greater focus on
interventions that drive neuroplasticity. The second section of this chapter (7.4-7.9) presents this argument in more detail.

7.2 Future Implications

Those who have used functional magnetic resonance imaging in stroke recovery studies will know that this type of research has some unique challenges, particularly in relation to recruiting patients in the first few days and weeks post-stroke [4, 5]. This thesis includes the first study [6] to use a randomised controlled trial design to image 23 patients during their acute and sub-acute recovery. However, if more knowledge is to be generated about the patterns of UL recovery and their associations with the brain’s reorganisational response, more research is required in the first month post-stroke, because this is the time when most patients experience the most improvement.

Research is also required to better define a “good” reorganisational response [7-10] and, in turn, to identify which UL interventions elicit that response [5]. To prove clinical benefit, studies investigating UL interventions must apply a randomised controlled trial design. However, researching patients in the first month post-stroke brings some unique design challenges, for example, the challenge of demonstrating significant differences in outcomes in a cohort who are known to be experiencing natural recovery, and the challenge of using a control group who, for ethical reasons, are receiving standard care. Despite this, generating evidence in a cohort who have recently experienced a stroke is very important to clinicians who are seeking to prescribe individualised treatment regimes that are evidence-based and known to drive brain reorganisation.

The new knowledge that this thesis has generated indicates that in those with a recent, stroke-affected UL, the sensorimotor regions in the ipsilesional hemisphere, which have been spared from the impact of the stroke, are important to UL recovery [4, 5]. In addition, it provides evidence that in the first 3 months post-stroke, other regions, such as the ipsilesional cingulate and inferior parietal areas, and Brodmann area 44, are also important to UL recovery [4, 5]. These regions may be recruited because they provide a connection between the cortex and the cerebellum [11] and are known for their involvement in attention, error detection and problem-solving [12]. The brain’s natural ability to reorganise is fundamental to UL recovery in the first few weeks post-stroke. This thesis has made an
important contribution to the understanding of ongoing potential for UL recovery. It has also informed the post-stroke approaches and strategies that should be prescribed and applied by clinicians.

7.3 Reorganising Therapy

This thesis provides impetus to the future consideration of the fact that stroke is a brain-based problem that requires a brain-based solution, and one that drives a neuroplastic, reorganisational response. In turn, this challenges the current focus of the assessments, interventions and approaches selected in the standard care of those with a stroke-affected UL. Whereas in the past, to maximise UL recovery, the focus has been on the arm and hand, in the future the focus must switch to what is happening in the brain [13]. This shift has important translational relevance to clinicians and, more particularly, to therapists. The remaining section of this chapter is a pre-peer-reviewed version of the following article: Hubbard IJ, Carey LM, Budd TW, Parsons MW. Reorganizing therapy: Changing the clinical approach to upper limb recovery post-stroke. Occupational Therapy International, 2015. 22(1): p. 28-35, which has been published in final form at http://onlinelibrary.wiley.com/doi/10.1002/oti.1381/abstract.
7.4 Abstract

Stroke is the leading cause of adult disability and, as a consequence, most therapists will provide health care to patients with stroke during their professional careers. An increasing number of studies are investigating the association between upper limb recovery and changes in brain activation patterns following stroke. In this paper we explore the translational implications of this research for health professionals working in stroke recovery. We argue that in light of the most recent evidence, therapists should consider how best to take full advantage of the brain’s natural ability to reorganise, when prescribing and applying interventions to those with a stroke-affected upper limb.

The authors propose that stroke is a brain-based or “upstairs” problem that needs a brain-based or “upstairs” solution. This paper addresses three topics: anticipating recovery, maximising recovery and predicting recovery. It proposes five practice-ready recommendations that are based on the evidence reviewed. The over-riding aim of this review and discussion is to challenge therapists to reconsider the health care they prescribe and apply to people with a stroke-affected upper limb.
7.5 Introduction

Stroke is the leading cause of adult disability, and as a consequence, most therapists will provide health care to patients with stroke during their professional careers. An increasing number of studies have investigated associations between upper limb (UL) recovery and changes in brain activation post-stroke [4, 5, 14-16]. Evidence indicates that the mechanisms supporting the brain’s learning processes are recruitment (reorganisation) of spared regions [17] and growth of new nerve cells (neurogenesis) [18]. Both processes, when combined, define what is now referred to as neuroplasticity [13, 19]. Whether or not neurogenesis can occur in the adult is as yet unclear, but sprouting of the axons from pre-existing neurons is possible. This, and similar types of structural plasticity, such as synaptogenesis and change in glial cells, are likely to be more widespread mechanisms underlying recovery than brain reorganisation alone [18]. In this paper, the authors will focus on the capacity of the brain to reorganise regions that support particular functions, and seek to answer the following question as reviewers of the evidence, researchers in the field and academic educators: What are the translational implications of this research for therapists working in stroke recovery?

