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Predicting recovery and outcomes for the lower limb after stroke

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Faculty of Medical and Health Sciences

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Health Science, the University of Auckland, 2017.
Abstract

Regaining the ability to walk after stroke is the most common rehabilitation goal for patients. Recovery from motor impairment plays a role in achieving independent walking and the symmetry of the walking pattern. The objectives of this thesis were to identify predictors of recovery from lower limb motor impairment and walking outcome at the sub-acute stage of stroke, and to investigate an intervention for improving gait symmetry at the chronic stage of stroke.

Two prediction studies were conducted using clinical measures, transcranial magnetic stimulation (TMS), and magnetic resonance imaging (MRI), within the first week of stroke, with follow-up assessments at 6 and 12 weeks post-stroke. The first study (n = 32) found that patients recovered about 70% of their initial lower limb motor impairment, with baseline motor impairment (lower limb Fugl-Meyer score) the only predictor of recovery. This is the first report of proportional recovery from lower limb motor impairment. The second study (n = 41) identified variables that predicted whether a patient would walk independently by six or 12 weeks, or remain dependent at 12 weeks post-stroke. The study produced the Time to Walking Independently after STroke (TWIST) algorithm that made accurate predictions for 95% of patients, and is the first to predict when a patient will walk independently post-stroke. TMS and MRI measures were not significant predictors in either study, which may be due to the presence of alternate descending pathways to the lower limb.

The final study investigated unilateral step training and conventional treadmill training in 20 patients with chronic stroke. The effects of training were dependent on the direction of gait asymmetry, as both types of training improved step-length asymmetry only for participants who took a shorter step with their paretic leg. This highlights the need to identify subsets of patients who are most likely to respond to a given intervention.
In summary, this thesis presents novel findings of proportional recovery from lower limb impairment, and the TWIST algorithm for predicting when a patient will achieve independent walking. Unilateral step training in the chronic stage had modest effects, but may have benefit at the subacute stage.
Acknowledgements

I would like to acknowledge the huge amount of support I have had throughout my PhD from my supervisors, colleagues, friends and family. Without their support, this thesis would not have been possible.

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- The patients and their families who generously volunteered to participate in the experiments at a time when they were most vulnerable. It has been a privilege to work with them.
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Lastly, I would like to thank my husband Matt Smith who has been incredibly supportive, always believed in me and has held everything together on the home front over the last few months; and my children Anya (4) and Zico (2) who joined us during this PhD and have only ever known life with a PhD mum. Their generosity of spirit and enthusiastic countdown to
finish my “book” helped me over the finish line. I am very grateful for the sacrifices my little family have made and hope I have made them proud.
Statement of contribution

During the course of my doctoral studies I have also had the opportunity to contribute to other projects, resulting in the following publications. This included patient recruitment, clinical and neurophysiological assessments, and providing patients and their therapy teams with prognostic information for their upper limb recovery and outcomes.


Preface

The aim of this thesis was to predict and improve recovery and outcomes for the lower limb and walking after stroke. Predicting when a patient will walk independently after stroke is important for patients, their family and their clinical team and may enable more effective discharge planning. Residual lower limb impairment is likely to affect gait asymmetry, which results in increased metabolic cost and reduced participation. Therefore, predicting recovery from lower limb impairment and improving gait symmetry after stroke may be of benefit.

The scope of this thesis is broad, encompassing prediction of recovery from impairment and walking outcomes in patients with sub-acute stroke, and investigating an intervention in patients at the chronic stage of stroke. One of the biggest challenges in neuroscience research is the implementation of findings into clinical practice. Throughout the thesis, the focus often returns to whether the findings are potentially translatable to clinical practice. One of the overall aims was to identify prediction information and present it in a format that is clinically relevant, accessible, and able to provide accurate information for an individual patient.

During the course of this research I have had the privilege of working alongside many of my clinical colleagues, and to witness their great enthusiasm and thirst for knowledge about the science behind stroke recovery and rehabilitation. This motivates me to focus my research on bridging the gap between neuroscience and clinical practice, to support the implementation of research findings for the benefit of our patients.

Thesis outline

This thesis contains five introduction chapters, four experiments and a final discussion. The first chapter reviews literature on the pathophysiology and acute medical care of stroke.

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Chapter 2 covers the neural control of walking. Chapter 3 is an abridged published invited commentary discussing neural plasticity after stroke. Chapter 4 is a methods section discussing clinical measures for lower limb impairment and walking. Chapter 5 reviews the literature on prediction in stroke, and includes technical methods information for transcranial magnetic stimulation (TMS) and magnetic resonance imaging (MRI). This chapter refers to a second published invited review on the use of TMS in stroke, which has been abridged and placed in Appendix 1 to aid the reader. The broad scope of the literature review provides the rationale for the following experiments.

The first experiment (Chapter 6) aimed to develop a protocol that optimises TMS for the lower limb, as lower limb TMS can be technically challenging, particularly early after stroke. This protocol was developed in healthy adults and then used with patients at the sub-acute stage of stroke in the next two studies. Chapter 7 describes a study conducted with patients recruited within one week of stroke. This study investigated and identified predictors of recovery from lower limb motor impairment. Chapter 8 describes another study conducted with patients within one week of stroke onset. This study investigated potential predictors for whether and when a patient would achieve independent walking after stroke, and generated the TWIST prediction algorithm. Chapter 9 investigated unilateral step training and conventional treadmill training with patients at the chronic stage of stroke as potential interventions to improve gait symmetry for those patients who recover independent walking. This chapter also contains an extended introduction section with a review of gait asymmetry after stroke and potential interventions. Chapter 10 discusses how these experiments relate to each other, identifies possible future directions, and provides concluding remarks.
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**Chapter 3: Plasticity and motor recovery after stroke**


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**Chapter 7: Proportional recovery from lower limb motor impairment after stroke**


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Chapter 8: The TWIST algorithm predicts Time to Walk Independently after STroke.
Smith M-C, Barber PA, Stinear CM. Submitted 2017 to Neurorehabilitation and Neural Repair

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Chapter 1. Stroke

Stroke is the third leading cause of death and the second leading cause of disability in the developed world (Lozano et al., 2012; Feigin et al., 2015b). In New Zealand over 45,000 people live with the effects of stroke with numbers expected to double by 2030 (Tobias et al., 2007; Feigin et al., 2014a). Advances in acute stroke care have led to stroke mortality rates dropping faster than stroke incidence rates (Feigin et al., 2015a). This increased survival rate combined with population growth means the number of people living with disability after stroke is increasing.

Stroke is caused by a disruption of the blood supply to the brain. The two most common types of stroke are ischaemic (defined by the American Heart Association as “an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction”) and intracerebral haemorrhage (defined as “rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma”) (Sacco et al., 2013). Depending on location and size, stroke may cause symptoms within a single domain such as movement, sensation, speech, vision or cognition, or may affect several domains. Larger lesions are generally associated with worse outcomes (Vogt et al., 2012), however the severity of the stroke is not always related to the size of the lesion (Bamford et al., 1991). For example, a smaller lesion located in the posterior limb of the internal capsule may damage fibres of the descending motor pathways resulting in a dense and severely disabling hemiplegia (Puig et al., 2011).

The purpose of this chapter is to outline the pathophysiology, acute medical management, and secondary prevention of stroke. It will also identify risk factors and the most commonly used stroke classification systems.
1.1. Cerebral circulation

The types of symptoms experienced after stroke depend on which part of the cerebral circulation is disrupted. The circulation to the brain is provided by the internal carotid arteries anteriorly, and the vertebral arteries posteriorly. The internal carotid arteries branch to form the anterior and middle cerebral arteries. The vertebral arteries come together at the level of the pons to form a single basilar artery which then branches into the posterior cerebral arteries. The anterior and posterior communicating arteries provide bridging circulation between the blood supply from the basilar artery and the internal carotid arteries, forming the circle of Willis. The circle of Willis provides collateral circulation in the case of an obstruction to the blood supply, allowing blood flow around the obstruction via the anterior and posterior communicating arteries. This may not completely prevent ischaemic damage but may reduce the severity of the damage occurring until medical intervention restores perfusion (Mikulik and Wahlgren, 2015).

Most strokes (70%) occur within the anterior circulation of the brain, with 96% of these occurring in the middle cerebral artery territory (Bogousslavsky et al., 1988). The middle cerebral artery supplies a large area of the cortex including the lateral parts of the frontal, parietal, temporal and occipital lobes and the insula. The deep lenticulostriate branches of the middle cerebral artery supply the basal ganglia and the posterior limb of the internal capsule. The middle cerebral artery is particularly susceptible to cardiac emboli due its large diameter and direct flow from the internal carotid artery. Symptoms of middle cerebral artery stroke are listed in Table 1.1.

The anterior cerebral artery supplies the cortex and white matter of the inferior frontal lobe, the medial surfaces of the frontal and parietal lobes and the corpus callosum. Anterior cerebral artery strokes account for only 3-4% of anterior circulation strokes (Bogousslavsky
This is largely due to effective collateral circulation supplied by the anterior communicating artery. Symptoms of anterior cerebral artery stroke are listed in Table 1.1.

**Table 1.1** Stroke symptoms in relation to affected cerebral blood supply

<table>
<thead>
<tr>
<th>Vascular territory affected</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle cerebral artery territory</td>
<td>Hemiplegia and/or sensory loss of the face, arm, trunk, leg contralateral to lesion (usually arm more than leg)</td>
</tr>
<tr>
<td></td>
<td>Aphasia (dominant hemisphere)</td>
</tr>
<tr>
<td></td>
<td>Visuospatial neglect</td>
</tr>
<tr>
<td></td>
<td>Homonymous hemianopia</td>
</tr>
<tr>
<td>Anterior cerebral artery territory</td>
<td>Weakness and/or sensory loss of the leg (distal more than proximal) contralateral to lesion</td>
</tr>
<tr>
<td></td>
<td>Cognitive impairment (apraxia, speech disturbance)</td>
</tr>
<tr>
<td>Posterior cerebral artery territory</td>
<td>Homonymous hemianopia</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Hemisensory loss</td>
</tr>
<tr>
<td></td>
<td>Hemiplegia</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral cranial nerve palsy (Horner’s syndrome, facial palsy, gaze palsy)</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Nystagmus</td>
</tr>
<tr>
<td></td>
<td>Diplopia</td>
</tr>
<tr>
<td></td>
<td>Dysarthria</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Nystagmus</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
</tr>
<tr>
<td></td>
<td>Dysmetria</td>
</tr>
<tr>
<td></td>
<td>Dysdiadochokinesia</td>
</tr>
<tr>
<td></td>
<td>Intention tremor</td>
</tr>
</tbody>
</table>
Posterior circulation strokes account for 20-30% of all strokes with 36% of these in the posterior cerebral artery territory, 48% in the brainstem, 7% in the cerebellum and 9% in multiple locations (Bogousslavsky et al., 1988). The posterior cerebral artery supplies the inferior temporal lobe, medial occipital lobe, the posterior corpus callosum and the brainstem. The deep branches of the posterior cerebral artery supply the thalamus, subthalamic nuclei and parts of the midbrain. The primary symptom of posterior cerebral artery stroke is contralateral homonymous hemianopia (Table 1.1). Circulation to the brainstem and cerebellum is supplied by the basilar artery and the superior and inferior cerebellar arteries. As the descending and ascending pathways between the brain and the spinal cord pass through and decussate at different levels of the brainstem, lesions in the brainstem produce symptoms specific to their level and location within the brainstem and the pathways affected (Table 1.1). Lesions in the cerebellum manifest in classic “cerebellar signs” including: ataxia, dysmetria and dysdiadochokinesia. Cerebellar lesions do not cause lower limb weakness and do not directly affect the descending motor control of the lower limb. Cerebellar stroke is not included in the scope of this thesis.

There are two types of stroke: Ischaemic stroke and haemorrhagic stroke. Up to 85% of all strokes are ischaemic, while the rest are haemorrhagic (Roger et al., 2012; Bhalla et al., 2013; O'Donnell et al., 2016). Ischaemic and haemorrhagic stroke differ in their pathophysiology, risk factors, acute management and secondary prevention and will be discussed separately.
1.2. Ischaemic stroke

Up to 85% of all strokes are ischaemic (Roger et al., 2012; Bhalla et al., 2013; O'Donnell et al., 2016). Ischaemic stroke is caused by an arterial occlusion resulting in reduced blood flow to part of the brain. This is usually due to thrombus formation around atheromatous plaques or thromboembolic debris travelling from the heart or large vessels supplying the brain. Thrombus formation typically occurs at the origin or bifurcation points of arteries supplying the brain. Approximately 25% of ischaemic strokes are lacunar strokes which are caused by occlusion of a single penetrating arterial branch of either the anterior or middle cerebral arteries affecting deep white and grey matter structures (Bejot et al., 2008).

Not all ischaemic strokes are due to occlusion of a main artery or its larger branches. Systemic hypoperfusion or microemboli may lead to the development of a watershed infarct. A watershed infarct is defined as ischaemia in an area bordering two vascular territories (Torvik, 1984). The distal parts of the circulation are particularly susceptible to reduced blood flow with few options for collateral circulation. Common causes of hypoperfusion are carotid stenosis, sudden hypotension, or cardiac arrest with prolonged resuscitation. A watershed infarct between the ACA and MCA territories may result in hemiplegia and sensory loss, particularly to the leg, and symptoms may be bilateral. Watershed infarcts account for 5-10% of all cerebral infarctions (Torvik, 1984; Sorgun et al., 2015).

1.2.1 Risk factors for ischaemic stroke

Risk factors for stroke can be separated into non-modifiable and modifiable risk factors. The strongest non-modifiable risk factor for ischaemic stroke is age. While stroke can affect people of all ages, the median age of first-ever stroke is 71 (Roger et al., 2012; Feigin et al., 2014a), with the risk of stroke doubling for every decade over the age of 55 (Ovbiagele and Nguyen-Huynh, 2011; Roger et al., 2012; Chyou et al., 2015). Other non-modifiable risk factors...
factors are listed in Table 1.2 (Feigin et al., 2014b). Modifiable risk factors for stroke are those which may potentially be reduced through medical management or lifestyle change and are the target of primary stroke prevention programmes and public awareness campaigns. The modifiable risk factors for ischaemic stroke are listed in Table 1.2 (Kannel et al., 1976; Ovbiagele and Nguyen-Huynh, 2011; Chyou et al., 2015; O'Donnell et al., 2016).

### Table 1.2 Risk factors for ischaemic stroke

<table>
<thead>
<tr>
<th>Non-modifiable risk factors</th>
<th>Modifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (risk doubles every decade over 55 years)</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Ethnicity (Māori, Pacifika, African American, Hispanic, Asian)</td>
<td>Cardiac disease</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>Current smoking</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Dyslipidaemia</td>
</tr>
<tr>
<td></td>
<td>Sedentary lifestyle</td>
</tr>
<tr>
<td></td>
<td>Abdominal obesity</td>
</tr>
<tr>
<td></td>
<td>Poor diet</td>
</tr>
<tr>
<td></td>
<td>Excessive alcohol intake</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>Psychosocial factors</td>
</tr>
</tbody>
</table>
1.2.2 Classification of ischaemic stroke

Stroke classification is a way of sub-typing stroke for a specific purpose. Several classification systems exist for stroke ranging from pathophysiological classifications, classification based on site and size of infarct, and classification based on clinical signs. Classification may assist clinicians in making rapid decisions about medical care in a time-constrained environment such as the first hours after stroke. Classification is also used to predict longer term outcomes for patients (Amarenco et al., 2009). The two most commonly used classification systems for ischaemic stroke are the Oxfordshire Community Stroke Project classification (Oxfordshire classification) and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification systems.

Bamford et al. (1991) developed the Oxfordshire classification for ischaemic stroke by subdividing patients into groups based on clinical features (Table 1.3). Four distinct categories were identified using clinical signs alone: Total Anterior Circulation Infarct (TACI), Partial Anterior Circulation Infarct (PACI), Lacunar Infarct (LACI) and Posterior Circulation Infarct (POCI). In the original study, these classifications were confirmed with computed tomography (CT) brain scans (Bamford et al., 1991). Strengths of the Oxfordshire classification system are that it is quick and doesn’t rely on expensive technology. It does not attempt to identify the cause of stroke, or the specific site of infarct, but rather identifies stroke severity and distinguishes between anterior and posterior circulation stroke. The Oxfordshire classification system has become the gold standard for classifying patients according to stroke type in rehabilitation trials, particularly those aimed at trying to predict recovery or best response to rehabilitation interventions.
Table 1.3 Oxfordshire classification system of ischaemic stroke

<table>
<thead>
<tr>
<th>Oxfordshire classification categories</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total anterior circulation infarct (TACI)</td>
<td>All three of:</td>
</tr>
<tr>
<td></td>
<td>• Motor and/or sensory symptoms of hands, face, arm and/or leg</td>
</tr>
<tr>
<td></td>
<td>• Higher level cognitive deficit (aphasia, visuospatial neglect, dyscalculia)</td>
</tr>
<tr>
<td></td>
<td>• Homonymous hemianopia</td>
</tr>
<tr>
<td>Partial anterior circulation infarct (PACI)</td>
<td>2 out of 3 of the above</td>
</tr>
<tr>
<td>Lacunar infarct (LACI)</td>
<td>One of the following:</td>
</tr>
<tr>
<td></td>
<td>• Pure motor</td>
</tr>
<tr>
<td></td>
<td>• Pure sensory</td>
</tr>
<tr>
<td></td>
<td>• Sensorimotor stroke</td>
</tr>
<tr>
<td></td>
<td>• Ataxic hemiparesis</td>
</tr>
<tr>
<td>Posterior circulation infarct (POCI)</td>
<td>Any of the following:</td>
</tr>
<tr>
<td></td>
<td>• Cranial nerve palsy with contralateral motor and/or sensory deficit</td>
</tr>
<tr>
<td></td>
<td>• Bilateral motor and/or sensory deficit</td>
</tr>
<tr>
<td></td>
<td>• Disorder of conjugate eye movement</td>
</tr>
<tr>
<td></td>
<td>• Cerebellar dysfunction without ipsilateral long-tract deficit</td>
</tr>
<tr>
<td></td>
<td>• Isolated homonymous hemianopia</td>
</tr>
</tbody>
</table>

In contrast to the Oxfordshire classification system, The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system aims to classify ischaemic stroke subtype based on aetiology (Adams et al., 1993). The TOAST classification consists of five categories: large-artery atherosclerosis; cardioembolism; small-vessel occlusion (lacune); stroke of other determined aetiology; or stroke of undetermined aetiology. Classification is based on a combination of the patient’s medical history/risk factors, brain imaging including
CT scan, CT angiogram or magnetic resonance imaging (MRI), cardiac imaging (echocardiography), imaging of extra cranial arteries such as carotid imaging and laboratory investigations for a pro-thrombotic state. TOAST is designed for clinicians making decisions about providing medical care and prevention of recurrent stroke. It is also useful to classify ischaemic stroke based on aetiology for researchers investigating the effectiveness of acute medical interventions such as thrombolysis and endovascular clot retrieval after stroke. TOAST does not provide a clinical picture of the patient or provide prognostic information beyond survival rates and broad disability categories.

1.2.3 Acute medical management of ischaemic stroke

Time from stroke onset to medical intervention is critical. The high metabolic rate of neurons means that they are highly susceptible to damage from deprivation of oxygen and glucose. For every minute that treatment does not occur to re-perfuse the affected area of the brain after large vessel ischaemic stroke, 1.9 million neurons, 3.8 billion synapses and 12 km of myelinated axonal fibres are lost (Saver, 2006). This equates to the loss of approximately 20 million neurons for every 10 minute delay in treatment providing justification for the phrase “time is brain” (Saver and Levine, 2010). Disruption of the blood supply to the affected area of the brain results in a focal area of cell death called the infarct core. The infarct core is tissue that has already infarcted or is going to infarct regardless of re-perfusion. Surrounding the infarct core is an area of reduced perfusion called the ischaemic penumbra. The ischaemic penumbra is tissue that is still salvageable, but is at risk of hypoxic cell death if perfusion is not restored quickly (Balami et al., 2013; Fisher and Saver, 2015). The potentially salvageable ischaemic penumbra is the target of acute stroke medical interventions.
In the last two decades, great advances have been made in the acute management of stroke. These interventions are time critical and rely on a patient presenting to hospital within hours of stroke onset. Treatments for ischaemic stroke include intravenous thrombolysis and endovascular clot retrieval. The primary goal of thrombolysis and clot retrieval is to rapidly restore perfusion through recanalization (either breaking down or mechanically removing the thrombus) (Balami et al., 2013). Early and successful recanalization with thrombolysis or endovascular clot retrieval significantly improves patient outcomes after stroke (Hacke et al., 2004; Fisher and Saver, 2015).