Stroke is an “upstairs” or brain-based problem that needs an “upstairs” or brain-based solution. To apply an evidence-based approach in our management of patients with a stroke-affected UL, we must be conversant with the research-generated knowledge and be able to evaluate its influence on clinical practice [20]. Applying an evidence-based approach means that we use scientific principles in our clinical decision-making, including our selection of stroke recovery assessments [21, 22], interventions [23, 24] and strategies [3]. This approach requires us to continually translate new knowledge that has been generated by research, into everyday clinical practice. This review will make practice-ready recommendations for therapists prescribing and applying health care to people with a stroke-affected UL.

7.6 Anticipating Recovery

In the past 15 years, evidence has demonstrated that the human brain has a natural and life-long capacity to reorganise in response to changes in behavioural demands [13, 25, 26]. Whereas just over a decade ago, therapists believed that the adult brain was relatively
static, we now know this to be entirely untrue. Therefore, as a result of this evidence, we should anticipate some recovery in most people diagnosed with stroke. Not only should this be our expectation in the acute and sub-acute phases post-stroke, it should also be our expectation in the chronic phase post-stroke [14, 27]. This is an excellent example of how new knowledge can challenge long-held beliefs, and it reinforces the benefits of applying a scientifically rigorous and evidence-based approach to health care [28]. As Hankey [29] stated, fortunately the days of “ignorance, nihilism and negativity” (Preface) in stroke are fast disappearing.

In healthy adults, Elbert et al [30] demonstrated that as a person learned to play the violin, the cortical representation of the non-dominant hand (the hand that takes the lead role in violin playing) increased over the learning period. Following stroke, evidence indicates that the non-lesioned areas of the brain, or those that have been “spared” from the impact of the stroke and are therefore still essentially healthy, reorganise [4, 5]. This reorganisation capacity is the theoretical mechanism supporting acute, sub-acute and long-term recovery [31], and the basis on which we argue that therapists should anticipate recovery in most people with a stroke-affected UL. The brain’s natural ability gives new hope and impetus to therapists and stroke survivors alike.

Rather than assessing and managing stroke as a body-based, or “downstairs” problem, management should be focussed on what is happening in the brain or “upstairs”. Thrombolysis is a contemporary example of an “upstairs” solution. It aims to salvage viable brain networks in the hyper-acute phase post-stroke [32], and, to validate its evidence-based credentials, it has been scientifically tested so that the right dose is prescribed to the right patient, at the right time and in the right way. This “upstairs” approach should also be applied to post-stroke rehabilitation with the same scientific rigour. On the basis of the evidence related to brain activation patterns post-stroke, the interventions being prescribed and applied to people recovering from stroke should take full advantage of their influence on the brain [33, 34]. Novel examples include imagery [35], mirror therapy [36] and SENSE [37] (a clinically proven approach to recovery of sensation post-stroke). Today’s stroke rehabilitation should focus on challenging the brain’s capacity to learn new ways of achieving already-familiar tasks.
The research investigating brain activation indicates that the patterns associated with recovery of a stroke-affected UL primarily involve the recruitment of two types of regions [4, 14, 38]. The first are perilesional; this term refers to regions of the brain that are directly adjacent to the area permanently damaged by the stroke. The second are “spared” regions; this term refers to regions that have been spared from the impact of the stroke and includes, but is not limited to, perilesional regions. In relation to UL recovery, these regions are often supplementary or secondary regions which, prior to the stroke, were not as actively involved in the UL task and/or behaviour, for example, the ipsilesional (same side as the lesion) supplementary motor area and premotor cortex [4, 5, 14]. What is interesting is that in the first month post-stroke, other regions often recruited include the ipsilesional anterior cingulate area and the bilateral cerebellum [39, 40]. This suggests that in the first few weeks post-stroke, the restoration of UL function needs additional support from regions more closely related to attention, learning and error detection [41-43].

**Recommendation 1: Anticipating recovery**

*In most patients with a stroke-affected UL, therapists should anticipate recovery and default to restorative strategies that seek to apply an “upstairs” approach which purposefully targets the brain’s natural ability to reorganise.*

The fact that the brain reorganises throughout a person’s lifetime demonstrates an ongoing potential for people to recover from stroke. There is compelling evidence that many stroke survivors can experience improvement months, and even years, post-event [14, 23, 44]. As Carey and Seitz [31] point out, different mechanisms underlie recovery at different phases post-stroke. In the hyperacute phase there is potential for recovery that is based on early reperfusion [45], but following this, most recovery relates to brain reorganisation or neuroplasticity [14, 31, 46]. Whilst there is more potential to experience recovery in the first few weeks post-stroke [31], in the chronic phase the evidence indicates that recovery is still possible in those who engage in targeted programs of behavioural UL training [14, 15]. On the basis of this evidence, we recommend that people with stroke be offered ongoing access to “Booster Clinics” that aim to improve, or at least maintain, long-term function, cardiovascular health and a sense of well-being [47]. We base this on the notions that firstly, the brain’s ability to reorganise is not dependent on just
the early weeks post-stroke, and secondly, the compelling evidence of recovery potential from the chronic, post-stroke literature. This could also overcome the sense of abandonment by health services, that patients can experience following discharge from hospital after a stroke [48]. In contrast to the long-term structure of chronic cardiac rehabilitation programs, however, the evidence indicates that patients in the chronic phase post-stroke would benefit more from short bursts of intensive, recovery initiatives which target tasks that are of interest to the patient and use “upstairs” approaches that are based on motivated learning [14, 49].

Recommendation 2: Ongoing recovery

*During their survival years, people with a stroke-affected UL, who are able to comply, should be offered the opportunity to attend “Booster Clinics” that use an intensive, repetitive, task-specific approach that is based on motivated learning.*

Anticipating recovery in most people with a stroke-affected UL must be followed up with strategies aimed at using the evidence of adaptive reorganisation of the brain. This will inform strategies aimed at maximising recovery in people with a stroke-affected UL and, in turn, inform our hypotheses about who is most likely to benefit.

### 7.7 Maximising Recovery

Current evidence indicates that to maximise recovery of a stroke-affected UL, therapists should apply intensive, repetitive task-specific training [14, 23], using everyday tasks that are meaningful and already familiar to the person with stroke [3]. However, the evidence indicates that there are significant challenges to applying an adequate intensity of UL intervention [50]. For the purposes of this paper, we define intensity as the amount of time patients with a stroke-affected UL are actively engaged in everyday activities at a level that will drive neuroplastic changes. The issue of intensity post-stroke has two distinct lines of emerging evidence; one line is “hot”, indicating that intensity matters, whilst the other line is “cold”, indicating that patients in hospital with stroke are often inactive. Our ability to overcome this hot/cold clinical dilemma is crucial to maximising UL recovery post-stroke.
The “hot” evidence

This evidence indicates that to maximise recovery, patients with stroke should engage in intensive, task-specific programs as early as possible post-event [13], as recommended in nationally-agreed clinical guidelines [51]. In our randomised controlled trial, patients in the intensive-training group, who were within one month of experiencing a first ischaemic stroke, all complied with the demands of a combined program of standard care and an additional two hours of intensive, task-specific UL training, for 5 days a week over 3 weeks [6]. We found this intensity to be clinically feasible and safe, on the basis that no participants withdrew, and no adverse events were recorded. All those in the intensive-training group were compliant with what some therapists may perceive as a fairly demanding UL regime for patients so soon after a stroke. Perhaps this is one of the problems; as therapists we may need to re-think our perceptions about what is “too demanding”, if we are to adhere to nationally-agreed clinical recommendations concerning intensity. Additionally, studies that have increased the intensity of early intervention post-stroke, including our own, rarely report adverse events related to post-stroke fatigue [23, 52, 53]. In our experience, fatigue is an issue that is often raised as a potential barrier when therapists discuss increasing the early intensity of training. We may need to challenge long-held assumptions about the impediment of post-stroke fatigue to early intervention. As therapists, our perceptions, beliefs and concerns may hinder our ability to bridge the evidence-practice gap [13, 51, 54].

Recommendation 3: Maximising intensity

In patients with a stroke-affected UL, strategies should be set in place that increase the intensity of UL behavioural training to at least 2 hours a day, 5 days a week for 3 weeks during the first month post-event.

The “cold” evidence

Whilst calls are made to increase the intensity of task-specific training, evidence is revealing that patients are doing very little in hospital [55, 56], which brings us to the “cold” line of evidence. It seems that the average hospital ward admitting patients with stroke is environmentally bereft and occupationally non-challenging [57]. This evidence is not only cold, but grim, if one adds issues such as a traditional reliance by most therapists on
individual face-to-face sessions [56] and “risk averse” protocols to patients mobilising around the ward [58]. All indications are that patients with stroke are often cared for in environments that actively discourage high levels of participation in everyday tasks. Could it be that today’s average hospital ward is contraindicated for patients recovering from stroke?

We believe this hot/cold clinical dilemma is currently the most pressing problem for those working to maximise recovery in patients with stroke. Unless it is resolved, these patients may not be able to achieve maximal UL recovery in the first month post-stroke, irrespective of the brain’s ability to reorganise.