**Intravenous thrombolysis**

Thrombolysis involves administering an intravenous recombinant tissue plasminogen activator (rtPA) called alteplase, with the aim of breaking down the thrombus to restore perfusion to affected areas. rtPA targets the breakdown of fibrin into fibrin degradation products and dissolves the thrombus allowing blood flow through the affected artery (Balami et al., 2013). The primary risk of harm from thrombolysis is secondary intracerebral haemorrhage which occurs in 7% of patients compared with 1% of patients who do not receive thrombolysis (Emberson et al., 2014). Contraindications are intracranial haemorrhage, history of bleeding disorders or coagulopathy, extremely high blood pressure unresponsive to treatment, active internal bleeding or recent trauma or surgery in the last 14 days (Balami et al., 2013). Thrombolysis is administered in accordance to established guidelines (European Stroke Organisation Executive and Committee, 2008; Jauch et al., 2013) which originally identified a treatment window of up to three hours after stroke onset (European Stroke Organisation Executive and Committee, 2008). However, more recent evidence has demonstrated that extending the treatment window from three to 4.5 hours is beneficial (Hacke et al., 2008; Wahlgren et al., 2008; Lees et al., 2010). This larger time window may make thrombolysis more accessible to patients.
The later thrombolysis is started after stroke onset, the less effective it is as the infarct size increases with prolonged loss of perfusion (Hacke et al., 2004; Lees et al., 2010). Patients treated within 90 minutes have better outcomes than those receiving alteplase later (Strbian et al., 2013). The risk of harm from thrombolysis outweighs the potential benefits for patients treated after 4.5 hours (Lansberg et al., 2009). For patients who receive thrombolysis within three hours of stroke onset, one in three patients achieves a better functional outcome and for those patients treated between three and 4.5 hrs, one in six achieves a better outcome than those who do not receive thrombolysis (Saver and Levine, 2010).

Despite the promising results from thrombolysis studies and rapid implementation into standard medical care, only 7-10% of patients with ischaemic stroke actually receive thrombolysis (Rosenberg and Steiner, 2016; Liu et al., 2017). One factor influencing this may be treatment delays occurring either before arrival to hospital or in the “door-to-needle” time after arrival at hospital, placing some patients outside the 4.5 hour treatment window. Late presentation to hospital may be due to: failure to recognise symptoms; waking with stroke symptoms and unsure of onset time; living alone and unable to contact an ambulance; or living a large distance from a tertiary care hospital.

Current guidelines require all patients to undergo CT scan to rule out primary intracerebral haemorrhage before beginning thrombolysis. This increases door-to-needle time and also prevents early administration of alteplase in the ambulance prior to arriving at hospital. Consideration of ways to determine patient safety for thrombolysis without CT scan is one controversial approach (Barrett and Gottesman, 2016; Rosenberg and Steiner, 2016). Other, more conventional, approaches include trialling mobile stroke ambulance services with portable CT scanners which have been demonstrated to reduce onset to needle time by 30 minutes (Kunz et al., 2016; Taqui et al., 2017).
**Endovascular clot retrieval**

Thrombolysis is a relatively safe treatment which is easy to administer within a hospital setting with appropriate facilities, but it does not work for all patients. This is particularly true for those with large clots affecting the internal carotid artery or proximal segment (M1) of the middle cerebral artery who are at high risk of very large infarction and more likely to experience poor outcomes such as severe disability or death (Saarinen *et al.*, 2012). In some specialist centres, patients with large vessel ischaemic stroke may undergo endovascular clot retrieval, usually after alteplase has been given. Patients are selected for endovascular clot retrieval on the basis of CT angiography or CT perfusion imaging which identifies patients with an occluded proximal artery in the anterior circulation and potentially salvageable penumbral tissue (Goyal *et al.*, 2015). The procedure is performed either under conscious sedation or general anaesthesia. A retrievable stent is deployed intra-arterially to aspirate the thrombus at the site of the occlusion.

The clot retrieval procedure must be started within six hours of stroke onset (Saver *et al.*, 2016). The removal of the clot within a short timeframe of symptom onset enables rapid reperfusion, minimising cell death. Patients with a small infarct core relative to a large area of perfusion loss are likely to benefit the most from this procedure. Patients who undergo endovascular clot retrieval are twice as likely to be functionally independent within 3 months of stroke (Broderick *et al.*, 2015).

Five large multicentre trials have been conducted with strong evidence in support of endovascular clot retrieval for successful recanalisation and improved functional outcomes (Berkhemer *et al.*, 2015; Campbell *et al.*, 2015; Goyal *et al.*, 2015; Jovin *et al.*, 2015; Saver *et al.*, 2015). The evidence was so strong that four of the five trials were stopped early due to the clear benefit of combined endovascular clot retrieval over thrombolysis alone. As with
thrombolysis, onset to treatment time is critical with endovascular clot retrieval. This time
constraint combined with the additional inclusion criteria and the reliance on resources and
expertise only available in a few large clinical centres means even fewer patients are treated
with endovascular clot retrieval than thrombolysis.

1.3. Intracerebral haemorrhage

Haemorrhagic stroke usually refers to intracerebral haemorrhage, which is bleeding from
intracerebral arteries into the surrounding brain parenchyma (Aguilar and Brott, 2011).
Another form of haemorrhagic stroke is subarachnoid haemorrhage, which refers to bleeding
into the subarachnoid space. Subarachnoid haemorrhage does not usually involve
haemorrhage into the brain parenchyma, and its mechanism, symptoms and recovery differ
from ischaemic stroke or intracerebral haemorrhage, therefore it is not included within the
scope of this thesis.

Intracerebral haemorrhage is usually the result of rupture of small penetrating arteries,
caused by hypertension-related degenerative changes in the vessels or cerebral amyloid
angiopathy (Qureshi et al., 2009; Aguilar and Brott, 2011). Secondary intracerebral
haemorrhage may be due to rupture of an arterio-venous malformation, an underlying
vasculopathy, haemorrhage from an intracerebral malignancy or be anticoagulant-induced
(Qureshi et al., 2009). Intracerebral haemorrhage has a high one month mortality rate of up
to 40% (Steiner et al., 2014).

Most studies report the incidence of intracerebral haemorrhage as approximately 15% of
all strokes (Roger et al., 2012; Bhalla et al., 2013). In New Zealand, primary intracerebral
haemorrhages account for 13% of new strokes (Feigin et al., 2015a). In contrast, a recent
epidemiological study reports the incidence of haemorrhagic stroke worldwide as 33%
(Feigin et al., 2015b). This discrepancy may be explained by the authors using a wider
definition of haemorrhagic stroke, which included all types of non-ischaemic stroke (such as subarachnoid haemorrhage). There are notable differences in the incidence of intracerebral haemorrhage by ethnic group and country. Incidence of intracerebral haemorrhage in Asian countries is more than twice as high as that of western regions such as Europe or North America where many stroke studies are conducted (van Asch et al., 2010; O'Donnell et al., 2016). Incidence and mortality from haemorrhagic stroke are also higher in developing countries than developed countries (Feigin et al., 2015b).

1.3.1 Risk factors for intracerebral haemorrhage

Although patients with intracerebral haemorrhage are usually slightly younger than those with ischaemic stroke, age remains an important risk factor (Bhalla et al., 2013), followed by poorly controlled hypertension and cerebral amyloid angiopathy (Qureshi et al., 2009). Male patients, current smokers, those with Māori, Pacific, Asian or African American descent and those with high alcohol intake are also at higher risk of intracerebral haemorrhage (Ariesen et al., 2003; van Asch et al., 2010; Feigin et al., 2015a). Patients taking antithrombotic or antiplatelet medication are at risk of secondary intracerebral haemorrhage (Howard et al., 2013).

1.3.2 Classification of intracerebral haemorrhage

There is no specific classification system for intracerebral haemorrhage. Intracerebral haemorrhage is described by type (primary or secondary), location (deep or lobar) and aetiology (chronic hypertension, amyloid angiopathy or secondary haemorrhage due to anticoagulation or antithrombotic therapy) (Aguilar and Brott, 2011). This aids in the acute medical management of intracerebral haemorrhage.
1.3.3 **Acute medical management of intracerebral haemorrhage**

The aim of acute management of intracerebral haemorrhage is to prevent complications such as haematoma expansion, perihematomal oedema and intraventricular haemorrhage with hydrocephalus. This includes blood pressure management to reduce hypertension, stopping or reversing anticoagulant medications, craniotomy to evacuate the haemorrhage, and hemicraniectomy to relieve intracranial pressure (Steiner *et al.*, 2014). Although these interventions do not reverse symptoms that have already occurred, they may limit further progression of the stroke and therefore improve outcomes (Balami and Buchan, 2012).

1.4. **Secondary stroke prevention**

Modification of lifestyle factors and medical management of risk factors are required for secondary prevention of stroke. Lifestyle modifications apply to both ischaemic stroke and intracerebral haemorrhage. The most common lifestyle modifications targeted in prevention programmes are smoking cessation advice, diet modification, and advice to participate in daily physical activity to increase cardiovascular fitness (European Stroke Organisation Executive and Committee, 2008; Kernan *et al.*, 2014). Walking, swimming and cycling are the most accessible forms of exercise for most people and yet these can be particularly difficult for patients after stroke with lower limb weakness, balance problems or cognitive changes. Consequently, patients often struggle to improve their cardiovascular fitness after stroke (Smith *et al.*, 2012).

Medical management in secondary prevention of ischaemic strokes includes identification and treatment of hypertension, diabetes mellitus, elevated lipid levels, atrial fibrillation and internal or other large artery stenosis (Kernan *et al.*, 2014). For intracerebral haemorrhage, identification and treatment of hypertension and diabetes mellitus is required (Steiner *et al.*, 2014).
Chapter 2. Neural control of walking and posture

This chapter will review the neural control of the lower limb and walking in healthy adults. I will then discuss the effects of stroke on walking. Finally, I will discuss rehabilitation and the recovery of walking after stroke.

Walking is a complex task that requires postural control of the trunk, rhythmic coordination of lower limb movements, and the ability to make rapid adjustments to maintain balance in response to unexpected perturbations, turning, walking on different surfaces, and avoiding obstacles. Sensory inputs including vision, proprioception, touch, pressure, and feedback from the vestibular apparatus, modify motor output in response to the environment. Although elements of walking are largely automated, with much of the rhythmic pattern of walking generated and controlled at a spinal cord level (Duysens and Van de Crommert, 1998; Dietz, 2003), it is increasingly recognised that supraspinal control and higher-level cognitive function also play important roles in walking (Schubert et al., 1997; Petersen et al., 2001; Petersen et al., 2012; Amboni et al., 2013).

2.1. Characteristics of human walking

Much of our knowledge about how walking is controlled comes from studies in quadruped animals. Human walking has some unique characteristics that mean the requirements of the neural circuitry for human walking may differ from other mammals (Nielsen, 2003). Firstly, humans walk with an upright bipedal gait which is inherently unstable. A stride cycle consists of 40% swing time, 40% single support time and two segments of 10% double support time for each leg (Lee and Hidler, 2008). Therefore 80% of the time is spent in single support with only one foot on the ground. During walking, the centre of mass is shifted forward, which places a person slightly off balance and helps to generate forward momentum. This forward momentum means that once walking is initiated,
each subsequent step requires less energy, reducing the metabolic cost of walking (Cavagna et al., 1963; Capaday, 2002). The combination of a long period of single support time and the forward shift of the centre of mass while stepping increases the risk of losing balance due to a sudden perturbation. This requires sophisticated sensorimotor integration and much greater reliance on supraspinal postural control than in a quadruped animal such as a cat (Nielsen, 2016).

The second unique characteristic of human walking is that the legs are almost fully extended during gait. The biomechanical stability of the extended knee joint requires minimal, and at times, no muscle activity in the quadriceps muscles to maintain extension, therefore reducing energy expenditure (Capaday, 2002). Thirdly, humans strike the floor heel-first (Capaday, 2002), which means that the hip and knee extensors are activated out of phase with the ankle plantar flexors, unlike toe-walking mammals such as cats that activate all extensor groups together (Capaday, 2002; Nielsen, 2003). These are important considerations when applying findings from animal studies to humans.
2.2. Neural control of walking

There are three components to the neural circuitry of walking: central pattern generators, sensory inputs, and supraspinal control. Although these are each described separately, these contributors to locomotion do not operate in isolation, but instead form a complex integrated control system capable of responding to environmental demands and perturbations (Duysens and Van de Crommert, 1998; Nielsen, 2016).

2.2.1 Central pattern generators for locomotion in animals

The discovery that the spinal cord is capable of generating spontaneous bursts of locomotor activity in motor neurons was first made in studies of decerebrate cats in the early 20th century by Graham Brown (Brown, 1911). The lower thoracic spinal cord was transected and dorsal roots were cut to isolate the spinal cord from supraspinal and peripheral afferent inputs. Electrical stimulation of the spinal cord produced rhythmic alternating flexion and extension movements of the hind limbs, indicating that this movement pattern is determined by a central mechanism located within the spinal cord (Brown, 1911). The term “central pattern generators” (CPG) refers to the neural networks which are able to produce this rhythmical motor pattern in the absence of peripheral feedback or supraspinal inputs (Armstrong, 1986; Duysens and Van de Crommert, 1998; Capaday, 2002; Frigon, 2012; Grillner and El Manira, 2015). More recent studies have provided conclusive evidence for the presence of a locomotor CPG in animals (Jankowska et al., 1967; Forssberg and Grillner, 1973; Andersson et al., 1978; Dietz, 2003).

The locomotor CPG does not spontaneously produce walking movements. Cats used in research are either spinalised with a lower thoracic spinal cord transection, or decerebrate (with a transection usually at the level of the brainstem), or both. The CPG is activated in spinalised animals by: stimulation of the spinal cord; administering monoaminergic
neurotransmitters; or stimulation of peripheral afferents when dorsal nerve roots are intact (Jankowska et al., 1967; Forssberg and Grillner, 1973; Armstrong, 1986; Nielsen, 2003). In decerebrate cats, with transection at the level of the brainstem, electrical stimulation of the mesencephalic and subthalamic locomotor regions in the brainstem also elicits locomotor movements (Armstrong, 1986). Afferent stimulation, brainstem stimulation, and the administration of neurotransmitters, provide non-specific excitatory drive to the CPG. This suggests that it is the CPG itself that selects and activates the correct muscles to produce a coordinated walking pattern rather than voluntary supraspinal control (Nielsen, 2003).

The CPG in spinalised cats produces stereotypic, automated movement on a treadmill (Armstrong, 1986). Without supraspinal inputs the movement is not under voluntary control, yet a cat with intact afferent inputs is able to adjust to different treadmill walking speeds, even changing gait pattern as required. This indicates that peripheral feedback actively modifies the output of the CPG in response to the changing environment (Andersson et al., 1978). CPG activation in response to brainstem stimulation in decerebrate cats occurs in the absence of an intact descending corticospinal tract. This suggests that the brainstem locomotor regions are important in driving the CPG (Drew et al., 2004). The exact mechanisms of how the CPG interacts with these peripheral and supraspinal inputs are not yet clear (Frigon and Gossard, 2010).

It is likely that a separate CPG exists for each limb, enabling limb-specific processing of sensory and supraspinal inputs. Interlimb coordination then occurs between the left and right hind limbs and between paired forelimbs and hind limbs (Duysens and Van de Crommert, 1998; Rossignol and Frigon, 2011; Frigon, 2017). Long and short descending and ascending axonal propriospinal projections contribute to interlimb coordination of the cervical and lumbar CPGs (Frigon, 2017). Crossed propriospinal projections enable left-right or diagonal
coordination (Juvin et al., 2012), allowing adjustments for each limb separately or while coupled with the opposite limb (Dietz, 2003).

2.2.2 Central pattern generators for locomotion in humans

Since the discovery of locomotor CPGs in animals, there has been considerable debate about whether a CPG exists in humans and if so, to what extent it controls locomotion. Translation from studies in quadrupeds to human walking control is inherently difficult due to differences in neural circuitry, gait patterns, and postural control requirements.

Most evidence for the existence of a CPG in humans comes from studies of pre-walking infants and of patients with spinal cord injuries. Infants demonstrate stepping behaviour either spontaneously or in response to peripheral stimuli (Yang and Gorassini, 2006). However, the walking pattern in infants is missing key features of the adult gait pattern such as heel strike, forward weight shift and knee-ankle coordination. Also, infants do not have the ability to maintain postural stability (Forssberg, 1985; Dominici et al., 2011). Analyses of movement patterns from infant to adulthood indicate that the basic walking pattern remains, but is refined as the nervous system matures (Yang and Gorassini, 2006; Dominici et al., 2011). This suggests that although CPGs may produce the basic rhythm of walking, maturation of descending pathways and integration of peripheral afferents are required to produce the gait pattern seen in adults (Forssberg, 1985; Dietz, 2003; Dominici et al., 2011).

People with complete spinal cord injury provide the best opportunity to examine the role of the CPG in adults. In patients with complete spinal cord injury, the spinal cord is reported to be capable of generating locomotor bursts (Dietz et al., 1995; Dobkin et al., 1995; Harkema et al., 1997; Lunenburger et al., 2006). It is not possible to isolate the human spinal cord from both descending pathways and afferent inputs, which makes it difficult to determine whether these locomotor bursts are truly generated from within the spinal cord or
whether they are a response to stretch reflexes or afferent inputs from limb loading (Capaday, 2002). One key difference between treadmill walking in spinalised animals and in people with spinal cord injury is that after a short period of training, the animals are able to support their own weight through their hind limbs (Forssberg and Grillner, 1973). In contrast, the CPG in humans generates insufficient force to support weight bearing, requiring the use of body-weight support harnesses during treadmill training (Dietz et al., 1995). This indicates that although the CPG may be present in humans it appears to be less robust than in animals and relies to a much greater extent on supraspinal input to generate enough muscle activation to support weight bearing (Capaday, 2002; Nielsen, 2003).

Neural coupling in humans is present between leg pairs (left and right), arm pairs and between the arms and legs, suggesting that separate CPGs exist for each limb. Neural coupling is stronger between leg pairs than arm pairs which reflects the primary role of the legs in bipedal locomotion. Leg movements influence movement of the arms (such as arm swing) more than arm movements influence the legs. This suggests a directional preference for interlimb coordination (Zehr et al., 2016).

In summary, the evidence indicates that a locomotor CPG exists in humans but it is likely that the human CPG receives more supraspinal control than in animals. The CPG acts as an automated producer of rhythmic motor output, generating the alternating flexion and extension pattern of walking. However, the CPG does not act in isolation, but relies on sensory feedback to adjust the CPG output in response to the environment and external perturbations (Grillner and El Manira, 2015). It also relies on supraspinal inputs to initiate movement, generate enough power for weight bearing, and produce fine control of movement and goal-directed walking.
2.2.3 Sensory input

Afferent inputs operating at a spinal level are either proprioceptive or cutaneous. Many of these afferent inputs also influence walking via supraspinal pathways. Proprioceptive inputs arising from muscle spindles, Golgi tendon organs, and joint receptors provide feedback on limb position and limb loading. Cutaneous afferents detect pressure, stretch, movement and vibration in the skin. These sensory inputs modify the timing and control of walking, enabling rapid corrections in response to perturbations or environmental demands (Nielsen, 2003; Rossignol and Frigon, 2011; Juvin et al., 2012; Choi et al., 2016). Sensory inputs may interact with the CPG by triggering the transition from stance phase to swing phase, and therefore contributing to changes in walking speed, and to reflexes which influence the CPG pattern (Prochazka and Ellaway, 2012).

The timing of the transition from stance to swing phase affects walking speed. In animals, walking speed increases as a result of a shorter stance phase, while swing phase remains fairly constant (Grillner and Rossignol, 1978; Prochazka and Ellaway, 2012). This means the earlier the stance-swing transition occurs, the faster the speed of walking. In humans, this reduction in stance duration is observed as a reduced double support time as the person increases walking speed. Hip and ankle joint position and loading of the lower limb may contribute to stance-swing phase transition (Andersson et al., 1978; Grillner and Rossignol, 1978; Pearson et al., 1998; Capaday, 2002; Yang and Gorassini, 2006; Rossignol and Frigon, 2011). Full hip extension triggers a flexion stepping response in cats and infants (Grillner and Rossignol, 1978), as do afferent inputs from the active ankle plantar flexors (Pearson et al., 1998). However, it is likely that phase transition is triggered by a combination of factors (Capaday, 2002). For example, for swing phase to be triggered, the leg must be in stance phase and the hip extended, and the contralateral limb must be loaded before swing phase is initiated (Prochazka and Ellaway, 2012). In this example, the position
and loading of each limb at the end of stance phase provides sensory feedback to the CPG to adjust the timing of the transition.

Reflexes produced by proprioceptive and cutaneous inputs also influence the gait cycle. Proprioceptive reflexes are continuously active through the gait cycle while cutaneous reflexes fire at specific times such as during ground contact (Prochazka and Ellaway, 2012). These reflexes help to form the building blocks of the gait cycle with the CPG and correct the gait pattern during walking. Reflexes act on the alpha motoneuron pool in the spinal cord. Sensitivity of the alpha motoneuron pool to afferent input is modulated according to the task (sitting, stance, or walking) and the phase of the gait cycle (Nielsen, 2003; Rossignol and Frigon, 2011; Juvin et al., 2012; Grey et al., 2013).

There is ongoing debate about the relative importance of each reflex type and their role during walking. There are two challenges to investigating the contribution of reflex activity during walking. Firstly, reflexes do not function in isolation. The descending motor pathways and sensory afferents involved in reflex activity both converge on common spinal motoneurons, which means that they are intrinsically linked (Nielsen, 2016). Secondly, reflexes are modulated both phasically and depending on task. This means the response to sensory inputs may differ substantially depending on whether they occur during swing phase or stance phase, or whether they occur while standing or walking. These challenges may be a contributing factor to the lack of consensus on the role of reflexes during walking. The next section contains an overview of some reflexes and their possible contribution to walking. These include: monosynaptic stretch reflexes (1a afferents), load receptor reflexes (1b afferents), and cutaneous inputs.
Monosynaptic stretch reflex (1a afferent)

The monosynaptic stretch reflex has received the most attention in studies of sensory inputs and walking. The monosynaptic stretch reflex loop consists of 1a afferents from the muscle spindle and alpha motoneurons in the spinal cord. As the stretch reflex can be difficult to measure in humans, the Hoffman reflex (H-reflex) is often used instead. Direct stimulation of the 1a afferents of the peripheral nerve triggers the monosynaptic reflex (Capaday, 2002; Grey et al., 2013). The soleus H-reflex is not fixed during walking, but is phasically modulated with greater amplitude during standing and stance phase in walking, than during swing phase (Capaday and Stein, 1986). This finding contributes to the theory that the stretch reflex (1a afferents) of the soleus muscle during late stance may be important in generating muscle activity for forward propulsion (Capaday and Stein, 1986; Grey et al., 2013).