Recommendation 4: Structuring the environment

*In patients with a stroke-affected UL, therapists should consider programs where the patients’ environment is structured in a way that stimulates them to participate in everyday tasks at a level and an intensity that is aimed at maximising recovery.*

A multi-modal approach

Maximising recovery is the “core business” of therapists who provide health care to people with a stroke-affected UL. In applying a task-specific approach, the evidence related to brain reorganisation post-stroke indicates that consideration must also be given to the fact that these tasks are now more complex [59, 60] and may require the brain to recruit regions that were not previously as engaged in undertaking the task, prior to the stroke. With this in mind, the authors propose that therapists apply strategies that purposefully build upon the task-specific approach [23] (Figure 7.1). An approach that targets brain reorganisation by value-adding to repetitive, task-specific training will be referred to as a “multi-modal” approach [1]. Some example of strategies that fall under a “multi-modal” approach include those that aim to prime the brain [37, 61], those that include mental practice [62] and those that aim to overcome problems specific to UL recovery, for example, overcoming learned non-use by applying constraint-based interventions [27, 63]. A multi-modal approach is recommended on the basis that it seeks to apply an “upstairs” solution to stroke recovery that drives the brain to use its natural ability to reorganise in response to changes in behavioural demands.
Figure 7.1: Graphic depicting a potential hierarchy of restorative approaches in post-stroke rehabilitation that target recovery of an affected upper limb

Recommendation 5: Applying multi-modal strategies

Therapists prescribing and applying health care to people with a stroke-affected UL should consider strategies that apply a multi-modal approach that seeks to take full advantage of the brain’s natural ability to reorganise.

7.8 Predicting Recovery

Our approaches to maximising recovery in people with a stroke-affected UL must be underpinned by an evidence-based approach to accurate prediction of those who are most likely to benefit from these approaches. If a patient has a stroke-affected UL, the standard pathway of care is a rehabilitation program that usually includes occupational therapy and physiotherapy [24]. However, with the increased pressure on health resources, therapists are often required to prioritise patient care, and this can be based on their prediction of whether or not a patient is likely to recover and/or go home [56]. Therefore, accurately
assessing and predicting recovery is a very important skill that therapists must master if they are to provide appropriate health care to those with a stroke-affected UL [64, 65]. Studies that use neuroimaging have made, and will continue to make, an important, evidence-based contribution to the matrix that therapists use to hypothesise a patient's recovery potential [66, 67].

Researchers are beginning to test algorithms that will assist therapists to apply an evidence-based approach in their recovery predictions and clinical prioritisation [64, 68]. Increasingly, studies investigating brain reorganisation are reporting differences between those who experience “good” recovery and those who experience “poor” recovery [7, 8, 69]. This research is making an important contribution to a standardised approach to assessing and predicting recovery post-stroke, and to a scientifically-based understanding of the mechanisms that support recovery.

Once recovery algorithms have been shown to demonstrate predictive validity in patients with a recent stroke, then recovery strategies can be more individually targeted. For example, future evidence may demonstrate that therapists providing health care to those who are predicted to experience very good recovery may only need to provide the patient and their family and/or carers with written information on the most effective strategies for maximising UL recovery post-stroke and access to ongoing review of a patient’s progress. For those who are predicted to experience very poor recovery, utilising compensatory strategies may be the most efficient approach. This would then allow therapists to allocate their time to those most likely to benefit from interventions that apply restorative approaches to UL recovery post-stroke. However, more research is required to test all such post-stroke recovery algorithms and prioritisation strategies.

**Recommendation 5: Predicting recovery**

_When therapists prioritise patient care on the basis of predicted recovery, consideration should be given to assessing and hypothesising recovery in patients with a stroke-affected UL, on the basis of the best available evidence._
7.9 Conclusion

Stroke is an “upstairs” problem that needs an “upstairs” solution. Following stroke, it is time to reconsider the evidence related to anticipating recovery, maximising recovery and predicting recovery, and time to reorganise how this is best applied in clinical practice. It is time to consider strategies that aim to ensure that the rehabilitation prescribed meets the intensity requirements of an effective task-specific approach. It is time to consider strategies and approaches that take full advantage of the brain’s natural ability to reorganise throughout a person’s lifetime.
7.10 References


APPENDICES
Appendix for Chapter 2
### Appendix 2.1: Non-intervention studies of subjects more than 1 month post-stroke

<table>
<thead>
<tr>
<th>Research</th>
<th>n</th>
<th>Baseline post-stroke</th>
<th>Stroke sub-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bestmann et al [64]</td>
<td>12</td>
<td>28.3 months</td>
<td>Cortical and subcortical, first ischaemic</td>
</tr>
<tr>
<td>Calautti et al [65]</td>
<td>9</td>
<td>&gt;36 days</td>
<td>Subcortical (n=16)</td>
</tr>
<tr>
<td>Cramer et al [66]</td>
<td>10</td>
<td>6.1 months</td>
<td>Cortical and subcortical, first ischaemic</td>
</tr>
<tr>
<td>Cramer et al [67]</td>
<td>11</td>
<td>Chronic phase</td>
<td>Spared M1</td>
</tr>
<tr>
<td>Feydy et al [39]</td>
<td>14</td>
<td>1.5 months</td>
<td>Cortical and subcortical, first ischaemic</td>
</tr>
<tr>
<td>Hanlon et al [49]</td>
<td>7</td>
<td>30–60 days</td>
<td>Cortical, first stroke, spared M1</td>
</tr>
<tr>
<td>Kimberley et al [68]</td>
<td>10</td>
<td>52.7 months</td>
<td>No active UL movement</td>
</tr>
<tr>
<td>Kokotilo et al [20]</td>
<td>10</td>
<td>6 months</td>
<td>Subcortical</td>
</tr>
<tr>
<td>Newton et al [69]</td>
<td>3</td>
<td>Mean 292.6 days</td>
<td>Cortical and subcortical, first ischaemic</td>
</tr>
<tr>
<td>Pineiro et al [70]</td>
<td>8</td>
<td>208 days</td>
<td>Subcortical, first ischaemic</td>
</tr>
<tr>
<td>Pineiro et al [71]</td>
<td>12</td>
<td>Mean 149 days</td>
<td>Subcortical, first ischaemic</td>
</tr>
<tr>
<td>Riecker et al [72]</td>
<td>8</td>
<td>Chronic phase</td>
<td>Subcortical, first ischaemic</td>
</tr>
<tr>
<td>Sharma et al [73]</td>
<td>20</td>
<td>171 days</td>
<td>Subcortical, first stroke</td>
</tr>
<tr>
<td>Schaechter et al [77]</td>
<td>9</td>
<td>3.3 years</td>
<td>First ischaemic, left hemispheric stroke</td>
</tr>
<tr>
<td>Small et al [74]</td>
<td>12</td>
<td>&lt;44 days</td>
<td>Cortical and subcortical</td>
</tr>
</tbody>
</table>
Appendices for Chapter 3
Appendix 3.1: Participants’ stroke locations

Using data from the diffusion-weighted images, Figures 1 to 23 each show sagittal, coronal and axial slices that include sections of each participant's lesions.

Figure 1: Participant 1

Figure 2: Participant 2

Figure 3: Participant 3
Figure 4: Participant 4

Figure 5: Participant 5

Figure 6: Participant 6
Figure 7: Participant 7

Figure 8: Participant 8

Figure 9: Participant 9
Figure 10: Participant 10

Figure 11: Participant 11

Figure 12: Participant 12
Figure 13: Participant 13

Figure 14: Participant 14

Figure 15: Participant 15
Figure 19: Participant 19

Figure 20: Participant 20

Figure 21: Participant 21
Figure 22: Participant 22

Figure 23: Participant 23
Appendix 3.2: Characteristics of standard care over the 12-month period preceding this study

<table>
<thead>
<tr>
<th>Characteristic (mean per patient)</th>
<th>Length of stay</th>
<th>Occasions of service</th>
<th>Time per session</th>
<th>Individual contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute stroke: Occupational Therapy</td>
<td>12 days</td>
<td>6</td>
<td>33 mins</td>
<td>90%</td>
</tr>
<tr>
<td>Acute stroke: Physiotherapy</td>
<td>11 days</td>
<td>6</td>
<td>30 mins</td>
<td>98%</td>
</tr>
<tr>
<td>Stroke rehabilitation: Occupational Therapy</td>
<td>31 days</td>
<td>14</td>
<td>42 mins</td>
<td>97%</td>
</tr>
<tr>
<td>Stroke rehabilitation: Physiotherapy</td>
<td>32 days</td>
<td>20</td>
<td>38 mins</td>
<td>99%</td>
</tr>
</tbody>
</table>
Appendix 3.3: Findings related to within-session movement

Table 2: Difference (95% CI) across all three sessions between the standard care group and the intensive-training group and associated *p*-value

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean difference (95% CI)</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard care relative to intensive-training</td>
<td></td>
</tr>
<tr>
<td>Affected UL x</td>
<td>0.0055 (-0.0124 to 0.0233)</td>
<td>0.5483</td>
</tr>
<tr>
<td>Affected UL y</td>
<td>0.0156 (-0.0195 to 0.0507)</td>
<td>0.3832</td>
</tr>
<tr>
<td>Affected UL z</td>
<td>0.0250 (-0.0176 to 0.0676)</td>
<td>0.2506</td>
</tr>
<tr>
<td>Unaffected UL x</td>
<td>0.0003 (-0.0003 to 0.0008)</td>
<td>0.3444</td>
</tr>
<tr>
<td>Unaffected UL y</td>
<td>0.0006 (-0.0002 to 0.0014)</td>
<td>0.1505</td>
</tr>
<tr>
<td>Unaffected UL z</td>
<td>0.0001 (-0.0001 to 0.0003)</td>
<td>0.3960</td>
</tr>
</tbody>
</table>