Subsequent studies of the stretch reflex during walking provided further support for soleus reflex-generated forward propulsion (Yang et al., 1991; Sinkjaer et al., 1996). However, these studies only investigated stretch reflex responses during unexpected perturbations (corrective responses). More recent findings suggest that a load-sensitive response generated by 1b afferents may play a more important role in soleus activity and modulating the timing of the gait cycle during normal walking than the 1a afferents. Instead, the role of the 1a afferent monosynaptic stretch reflex may be to respond to perturbations during walking such as walking over uneven ground (Sinkjaer et al., 2000; Grey et al., 2004; af Klint et al., 2010b; Grey et al., 2013; Nielsen, 2016).
Load-receptor reflexes (1b afferent)

Load sensitive 1b afferents arise from the Golgi tendon organs (Duysens et al., 2000) and may be responsible for the generation of muscle power in the extensor muscles of the lower limb and influence CPG timing. Load sensitive sensory input is also important in modulating other reflexes such as suppression of the pain-withdrawal reflex response in situations requiring high levels of postural control (Bastiaanse et al., 2000).

Weight bearing has a facilitatory effect on extensor muscles in both cats and humans, and has minimal effect on the flexors. This prevents unintentional lower limb flexion during stance and walking (Bastiaanse et al., 2000). As the limb is loaded, 1b afferents from the extensors reinforce the ongoing extensor activity during stance and flexor inhibition blocks the initiation of swing (Duysens et al., 2000). 1b afferents contribute to soleus muscle activity during late stance as the load on the plantar flexors increases. Unloading the limb also assists in the transition from stance to swing phase (Harkema et al., 1997; Zehr and Stein, 1999; af Klint et al., 2010a; af Klint et al., 2010b; Grey et al., 2013).

It is likely that the 1b load-receptor and the 1a stretch reflexes work in partnership. The combination of force and stretch inputs provides more detail to the central nervous system about the nature of a perturbation than information from a stretch reflex alone, leading to the ability to take more effective corrective action (af Klint et al., 2010b).

There are important clinical applications of the load-receptor reflex in rehabilitation. Harkema et al. (1997) conducted a study with spinal cord injured patients participating in body-weight supported treadmill training at varying levels of body-weight support. They reported that soleus activity increased as the patient increased their self-supported weight bearing. This suggests that the common practice of training patients with lower limb weakness in weight bearing positions is not only beneficial as a task-oriented exercise but
may capitalise on the effects of load-sensitive reflexes to increase extensor muscle activity and trigger stepping phases within the CPG (Dietz et al., 1995; Dietz, 2003).

Cutaneous reflexes

Cutaneous inputs have two main roles during walking: flexor withdrawal response to stimuli; and corrective response to maintain balance (Zehr and Stein, 1999). Cutaneous receptors allow the detection of unexpected foot contact when encountering obstacles or walking over uneven ground (Zehr and Stein, 1999; Choi et al., 2016). Pressure sensitive cutaneous afferents in the skin also provide feedback on limb loading, which likely contributes to the stance-swing transition and to balance reactions (Bastiaanse et al., 2000).

Similarly to the stretch and load-receptor reflexes, cutaneous reflexes are also modulated depending on the phase of the step cycle (Grey et al., 2013). During early swing, stimulation to the dorsum of the foot produces a contraction in tibialis anterior, dorsiflexing the foot. At the end of swing phase, the same stimulation results in inhibition of tibialis anterior, preventing dorsiflexion just before heel strike (Duysens et al., 1992; Grey et al., 2013). The purpose of this reflex reversal is unclear.

In summary, the role of somatosensory feedback is to provide the central nervous system with enough information to adapt to the environment and provide functionally appropriate output. This is achieved through afferents such as stretch and load receptors, and cutaneous afferents that act at the spinal level and form reflex arcs. These afferents are phasically modulated by the CPG and supraspinal input. They provide input to the CPG, influencing the timing of muscle contractions during walking, and enabling corrections after perturbations or in response to the environment.
2.2.4 Supraspinal control of walking

The fact that walking generally requires little conscious attention may lead to the conclusion that the motor cortex plays only a minor corrective role during walking. However, a relatively low level of voluntary effort, decision making, or attention required by walking should not be used to infer a lack of supraspinal neuronal activity during walking (Barthelemy and Nielsen, 2010). Although the CPG may produce the basic locomotor pattern, evidence presented in this section will make it clear that supraspinal control is required to initiate walking, is involved in modulating both the CPG and sensory inputs, and in generating sufficient motor activity to support weight bearing (Petersen et al., 2012). The cortex is also important in processing visual inputs, and for executive function and attention during walking, which are important for goal direction, anticipation, and negotiation of the environment (Shumway-Cook et al., 1997; Drew et al., 2008; Yogev-Seligmann et al., 2008; Petersen et al., 2012). People with deficits in executive function and attention exhibit gait disturbances and are at higher risk of falls (Shumway-Cook et al., 2000; Yogev-Seligmann et al., 2008). This section will describe the descending motor pathways and supraspinal control of posture and walking.

Descending motor pathways

Drew et al. (2004) state that supraspinal structures have two main roles during walking: Firstly to provide fine control of locomotion and voluntary modification of the basic locomotor rhythm via lateral descending motor pathways; and secondly, to provide postural support via the medial descending motor pathways. This is a reasonable simplification of the functional and anatomical division of the descending pathways. The lateral descending pathways include the corticospinal tract and the rubrospinal tract which are responsible for fine motor control, particularly in the distal limbs. The medial pathways are the
reticulospinal and vestibulospinal tracts which are responsible for gross movements of the proximal limbs and trunk, and postural control (Lemon, 2008).

**Corticospinal tract**

The corticospinal tract (CST) arises in the cortex and is responsible for voluntary and fine motor control of the contralateral limb. Although the CST is involved in voluntary movement of the whole limb, it has a greater role in distal limb control (Armstrong, 1986; Brouwer and Ashby, 1992). About 30-40% of the CST fibres originate in the primary motor cortex located on the precentral gyrus (Brodman’s area 4). The neurons within the primary motor cortex are arranged somatotopically. The leg and foot representations are positioned medially, deep within the longitudinal fissure, while the hand and face representations are positioned laterally. Areas that require more precise motor control such as the face, tongue, hands and feet have greater representation than areas that rely on less skilled movements such as the trunk and legs (Rhoades and Bell, 2013). 30% of CST fibres arise from the premotor and supplementary motor areas (Brodman’s area 6). The premotor and supplementary motor areas are located in the frontal lobe rostral to the primary motor cortex and are involved in motor planning and learning of motor sequences. Somatotopic representation is also present in these areas but is less well defined. The final 30% of CST fibres arise from neurons in the parietal lobe responsible for sensory processing. These fibres play an important role in integrating visual and sensory information and modulating sensory reflexes during voluntary movement (Drew et al., 2008; Nichols-Larsen et al., 2016).

The fibres within the CST are also somatotopically organised. They descend through the posterior limb of the internal capsule, the midbrain, and the pons to the pyramids of the medulla (giving rise to the name “pyramidal tract”). At the medullary pyramids, 90% of fibres cross the midline and descend within the lateral funiculus of the spinal cord white
matter. Some of these fibres terminate directly on the alpha motoneurons in the ventral horn, while the rest act on the alpha motoneurons via interneurons (Rhoades and Bell, 2013; Rothwell and Nielsen, 2013). 10% of the fibres do not cross over, forming the anterior corticospinal tract.

**Rubrospinal tract**

The rubrospinal tract originates in the red nucleus of the midbrain. The red nucleus integrates inputs from the motor cortex and the cerebellum, contributing to its function as a coordination centre (Nichols-Larsen *et al.*, 2016). Fibres of the rubrospinal tract cross the midline at the level of the midbrain and descend in the lateral funiculus to terminate in the lateral spinal intermediate zone. The precise role of the rubrospinal tract in humans is not well understood and may be overshadowed by the much larger CST which also controls distal musculature. It has been suggested that the rubrospinal tract preferentially activates distal flexor muscles of the contralateral limb (Rhoades and Bell, 2013). However other authors suggest that in humans and primates the main role of the rubrospinal tract may be to facilitate end-point accuracy. End-point accuracy relies on rapid coordination of the distal limb in tasks during which the positioning of limb movement must be precisely controlled, such as an upper limb reaching task, or foot placement during skilled walking (van Kan and McCurdy, 2001; Drew *et al.*, 2008; Nichols-Larsen *et al.*, 2016).

**Reticulospinal tract**

In cats, the reticulospinal tract is the primary descending motor pathway and is responsible for driving the CPG during walking (Armstrong, 1986; Drew *et al.*, 2004; Grey *et al.*, 2013). The reticular formation is a group of neurons located in the pons and medulla that receives inputs from the premotor and supplementary motor areas, primary motor cortex, and the cerebellum (Drew *et al.*, 2004). Reticulospinal fibres originating from the reticular nuclei
then descend ipsilaterally and terminate on motoneurons and interneurons involved in the control of axial and proximal limb muscles. The reticulospinal tract has some bilateral influence at the level of the spinal cord due to commissural interneurons. Lateral reticulospinal fibres have relatively small axons with slow conduction velocities and may contribute to initiating CPG output via the motoneurons of the proximal leg flexors (Buford, 2009). The medial fibres consist of large, fast conducting axons that contribute to rapid postural adjustments (Buford, 2009). The reticulospinal fibres produce gross movements of the proximal limbs and trunk. The cortical and cerebellar projections onto the reticular nuclei enable anticipatory postural adjustments to occur during movement planning, providing a stable base from which to perform fine manipulation of the distal limb (Buford, 2009; Nichols-Larsen et al., 2016).

**Vestibulospinal tract**

The vestibular nuclei in the brainstem integrate afferent inputs from the vestibular apparatus and cerebellum. A small number of cortical projections also act on the vestibular nuclei and are thought to subconsciously inhibit vestibular reflexes that are likely to interfere with voluntary movement (Nichols-Larsen et al., 2016). Medial vestibulospinal fibres descend bilaterally and project to the medial part of the cervical and thoracic spinal cord to act on axial muscles. The medial fibres also produce the vestibulo-ocular reflex. The lateral fibres descend ipsilaterally down the length of the spinal cord and produce extension of both axial and limb muscles in response to challenges to upright posture. The vestibulospinal tract in conjunction with the reticulospinal tract is responsible for the control of posture and balance (Buford, 2009; Nichols-Larsen et al., 2016).
Role of descending pathways in walking

Although each of the descending motor pathways described above may play a role in walking, two are of particular importance. These are the reticulospinal tract and the CST. In decerebrate cats, locomotion is initiated by stimulating the mesencephalic locomotor region and subthalamic motor regions in the brainstem (Grey et al., 2013). These brainstem locomotor regions generate supraspinal control of the CPG via the reticulospinal pathways (Armstrong, 1986, 1988; Grillner and El Manira, 2015), which modify the activity of both flexor and extensor muscles during walking, depending on the phase of the gait cycle (Drew et al., 2004). These sets of neurons within the brainstem and hypothalamus are also likely to exist in humans (Grey et al., 2013). Certainly, in animals, the reticulospinal tract appears to be more important in walking than the CST as the basic motions of walking are mostly dependent on proximal muscle control.

The role of the CST in walking is the most debated of all descending pathways in humans. The CST has a critical role in the upper limb, producing the fine distal motor control that almost all upper limb tasks require. As a result, lesions affecting the CST result in severe and often permanent upper limb impairment and disability (Stinear et al., 2007; Puig et al., 2017). In contrast, movements of the lower limb rarely require the same level of fine motor control, with the exception of foot clearance (ankle dorsiflexion) during swing phase of walking.

Findings from animal studies have driven conclusions that the role of the CST during walking is merely corrective and that, provided the mesencephalic locomotor region in the brainstem is intact, the CST is not essential for basic walking. In an early study by Liddell and Phillips (1944), lesions of the pyramidal tracts in animals produced only mild difficulties in walking, that resolved within two weeks (Liddell and Phillips, 1944; Armstrong, 1986).
Even immediately after recovery from anaesthesia these animals were able to walk independently over level surfaces with only minor gait changes such as foot drop and hip circumduction. However, when challenged with more difficult locomotor tasks such as stepping over a horizontal ladder or walking on a narrow beam, the animals were unable to complete the task (Liddell and Phillips, 1944). These findings have been supported in several studies showing activity of the pyramidal tract neurons is increased during skilled locomotion (Drew, 1988; Amos et al., 1990; Beloozerova and Sirota, 1993; Drew, 1993). This provides further evidence that the CST is not required for basic walking, but does play an essential role in obstacle avoidance and skilled voluntary movements in cats (Armstrong, 1986; Nielsen, 2003; Drew et al., 2004).

It is clear from clinical observation that these studies in animals do not translate well to human walking. Stroke lesions affecting the CST are more devastating in humans than in other animals (Nielsen, 2003). Although patients with complete CST injury may be able to walk eventually, this process takes several months of rehabilitation and substantial gait deficits remain (Ahn et al., 2006). If the only purpose of the human CST during walking is to refine or correct the walking pattern, it would be expected that with support these patients would be able to use the reticulospinal tract, the CPG, and reflex activity to produce fairly functional walking.

Although studies in cats and other quadrupeds have been invaluable in identifying some of the basic neural circuitry controlling walking across different species, the different biomechanics of quadrupedal and bipedal gait mean that the “weighting” of each of the neural components contributing to locomotion (CPG, sensory inputs, and supraspinal control) must also be different. For example, while the reticulospinal pathway is the primary descending motor pathway in cats (Drew et al., 2004), the CST is the major descending motor pathway in humans (Lemon, 1993). This may reflect the greater need for fine motor
control in humans, particularly in the upper limb and for foot clearance during walking (Lemon, 1993; Nielsen, 2003; Petersen et al., 2003). During walking in cats, the foot strike is through the toes, whereas in humans, the heel makes contact with the ground first (Capaday, 2002). This important difference in gait biomechanics means that humans require great precision in the degree of dorsiflexion produced at the ankle, to scale it appropriately with the degree of hip and knee flexion and efficiently clear the ground (Nielsen, 2003). The CST in cats and humans is also neuroanatomically different. CST fibres in the cat do not have any direct terminations on motoneurons, but instead act on the alpha motoneurons via interneurons. In contrast, up to half of CST fibres in humans may directly synapse with the alpha motoneuron (Petersen et al., 2003; Nielsen, 2016).

Recent advances in neurophysiological techniques such as transcranial magnetic stimulation (TMS) have enabled non-invasive examination of the corticomotor pathways in humans. The technical aspects and applications of TMS are discussed in greater depth in Chapters 5 and 6 of this thesis. But in short, TMS involves delivering a magnetic stimulus over the scalp which excites the neurons of the primary motor cortex. Measures of the resulting motor-evoked potential (MEP) in the target muscle are taken as indicators of excitability of the corticomotor pathways, of which the greatest contributor is the CST.

Early TMS studies in healthy adults reported that the corticomotor pathways to both the proximal and distal leg muscles are more excitable during different phases of the gait cycle, providing evidence that the CST may be actively involved throughout walking in humans (Schubert et al., 1997; Capaday et al., 1999; Schubert et al., 1999; Bonnard et al., 2002). However, it is possible that this phasic modulation of motor evoked potentials could occur at any point along the corticomotor pathway, reflecting modulation of excitability at a subcortical level or spinal level rather than being driven by the CST (Petersen et al., 2001; Grey et al., 2013). Petersen et al. (2001) delivered sub-threshold TMS pulses during walking
with the aim of identifying whether the corticospinal neurons were contributing to this phasic modulation. Sub-threshold TMS causes intracortical inhibition of the cortical neurons (Davey et al., 1994). During walking, the sub-threshold TMS pulse suppressed ankle dorsiflexor EMG, providing robust evidence that cortical neurons are involved in transmitting motor commands to the ankle dorsiflexors during walking (Petersen et al., 2001).

TMS studies and neuroimaging studies have also been conducted in patients at the chronic stage of stroke to determine the effect of CST damage on walking after stroke (Ahn et al., 2006; Dawes et al., 2008; Madhavan et al., 2010; Cho et al., 2012; Jayaram et al., 2012; Jones et al., 2016). The neuroimaging studies use magnetic resonance imaging (MRI) to quantify the degree of damage to the CST. The various MRI techniques used are discussed in detail in Chapter 5. These studies provide evidence that although walking speed is related to the degree of damage to the CST, this relationship is much weaker than the relationship between upper limb function and CST damage (Dawes et al., 2008; Jayaram et al., 2012; Jones et al., 2016). These findings suggest that the CST is less important in walking than it is in upper limb function.

This does not mean the CST is not important at all in walking. CST damage correlates with knee extensor weakness after stroke (Madhavan et al., 2011) and even greater weakness of the distal leg, resulting in foot drop (Ahn et al., 2006). This affects the patient’s ability to generate enough power to sustain weight bearing and to lift the foot during swing phase. The CST has greater control over distal than proximal lower limb muscles (Schubert et al., 1997; Petersen et al., 2003; Iglesias et al., 2012). Distal motor weakness and poor distal control likely affects walking performance (walking speed and gait pattern) more than the ability to walk independently which relies heavily on postural and proximal limb control. It is possible to compensate for mild to moderate lower limb weakness, foot drop and reduced accuracy of foot placement, as described in Section 2.6. However, compensatory strategies produce a
gait pattern that is inefficient and slow, affecting walking speed and symmetry. Regardless, this compensation may enable safe and independent walking even in the absence of a functional CST. This distinction is important when considering results from studies of the CST in walking.

Some patients with CST damage recover the ability to walk independently (Ahn et al., 2006). There is some evidence that this occurs via alternative descending pathways. Patients with severe CST damage have greater ipsilateral connectivity from the non-lesioned hemisphere to the affected leg than those who have an intact CST (Jayaram et al., 2012). Although this may provide a benefit in regaining the ability to walk, ipsilateral connectivity may also be maladaptive, resulting in poor coordination of the lower limbs in gait (Madhavan et al., 2010) and therefore slower walking with a poor gait pattern.

In summary, the descending pathways play an important role in walking, with the reticulospinal tract likely contributing to the rhythmic pattern, posture, and proximal limb control. Evidence suggests the CST plays a greater role in walking in humans than in animals. Damage to the CST results in weakness, particularly distally, but unlike the upper limb, patients with CST damage may be able to access alternative descending pathways to the lower limb in order to achieve a return to independent walking. Despite this, the distal weakness caused by CST damage is difficult to compensate for as the alternative descending pathways (reticulospinal and vestibulospinal) primarily control the proximal limb and axial muscles. Therefore, CST damage is likely to affect walking speed and gait pattern.
2.3. Motor planning in walking

Motor planning in locomotion involves initiating walking and modifying gait through the processing of visual and sensory inputs. The areas likely to be involved in this are the same as those involved in the planning of voluntary movement: the premotor cortex, supplementary motor area and the posterior parietal cortex. These areas provide projections to the corticospinal tract (Rothwell and Nielsen, 2013). The posterior parietal cortex may be particularly important during the avoidance of obstacles as it processes sensory and spatial inputs, and may also play a role in the working memory of already traversed obstacles (Drew et al., 2008; Grey et al., 2013).

The basal ganglia and cerebellum also play an important role in the planning of movement. The basal ganglia initiate movement and select goal-directed movement patterns (Grillner et al., 2008; Grey et al., 2013). The effects of basal ganglia dysfunction can be observed in patients with Parkinson’s disease with symptoms of bradykinesia, difficulty initiating walking, changing direction, and stopping.

The cerebellum is involved in postural control and coordination. It also plays a role in motor learning and adaptation that will be discussed in Chapter 9. The cerebellum can assist with both anticipatory and reactionary postural adjustments, and the control of coordinated movements required for skilled walking (Morton and Bastian, 2006; Grey et al., 2013). The cerebellum receives and processes inputs from the vestibular nuclei, sensory feedback from the limbs, and input from the motor cortex. It uses this information to make anticipatory postural adjustments and adapt walking through trial-and-error practice. This means it acts as a comparator between expected movement and actual movement, and adapts the motor output accordingly using predictive feed-forward control (Morton and Bastian, 2007).
2.4. Postural control in walking

One of the most important aspects of walking is the ability to maintain posture and balance. Without the ability to maintain an upright posture, independent walking is not possible; despite this, few studies consider the role of posture during walking. Postural adjustment is needed to maintain balance during normal walking, while negotiating obstacles, and in response to perturbations. Anticipatory postural adjustment is needed to counter the inertial forces of lifting the leg to initiate stepping, preventing the body moving backwards in response (Buford, 2009). These small and usually unnoticed postural adjustments occur on a subconscious level during movement planning (Nichols-Larsen et al., 2016). Larger scale postural adjustments occur in response to unexpected perturbations or to visual feedback.

Postural control is mediated by the cerebellum via the vestibulospinal and reticulospinal tracts in response to feedback from the vestibular apparatus, visual and somatosensory inputs (Nichols-Larsen et al., 2016). The vestibular apparatus provides information on the position of the head in space, and the direction and speed of movement in relation to the upright, neutral head position. Visual input provides information about the orientation of the body in space in relation to the environment, and enables anticipatory postural adjustment in response to approaching obstacles or changes in terrain (Drew et al., 2008). Sensory inputs provide proprioceptive information about body position and cutaneous feedback provides information about contact with an obstacle to allow rapid postural adjustments (Zehr and Stein, 1999; Nielsen, 2003; Choi et al., 2016). One final key element in postural control is sufficient motor power to maintain the trunk and legs in extension, and produce the movement patterns required to maintain balance.