Table 3: Difference (95% CI) subgroups (of the whole population) and associated *p*-value

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Mean difference (95% CI)</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard care relative to intensive-training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Session</td>
<td>1</td>
<td>0.0076 (0.0017 to 0.0136)</td>
<td>0.0120</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.0037 (-0.0041 to 0.0115)</td>
<td>0.3542</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Side</td>
<td>Affected UL</td>
<td>0.0856 (0.0705 to 0.1007)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Unaffected UL</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Standard care</td>
<td>0.0001 (-0.0001 to 0.0003)</td>
<td>0.3960</td>
</tr>
<tr>
<td></td>
<td>Intensive-training</td>
<td>Referent</td>
<td></td>
</tr>
</tbody>
</table>
Figures 1-23: Comparison of each participant’s EPI and T1 images
The symmetrical template and the “check registration” facility in SPM5 have been used to create the images shown below. For each participant, the first three images show the sagittal, coronal and axial slices on the symmetrical template; the second three show the mean EPI sagittal, coronal and axial images across all three sessions, and the final three show the mean T1 sagittal, coronal and axial slices images across all three sessions.

Figure 2: Participant 1

Figure 3: Participant 2
Figure 4: Participant 3

Figure 5: Participant 4

Figure 6: Participant 5
Figure 7: Participant 6

Figure 8: Participant 7

Figure 9: Participant 8
Figure 10: Participant 9

Figure 11: Participant 10

Figure 12: Participant 11
Figure 13: Participant 12

Figure 14: Participant 13

Figure 15: Participant 14
Figure 19: Participant 18

Figure 20: Participant 19

Figure 21: Participant 20
Figure 22: Participant 21

Figure 23: Participant 22

Figure 24: Participant 23
Appendix 3.4: Findings for rigour of the finger-tapping task

The figures provide evidence demonstrating the rigour of the finger-tapping task, with the uncorrected $p=0.001$ and the cluster threshold set at zero. (These findings include data from a left-handed patient whose data were not included in the study.)

Figure 25: Left and right finger-tapping > rest across all time points

Figure 26: Left and right finger-tapping > rest at 1 week
Figure 27: Left and Right Finger-tapping > rest at 1 month

Figure 28: Left and right finger-tapping > rest at 3 months
### Appendix 3.5: Results from between-group variability in motor function of the affected upper limb using Levene’s robust test

<table>
<thead>
<tr>
<th>Time post-stroke</th>
<th>Result</th>
<th>( w_0 )</th>
<th>( w_{50} )</th>
<th>( w_{10} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>No difference</td>
<td>( w_0=0.971, \text{Pr}&gt;F=0.336 )</td>
<td>( w_{50}=0.362, \text{Pr}&gt;F=0.554 )</td>
<td>( w_{10}=1.650, \text{Pr}&gt;F=0.213 )</td>
</tr>
<tr>
<td>1 month</td>
<td>Less variable in the intensive-training group</td>
<td>( w_0=6.776, \text{Pr}&gt;F=0.0166 )</td>
<td>( w_{50}=3.086, \text{Pr}&gt;F=0.094 )</td>
<td>( w_{10}=4.857, \text{Pr}&gt;F=0.039 )</td>
</tr>
<tr>
<td>3 months</td>
<td>Less variable in the intensive-training group</td>
<td>( w_0=9.244, \text{Pr}&gt;F=0.006 )</td>
<td>( w_{50}=2.184, \text{Pr}&gt;F=0.154 )</td>
<td>( w_{10}=5.176, \text{Pr}&gt;F=0.033 )</td>
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## Appendix 3.6: Participants' characteristics and clinical scores at 1 week, 1 month and 3 months post-stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>Age</th>
<th>Lesioned hemisphere</th>
<th>1 week post-stroke</th>
<th>1 month post-stroke</th>
<th>Positive shift in UL–MAS in the first month</th>
<th>3 months post-stroke</th>
<th>Positive shift in UL–MAS in first 3 months</th>
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<tr>
<td>SC</td>
<td>M</td>
<td>83</td>
<td>R</td>
<td>2</td>
<td>14</td>
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<td>2</td>
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<td>1</td>
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<tr>
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<td>2</td>
<td>14</td>
<td>4</td>
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<tr>
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<td>F</td>
<td>69</td>
<td>R</td>
<td>4</td>
<td>7</td>
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<td>16</td>
<td>9</td>
</tr>
<tr>
<td>SC</td>
<td>F</td>
<td>69</td>
<td>L</td>
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<td>12</td>
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<td>16</td>
<td>4</td>
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<td>F</td>
<td>47</td>
<td>R</td>
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<td>M</td>
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<td>5</td>
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<td>17</td>
<td>12</td>
</tr>
<tr>
<td>IT</td>
<td>M</td>
<td>72</td>
<td>L</td>
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<td>16</td>
<td>2</td>
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<td>R</td>
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<td>IT</td>
<td>F</td>
<td>37</td>
<td>L</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