After stroke, patients often experience difficulties with trunk control due to weakness, although less so than leg control (Verheyden et al., 2008). Although this thesis focuses on
patients with weakness after stroke, several other factors may contribute to postural instability. Patients with lesions affecting their parietal lobe may experience visuospatial inattention affecting their midline orientation and their ability to maintain balance in sitting or standing. Patients with cerebellar and brainstem stroke may also experience severe loss of postural control due to ataxia, particularly during tasks requiring proximal control (Morton and Bastian, 2007). These patients typically perform better with stepping accuracy when using walking aids to provide proximal postural support. The presence of hemianopia due to a lesion affecting the occipital lobe may also affect a person’s ability to balance and avoid obstacles. There is clear evidence that patients who are able to walk independently have better trunk control than those who require assistance or who are non-ambulatory (Kollen et al., 2005; Verheyden et al., 2006; Veerbeek et al., 2011b). This highlights the importance of trunk control and posture in walking recovery after stroke.

2.5. Cognition

The role of cognition and attention in postural control and walking has become clearer in recent years. Walking requires attention, even if we are not aware of it. Performing a cognitive task while walking creates competition for attention (Yoge v-Seligmann et al., 2012). It has been suggested that if a person is asked to complete a cognitively challenging task during walking or a balance activity, they will prioritise posture over the cognitive task to avoid falling. This was termed the “posture-first” strategy (Shumway-Cook et al., 1997). However, several studies have used this dual-task design to demonstrate that this is often not the case even in healthy young adults, and in fact decrements in performance occur in the postural task rather than the cognitive task (Lindenberger et al., 2000; Siu et al., 2008; Schaefer et al., 2015). This suggests that prioritisation during dual task conditions may be more complex and involve aspects such as the person’s postural reserve (their capacity to
respond to perturbations), the perceived risks of the situation, the complexity of the task, skill level, and mood or personality (Yoge-Seligmann et al., 2012).

Balance deteriorates as people age, increasing the attentional demand of walking. Even with explicit instructions to focus on walking, healthy older adults do less well at performing dual tasks than young adults, failing to prioritise walking and resulting in increased gait variability (Yoge-Seligmann et al., 2010). Older patients with dementia have poor executive function, reduced visuospatial awareness and poor memory, reducing their ability to prioritise tasks. These factors combined with reduced postural reserve associated with aging, lead to an increased risk of falling for these patients (Amboni et al., 2013). Similarly, patients with neurological diseases affecting their balance and walking such as stroke have a higher attentional demand during walking. Cognitive deficits after stroke may increase the risk of falls and affect the ability to live independently (Shumway-Cook et al., 1997; Yoge-Seligmann et al., 2008; Cumming et al., 2014).

2.6. Walking recovery after stroke

One of the main rehabilitation goals after stroke is the recovery of walking (Bohannon et al., 1988). A stroke lesion in any of the areas discussed in this chapter may affect a person’s ability to walk. These structures include: premotor cortex, supplementary motor area, primary motor cortex, somatosensory cortex, occipital lobe, brainstem, basal ganglia and cerebellum (Jones et al., 2016). Due to the somatotopic organisation of the motor cortex, the leg representation sits within the territory of the anterior cerebral artery. This means that stroke affecting cortical leg representation is rare, and therefore lower limb and walking deficits are more likely to be caused by stroke in one of the other areas listed above. Lesions affecting the white matter of the descending pathways or the corticocortical and cortico-subcortical connections also affect walking. In areas such as the posterior limb of the internal
capsule, a relatively small lesion can damage the entire CST (Puig et al., 2011). The specific effects of the stroke on the lower limb and walking depend on the location of the lesion and the descending pathways affected. Symptoms can include weakness of the affected leg, poor trunk control and balance, cognitive and visuospatial deficits, reduced sensation and altered muscle tone.

The stroke recovery process starts soon after stroke onset and is not linear, with most recovery occurring within the first three months (Jorgensen et al., 1995). Early peri-infarct ischaemia triggers a cascade of cellular changes, initiating a period of spontaneous biological recovery and heightened neural plasticity. This process occurs during the first three months after stroke and contributes to rapid improvements. At the same time, the nervous system begins to reorganise through use-dependent plasticity which contributes to the return of function after stroke. Neural plasticity in the context of stroke recovery is discussed in detail in the next chapter.

Patients who experience lower limb weakness and difficulty walking after stroke are typically admitted to an inpatient rehabilitation unit for a period of intensive rehabilitation. Rehabilitation of walking is usually provided by physiotherapists, with occupational therapists building on these skills during other functional tasks. Rehabilitation typically consists of a combination of lower limb, trunk, balance, and walking exercises with a focus on task-oriented training (Winstein and Kay, 2015). The New Zealand Stroke Guidelines state that patients should receive one hour of physiotherapy a day (2010), although in reality it is likely that this does not always happen due to caseload demands, patient illness, medical appointments, and patient motivation (McNaughton et al., 2014). Also, therapy time does not equate to actual time in active rehabilitation (Bernhardt et al., 2007).
Despite potentially lower than recommended doses of lower limb therapy, outcomes for walking are typically better than for the upper limb. The upper limb relies on an intact corticospinal tract to perform fine distal manipulation tasks which are required for virtually all upper limb activities. This means that damage to the corticospinal tract can be devastating for upper limb recovery as alternative descending pathways to the upper limb only have minimal contribution to the distal limb. It is not possible to compensate for a non-functional hand and arm except by using the other arm to achieve the task.

In contrast, walking primarily requires postural control and proximal control of the legs in conjunction with the CPG. Compensation for distal weakness occurs during swing phase with the activation of proximal muscle groups to exaggerate hip flexion or to circumduct the hip. The use of an ankle splint is also common for foot drop. Another important compensation strategy is the shifting of weight to the intact side and using trunk rotation to assist with swing phase. During stance, shifting weight to the intact side, utilising a hyperextended paretic knee as a “strut”, reducing the length of time spent in single support on the affected leg, or using a stick, minimises the requirement for lower limb control during weight bearing. Patients with damage to the corticospinal tract may still have access to alternative descending motor pathways such as the reticulospinal tract and the vestibulospinal tract. This may lead to the ability to regain enough postural and proximal control to perform these compensatory adjustments and walk independently. Yet, despite these advantages over the upper limb, even with a period of rehabilitation, only 40-60% of patients with stroke who are initially unable to walk independently recover independent walking (Jorgensen et al., 1995; Kollen et al., 2006). This means the impact of stroke on walking is significant and the ability to predict recovery from walking and improve walking after stroke is highly clinically relevant.
The next chapter is an invited review which discusses the neuroplastic mechanisms of stroke recovery and implications for clinical practice. This will lead into chapter 4 which will discuss the different types of walking outcomes considered in stroke research and rationale for the selection of outcome measures used in this thesis.
Chapter 3. Plasticity and motor recovery after stroke

This chapter is abridged with permission from the full literature review published in the New Zealand Journal of Physiotherapy:


3.1. Introduction

The purpose of this commentary is two-fold. Firstly, to consider recent developments in the study of spontaneous biological recovery and use-dependent plasticity after stroke, and secondly, to discuss how motor training interacts with recovery mechanisms. We then consider what this means for the practising physiotherapist.

3.2. Distinction between impairment and function

One challenge in reviewing the literature in stroke rehabilitation is the interchangeable use of terms such as functional recovery, motor recovery, motor impairment and compensation (Levin et al., 2009). Defining these terms clearly will reduce confusion. Levin and colleagues (2009) suggest aligning these terms with the World Health Organisation International Classification of Functioning (ICF) items of “body structure and function” and “activity”. For the purposes of this commentary, motor impairment refers to the ability to perform a movement (“body structure and function” level of the ICF) and can be evaluated with measures of strength and motor control. Function refers to the ability to perform a task (“activity” level of the ICF) and can be measured as task completion or time taken to complete the task.

True neurological recovery requires resolution of impairment, which allows movements and activities to be performed in the same way as before the stroke (using the same neural
connections and motor patterns). Functional recovery, however, can still occur without full resolution of impairment. Compensation for residual impairment enables the recovery of function by using alternative neural connections and/or different patterns of muscle activity. For example, during a reaching task, the patient may compensate by: accessing different neural connections; altering the timing of muscle activation resulting in an altered movement pattern; using a combination of shoulder abduction and flexion instead of pure flexion; using an alternate grip; and/or they may lean forward with the trunk. These compensations allow the patient to achieve a functional reach, despite their residual impairment.

Improvement in function can occur without any change in impairment, and recovery from impairment does not always lead to functional improvement (Buma et al., 2013; Kitago et al., 2013; Kwakkel et al., 2015). As the use of task-specific training has become established in stroke rehabilitation (Winstein and Kay, 2015), most motor outcome measures assess functional recovery. These measures assess whether a task is completed or not, or how fast it is completed, rather than how well it is completed. They are unable to distinguish between an improvement in function due to a reduction in impairment, or an improvement in function due to compensation (Kitago and Krakauer, 2013). Yet, this distinction is critical in understanding the biological mechanisms of recovery and therefore in understanding the role of physiotherapy in this process (Zeiler and Krakauer, 2013).

3.3. Spontaneous biological recovery and proportional resolution of impairment

Spontaneous biological recovery is motor recovery that occurs in the absence of motor training after ischaemic injury to the brain (Cramer, 2008; Nudo, 2011; Zeiler and Krakauer, 2013) and has been reported in both animals and humans after stroke (Carmichael, 2010; Nudo, 2011; Krakauer et al., 2012). Ischaemia in the peri-infarct area triggers a cascade of
effects (Xing et al., 2012) ultimately resulting in upregulation of genes responsible for
neuronal growth (heightened neuroplasticity), increases in long term potentiation (enabling
strengthening of synapses and improved neurotransmission), alterations in excitation and
inhibition via neurotransmitters in the lesioned cortex, and axonal sprouting around the
infarct site (Hagemann et al., 1998; Carmichael, 2006; Brown et al., 2007; Zeiler and
Krakauer, 2013). This period of heightened sensitivity in the brain begins within hours of
stroke onset and lasts up to one month in animals and around three months in humans,
although the time frame may vary with individuals or stroke severity (Carmichael, 2006;
Cramer, 2008; Krakauer et al., 2012). Rapid improvements occur in both impairment and
function during this sensitive period.

The importance of spontaneous biological recovery in the resolution of impairment after
stroke has been established by the discovery of the Proportional Recovery Rule. Prabhakaran
et al. (2008) investigated the resolution of impairment in the upper limb using the Fugl-
Meyer scale (FM) in 41 patients with stroke. The FM scale is used to measure strength and
motor control in the affected limb (Fugl-Meyer, 1980). Patients were assessed within 72
hours of stroke and again three and six months after stroke. The degree of initial impairment
was defined as the maximum FM score possible minus the baseline FM score. For example,
if a patient scores 26/66 on baseline FM, their initial impairment is 66 – 26 = 40 points.
Prabhakaran et al. (2008) discovered that by three months after stroke, patients reduced their
impairment by an almost fixed amount of 70%. In other words, patients recovered 70% of
the movement (at an impairment level) that they lost due to the stroke. Using the example
above, this means that although the maximum improvement available was 40, the actual
increase in FM score was only 0.7 x 40 = 28, making the final FM score 26 + 28 = 54.

This phenomenon of proportional resolution of impairment in the upper limb after stroke
has since been replicated in several other studies (Marshall et al., 2009; Zarahn et al., 2011;
Byblow et al., 2015; Feng et al., 2015; Winters et al., 2015). A study by Lazar et al. (2010) examined resolution of impairment in aphasia after stroke and reported that it also follows proportional recovery between baseline and 90 days. This finding supports the theory that proportional recovery may be generalizable across other functional domains (Winters et al., 2015). The proportional resolution of impairment is consistent across patient samples from four different countries, with different rehabilitation services and for patients of both genders, all ages and ethnicities. This indicates that it is likely to reflect a fundamental spontaneous biological recovery mechanism, about which we currently know very little (Prabhakaran et al., 2008; Byblow et al., 2015b; Krakauer and Marshall, 2015).

Another interesting finding is the lack of influence of physiotherapy and occupational therapy on proportional resolution of impairment. Byblow et al. (2015) measured impairment using the FM at 2, 6, 12 and 26 weeks after stroke in 93 patients. Patients were separated into: 1) a standardised therapy cohort who received 30 minutes of upper limb therapy five days a week for four weeks in addition to standard care, and 2) a variable therapy cohort who received standard care with therapy dose determined by the treating therapist based on clinical judgement (ranging from 0 to 803 minutes of total upper limb therapy time). Participants with functionally intact corticospinal tracts (CST) followed the proportional recovery rule regardless of their initial impairment, the group they were in or their therapy dose, indicating that therapy did not have an influence on resolution of impairment (Byblow et al., 2015; Krakauer and Marshall, 2015). These results indicate that current physiotherapy practice has not yet found a way to enhance spontaneous biological recovery (resolution of impairment) early after stroke.

Some patients with severe initial impairment exhibit proportional recovery, while others do not and recover by less than 70%, or not at all. Unfortunately, there is no clinical assessment that can identify which patients will follow the 70% rule and which ones will not.
A recent study showed that a functional CST is required to achieve proportional resolution of impairment. Patients whose CST is no longer able to transmit descending motor commands do not exhibit proportional resolution of impairment (Byblow et al., 2015), and these patients also achieve a poor functional recovery of the upper limb (Stinear, 2010a; Stinear et al., 2012). These findings demonstrate that without a viable connection between the brain and the muscles, any neuroplastic reorganisation occurring in the cortex, whether due to spontaneous biological processes or use-dependent plasticity, is largely redundant.

It is not clear why impairment resolves by around 70%, and not some other number. This threshold may reflect inefficient and incomplete re-myelination of damaged axons in the descending motor pathways (El Waly et al., 2014; Byblow et al., 2015). This possibility, and other potential mechanisms, remain to be explored.

To date, there have been no published studies investigating proportional recovery in the lower limb. For the lower limb, there are more projections to the corticospinal pathway from the contralesional (unaffected) cortex than for the upper limb (Jang et al., 2005; Dawes et al., 2008). There are also several alternative pathways involved in generating movement in the legs and trunk such as the vestibulospinal and reticulospinal tracts which receive bilateral inputs (Nathan et al., 1996; Matsuyama and Drew, 2000; Jang et al., 2013a). This means the damage from the stroke may be compensated for by other existing motor pathways and descending control from the contralesional cortex. For these reasons, it is possible that if proportional recovery of the lower limb does occur, it may differ from the upper limb.

The proportional recovery rule enables clinicians and researchers alike, for the first time, to quantify spontaneous biological recovery after stroke in humans. While using functional outcome measures remains an essential part of research into interventions aimed at improving function, the inclusion of impairment-based measures may assist in understanding the
neurobiological mechanisms underpinning the recovery process, ultimately targeting future therapies more effectively.

To summarise these findings, return of movement at an impairment level after stroke is a spontaneous process controlled by biological mechanisms, which occurs in the first three months after stroke and is not influenced by current therapy practices. This does not mean that rehabilitation early after stroke is ineffective but rather that it promotes neurological compensation (such as cortical reorganisation) in order to improve function rather than restoring damaged neural networks.

3.4. Use-dependent plasticity

Neuroplasticity can be defined as “the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganising its structure, function and connections” (Cramer et al., 2011). The discovery that the brain has the capacity to change in response to both experience and injury transformed our understanding of mechanisms underlying training effects and learning both in the healthy and injured brain (Nudo, 2006; Winstein and Kay, 2015).

Use-dependent or experience-dependent plasticity was originally discovered in animal models. Motor training was found to increase synaptic efficacy and long term potentiation (strengthening of synapses), and induce synaptogenesis, axonal sprouting and formation of dendritic spines (Jones et al., 1999; Carmichael, 2006; Brown et al., 2009; Krakauer et al., 2012). These cellular effects are accompanied by enlargement of the cortical motor map specific to the limb involved in the training (Nudo et al., 1996a; Nudo, 2006).

The concept of plasticity has driven our rationale for rehabilitation, however there are some challenges inherent in applying research in animal models to stroke recovery in humans. Firstly, the rodent brain is structurally quite different from the human brain with
much less white matter relative to grey matter (Wang et al., 2016). Secondly, in animals, a stroke is artificially induced in a specific and localised area (usually the motor cortex). This creates a pure cortical infarct which spares adjacent cortical areas and white matter pathways (Wang et al., 2016). In contrast, in humans, the majority of stroke damage is likely to be in subcortical regions (Bogousslavsky et al., 1988; Kang et al., 2003; Wessels et al., 2006; Corbetta et al., 2015), with damage not only to grey matter but also to ascending and descending white matter tracts and white matter connections between cortical and subcortical structures (Corbetta et al., 2015; Wang et al., 2016). This results in a disruption in the brain’s ability to transmit a message not only via descending pathways to the muscles, but also between cortical regions.

In other words, our understanding of neuroplasticity comes from examining pure cortical infarcts in animals with great capacity for reorganisation within surrounding grey matter, and is being applied to stroke in humans, which is predominantly a white matter disconnection problem (Corbetta et al., 2015).

The distinction between pure cortical damage and subcortical damage is important when considering the effects of stroke and how neuroplasticity shapes stroke recovery. Stinear and colleagues (2012) reported that recovery of upper limb function after stroke requires a functional CST. No amount of training-induced cortical plasticity will enable motor function to improve if the white matter motor pathways are irreparably damaged, as there is very little capacity within the human motor system to use alternative pathways (Krakauer and Marshall, 2015).

3.4.1 **Synaptic (grey matter) plasticity**

Synaptic plasticity occurs in the cortical grey matter through mechanisms such as synaptogenesis, increased synaptic efficacy and altered neurotransmitter levels. Animal
research forms the basis of our understanding of synaptic plasticity in the human brain, and provides some fundamental concepts of motor learning and plasticity such as the importance of therapy intensity (MacLellan et al., 2011), time-sensitivity (Biernaskie and Corbett, 2001; Biernaskie et al., 2004; Carmichael, 2006) and the effect of environmental enrichment (Johansson and Ohlsson, 1996; Biernaskie and Corbett, 2001; Krakauer et al., 2012).

Synaptic plasticity is sensitive to many inputs from other regions of the cortex (Murphy and Corbett, 2009), which is why reward, motivation, attention, the environment, task variation and challenge are important (Biernaskie and Corbett, 2001; Wulf et al., 2012; Winstein and Kay, 2015). A study in squirrel monkeys compared the effects of simple task repetition (practice) with learning a new task and reported that changes in cortical motor map representation only occurred after training on the new task, not with simple high repetition practice (Plautz et al., 2000). This means that synaptic plasticity occurs with motor learning not with repetitive practice alone (Remple et al., 2001).

Further research in motor learning in both healthy adults and adults with stroke has highlighted three main principles for motor learning. In order for learning to occur, the motor training must be challenging (both in intensity and difficulty), it must be progressive and adapted over the practice period (variability and novelty are important), and the patient must be motivated (the task must be meaningful). These principles have led to the development of task-oriented training as the recommended rehabilitation focus for motor skill learning after stroke (Cramer et al., 2011; Winstein and Kay, 2015).

Synaptic plasticity drives functional recovery after stroke, and large gains may be made early after stroke, often in the face of residual impairment. This is achieved through the use of neurological compensation (cortical reorganisation and increasing efficiency of surrounding synapses) (Whishaw et al., 2008; Moon et al., 2009; Buma et al., 2013; Kitago
and Krakauer, 2013). There are two important points to remember when embarking on a
rehabilitation programme aimed at improving synaptic plasticity. Firstly, time frame is
critical. Once outside the sensitive period of the first three months after stroke, the capacity
for neuroplasticity in the stroke brain returns to that of the non-injured brain (Biernaskie et
al., 2004; Carmichael, 2006; Krakauer et al., 2012). Harnessing the heightened plasticity in
the first three months is essential.

Secondly, although functional recovery occurs largely through synaptic plasticity, it is
still reliant on intact white matter (Jang et al., 2010; Borich et al., 2014; Corbetta et al.,
2015). Irreparably damaged motor tracts prevent the message from being sent to the muscles.
For the upper limb, it is possible to identify which patients have sustained severe damage to
the white matter pathways and which patients have spared white matter pathways using a
combination of clinical assessments, transcranial magnetic stimulation and magnetic
resonance imaging (Stinear et al., 2012). Unfortunately, this type of prediction algorithm has
not yet been established in the lower limb.

3.4.2 White matter plasticity

White matter plasticity occurs in the white matter tracts through mechanisms which
promote structural changes such as remyelination of axons and axonal sprouting (Fields,
2005; Brown et al., 2007; McIver et al., 2010; Clarkson et al., 2013; Zheng and Schlaug,
2015; Wang et al., 2016). These changes may contribute to recovery of transmission in the
motor pathways. White matter plasticity may contribute to spontaneous biological recovery
(Dancause et al., 2005; Carmichael, 2006; Zeiler and Krakauer, 2013) and research in animal
models has shown that it is also use-dependent (Sanchez et al., 1998; Fang et al., 2010;
Clarkson et al., 2013). Increased axonal firing in response to activity stimulates the
proliferation of oligodendrocytes which are responsible for remyelination of the axons and
may also provide the stimulus for axonal sprouting, and synaptogenesis (Juraska and Kopceik, 1988; Carmichael and Chesselet, 2002; McIver et al., 2010; Simon et al., 2011)

We do not know yet how to promote white matter plasticity after stroke, but the hypothesis is that there is a training response that is dose-dependent (Bengtsson et al., 2005; Fields, 2005; Nudo, 2011; Kwon et al., 2012). Exactly how many repetitions are required to generate a change in white matter has not been investigated in humans, but it is expected to be very high (Krakauer et al., 2012). One study in humans has attempted to look at the effects of training on white matter (Scholz et al., 2009). Twenty-four healthy adults underwent a six-week training programme for a juggling task. The authors concluded that training improved the structural organisation of the axonal bundles, possibly due to increased myelination and/or axon calibre. They hypothesised that this may lead to increased conduction velocity and better synchronisation of descending motor commands (Scholz et al., 2009). This preliminary work in healthy adults provides some direction for future research into promoting white matter plasticity in humans. Other potential avenues for investigating white matter plasticity interventions after stroke are pharmacological interventions such as medications that interact with myelin formation, neurophysiological interventions, such as non-invasive brain stimulation, or robotics to support high-repetition practice.

3.5. Motor training and use-dependent plasticity

Motor training makes up the bulk of physiotherapy rehabilitation after stroke and aims to improve function through skill learning and adaptation. The highly neuroplastic state that exists in the first months after stroke means that the brain is primed for growth and change. However this plasticity is not targeted, but occurs indiscriminately throughout the cortex (Zeiler and Krakauer, 2013). This means the plasticity can be either adaptive, leading to an improvement in function (Cohen et al., 1997; Dancause and Nudo, 2011), or maladaptive,
leading to loss of function or other negative consequences such as seizures or pain disorders (Karl et al., 2001; Nudo, 2006; Prince et al., 2009).

Examples of maladaptive motor plasticity after stroke are the development of compensatory movement patterns out of proportion to the level of impairment and cortical reorganisation due to learned non-use (Sunderland and Tuke, 2005; Krakauer, 2006; Wolf et al., 2006; Whishaw et al., 2008; Winstein and Kay, 2015). Motor training may facilitate adaptation and prevent maladaptation by directing and shaping the cortical reorganisation as it occurs (Nudo et al., 1996b; Huang et al., 2008; Carmichael, 2010; Kitago and Krakauer, 2013). A useful analogy for this is to imagine a tree planted in exceptionally fertile ground. Rapid growth occurs randomly in all directions and requires pruning to shape and increase the efficiency of the growth, analogous to the role of the physiotherapist in rehabilitation after stroke.

One reason that task specific functional training may primarily promote compensatory reorganisation is that there is usually an incentive and a requirement for the task to be completed immediately. This means that the brain may choose to bypass the damaged networks in favour of compensation in order to achieve the goal. This form of reinforcement learning may lead to preferential selection of these alternative motor strategies in the future and establishing a new motor pattern to complete the task (Huang et al., 2011; Kitago and Krakauer, 2013).

There have been suggestions that early motor training should only include very high intensity impairment training in the absence of functional training, in order to reduce early compensation and to promote attempts to access the damaged neural pathways (Krakauer et al., 2012). However, this approach is highly impractical in a setting where health resources are limited and patients are intent on getting home as soon as possible. Returning some focus
to impairment training and increasing focus on quality of movement rather than task completion may start to lead us in the right direction.

Gains in function produced by motor training carried out six months or more after stroke are almost certainly due to compensatory mechanisms, and for this reason, improvements will be relatively small (Raghavan et al., 2010; Zeiler and Krakauer, 2013; Lefebvre et al., 2015). By this time, the impairment resolution process is complete. Training in the chronic stage teaches the patient how to use the movement that they already have in a more effective way (Kwakkel et al., 2015). There is evidence that improving function occurs in the absence of further impairment resolution, however, the effects of the residual impairment do contribute to the poor quality and increased energy expenditure of the movement (Page et al., 2008; Massie et al., 2009).

A small study recently investigated the neurological basis for constraint-induced movement therapy (CIMT) in patients with chronic stroke (Kitago et al., 2013). They demonstrated that a two-week programme of CIMT improved functional use of the arm as assessed with the action research arm test (ARAT). However, joint kinematic data and upper limb motor impairment (FM) showed no improvement after CIMT (Kitago et al., 2013). In other words, CIMT did not improve their movement patterns or underlying impairment. This is an example of using an impairment assessment alongside a functional one to establish that functional improvements were a result of neurological compensation rather than restoring damaged networks.
3.6. What does this mean for rehabilitation after stroke?

Spontaneous biological recovery and use-dependent plasticity are powerful drivers towards recovery early after stroke. Understanding the difference between neurological recovery in the first 12 weeks after stroke and in the chronic stage will help direct the physiotherapist in decision making about a particular treatment modality in both stages of stroke recovery.

The discovery of proportional recovery from impairment, for the first time, provides insight into the ceiling effect on stroke recovery we so often see in our patients. This research necessitates a shift in thinking away from the classic neuroplasticity model which has long suggested that the brain has unlimited capacity to keep remodelling and changing with skill learning throughout adulthood. Although the capacity of the cortex to undergo synaptic plasticity after stroke is the same as in a healthy adult, damage to white matter structures places some definite limitations on the beneficial effects of this reorganisation. Quite simply, if there is no way to communicate between the brain and the body, there is no capacity for motor recovery no matter how much cortical reorganisation occurs. Fortunately, in most patients with stroke, damage to the white matter connections is not complete, providing a substrate for communication between the reorganised cortex and body.

The next chapter will discuss clinical measures of lower limb impairment and walking function and how they may be used to measure walking recovery after stroke.
Chapter 4. Clinical measures of the lower limb and walking after stroke

Clinical measures are commonly used to assess impairment or function after stroke. In research, they may be used for selection and baseline characterisation of patients, to measure recovery between two time points, to measure outcomes at a single time point, or to measure the response to an intervention. By distinguishing between impairment and function, clinical measures may also provide useful information about the biological mechanisms underpinning recovery or the response to an intervention (Buma et al., 2013; Kitago et al., 2013). This chapter will provide a detailed review of the most commonly used clinical measures for the lower limb and walking in stroke and provide rationale for the selection of the measures used in this thesis.

4.1. What is walking recovery?

Full recovery of walking after stroke can be defined as regaining pre-stroke walking ability. For most patients this means being able to walk in the community and participate in meaningful activities such as returning to work or study, going shopping or meeting with friends and family (Bohannon et al., 1988). This complex ability can be broken down into smaller areas of focus. To walk in the community, the patient must first achieve independent walking. Walking indoors on a flat surface is key to being able to live independently, while walking outside provides greater challenges and requires the ability to safely negotiate slopes, kerbs, steps, and uneven ground. A second contributor to community ambulation is walking performance, or how well a person walks. Increasing walking speed, improving the quality of the walking pattern by reducing compensatory movements, improving symmetry, and increasing walking endurance may increase the likelihood of successful community ambulation (Perry et al., 1995; Hill et al., 1997; Shumway-Cook et al., 2002; Lord et al.,
2004; Fulk et al., 2010; Veerbeek et al., 2014; Awad et al., 2015b). Thirdly, an important consideration is not only whether a patient is able to walk in the community, but whether they actually do it in daily life. Walking recovery can therefore be divided into three main areas of focus: independent walking, walking performance, and participation (figure 4.1).

**Figure 4.1** Recovery of walking

Contributors to community ambulation after stroke include the recovery of independent walking, improved walking performance, and participation. Independent walking is achieved first, followed by improved walking performance. Once the patient has achieved the necessary physical skills to walk in the community, factors influencing participation largely determine whether community ambulation is achieved.

The ability to walk independently may facilitate discharge home from hospital rather than to a residential care facility, and reduces the burden on carers and family (Hill et al., 1997). Walking independently within the home usually requires the ability to walk over a flat surface for a short distance but doesn’t require the person to walk quickly (Perry et al., 1995; Schmid et al., 2007). Many homes have stairs but it is usually possible to modify living
arrangements to allow someone to stay on one level. The rehabilitation team usually advises the patient and family member whether the patient is safe to walk independently within the home but final decisions about living arrangements are made by the patient and their family.

Walking performance refers to how well a person can walk and therefore influences whether they are limited to household ambulation or are able to walk outside and participate in community activities. There is a clear relationship between walking speed and the ability to walk in the community (Perry et al., 1995; Shumway-Cook et al., 2002; Lord et al., 2004; Schmid et al., 2007; Fulk et al., 2010), and also between walking speed and falls risk (Forster and Young, 1995). Perry et al. (1995) reported that a walking speed of less than 0.4 metres per second (m/s) equates to indoor walking only, a walking speed between 0.4 to 0.8 m/s equates to limited walking in the community, and a walking speed greater than 0.8 m/s enables unlimited community ambulation. These speed-based stratifications have been replicated in a later study (Schmid et al., 2007), and have been used as an indicator of community ambulation ability in prediction studies (Bland et al., 2012).

However, walking speed alone is not enough to determine whether a person is able to walk in the community (Hill et al., 1997; Lord and Rochester, 2008; Mudge and Stott, 2009). A person needs to be able to walk at least 300 m without stopping at an average speed of 0.8 m/s in order to walk comfortably in the community (Shumway-Cook et al., 2002; Lord et al., 2004; Schmid et al., 2007; Lord et al., 2008; Fulk et al., 2010). The ability to walk at 0.8 m/s over the commonly used test distance of 10 metres does not necessarily mean a person is able to walk 300 m at the same speed and therefore whether they will achieve community ambulation (Dean et al., 2001; Taylor et al., 2006; Fulk et al., 2010).

Asymmetrical and compensatory walking patterns contribute to slower walking speeds (Awad et al., 2015b). Walking asymmetry is also associated with an increased metabolic
cost of walking (Ellis et al., 2013; Finley et al., 2013; Awad et al., 2015a; Finley and Bastian, 2017), which may reduce walking endurance. The greater energy requirements of walking after stroke may lead to inactivity, further reducing endurance and limiting community ambulation. Walking activity after stroke is very low, with stroke survivors taking only half the number of steps per day that sedentary older adults take (Michael et al., 2005).

Mahendran et al. (2016) reported that over the first six months after hospital discharge, people increase the amount of time spent sitting and most bouts of walking consist of fewer than 40 steps. Improving walking pattern and symmetry may reduce the metabolic cost of walking, reducing one of the barriers to physical activity after stroke.

The complexity of community ambulation means that improvements in walking speed, endurance or gait symmetry do not always translate into participation in community ambulation and community activities (Hill et al., 1997; Lord et al., 2004; Lord and Rochester, 2008). A New Zealand based study of thirty patients at the subacute stage of stroke reported that despite substantial gains in walking speed after a physiotherapy programme on discharge from hospital, only a small number of patients achieved self-reported independence in the community (Lord et al., 2008). This suggests that while walking performance contributes to whether a patient participates in community ambulation after stroke, it does not explain inter-individual variability in participation. Cognition, balance, depression, and self-efficacy may be strong determinants for community ambulation (Robinson et al., 2011). Other factors include: a person’s environment such as weather (snow/ice); living rurally or living on a steep hill; difficulties accessing transport; level of social support; and fears of how they may be perceived in the community (Shumway-Cook et al., 2002; Robinson et al., 2011).

In summary, the end-goal of walking recovery is walking in the community. There are three elements needed for successful community ambulation: independent walking; walking
performance; and participation. This thesis focuses on two of these aspects: firstly, the recovery of independent walking, as this is the primary inpatient rehabilitation goal and facilitates discharge from hospital (Bohannon et al., 1988); and secondly, for those patients who can walk independently, improving walking performance by reducing asymmetry.

4.2. Selection of clinical measures

Clinical measure selection requires careful consideration of what aspect of walking the prediction study or rehabilitation trial is targeting and the underlying biological mechanisms of interest (Kitago and Krakauer, 2013; Veerbeek et al., 2014; Bernhardt et al., 2016). It is important to be clear whether improvements are expected in impairment or function and to select outcome measures accordingly (Levin et al., 2009). It may also be useful to include measures of both function and impairment to determine whether functional improvements are a reflection of restoring damaged neural networks (reducing impairment), compensation through motor learning, or both (Buma et al., 2013; Kitago et al., 2013). Finally, the clinical measures need to be both specific and sensitive to the target behaviour (Veerbeek et al., 2014). For example, a global disability measure such as the modified Rankin scale (mRS) (van Swieten et al., 1988) is unlikely to detect a significant effect in a study aimed at improving walking or activity levels after stroke.

Impairments in a range of domains can affect walking function. These impairments depend on the location of the stroke and may include lower limb weakness, lower limb spasticity or abnormal muscle tone, loss of lower limb sensation, poor trunk control and balance, visuospatial neglect, vision loss, and cognitive impairment. This chapter will discuss the selection of measures of impairment in lower limb strength and trunk control, as these are strongly related to regaining independent walking after stroke (Collin and Wade, 1990; Friedman, 1990; Jorgensen et al., 1995; Sánchez-Blanco et al., 1999; Kollen et al.,
Lower limb muscle power, particularly plantar flexion propulsion, is also strongly related to speed and symmetry of walking after stroke (Balasubramanian et al., 2007, Allen et al., 2011). This chapter will also discuss the selection of functional measures of independent walking and walking performance (speed and symmetry) and identify the most commonly used measures in each of these categories (Figure 4.2).

**Figure 4.2** Most commonly used clinical measures for the recovery of the lower limb and walking.

FAC = Functional Ambulation Categories; FIM = Functional Independence Measure; SSC = Scandinavian Stroke Scale; TUG = Timed Up and Go; MRC = Medical Research Council grade; MI = Motricity Index; PASS = Postural Assessment Scale for Stroke.
This thesis includes three studies with patients who have experienced a stroke: two prediction studies at the subacute stage, and one intervention study at the chronic stage. The first prediction study (Chapter 7) investigated recovery from motor impairment of the lower limb, while the second prediction study (Chapter 8) investigated potential predictors for the time taken to recover independent walking after stroke. These studies required an impairment measure of lower limb movement and a functional measure of independent walking, respectively. Both of these studies also required measures that could be used at baseline to predict subsequent recovery and outcome. The intervention study (Chapter 9) investigated the effects of unilateral step training on walking performance (symmetry and speed). This required a walking speed measure suitable for a clinic setting and a laboratory research tool for measuring walking symmetry.

The following databases of clinical measures were searched: Academy of Neurologic Physiotherapy (strokEDGE), EBRSR.com (Outcome measures in stroke rehabilitation), Canadian Partnership for Stroke Recovery (Stroke Engine), and Shirley Ryan Ability Lab Rehabilitation Measures Database. Measures were selected by taking into account their validity, reliability, floor and ceiling effects, and for the prediction studies, their practical use by clinicians in the busy ward environment in patients within 3 - 7 days of stroke. When considering the recommendations from the above databases, the intended use of the tool (which may be different to that in the clinical setting referred to in these databases), the stroke severity of the target population, and the robustness of the reliability and validation studies were also taken into account. This section is not intended as a critique of the reliability and validation studies but rather a critique of the relative advantages and disadvantages of the measures themselves in the context of this thesis. The measures selected for use in this thesis are summarised in Table 4.1.
Table 4.1 Selected clinical measures for the lower limb and walking

<table>
<thead>
<tr>
<th>Measure</th>
<th>Summary</th>
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<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
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<tr>
<td><strong>Lower limb strength and movement</strong></td>
<td></td>
</tr>
<tr>
<td>Medical Research Council grade (MRC)</td>
<td>Assesses:</td>
</tr>
<tr>
<td></td>
<td>Strength of muscles performing a single movement at a joint</td>
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<tr>
<td></td>
<td>Scoring:</td>
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<tr>
<td></td>
<td>Each movement is scored out of 5, with zero being no movement and 5 being full power</td>
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<tr>
<td></td>
<td>Scores are not summed</td>
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<tr>
<td></td>
<td>Specificity:</td>
</tr>
<tr>
<td></td>
<td>Not specific to stroke</td>
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<tr>
<td></td>
<td>Use:</td>
</tr>
<tr>
<td></td>
<td>Frequently used clinically</td>
</tr>
<tr>
<td></td>
<td>Rarely used in stroke research as a measure of recovery or outcome</td>
</tr>
<tr>
<td></td>
<td>Resources:</td>
</tr>
<tr>
<td></td>
<td>No equipment required, takes 5 minutes</td>
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<tr>
<td>Motricity index</td>
<td>Assesses:</td>
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<tr>
<td></td>
<td>Provides overall indication of motor impairment after stroke</td>
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<tr>
<td></td>
<td>Scoring:</td>
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<tr>
<td></td>
<td>Three movements, each scored out of 33, with zero being no movement and 33 being full power</td>
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<tr>
<td></td>
<td>Hip flexion, knee extension, ankle dorsiflexion</td>
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<tr>
<td></td>
<td>Maximum score = 100 (99 + 1 point)</td>
</tr>
<tr>
<td></td>
<td>Specificity:</td>
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<tr>
<td></td>
<td>Specific to stroke</td>
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<td></td>
<td>Use:</td>
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<td></td>
<td>Rarely used clinically</td>
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<td></td>
<td>Frequently used in research</td>
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<td></td>
<td>Resources:</td>
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<td></td>
<td>No equipment required, takes 5 minutes</td>
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</tbody>
</table>
| Fugl-Meyer Scale, Lower limb (FM) | **Assesses:**  
| | Impairment of limb movement, reflexes, coordination, balance, sensation  
| | Only the motor component is commonly used  
| **Scoring:**  
| | Seventeen items scored 0, 1 or 2  
| | Maximum score = 34  
| **Specificity:**  
| | Specific to stroke  
| **Use:**  
| | Rarely used clinically  
| | Most commonly used motor impairment measure in research  
| **Resources:**  
| | Reflex hammer  
| | Takes 10 minutes for the lower limb component  
| **Postural control**  
| **Trunk control test (TCT)** | **Assesses:**  
| | Static and dynamic trunk control  
| | Rolling to each side, lie to sit, and static sitting balance  
| **Scoring:**  
| | Four items, each scored 0, 12 or 25  
| | 0 = unable; 12 = independent with aid or abnormal movement; 25 = independent with normal movement  
| | Maximum score = 100  
| **Specificity:**  
| | Specific to stroke  
| **Use:**  
| | Rarely used clinically  
| | Used in prediction research  
| **Resources:**  
| | No equipment required  
| | Takes 5 minutes  

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<table>
<thead>
<tr>
<th><strong>Function</strong></th>
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<tbody>
<tr>
<td><strong>Independent walking</strong></td>
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<tr>
<td><strong>Functional ambulation categories (FAC)</strong></td>
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<table>
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<tr>
<th><strong>Walking performance</strong></th>
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<tr>
<td><strong>10 metre walk test</strong></td>
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<td>GAITRite®</td>
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<tr>
<td>Spatiotemporal parameters of gait</td>
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</tbody>
</table>

**Scoring:**
- Spatiotemporal parameters recorded while patient walks on a 4 metre long instrumented mat

**Specificity:**
- Not specific to stroke

**Use:**
- Rarely used clinically
- Commonly used in biomechanical research

**Resources:**
- Specialised laboratory equipment: GAITRite instrumented mat, computer and software for processing data
- Time taken depends on number of walks
- Requires time for processing data
4.3. Impairment: lower limb strength and movement

The two most commonly used measures for lower limb strength are the Motricity Index and the Medical Research Council (MRC) grading. The lower limb component of the Fugl-Meyer scale is a detailed assessment of lower limb movement including movement synergies, reflexes and coordination (Table 4.1). All three of these measures are used in this thesis for different purposes, as will be discussed below.

Medical research council (MRC) grade and lower limb Motricity Index

The MRC grades and Motricity Index are forms of manual muscle testing used to measure muscle strength. The key difference between these two measures is that the MRC provides an individual score for a specific movement at any joint, whereas the lower limb Motricity Index provides a more global picture of lower limb strength with the selection of only three muscle groups and a single summed total (Demeurisse et al., 1980; Collin and Wade, 1990). The MRC is an ordinal scale, whereas although the test procedure for the Motricity Index is the same as the MRC, the Motricity Index scores are weighted, with a larger gap between scores when progression to the next score is more difficult to achieve. Despite well-established overall reliability (ICC > 0.86) and validity (r > 0.77) (Bohannon, 1986; Wadsworth et al., 1987; Collen et al., 1990; Collin and Wade, 1990; Cameron and Bohannon, 2000), both scales are slightly less reliable for higher scores which require the application of resistance by the assessor, due to the subjective nature of this component (Bohannon, 1986; Aitkens et al., 1989; Collen et al., 1990).

This reduction in reliability during manual muscle testing at higher levels of resistance suggests that the use of an objective tool such as hand-held dynamometry may be of benefit. The reliability (ICC > 0.78) (Bohannon, 1986; Wadsworth et al., 1987; Riddell et al., 1989; Cameron and Bohannon, 2000), and validity (r > 0.76) (Cameron and Bohannon, 2000) of
hand-held dynamometry is established. The reliability and validity statistics are comparable to manual muscle testing, with dynamometry demonstrating similar reduced accuracy when higher levels of resistance were needed from the examiner, particularly when testing stronger lower limb muscle groups (Wadsworth et al., 1987). However, dynamometry requires the purchase of equipment which is not commonly accessible in the acute hospital setting, therefore it was not used as a strength measure in this thesis.

Another challenge with using manual muscle testing is that some muscle groups in the lower limb are difficult to test in an antigravity position. This has led to the development of timed sit to stand tests as a proxy measure for lower limb strength (Csuka and McCarty, 1985). These have the advantage of being quick to administer and requiring no specialised equipment. However it has since been reported that in patients with stroke, balance rather than lower limb strength is the main contributor to the timed sit to stand test scores (Ng, 2010). In addition, there is a substantial floor effect as the patient must be able to stand up independently with arms folded across their chest. This means that patients with moderate to severe stroke cannot complete the test, while those who can complete the test are likely already walking. Therefore the timed sit to stand tests are not a suitable alternative to manual muscle testing such as the MRC scale or motricity index as potential predictors for independent walking in this thesis.