**Key:** SC=standard care; IT=intensive-training; mRS=modified Rankin score; UL–MAS=upper limb component of the Motor Assessment Scale
Appendices for Chapter 4
Appendix 4.1: Non-significant results for good recovery versus poor recovery

These results display the clusters of brain activity associated with the stroke-affected upper limb. They compare results between finger-tapping versus rest, and between those who experienced good and poor recovery. For Figures 4.1 to 4.3, a small-volume correction used a combined region of interest that included the bilateral inferior parietal lobe, cingulate area, primary motor area and Brodmann Area (BA) 6.
Figure 4.1: Sagittal, coronal and axial slices showing clusters of whole-brain activation significantly greater in the good recovery cohort when compared with the poor recovery cohort at 3 months post-stroke. The SPM t-images are displayed at a voxel-wise significance threshold of $p<0.001$ uncorrected and a family-wise error cluster threshold at $p<0.05$. Data have not been smoothed.
Figure 4.2: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the good-recovery cohort when compared with the poor-recovery cohort at 1 week post-stroke. The SPM t-images are displayed following a small-volume correction and at a voxel-wise significance threshold of $p<0.005$ uncorrected and a family-wise error cluster threshold at $p<0.05$. 

### Table 4.2: Statistical results

<table>
<thead>
<tr>
<th>set-level</th>
<th>cluster-level</th>
<th>voxel-level</th>
<th>$T$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>$c$</td>
<td>$\rho_{\text{corrected}}$</td>
<td>$k_E$</td>
<td>$\rho_{\text{uncorrected}}$</td>
</tr>
<tr>
<td>0.4226</td>
<td>0.986</td>
<td>0.960</td>
<td>0.936</td>
<td>0.960</td>
</tr>
<tr>
<td>0.500</td>
<td>0.930</td>
<td>0.916</td>
<td>0.918</td>
<td>0.918</td>
</tr>
<tr>
<td>0.666</td>
<td>0.931</td>
<td>0.918</td>
<td>0.918</td>
<td>0.918</td>
</tr>
<tr>
<td>0.833</td>
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<td>0.920</td>
<td>0.924</td>
<td>0.924</td>
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<tr>
<td>1.000</td>
<td>0.906</td>
<td>0.920</td>
<td>0.993</td>
<td>0.993</td>
</tr>
</tbody>
</table>

Table shows 16 local maxima more than 4.00 mm apart.

- **Height threshold** $T = 2.23$, $p = 0.005 (0.955)$ ($p<0.005$ (degrees of freedom = 10, 21.9))
- **Extent threshold** $k = 0$ voxels, $p = 1.000 (0.995)$
- **False discovery rate** $\alpha = 0.05$
- **Expected voxels per cluster** $d = 14.971$
- **Expected number of clusters** $<\alpha> = 5.22$
- **Voxel size** $3.0 \times 3.0 \times 3.0 \text{ mm}$

Expected false-discovery rate, $\alpha = 0.84$.
Figure 4.3: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the good-recovery cohort when compared with the poor-recovery cohort at 1 month post-stroke. The SPM $t$-images are displayed following a small-volume correction and at a voxel-wise significance threshold of $p<0.005$ uncorrected and a family-wise error cluster threshold at $p<0.05$. 

Table shows: 16 local maxima more than 4.3mm apart.

| Height threshold: $T = 2.83, p = 0.005$ (99.9%) $p<0.005$ (degrees of freedom = [1, 21.0]) |
|---|---|---|---|---|---|---|
| Extent threshold: $k = 0$ voxels, $p = 1000$ (99.9%) |
| Expected voxels per cluster, $k = 17,416$ |
| Expected number of clusters, $k = 4.68$ |
| Expected false discovery rate, $k = 0.39$ |

Volume: 209412 voxels = 52.5 voxels
Voxel size: 3.0 x 3.0 x 3.0 mm mm mm; (resel = 106.54 voxels)
Appendix 4.2: Additional detail on the significant results for good recovery versus poor recovery

The results in Figure 4.4 display the clusters of brain activity associated with the stroke-affected (right) upper limb and comparing results between finger-tapping versus rest, and when comparing those who experienced good recovery to those who experienced poor recovery. The small-volume correction used a combined region of interest that included the bilateral inferior parietal lobe, cingulate area, primary motor area and BA6.
Figure 4.4: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the good-recovery cohort when compared with the poor-recovery cohort at 3 months post-stroke. The SPM t-images are displayed following a small-volume correction and at a voxel-wise significance threshold of $p<0.005$ uncorrected and a family-wise error cluster threshold at $p<0.05$. 