Clinically, the MRC grading scale is useful as it enables clinicians to assess each muscle group separately. The MRC grades have also been used as predictors for the recovery of independent walking (Friedman, 1990; Olsen, 1990). However in both of these studies, a selection of only two or three muscle groups was used, with no rationale provided for the selection. This removes the potential advantages of considering all major lower limb muscle groups individually and in combination as potential predictors for walking recovery.
The Motricity Index is more commonly used than MRC grades in stroke research. The Motricity Index is very quick to administer and the use of a single score as an overview of lower limb strength allows classification of patients at baseline and measurement of improvement over time. However, a substantial limitation of the Motricity Index in the prediction of walking recovery is the inclusion of only three movements (hip flexion, knee extension and ankle dorsiflexion). Furthermore, the hip extensors and plantar flexors are not assessed but are arguably more important in walking than those assessed by the Motricity Index. Also, the use of a single score does not allow differentiation between patients with proximal or distal weakness, or varying degrees of weakness between the muscle groups. These limitations may affect the predictive value of the Motricity Index for the recovery of walking.

The Motricity Index, as a global measure of lower limb movement, is an important predictor of independent walking at six months (Sánchez-Blanco et al., 1999; Kollen et al., 2006; Veerbeek et al., 2011b). But for studies attempting to make finer grained predictions on an individual level, using individual MRC grades may provide a greater capacity to differentiate between individual patients. For these reasons, both the Motricity Index and individual MRC grades for lower limb muscle strength are included as potential predictors for the recovery of walking in this thesis.

Fugl-Meyer scale

The Fugl-Meyer (FM) scale is a stroke-specific impairment level measure of upper and lower limb movement, sensation and balance after stroke (Fugl-Meyer et al., 1975). The motor component of the FM is reliable (ICC > 0.86) and valid in the stroke population (r > 0.73) (Fugl-Meyer, 1980; Duncan et al., 1983; Sanford et al., 1993; Gladstone et al., 2002; Hsueh et al., 2008; Sullivan et al., 2011) and administration of the FM was standardised in
2011 (Sullivan et al., 2011). The motor FM is the most commonly used impairment measure in stroke (Gladstone et al., 2002). It is particularly responsive to change in the subacute stage after stroke, which reflects the timeframe during which most recovery from impairment occurs (Duncan et al., 2000; van der Lee et al., 2001; Krakauer et al., 2012). The use of the motor FM alongside functional measures has also provided important insights into the neurobiological effects of interventions during the chronic stage after stroke, identifying that most of these interventions produce modest improvements in function and do not reduce impairment (van der Lee et al., 2001). The most notable recent use of the motor FM is to measure proportional recovery from impairment in the upper limb (Prabhakaran et al., 2008; Marshall et al., 2009; Zarahn et al., 2011; Byblow et al., 2015; Feng et al., 2015; Winters et al., 2015; Stinear et al., 2017b).

A limitation of the motor FM is the ceiling effect, with responsiveness greatest in patients with moderate to severe impairment (Gladstone et al., 2002; Hsueh et al., 2008). This may be due to the omission of tests of fine distal control in either the hand or the foot. This is of particular concern when using the FM to measure proportional recovery in patients with mild stroke. Another limitation is the use of a three point ordinal scale (0, 1 or 2) to score items, potentially reducing responsiveness to change (Gladstone et al., 2002; Kitago et al., 2013). The lower total score of 34 points for the leg may be an important consideration when measuring proportional recovery from lower limb impairment, as there is less “room to move” on the scale than there is for the upper limb which has a total score of 66 points. Despite these limitations, the motor FM is the current standard for measuring motor impairment after stroke.

In summary, the MRC, Motricity Index and lower limb FM all provide important but different information about lower limb impairment after stroke. In this thesis, the Motricity Index is used to characterise patients at baseline, and both the Motricity Index and MRC
grades are used as potential predictors for the recovery of independent walking (Chapter 8). Although the inclusion of individual muscle MRC grades takes longer to assess and is challenging from a statistical perspective, this approach is novel and may provide important information that has been missed previously by using the more global Motricity Index. Finally, the FM is used here to determine whether recovery from lower limb motor impairment is proportional to initial impairment in the first three months after stroke (Chapter 7).

4.4. Impairment: trunk control

Trunk control early after stroke is a predictor for the recovery of independent walking (Franchignoni et al., 1997; Tsang and Mak, 2004; Masiero et al., 2007; Veerbeek et al., 2011b) and may therefore be an important independent variable for the second prediction study (Chapter 8). Trunk control and balance are often combined into a single clinical measure. In both clinical and research settings, a commonly used measure for trunk control and balance after stroke is the Berg balance scale. Other scales include the Trunk Control Test, the Trunk Impairment Scale and the Postural Assessment Scale for Stroke (PASS) (Figure 4.2). This section will explain the rationale for selecting the Trunk Control Test as the clinical measure for trunk control in the prediction of independent walking in Chapter 8 of this thesis.

Berg balance scale

The Berg balance scale is well established (reliability ICC > 0.87); validity r > 0.66) and used extensively to assess balance and predict falls risk in patients with stroke (Berg et al., 1992; Berg et al., 1995; Stevenson, 2001; Salbach et al., 2001; Mao et al., 2002; Flansbjer et al., 2012). The Berg balance scale was designed to detect improvement in balance in a clinical setting (Stevenson, 2001). However in the prediction study in this thesis, the
dependent outcome is time taken to achieve independent walking and not an improvement in balance. The posture or balance measure must therefore be sensitive enough to differentiate at one week after stroke between those who will recover independent walking early, those who will recover later, and those who will not recover independent walking at all. Floor effects may result in patients with moderate to severe stroke being grouped together rather than being differentiated. The Berg balance scale has substantial floor effects for patients early after severe stroke as most items are standing balance activities, with only one seated item (Mao et al., 2002). A measure specifically targeting trunk control in sitting and lying is more likely to be a sensitive predictor of walking outcomes in the moderate to severe patient group.

**Trunk Control Test**

The Trunk Control Test and the Trunk Impairment Scale both target trunk control rather than combining trunk control with standing balance (Collin and Wade, 1990; Verheyden et al., 2004). The Trunk Control Test is reliable ($r = 0.76$) and valid ($r > 0.80$) in the stroke population (Collin and Wade, 1990; Franchignoni et al., 1997). It only takes five minutes to administer and has predictive value for the recovery of independent walking and walking performance (Collin and Wade, 1990; Duarte et al., 2002; Kollen et al., 2006; Masiero et al., 2007). The lack of a floor effect means that this test is more likely to be able to differentiate between moderate and severely impaired patients at baseline than the Berg balance scale (Verheyden et al., 2006). The four items in the Trunk Control Test reflect what a physiotherapist is likely to evaluate as part of their first assessment of a patient, and therefore this test is practical to include in an algorithm that predicts walking recovery and that is intended for translation to clinical practice. One limitation of the Trunk Control Test is the ceiling effect as it only measures four simple movements in sitting and lying and does not capture minor trunk impairments in patients with mild stroke (Verheyden et al., 2006). Each
item is scored on an ordinal scale of 0, 12 or 25 points per item, which reduces the sensitivity to change and adds to the ceiling effect. These factors also limit the usefulness of the Trunk Control Test in a clinical setting for measuring improvements in trunk control after rehabilitation.

Trunk Impairment Scale

The Trunk Impairment Scale is a comprehensive measure of a range of trunk movements, has no ceiling effect, and is reliable (ICC > 0.84) and valid (r > 0.82) in a stroke population (Verheyden et al., 2004; Verheyden et al., 2006). The Trunk Impairment Scale consists of 17 items including static sitting balance, sitting with legs crossed, trunk side flexion, hip hitching, and trunk rotation in sitting. Patients are scored according to the ability to complete each item, the quality of the movement, and the amount of compensatory movement used (Verheyden et al., 2004). These finer grained assessments are useful for planning and measuring the effects of a rehabilitation programme. However, a patient will score zero for the whole test if they do not have independent sitting balance. This means although it is more sensitive to change than the Trunk Control Test due to the lack of a ceiling effect (Verheyden et al., 2006), it is likely to be less useful for patients with moderate to severe stroke. One study has reported that the Trunk Impairment scale is a predictor for overall functional recovery (measured with the Barthel Index) (Verheyden et al., 2007), but no studies have reported the use of the Trunk Impairment Scale as a predictor for recovery of independent walking. Another limitation of the Trunk Impairment Scale is that it takes up to 20 minutes to administer, which is similar to the Berg balance scale.

Postural Assessment Scale for Stroke (PASS)

The Postural Assessment Scale for Stroke (PASS) includes 12 lying, sitting, and standing balance items. It was developed with the aim of providing a single scale that was suitable for
patients with severe stroke while still including items with enough variation in difficulty to avoid ceiling effects for patients with mild or moderate stroke and increase sensitivity to change (Benaim et al., 1999). It is reliable (ICC > 0.92) and valid (r > 0.72) in a stroke population (Benaim et al., 1999; Mao et al., 2002; Chien et al., 2007a). The predictive value of the PASS for walking recovery is unclear, with only one study so far investigating the use of the PASS as a predictor for the recovery of independent walking (Huang et al., 2016).

Like the Berg balance scale and the Trunk Impairment Scale, the PASS takes up to 20 minutes to administer. This is a limitation when considering its use as a predictor for the recovery of independent walking. A shorter 5 item version was developed that has similar psychometric properties to the complete PASS, but the removal of three lying and sitting items created a notable floor effect (Chien et al., 2007b). The PASS contains all of the items included in the Trunk Control Test. These items, plus a fifth item, have been combined into another short version of the PASS (PASS-TC) (Hsieh et al., 2002). The PASS-TC has similar predictive value for the recovery of overall function as the Trunk Control Test, with no clear advantages regarding the ceiling effect or sensitivity to change (Hsieh et al., 2002; Wang et al., 2005). Its predictive value for the recovery of independent walking has not been established but it is reasonable to suggest it has similar predictive value to the Trunk Control Test considering the similarities with the Trunk Control Test. It is difficult to justify using the full PASS or PASS-TC in place of the Trunk Control Test as they do not add predictive value to that already provided by the Trunk Control Test for the recovery of independent walking, and are less well established.

In summary, the Trunk Control Test was selected as the baseline measure of trunk control for the prediction study in Chapter 8. The requirements for the selected measure were that it: is easy to administer in a clinical setting early after stroke; has minimal floor effects which may assist in differentiating between patients with moderate to severe stroke at
baseline; is reliable and valid early after stroke; and has established predictive value for the recovery of independent walking at a set time point after stroke. Sensitivity to change and ceiling effects were less important for this study, although they may be important considerations in future studies attempting to predict the recovery of independent walking at more frequent time points after stroke, particularly for patients with mild to moderate stroke. While it has its limitations, the Trunk Control test specifically targets trunk control in lying and sitting which removes floor effects for severe patients and it is the best fit for the criteria listed above.

4.5. Function: independent walking

The most commonly used clinical measure for independent walking is the Functional Ambulation Categories score (FAC), which is reliable (kappa = > 0.90) and valid (r > 0.67) in the stroke population (Holden et al., 1984; Holden et al., 1986; Collen et al., 1990; Mehrholz et al., 2007) (Table 4.1). The FAC categorises patients according to the level of assistance they need to walk on a flat surface and whether they are able to walk over uneven ground, slopes and stairs (Holden et al., 1984). In prediction studies, the FAC is used as the dependent variable and is usually dichotomised into independent (FAC = 4 or 5) or dependent (FAC ≤ 3) walking. Several other more global scales such as the Barthel Index, the Functional Independence Measure (FIM), and the Scandinavian Stroke Scale (Figure 4.2), contain an item for walking independence and are also commonly used in prediction studies (Loewen and Anderson, 1990; Jorgensen et al., 1995; Wandel et al., 2000; Tsang and Mak, 2004). The Barthel Index and FIM differ slightly from the FAC as they score ambulation on flat surfaces as a separate item to ambulation on stairs (Mahoney and Barthel, 1965; Keith et al., 1987), while the Scandinavian stroke scale only scores patients for walking on flat surfaces (Scandinavian Stroke Study Group, 1985). It is still possible to compare results across studies using these different measures provided they score ambulation on flat surfaces.
and the cut off for independent walking is at the same level as FAC ≥ 4. All of the scales for independent walking have similar limitations of few scoring levels and a reliance on either the subjective opinion of the assessor or self-report from the patient as to whether the patient is safe to be walking with a certain level of assistance. They do not assess whether this level of walking occurs routinely for the patient, but score on the best performance at the time of the assessment. The assessments only occur over a short walking distance of between 3 and 50 metres which means they do not assess the ability to walk independently over a long distance.

The FAC was used in this thesis as it is a clear and simple measure specifically focused on walking independence. It is also the only one of these measures to include elements of outdoor walking, which may be useful information in future analyses of the data. Although the FAC usually allows the use of any type of walking aid to be scored as a grade 4 or 5, we have allowed the use of a stick or lower limb orthosis but not walking frames. The prediction study in Chapter 8 is not just investigating factors which predict walking recovery at a single time point, but also those which predict when a patient will become independent. The provision of walking frames is a highly subjective decision made by a physiotherapist, influenced by different treatment philosophies and training. The timing of this provision may artificially influence the results of the prediction study, resulting in two patients who have similar physical capabilities achieving “independence” at quite different time points. For this reason, all patients who were provided with a walking frame were asked to walk without one for the purposes of scoring the FAC.
4.6. Function: walking performance

The selection of tests for walking performance is determined by the aspect of walking performance being measured. Gait speed can be measured with the 10 metre walk test, the Timed Up and Go (TUG) and the six minute walk test. These tests however, do not measure the patient’s walking pattern. In order to measure specific spatiotemporal aspects of walking, such as symmetry it is necessary to consider using more sophisticated analysis tools such as a pressure-sensitive gait mat or three-dimensional motion capture video recording. This section explains the rationale for the selection of tests of walking speed and symmetry used in the treadmill training study in Chapter 9.

10 metre walk test

The 10 metre walk test is the gold standard measure for walking speed with established excellent reliability (ICC > 0.86) and validity (r > 0.76) (Collen et al., 1990; Flansbjer et al., 2005; Perera et al., 2006; Schmid et al., 2007), and is also used to infer the ability to walk in the community. The test involves walking over a 14 metre distance with walking speed and number of steps measured over the middle 10 metres (Table 4.1). Strengths of the 10 metre walk test are that it is quick and easy to administer, is sensitive to change with no ceiling effect, and may be ideal for use as a measure of improvement in walking speed after an intervention (Perera et al., 2006; Tilson et al., 2010). One limitation is the requirement for a long flat walking surface. This often limits the use of the 10 metre walk test to a clinic setting as this distance is often unavailable in a patient’s home or environment. Careful consideration should be given to the interpretation of 10 metre walk test results in relation to the ability to walk in the community as it is only a measure of speed, not endurance, and does not take into account participation factors (Dean et al., 2001; Mudge and Stott, 2009). In this thesis, the 10 metre walk test was used as a measure of walking performance before and after the intervention for walking asymmetry detailed in Chapter 9. It was not used in the
prediction study as patients must already be independently walking in order to complete the test.

*Timed Up and Go (TUG)*

The Timed Up and Go (TUG) test measures the ability to get up from a chair, walk, turn and return to the chair. The TUG has excellent reliability (ICC > 0.94) and validity (r > 0.83) in patients with stroke (Flansbjer *et al.*, 2005; Ng and Hui-Chan, 2005). There is no ceiling effect and as it is a timed test, it is highly responsive to change. The TUG has a slightly greater floor effect than the 10 metre walk test as a patient must be able to both stand *and* walk independently in order to complete the test. As the intervention study in this thesis did not involve any training aimed at standing up from a chair, balance or turning, this test was not selected as an outcome measure.

*6-minute walk test (6MWT)*

The 6-minute walk test measures both gait velocity and endurance over six minutes. It requires the patient to walk as many lengths of a 30 metre walkway in six minutes as possible, while cardiovascular measures such as vital signs and rate of perceived exertion are recorded. This test has high reliability (ICC > 0.73) and validity (0.69) and has no ceiling effects (Kosak and Smith, 2005; Flansbjer *et al.*, 2005; Fulk *et al.*, 2010). While the 6-minute walk test has a walking speed component, the emphasis is on distance covered and endurance. Its main strength lies in its use as a predictor for community ambulation (Mudge and Stott, 2009; Fulk *et al.*, 2010). The 6-minute walk test takes longer to administer than the 10 metre walk and requires a much longer walkway. For these reasons, and because this thesis was not specifically aimed at improving participation in community ambulation the 6-minute walk test was not used as the walking speed measure in this thesis.
The second tool for measuring walking performance used in this thesis is the GAITRite® Electronic Walkway (CIR Systems Inc. US). This instrumented mat enables detailed measurement of spatiotemporal gait parameters and is particularly useful in measuring walking asymmetry. The GAITRite® system is reliable (ICC = 0.72 – 0.94) in the stroke population (Kuys et al., 2011). The limitations of this system are the cost, need for clinic space, and the limited length of the instrumented mat. This means that only a small number of steps are recorded on each walking trial and there is a risk of capturing acceleration and deceleration data during the trial rather than the patient’s usual walking pattern. This can be mitigated by starting the patient walking two metres before the instrumented mat and asking them to continue walking until two metres off the mat, as is standard practice with the 10 metre walk test.

Another limitation of the GAITRite® system is that it is not able to differentiate between simple changes in step length and changes in where the foot is placed in relation to the trunk (Finley and Bastian, 2017). This information can be captured with three-dimensional motion capture systems using positional sensors on segments of the limbs and trunk. These kinematic systems can be cost-prohibitive and were not available for use in these experiments. The GAITRite® system was used in the final experiment (Chapter 9) to analyse walking asymmetry before and after the intervention.
4.7. Summary

In summary, recovery of independent walking, improved walking performance and participation all contribute to walking in the community. Careful selection of clinical measures that reflect both the focus of walking recovery (independence or performance) and the level at which improvement is expected to occur (impairment or function) is important. The next chapter will discuss clinical, neurophysiological and neuroimaging predictors of independent walking after stroke.
Chapter 5. Prediction of lower limb recovery and walking outcomes after stroke

Predicting recovery after stroke has the potential to equip clinicians, patients and their families with vital information, guiding expectations for recovery and assisting with realistic and attainable goal setting during rehabilitation (Kwakkel et al., 1996; Stinear, 2010b). The tailoring of an effective and efficient rehabilitation programme to suit the individual may improve patient outcomes and quality of life after stroke. Providing prognostic recovery information can also increase rehabilitation efficiency (Stinear et al., 2017a).

Early information about whether a patient is expected to walk independently after stroke could aid decision making about the type and duration of rehabilitation provided, the level of support required after discharge, and likely discharge destination (Kollen et al., 2006; Bland et al., 2012). Previous studies predict walking outcome at a single time point (Sánchez-Blanco et al., 1999; Kollen et al., 2006; van de Port et al., 2006a; Veerbeek et al., 2011b; Kwah et al., 2013; Shum et al., 2014), or at the end of rehabilitation (Loewen and Anderson, 1990; Wandel et al., 2000; Thornton et al., 2001; Tsang and Mak, 2004; Masiero et al., 2007; Bland et al., 2012). Several studies have also tracked the time course of walking recovery after stroke, reporting that recovery is greatest within the first month after stroke and peaks for most patients within three months (Wade et al., 1987; Friedman, 1990; Jorgensen et al., 1995; Kollen et al., 2005).

Clinicians are able to make fairly accurate predictions about whether a patient will eventually recover independent walking (Korner-Bitensky et al., 1989; Kent et al., 1993; Kwakkel et al., 2000). However, they are poor at predicting when a patient will achieve this because of the variable and non-linear nature of recovery after stroke (Kent et al., 1993; Kwakkel et al., 2000). As walking independently is usually one of the criteria for discharge
home from hospital, the ability to predict not just whether but also when a patient will walk independently may improve the timeliness of discharge planning.

Patient safety after discharge is a primary concern, as up to 73% of patients with stroke experience a fall within six months of discharge (Forster and Young, 1995; Weerdesteyn et al., 2008; Bland et al., 2012). Providing an accurate picture of the type and duration of support the patient will need at home may enable the patient, family, and rehabilitation team to more effectively make arrangements for home support, leading to improved safety and reducing the risk of carer burnout (Bland et al., 2012). Early discharge planning might also enable earlier referral to community rehabilitation and support services, lowering the risk of a patient being placed on a wait list and improving continuity of care.

This chapter will describe important considerations in prediction studies relating to the lower limb and walking. This will include discussion of findings from studies that predict independent walking after stroke using clinical, neuroimaging and neurophysiological predictors, providing context for the walking prediction study in Chapter 8 of this thesis.

5.1. Important considerations for prediction studies

Prediction studies are often difficult to compare because of variations in terminology, clinical predictors, timing of assessments, and choice of measures, as well as the heterogeneity of the sample of patients (Kwakkel et al., 1996). The term “prediction” is commonly used to describe a relationship between two variables at a single point in time. For example, several studies report that imaging measures or limb strength “predict” the functional status of a patient (Carter et al., 2010; Peterson et al., 2010a; Zhu et al., 2010; Fulk et al., 2017). However, as these studies performed all measures at the same time point, they are actually reporting an association between the two variables, rather than showing that an independent variable at baseline predicts the dependent variable at a time point in the future.
For this thesis, prediction always refers to using a baseline variable to predict recovery or outcome at a later time point.

It is important to consider whether a study is predicting an outcome at a single point in time or recovery between two time points. Prediction studies often use the terms “recovery” and “outcome” interchangeably when they are different things. “Recovery” is a broad term used to describe the patient’s progress from disability towards normal life after stroke. More specifically, recovery can be defined as improvement over time. This means motor recovery refers to the amount of movement or walking ability that the patient regains after the stroke. It is not possible to quantify how much movement or walking ability a patient has regained without first knowing how much they lost after the stroke. Therefore, the same measures must be performed on at least two time points, with the difference between the scores at baseline and the primary endpoint used as the dependent variable. In contrast, “outcome” is measured only once, at the primary end point, and refers to what the patient is able to do at that specific time point (e.g. independent walking or walking performance). Outcome measures do not detect whether the patient’s performance improved, remained stable, or deteriorated, relative to early after stroke. Measures of both recovery and outcome are potentially useful, but the choice and timing of assessments must have a clear rationale based on the study’s hypothesis.

From a patient’s perspective, their outcome is of great importance in determining their ability to continue with their daily lives. However, measuring and understanding recovery over time gives us the opportunity to understand the neurobiological processes underlying recovery. It also enables us to ask questions about why two patients who start with the same baseline scores recover differently and achieve different outcomes, and to identify which patients may benefit from specific rehabilitation interventions (Burke et al., 2014; Jones et
This thesis investigates recovery from lower limb motor impairment in Chapter 7 and prediction of a functional walking outcome (independent walking) in Chapter 8.

5.1.1 Methodological criteria for prediction studies

Many prediction studies have been conducted, although few have been of high quality. Kwakkel et al. (1996) evaluated 78 studies aimed at predicting functional outcome (activities of daily living) after stroke against a set of eleven criteria considered important for valid prognostic research (Table 5.1). Only 13 studies met eight or more criteria (Kwakkel et al., 1996). More recently, Veerbeek et al. (2011a) conducted a systematic review of 48 studies predicting functional outcomes, with an expanded set of 27 criteria. The notable additions to this set are that: the predictors and dependent variable must be clearly defined; the rationale for cut-off points (if dichotomised) are clearly explained; the data for all candidate predictors are presented; and that the primary endpoint is a fixed point in time rather than discharge from rehabilitation (Veerbeek et al., 2011a). Of these 48 studies, only six met 20 or more out of 27 criteria and were classified as having a low risk of bias.

Craig et al. (2011) conducted a systematic review of studies predicting walking outcomes after stroke. With tight inclusion criteria of completing baseline assessment within one week of stroke onset, and predicting independent walking ability at one month post-stroke, they found only five studies for critical review (Friedman, 1990; Jorgensen et al., 1995; Matsunaga et al., 1997; Smith and Baer, 1999; Baer and Smith, 2001). However, three of these studies included patients in their statistical analyses who were already walking independently at baseline (Matsunaga et al., 1997; Smith and Baer, 1999; Baer and Smith, 2001). The other two studies also included patients who were independent, but analysed the data for dependent patients separately from the whole group analyses.
These reviews highlight the lack of high quality studies of patients early after stroke, making systematic review difficult. This gap in the literature means no conclusions can yet be drawn about the strongest predictors for the recovery of independent walking, when they should be measured, and how this information can be applied in clinical practice.

Table 5.1 Methodological criteria for prediction studies (Kwakkel et al., 1996)

<table>
<thead>
<tr>
<th>Methodological criteria</th>
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<tr>
<td>Evidence that the dependent variables are valid and reliable</td>
</tr>
<tr>
<td>Evidence that the independent variables are valid and reliable</td>
</tr>
<tr>
<td>Observation started within 2 weeks of stroke onset</td>
</tr>
<tr>
<td>A follow-up period of at least 6 months</td>
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<tr>
<td>Control for drop-outs: must be specified</td>
</tr>
<tr>
<td>The relationship between the dependent and independent variable is tested for significance</td>
</tr>
<tr>
<td>Adequate sample size: at least 10 participants for each variable tested</td>
</tr>
<tr>
<td>Control for multi-collinearity: interaction between two or more independent variables is tested in the prediction model</td>
</tr>
<tr>
<td>Specification of relevant patient characteristics</td>
</tr>
<tr>
<td>Description of additional medical/paramedical interventions</td>
</tr>
<tr>
<td>Cross-validation of the model in a second independent group</td>
</tr>
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</table>

The methodological criteria for systematic reviews of prediction studies (Table 5.1) ensure robustness of research processes. However, what they do not do is evaluate whether the studies’ findings are translatable into clinical practice. Factors that influence this include: high accuracy of predictions, accessibility of the measures to clinicians, ability to predict outcomes for individual patients, and clinical relevance of the outcome measure.
The next sections will critically evaluate some of the literature on the prediction of independent walking after stroke. The purpose of this evaluation is not to conduct a systematic review of all studies predicting independent walking outcome, but to highlight methodological inconsistencies which contribute to the difficulty in drawing conclusions about potential prediction models, and to provide a rationale for the methodology used for the experiments in Chapters 6, 7 and 8.

5.2. Regaining independent walking after stroke

The reported percentage of patients who regain independent walking after stroke varies greatly, from 34% to 85% (Wade and Hewer, 1987; Friedman, 1990; Jorgensen et al., 1995; Hill et al., 1997; Kollen et al., 2006; Veerbeek et al., 2011b; Kwah et al., 2013). The variation in reports may be due to differences in inclusion criteria, differences in the timing of initial and final assessments, and how the data are reported. Some studies report the percentage of patients who walk independently, but include patients who were already independent on admission to the study rather than the percentage of patients who actually recover independent walking (Matsunaga et al., 1997; Smith and Baer, 1999; Baer and Smith, 2001). This may produce higher “recovery” percentages. In order to identify predictors for independent walking, the patients who have already achieved this goal should be excluded from the analysis.

One of the largest, and most frequently cited, studies on walking outcomes after stroke is the Copenhagen Stroke Study. Jorgensen et al. (1995) reported in this study that out of a large sample of 804 patients admitted within 12 hours of stroke onset, 50% of the patients were walking independently by the time they were discharged from rehabilitation. However, a closer look at the data reveals that 172 (21%) of the patients died before completing rehabilitation but were still included in this figure, and a third of the patients in this study
were already walking independently on admission. Of the patients who were unable to walk independently on admission, and who survived to the end of rehabilitation (349 patients), only 34% actually achieved independent walking. This is much lower than the 50% of all patients reported in the abstract or the 64% of all survivors reported in the conclusion (Jorgensen et al., 1995). This highlights the importance of clear and unambiguous reporting.

Strengths of this study are: the very large sample size; consecutive patient recruitment; and that despite including all patients in the analysis, the data were also reported for separate sub-groups, enabling a more detailed review.

In contrast to these findings, Friedman et al. (1990) reported that, of the patients who were unable to walk without assistance at seven days post-stroke, 57% recovered independent walking by six months (Friedman, 1990). This figure of almost 60% aligns more closely with other studies reporting that 60 - 70% of patients initially unable or requiring assistance to walk after stroke recovered independent walking by six months (Kollen et al., 2006; Veerbeek et al., 2011b; Kwah et al., 2013). Thus, the Copenhagen Stroke Study (Jorgensen et al., 1995) stands out as having the worst walking outcomes of the stroke prediction studies.

While it may be tempting to consider this low figure an arbitrary outlier, it is possible that the sample was not representative of the generally studied stroke population, and may instead be more representative of the general stroke population. This study attempted to include all consecutive patients admitted with stroke over an 18 month period. In contrast, most stroke prediction studies have strict inclusion and exclusion criteria such as: type of stroke (infarct); stroke location (anterior circulation); no previous stroke; no complicated medical history; no difficulties communicating; minimal cognitive impairment; upper age limits; degree of lower limb and trunk impairment; and suitability for admission to a rehabilitation unit (Friedman, 1990; Loewen and Anderson, 1990; Sánchez-Blanco et al., 1999; Tsang and Mak, 2004; Kollen et al., 2006; Masiero et al., 2007; Veerbeek et al., 2011b; Bland et al., 2012). Many
of these studies therefore exclude the most severely affected patients. These examples highlight the difficulty faced in prediction research of finding a balance between designing a study that is comparable to other prediction studies, by attempting to reduce the heterogeneity of the sample cohort, while also making the research applicable to the general stroke population.

Overall, it seems that around 30 – 40 % of patients fail to regain independent walking after stroke, which means the prediction of who will and who will not achieve this outcome is relevant for a large number of patients. It is important to keep in mind that findings from prediction studies may only be transferrable to some patients within the general stroke population, depending on the selection of patients in the study. Prediction studies can be grouped into those that use clinical, neuroimaging, or neurophysiological independent variables. Each of these groups will be discussed separately in the next sections.

5.2.1 Clinical predictors for independent walking

Most prediction studies test only clinical measures as potential variables for predicting independent walking, despite evidence in the upper limb that a combination of clinical, neurophysiological and imaging biomarkers may be beneficial for predicting recovery from impairment and functional outcomes (Stinear et al., 2012; Kim and Weinstein, 2017; Stinear et al., 2017b). This probably reflects the low cost and high accessibility of clinical measures compared with neurophysiological and imaging measures. The use of clinical measures in an algorithm or prediction model may facilitate translation of the prediction tool into clinical practice.

Several clinical predictors have been associated with independent walking after stroke. These include: age; lower limb motor impairment; lower limb sensory impairment; homonymous hemianopia or visuospatial neglect; trunk control in lying and/or sitting; initial
disability in activities of daily living; initial ambulation level; overall stroke severity; and urinary continence. The studies identifying these predictors are provided in Table 5.2. Oxfordshire stroke classification was also a predictor in two studies reporting that patients with total anterior circulation infarct were less likely to achieve independent walking (Smith and Baer, 1999; Baer and Smith, 2001). However these two studies are excluded from further discussion as they both included patients who were already independent. I found no studies that aimed to predict when a patient would achieve independent walking.

Table 5.2 Potential clinical predictors for independent walking after stroke

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Age</td>
<td>Friedman, 1990; Sánchez-Blanco et al., 1999; Kollen et al., 2006; Masiero et al., 2007; Kwah et al., 2013</td>
</tr>
<tr>
<td>Lower limb motor impairment</td>
<td>Friedman, 1990; Olsen, 1990; Jorgensen et al., 1995; Sánchez-Blanco et al., 1999; Veerbeek et al., 2011b</td>
</tr>
<tr>
<td>Lower limb sensory impairment</td>
<td>Sánchez-Blanco et al., 1999; Patel et al., 2000</td>
</tr>
<tr>
<td>Homonymous hemianopia or visuospatial neglect</td>
<td>Friedman, 1990; Sánchez-Blanco et al., 1999; Patel et al., 2000</td>
</tr>
<tr>
<td>Trunk control in lying or sitting</td>
<td>Loewen and Anderson, 1990; Tsang and Mak, 2004; Masiero et al., 2007; Duarte et al., 2010; Veerbeek et al., 2011b</td>
</tr>
<tr>
<td>Initial disability in activities of daily living (Barthel Index or Functional Independence Measure)</td>
<td>Wandel et al., 2000; Kollen et al., 2006; van de Port et al., 2006a; Masiero et al., 2007</td>
</tr>
<tr>
<td>Initial ambulation</td>
<td>Jorgensen et al., 1995; Shum et al., 2014</td>
</tr>
<tr>
<td>Stroke severity (NIHSS)</td>
<td>Kwah et al., 2013</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Loewen and Anderson, 1990</td>
</tr>
</tbody>
</table>
The wide range of potential predictors reported by these studies means it is difficult to draw conclusions. The strengths and limitations of some of these studies will be discussed with reference to two factors that affect clinical relevance and translation to clinical practice: the selection of variables, and the timing of the assessments.

Selection of variables to predict independent walking

The importance of careful selection of measures was discussed in Chapter 4. Many studies have used the dichotomised Functional Ambulation Categories (FAC) score of $\geq 4$ to define independent walking when exploring predictors of walking outcome (Sánchez-Blanco et al., 1999; Kollen et al., 2006; Duarte et al., 2010; Veerbeek et al., 2011b). Other valid and reliable outcome measures used to identify patients who walked independently were the dichotomised walking sub-scores of the Barthel Index, the Functional Independence Measure (FIM), the Scandinavian Stroke Scale, and the Motor Assessment Scale (Jorgensen et al., 1995; Patel et al., 2000; Wandel et al., 2000; Kwah et al., 2013). The strength of these studies is the selection of a clear dichotomised outcome variable, each with the same definition for independent walking. This means that, despite using different outcome measures, the findings from these studies can be compared with each other. However, there is little overlap in the predictors identified by these studies (Table 5.1), suggesting that methodological factors contributed to their variable results.

Several other studies had poor outcome variable selection. One used the FAC but chose to dichotomise the score at FAC $\geq 3$ (Masiero et al., 2007), while another study dichotomised the walking FIM score at $\geq 5$ (Singh et al., 2006). In both studies, patients requiring supervision to walk were included in the “independent” group, preventing these studies from being compared with other prediction studies. Other studies either used un-validated measurement scales, or did not dichotomise the dependent variable and therefore were not
specifically predicting whether patients regained independent walking or not (Loewen and Anderson, 1990; Nitz and Gage, 1995; Feigin et al., 1996; van de Port et al., 2006a). These variations in the selection and dichotomising of outcome variables highlight some of the challenges in interpreting findings from prediction studies.

Careful selection of the independent variables is also important. A recent study reports that stroke severity and age are predictors of independent walking at six months post-stroke (Kwah et al., 2013). This study has several strengths: a large patient sample (n = 114); patients with ischaemic and haemorrhagic stroke recruited consecutively within a median time of six days after stroke onset; identification and removal from analysis of patients already walking at enrolment to the study; more than 10 patients per predictor entered into the analysis; and selection of valid and reliable assessment tools. However, despite noting that the Trunk Control Test and Motricity Index were predictors in a previous and important study by Veerbeek et al. (2011b), the authors instead used age, stroke severity (NIHSS), ability to stand from sitting, premorbid function, and lower limb spasticity in their model. Their rationale for the selection of their predictors was clinical relevance, common clinical use, and availability (Kwah et al., 2013). They also stated that external validation of models using the Trunk Control Test and Motricity Index is challenging in Australia due to low use of these measures in clinical practice (Kwah et al., 2013). Yet these clinical measures are very quick to use, freely accessible, and reflect what a physiotherapist is likely to assess early after stroke, making them relatively simple to validate in a prospective prediction study and translatable to clinical practice. The exclusion of these measures is therefore not well-justified.

The main limitation of this study was that it was a secondary analysis of data from a previous study. Therefore the selection of predictor variables was limited to those that were used in the original study investigating the development of contractures after stroke (Kwah et
al., 2012). The selection of a small number of “convenience” variables introduces bias into the study, which is an important consideration when conducting retrospective studies or secondary analyses of a dataset collected for a different purpose. This approach may cause the researchers to miss important predictors simply because they were not in clinical use at the time. Another limitation is despite the inclusion of both ischaemic and haemorrhagic stroke in the study, type of stroke was not identified or ruled out as a potential predictor for walking outcome. Stroke location (anterior or posterior circulation) was also not reported in this study. These limitations mean that, while this study had several strengths, the results need to be treated with caution.

Good selection of the outcome variable enables clear and accurate reporting of findings and comparability between studies, while poor selection of the independent variables may bias study findings. Some of the differences in study findings may simply be due to the differences in variables selected for analysis. Clear rationale needs to be provided for variable selection and for why others were omitted.

Timing of baseline assessments

Another important factor to consider when evaluating prediction research is the timing of the initial assessment in relation to stroke onset. Assessment timing is important due to the non-linear trajectory of stroke recovery and the different neurobiological mechanisms of recovery during the subacute and chronic stages (Jorgensen et al., 1995; Kollen et al., 2005; Kitago and Krakauer, 2013).

Several studies have completed baseline assessments within one week (Friedman, 1990; Loewen and Anderson, 1990; Jorgensen et al., 1995; Wandel et al., 2000; Kollen et al., 2006; Veerbeek et al., 2011b; Kwah et al., 2013; Shum et al., 2014), and a few have assessed patients within two weeks of stroke onset (Sánchez-Blanco et al., 1999; Duarte et al., 2010).
The bulk of walking prediction studies, however, perform baseline measures on admission to inpatient rehabilitation rather than at a specified point in time (Mayo et al., 1991; Sánchez-Blanco et al., 1999; Thornton et al., 2001; Singh et al., 2006; van de Port et al., 2006a; Masiero et al., 2007; Hirano et al., 2016). Even though the mean or median time of admission to rehabilitation is reported as within one month or a few weeks of stroke onset, the range of admission times can vary widely. For example, while van de Port et al. (2006a) reported mean time between onset and admission as 45 days, and Singh et al. (2006) reported median admission of 17.5 days, they included patients up to 100 and 623 days post stroke, respectively. This results in data from patients at the early and late subacute recovery phase, and patients in the subacute and chronic stage, being analysed together.

Two quite contrasting studies have prospectively investigated whether it is possible to accurately predict independent walking in non-ambulatory patients using clinical variables assessed within 72 hours after stroke onset (Veerbeek et al., 2011b; Shum et al., 2014). Both studies included a large patient sample (n > 150 each) with first-ever stroke and measured independent walking using the FAC. Shum et al. (2014) evaluated whether the modified Rivermead Mobility Index (mRMI) at baseline could predict independent walking one month after stroke. They report that patients with a baseline mRMI score of 18.5 or more out of 40 have an 88% chance of walking independently by one month. Significant limitations of this study are: no identification of stroke type or location; lack of clarity about the mobility status of the patients included in the study; no reporting of the baseline variable scores; selection of only one independent variable; and a primary endpoint of one month after admission without any later assessments. These substantial limitations mean that results from this study are not comparable to other studies.

Veerbeek et al. (2011b) used multivariable logistic regression analysis of 15 variables to develop a prediction model for independent walking at six months in patients with first-ever
ischaemic stroke. Initial assessments took place within 72 hours, at five days, and nine days post stroke. Patients who had sitting balance and some voluntary movement in the lower limb (Motricity Index ≥ 25) at 72 hours post-stroke had a 98% chance of recovering independent gait within six months (achieving FAC ≥ 4). However, patients unable to sit for 30 seconds unsupported, and with only a flicker of movement or no movement in the lower extremity, only had a 27% chance of recovering independent walking. The impact of recovery trajectory in the first nine days after stroke is clear in this study. By day nine, if the patient had not achieved independent sitting balance and a Motricity Index score ≥ 25, the probability of regaining independent gait fell to 10% (Veerbeek et al., 2011b). No other significant predictors were identified in the final model.

This study represents some of the most promising research so far into using clinical variables to predict independent walking after stroke. It has several strengths such as: early assessments; valid and reliable assessment measures; selection of a wide range of independent variables; multiple time points for assessments; a fixed primary endpoint; and a large sample of 154 patients. The authors used bivariate logistic regression for each variable and tested for collinearity to reduce the number of variables entered into the multivariate logistic regression from 19 to 15, which is appropriate for the sample size. This contrasts with Sánchez-Blanco et al. (1999) who entered 17 variables for a sample size of only 92 patients, resulting in possible overfitting of their model.

The findings of Veerbeek et al. (2011b) support those of earlier studies showing that lower limb strength (Friedman, 1990; Jorgensen et al., 1995; Sánchez-Blanco et al., 1999) and trunk control (Loewen and Anderson, 1990; Masiero et al., 2007; Duarte et al., 2010) are predictors for the recovery of independent walking. These other studies also identified age, visuospatial impairment, sensory impairment, homonymous hemianopia, baseline walking, and baseline activities of daily living function as predictors for independent walking. These
variables were also included in the study by Veerbeek et al. (2011b), but did not make it into the final model as significant predictors, suggesting that lower limb impairment and trunk control may be more important predictors.

There are, however, also several limitations. First, the study did not validate the prediction model in an independent sample of patients. Secondly, the use of forward step-wise logistic regression is a limitation as it can over-estimate $R^2$ values, generate falsely narrow confidence intervals, and is highly influenced by collinearity. The backwards step-wise multiple regression analysis used in other studies (Bland et al., 2012; Kwah et al., 2013) has similar issues, and results produced by both methods should be interpreted with caution. Positive predictive value (0.93) and sensitivity (0.93) of the model were high, but the negative predictive value (0.63) and specificity (0.63) were low, with a fairly high error rate for individual patients resulting in 37% false negatives and 7% false positives at 72 hours (Veerbeek et al., 2011b). This contrasts with the accuracy of clinician’s predictions which tend to be too optimistic (Korner-Bitensky et al., 1989; Kent et al., 1993), and raises concerns about patients missing out on rehabilitation services if decisions about their rehabilitation potential are based on this model. The positive and negative predictive values increased between day two and day nine, suggesting that the accuracy of prediction models or prediction algorithms is greater as time passes after stroke (Loewen and Anderson, 1990). It can be difficult to find the balance between accuracy of prediction and clinical usefulness when choosing the baseline assessment time point. A final limitation is that the complex regression equation required for calculating a probability value for an individual patient is a barrier to translation into clinical practice. This is a common limitation of prediction studies that use regression modelling techniques.
Timing of primary endpoint

The timing of the primary endpoint also varies in the literature and may have an impact on studies’ findings. Achieving independent walking by the time of discharge from hospital (Loewen and Anderson, 1990; Jorgensen et al., 1995; Wandel et al., 2000; Masiero et al., 2007) may have different predictors than achieving independent gait six months or one year after stroke (Kollen et al., 2006; Duarte et al., 2010; Veerbeek et al., 2011b; Kwah et al., 2013).