<table>
<thead>
<tr>
<th>statistic</th>
<th>search volume: image mask: \text{\textit{W bilateral CA, IPL, M1, BA6, ml}}</th>
<th>voxel-level</th>
<th>mm mm mm</th>
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</thead>
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<td>$c$</td>
<td>$k_E$</td>
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<tr>
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</tr>
<tr>
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<td>0.000</td>
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<td>0.005 0.006 6.58 4.79 0.000 3 -3 39</td>
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<td>0.000</td>
<td>0.002</td>
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</tr>
<tr>
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<tr>
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<td>0.000</td>
<td>0.002</td>
<td>0.005 0.006 6.58 4.79 0.000 3 -3 39</td>
</tr>
</tbody>
</table>

Table: 16 local maxima more than 4.1 mm apart

Height threshold: $T = 2.33, p = 0.006 (0.997)$; $p<0.005$ (degrees of freedom $= [1.0, 21.0]$)

Extent threshold: $k = 0$ voxels, $p = 1000 (0.997)$

Volume threshold: $V = 15.3, 14.2, 13.9$ mm mm mm; $5.1, 4.9, 4.7$ voxels

Expected number of clusters, $<\phi> = 4.36$

Volume size: $3.0, 3.0, 3.0$ mm mm mm; $<\text{voxels}> = 117.62$ voxels

Expected false discovery rate, $<\text{FDR}> = 0.38$
Appendix 4.3: Non-significant results for subcortical versus cortical stroke

These results are those displaying the clusters of brain activity associated with the stroke-affected upper limb and comparing results between finger-tapping versus rest, and those diagnosed with subcortical versus cortical stroke. For Figures 4.6 to 4.8, a small-volume correction used a combined region of interest that included the bilateral inferior parietal lobe, cingulate area, primary motor area and BA6.
Figure 4.5: Sagittal, coronal and axial slices showing clusters of whole-brain activation significantly greater in the subcortical cohort when compared with the cortical cohort at 3 months post-stroke. The SPM t-images are displayed at a voxel-wise significance threshold of $p < 0.001$ uncorrected and a family-wise error cluster threshold at $p < 0.05$. Data have not been smoothed.
Figure 4.6: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the subcortical cohort when compared with the cortical cohort at 1 week post-stroke. The SPM t-images are displayed following a small-volume correction and at a voxel-wise significance threshold of $p<0.005$ uncorrected and a family-wise error cluster threshold at $p<0.05$. 
Figure 4.7: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the subcortical cohort when compared with the cortical cohort at 1 month post-stroke. The SPM t-images are displayed following a small-volume correction and at a voxel-wise significance threshold of \( p < 0.005 \) uncorrected and a family-wise error cluster threshold at \( p < 0.05 \).
Figure 4.8: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the subcortical cohort when compared with the cortical cohort at 3 months post-stroke. The SPM t-images are displayed following a small-volume correction and at a voxel-wise significance threshold of $p<0.005$ uncorrected and a family-wise error cluster threshold at $p<0.05$. The table shows 16 local maxima more than 4.00 mm apart.
Appendix 4.4 Non-significant results for cortical versus subcortical stroke

These results display the clusters of brain activity associated with the stroke-affected upper limb and comparing results between finger-tapping versus rest, and between those diagnosed with cortical versus subcortical stroke. A small-volume correction used a combined region of interest that included the bilateral inferior parietal lobe, cingulate area, primary motor area and BA6.
Figure 4.9: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the cortical cohort when compared with the subcortical cohort at 1 week post-stroke. The SPM t-images are displayed following a small-volume correction and at a voxel-wise significance threshold of $p<0.005$ uncorrected and a family-wise error cluster threshold at $p<0.05$. 
Figure 4.10: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the cortical cohort when compared with the subcortical cohort at 1 month post-stroke. The SPM t-images are displayed following a small-volume correction and at a voxel-wise significance threshold of \( p < 0.005 \) uncorrected and a family-wise error cluster threshold at \( p < 0.05 \).
Figure 4.11: Sagittal, coronal and axial slices and rendered images showing clusters of brain activation significantly greater in the cortical cohort when compared with the subcortical cohort at 3 months post-stroke. The SPM t-images are displayed following a small-volume correction and at a voxel-wise significance threshold of $p<0.005$ uncorrected and a family-wise error cluster threshold at $p<0.05$. 

```
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<th>mm</th>
<th>mm</th>
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</thead>
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<td>$E$</td>
<td>$F$</td>
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```

Table shows 16 local maxima more than 4.0mm apart.