Predicting independent walking at a fixed primary endpoint is preferable to a flexible time point such as discharge from rehabilitation (Veerbeek et al., 2011a). Time spent in rehabilitation is usually different for each patient. One of the main determinants for discharge from rehabilitation is the ability to walk independently, although criteria for discharge often vary between health services. This means prediction tools for independent walking by the end of rehabilitation in a given clinical setting are difficult to generalise to other settings. Also, if the level of walking ability influences the timing of discharge, predicting the level of walking at discharge becomes circular and a self-fulfilling prophecy. One situation where this might not be the case is in a health system with a pre-determined length of stay in rehabilitation.

The timing of the primary endpoint may also determine the relevance of the prediction to the clinician and patient. Predicting whether a patient will walk independently by six months may not be useful for rehabilitation or discharge planning, as six months is well beyond the usual inpatient rehabilitation duration. Also, many patients will reach maximum recovery much earlier than six months. Another limitation of a primary endpoint at six months or one year is that after the initial recovery period some patients begin to deteriorate due to factors such as deconditioning, cognitive problems, fatigue and depression (van de Port et al.,
2006b). It may be more beneficial to measure the primary outcome at a time point that best reflects the peak of recovery at around three months, in order to avoid results being affected by subsequently declining mobility (Friedman, 1990; Jorgensen et al., 1995). An additional follow up assessment point at six months may also be beneficial to ensure the later walking status of all patients is captured.

Drawing conclusions from the clinical studies discussed here is difficult as few studies had the same time-points for baseline assessments, type of clinical variables used as predictors, measures of independent walking, or primary endpoints. No studies were found that attempted to predict when a patient would achieve independent walking after stroke, which is the aim of the experiment in Chapter 8. However, it is likely that clinical predictors for regaining independent walking at a fixed time point may also be predictors for when this will occur. One of the most methodologically robust and clinically relevant studies discussed is that by Veerbeek et al. (2011b), which identifies trunk control and lower limb impairment as potential clinical predictors for independent walking, supporting earlier findings. This suggests that these two measures should be included in future prediction studies. Age, baseline activities of daily living function, baseline walking ability, and visual or sensory impairment have also been identified in more than one study, and should also be considered as potential clinical predictors in future studies.

A limitation of using clinical measures as predictors is that they tell us what a patient is able to do after stroke, but do not tell us how the stroke has affected the structure and function of the brain, and its potential for recovery. Obtaining this information with neuroimaging or neurophysiological tools may help to differentiate between patients with similar baseline impairments who will and will not achieve independent walking.
5.2.2 Imaging predictors for independent walking

Magnetic resonance imaging (MRI) is accessible to most hospital-based clinical teams, and MRI techniques are well established for examining motor recovery and outcomes after stroke. As few studies have investigated the use of MRI measures in predicting lower limb and walking outcomes early after stroke, this section will briefly describe structural and functional MRI techniques that are currently used in upper limb prediction research and emerging in lower limb research. This section will also evaluate studies that used MRI measures to predict independent walking after stroke.

MRI techniques

MRI can be used to examine the structural effects of stroke on the brain, such as lesion size and location (Chen et al., 2000; Alexander et al., 2009; Jayaram et al., 2012; Jones et al., 2016) and the microstructural integrity of white matter pathways (Basser, 1995; Liang et al., 2007; Dawes et al., 2008; Lindenberg et al., 2010; Zhu et al., 2010; Jayaram et al., 2012; Stinear et al., 2012). Functional MRI (fMRI) can be used to examine cortical activation patterns after stroke (Cramer et al., 1997; Ward et al., 2003; Enzinger et al., 2008; Marshall et al., 2009; Zarahn et al., 2011). MRI studies often correlate imaging measures with clinical measures at the time of imaging rather than predicting a future outcome, with most studies conducted in patients at the chronic stage of stroke (Cramer et al., 1997; Enzinger et al., 2008; Lindenberg et al., 2010; Zhu et al., 2010; Cho et al., 2012; Jayaram et al., 2012; Moon et al., 2016). MRI studies have also been conducted to predict motor and functional recovery after a period of rehabilitation (Cramer et al., 2007; Stinear et al., 2007; Dawes et al., 2008; Lindenberg et al., 2012; Burke et al., 2014; Jones et al., 2016).

In studies beginning early after stroke, structural MRI measures have been used to predict upper limb outcomes (motor impairment and function) (Puig et al., 2011; Stinear et al., 2012;
Puig et al., 2013) and both structural and functional MRI measures have been used to predict recovery over time from upper limb motor impairment (Marshall et al., 2009; Zarahn et al., 2011; Byblow et al., 2015; Feng et al., 2015; Buch et al., 2016). Structural MRI measures may be particularly useful in predicting recovery potential for patients who initially experience severe upper limb motor impairment (Stinear et al., 2012; Feng et al., 2015; Buch et al., 2016; Puig et al., 2017). Unlike the upper limb, with an abundance of research into MRI biomarkers in stroke, the paucity of research in the lower limb means the use of MRI measures as predictors for walking recovery or outcomes has yet to be established.

Structural MRI to determine lesion volume and location

Structural MRI can be used to determine lesion location and volume (Puig et al., 2017). Lesion volume can be calculated by manually outlining the lesion on each slice of a T1-weighted image (Chen et al., 2000), T2-weighted image (Chen et al., 2014), or diffusion weighted image (Puig et al., 2011). The areas of the lesion in each slice are then summed and multiplied by the thickness of the slices to calculate lesion volume in cm$^3$ (Chen et al., 2000; Puig et al., 2011). Although patients with a larger stroke volume are more likely to have poor outcomes, lesion location is a stronger predictor for motor recovery and functional outcomes after stroke (Chen et al., 2000; Puig et al., 2013; Chen et al., 2014; Jones et al., 2016).

The relationship between lesion location and motor behaviour can be evaluated in groups of patients with voxel-based lesion symptom mapping (VLSM) (Bates et al., 2003; Moon et al., 2016). The stroke lesion is manually outlined on each slice of a fluid-attenuated inversion recovery (FLAIR) image, and then compared with a diffusion-weighted image and adjusted for accuracy (Cheng et al., 2014; Meyer et al., 2016). The FLAIR images are registered to the patient’s T1-weighted image, and normalised to the Montreal Neurologic...
Institute (MNI) standard space (Jones et al., 2016; Moon et al., 2016). To improve statistical power, all lesion masks are flipped over to the same hemisphere (Meyer et al., 2016), and then combined to create an overlay map of lesioned voxels across all patients. Voxel-by-voxel t-tests are then conducted to compare behavioural scores between patients with or without a lesion in each voxel (Bates et al., 2003; Cheng et al., 2014). Only voxels affected in at least 10% of subjects are analysed (Jones et al., 2016; Meyer et al., 2016; Moon et al., 2016).

By mapping structural lesions to a behavioural scale, VLSM identifies which lesioned neural structures are associated with specific motor deficits (Cheng et al., 2014). In chronic stroke, lesions affecting the basal ganglia, insula, internal capsule, and subgyral white matter adjacent to the corona radiata, are associated with poor lower limb Fugl-Meyer scores (Moon et al., 2016); while lesions affecting the posterolateral putamen are associated with temporal walking asymmetry (Alexander et al., 2009). Recent studies reported that lesions in the insula, putamen, external capsule, internal capsule, and surrounding white matter, were significantly related to poor gains in walking speed after rehabilitation in patients at the subacute stage of stroke (Jones et al., 2016; Moon et al., 2017), but there was no significant relationship between lesion location and improvements in independent walking. Several of these lesion locations do not overlap with the CST, suggesting that CST integrity may be less important for improvements in walking speed than other brain regions and white matter connections (Jones et al., 2016).

The strengths of VLSM are that it provides valuable insight into which brain areas may be related to lower limb and walking function; it may identify which patients (based on lesion location) are more or less receptive to specific types of rehabilitation; and it may identify in retrospect which patients were more likely to have good walking outcomes after stroke. No studies have attempted to use VLSM to prospectively predict motor outcomes in a new group
of patients or in individual patients. One research group is creating a large data repository of MRI images, behavioural assessment scores for aphasia and cognition, and demographic information (PLORAS database) (Seghier et al., 2016). This group aims to collect a very large set of data, including lesion location mapping, and use this information to make predictions for individuals based on how other patients with similar lesions, behavioural scores and demographic characteristics recovered language abilities after stroke. This approach needs a very large number of patients, and the study is ongoing. VLSM may also be useful to identify the structures most related to good walking outcomes. But without the benefit of a very large database from which to draw predictive information, a different approach is likely required to make accurate predictions for individual patients.

*MRI to examine white matter pathways – FA asymmetry*

Structural MRI can also be used to examine damage to the structure of white matter pathways after stroke with diffusion tensor imaging and tractography. These techniques can be used to characterise the microstructure of white matter pathways using information from the diffusion weighted image. Diffusion tensor imaging is sensitive to the magnitude and direction of the movement of water molecules in tissue (Ciccarelli et al., 2008). A diffusion tensor is estimated within each voxel, with three perpendicular eigenvectors (Basser et al., 1994). The eigenvector with the largest eigenvalue reflects the principal direction and magnitude of water diffusion in each voxel (Basser et al., 1994; Pierpaoli et al., 1996; Werring et al., 2000). Fractional anisotropy (FA) is a scalar value calculated from the eigenvectors to quantify the directionality of water molecule movement, where a value of 1 indicates perfectly anisotropic diffusion (uniform in direction) and a value of zero indicates completely isotropic diffusion (Basser, 1995). Water molecules within the white matter are constrained by cell membranes and the myelin sheath of the axon, which causes them to travel primarily along the axons instead of across the axons. White matter tracts contain
bundles of axons orientated in the same direction, which therefore have high mean FA values (Basser et al., 1994; Pierpaoli et al., 1996). Disruption of white matter tracts by stroke results in a lower mean FA value, reflecting a loss of axonal structural integrity and organisation (Werring et al., 2000).

Calculating FA asymmetry between the lesioned and non-lesioned white matter tracts can provide information about structural damage to the white matter. The FA maps generated from diffusion-weighted images are registered to the participant’s T1-weighted image and overlaid by a template of the volume of interest (VOI) from the Montreal Neurologic Institute standard space (Ciccarelli et al., 2008). Manual correction for any errors is conducted using the T1-weighted image as a reference for the anatomical location of structures. The VOIs for upper limb studies are usually the posterior limbs of the internal capsules (Puig et al., 2011; Byblow et al., 2015) or the pons (Lindenberg et al., 2010; Puig et al., 2013). An FA asymmetry value is calculated from the mean FA values in the VOIs of the lesioned and non-lesioned hemispheres. A greater FA asymmetry indicates greater structural damage to the VOI in the lesioned hemisphere, and predicts poor motor recovery and outcomes for the upper limb after stroke (Stinear et al., 2012; Byblow et al., 2015; Buch et al., 2016).

One of the limitations of FA asymmetry calculated in a specific VOI or slice is that stroke damage that does not occur within the target VOI may be missed. This can be overcome by using diffusion tensor tractography (DTT) to construct the tract, then calculating mean FA along the entire tract and calculating FA asymmetry as above. Tensors calculated from diffusion weighted images are used to produce a three-dimensional representation of white matter tracts by following the path of preferred water diffusion (Ciccarelli et al., 2008; Zhu et al., 2010). Briefly, for the CST, a seed region is typically defined in the pre-central gyrus, with a way point in the posterior limb of the internal capsule, and end point in the pons (Zhu et al., 2010; Feng et al., 2015; Stinear et al., 2017b).
Tractography then generates tracts that run from the seed region to the target area, allowing visualisation of the extent and level of CST damage (Puig et al., 2011). One of the limitations of DTT is that there are several user-defined tracking ‘rules’, such as minimum FA values and maximum ‘bend’ values, that can vary between studies (Behrens et al., 2003b). DTT is also unable to reliably construct tracts that pass directly through a stroke lesion, although this still allows researchers to determine whether the CST is completely disrupted or not. Four studies have used DTT early after stroke to determine CST disruption and evaluate whether this is a predictor of independent walking later after stroke (Cho et al., 2007b; Jang et al., 2008; Kim et al., 2013; Kim et al., 2016). One of these studies also evaluated FA asymmetry along the CST (Kim et al., 2013). These were the only studies found that used MRI within two months after stroke to predict subsequent independent walking. They are described in Table 5.3 and discussed in detail later in this chapter.

The problems associated with attempting to construct tracts that pass directly through the stroke lesion can be overcome by constructing a template CST from diffusion weighted images of the contralesional hemisphere of patients with stroke or from healthy age-matched controls. The template CST can then be overlaid on the ipsilesional hemisphere, and the mean FA calculated within the ipsilesional CST.

**MRI to examine white matter pathways – Lesion load**

CST templates can also be used to calculate stroke lesion load on the CST. Lesion masks are hand-drawn on the T1 weighted image of individual participants, which is overlaid with the CST template. The lesion load is calculated as the percentage of CST voxels that are overlapped by the lesion (Zhu et al., 2010; Feng et al., 2015). CST lesion load is a significant predictor for recovery from upper limb impairment (Feng et al., 2015; Stinear et al., 2017b) and functional upper limb outcomes (Stinear et al., 2017a).
In chronic stroke, CST lesion load is a weak predictor for walking speed response to rehabilitation in patients with mild lower limb impairment (Dawes et al., 2008) but not for patients with moderate lower limb impairment (Burke et al., 2014). Both of these studies had small sample sizes (both n ≤ 25), participants had a relatively young mean age, and all participants were able to walk independently. One study provided four weeks of body-weight support treadmill training three times a week (Dawes et al., 2008), while the other provided four weeks of “standardised” physiotherapy gait training twice a week, beginning four weeks after baseline assessments and finishing three weeks before the final assessment (total 12 week block) (Burke et al., 2014). Both studies reported other, stronger predictors for walking speed response to rehabilitation, which were baseline walking speed (Dawes et al., 2008), baseline lower limb impairment, and fMRI activation volume within the ipsilesional foot sensorimotor cortex (Burke et al., 2014). The study by Burke et al. (2014) included participants from as early as two months after stroke to over a year post-stroke; including participants at different stages of the recovery trajectory may have affected results. The different participant populations and training interventions used by these studies mean it is not possible to draw firm conclusions about whether CST lesion load is a predictor for walking speed response to rehabilitation in the chronic stage of stroke. It seems likely that other predictors are more important than CST lesion load for mildly affected patients, supporting the findings from VLSM studies that suggest walking speed response to rehabilitation may be related to structures outside the CST.

One study has used CST lesion load to investigate walking speed response and change in FAC in 50 participants with moderate to severe gait deficits (Jones et al., 2016). Participants were recruited within six weeks of stroke onset and received six weeks of usual care rehabilitation. CST lesion load was a significant predictor for increased FAC score, but not increased walking speed (Jones et al., 2016). Age and baseline walking ability were both
stronger predictors than CST lesion load for increased FAC score in these participants. Unfortunately, this study did not clearly state the baseline walking ability of all participants, or dichotomise final FAC score, but instead used a change score, which makes it difficult to determine whether CST lesion load was a predictor for independent walking. For these reasons it has not been included in the discussion relating to Table 5.3.

The strength of using measures of the structural integrity of white matter tracts, such as FA asymmetry and CST lesion load, is that they reflect the stroke damage for each individual patient, and can therefore help to explain why some patients with similar baseline motor impairment have different recovery and outcomes. Cut-off points have been determined for both FA asymmetry and CST lesion load as predictors for upper limb function after stroke (Stinear et al., 2012; Stinear et al., 2017a), which means they are able to be used as predictors for individual patients. This is encouraging for the potential use of MRI biomarkers for predicting lower limb motor recovery and outcomes. The main limitation of these measures is the potential complexity of processing the data with software and specialist knowledge that may not be accessible to clinicians. Also, studies have used a wide variety of MRI measures when predicting motor recovery and outcomes after stroke, and there is currently no widely accepted ‘gold standard’. Further work with larger samples of patients is needed.

Functional MRI

While structural MRI allows quantification of stroke lesion volume and microstructural damage to white matter, it doesn’t tell us how well the sensorimotor network is working after stroke. Functional MRI (fMRI) provides information about the function of the entire sensorimotor network (Ward, 2011) and can also be used to visualise increased cortical activity in response to training after stroke (Enzinger et al., 2009). Patients typically perform a motor task such as finger tapping, hand grip, or ankle movement during the MRI scan
(Ward et al., 2003; Enzinger et al., 2008). This raises the issue of highly selective recruitment as patients need to be able to perform the task, effectively excluding severely impaired patients and those with aphasia or neglect.

During the fMRI task, patients with greater upper and lower limb motor impairment have greater activation in secondary motor areas such as the premotor and supplementary motor cortices, and more bilateral activation, than patients who are well recovered from stroke (Enzinger et al., 2008; Ward, 2011). This suggests that greater damage to the descending motor pathways from the primary motor cortex results in attempts to use secondary motor areas to generate movement (Ward, 2011).

Most studies using fMRI have reported associations between cortical activation patterns and levels of impairment and function at the same point in time (Cramer et al., 1997; Ward et al., 2003; Luft et al., 2005; Enzinger et al., 2008). fMRI has also been used to predict upper limb function (Cramer et al., 2007) and walking speed response to rehabilitation at the chronic stage (Burke et al., 2014). Burke et al. (2014) reported that lower limb impairment (lower limb FM score) and fMRI activation volume of the ipsilesional foot primary sensorimotor cortex, in combination, were strong predictors for walking speed response to rehabilitation in chronic stroke. Limitations of the study were discussed previously in the CST lesion load section. This study improves on other studies in that it includes clinical, structural MRI and fMRI measures as potential predictors. However, eight variables were entered into a forward stepwise multivariate model, for a sample of 20 participants, resulting in a high likelihood of overfitting the data. Additionally, they conclude that lower limb FM and fMRI activation volume are strong predictors for walking speed response to rehabilitation, but do not provide cut-off points for the measures or provide a way of using this information in clinical practice.
Two studies of the upper limb investigated fMRI within three days of stroke as a predictor for recovery from upper limb motor impairment, with one study reporting a weak correlation and the other reporting no significant relationship (Marshall et al., 2009; Zarahn et al., 2011). No studies were found to have investigated whether fMRI measures early after stroke can predict independent walking outcomes. In order to be used as a predictor an fMRI measure would need to be related to subsequent walking status for an individual patient, but fMRI studies typically rely on averaging data from groups of patients in order to identify common areas of cortical activity. While fMRI provides information about cortical activation at the time of the movement, it is unclear whether these patterns of activity can be used to predict later behavioural outcomes at the group level or for individual patients.

Regardless of the type of MRI technique used, MRI prediction studies are susceptible to the same methodological challenges as studies of clinical predictors including: type and size of patient sample; timing of the initial assessment; and selection and timing of the primary outcome measure. They typically have smaller sample sizes and use fewer independent variables in their prediction models than studies investigating clinical predictors for walking outcome (Table 5.3).
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Stroke characteristics</th>
<th>Baseline clinical</th>
<th>Days from onset</th>
<th>MRI measures</th>
<th>Outcome measure</th>
<th>Endpoint results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho et al.</td>
<td>40</td>
<td>ICH – basal ganglia or corona radiata</td>
<td>FAC</td>
<td>Clinical at stroke onset</td>
<td>DTT: Type A CST preserved</td>
<td>Final FAC</td>
<td>6 months % reached FAC ≥ 4 at 6 months: 100% of Type A patients 75% of Type B patients 60% of Type C patients 38% of Type D patients Significant difference between groups P &lt; 0.05</td>
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<tr>
<td></td>
<td></td>
<td>First stroke</td>
<td></td>
<td></td>
<td>Type B CST preserved but fibres not from M1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Complete paralysis at ankle and hand</td>
<td>MRI</td>
<td>23 days</td>
<td>Type C CST interrupted at haematoma site</td>
<td></td>
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<td></td>
<td></td>
<td>FAC = 0</td>
<td></td>
<td></td>
<td>Type D CST does not reach haematoma due to degeneration</td>
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<tr>
<td>Jang et al.</td>
<td>25</td>
<td>Infarct including CST at base of pons</td>
<td>FAC</td>
<td>Clinical &lt; 24 hours</td>
<td>DTT: Type A CST intact</td>
<td>Δ FAC</td>
<td>6 months Δ FAC greater in group A than B p = 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First stroke</td>
<td></td>
<td></td>
<td>Type B CST interrupted</td>
<td>Final FAC</td>
<td>All patients had a final FAC ≥ 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRC &lt; 2 in lower limb</td>
<td>MRI</td>
<td>15 days</td>
<td></td>
<td></td>
<td>77% of Type A reached FAC = 5</td>
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<tr>
<td></td>
<td></td>
<td>No sensory, cognitive, ataxic or autonomic symptoms</td>
<td></td>
<td></td>
<td>DTT was a significant predictor of final FAC: AUC = 0.843, SE = 0.09, p = 0.004</td>
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<tr>
<td>Kim et al.</td>
<td>37</td>
<td>Large MCA infarct</td>
<td>FAC</td>
<td>Clinical &lt; 24 hours</td>
<td>DTT: Type A CST preserved</td>
<td>Δ FAC</td>
<td>6 months Δ FAC greater in Type A than B or C p &lt; 0.001, but no difference between B or C p = 0.862</td>
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<td></td>
<td></td>
<td>First stroke</td>
<td></td>
<td></td>
<td>Type B CST preserved at infarct</td>
<td>Final FAC</td>
<td>Only Type A reached FAC ≥ 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRC &lt; 3 in lower limb</td>
<td>MRI</td>
<td>19 days</td>
<td>Type C CST does not reach infarct</td>
<td></td>
<td>Final FAC scores for Type A were significantly higher than B or C p &lt; 0.05</td>
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<tr>
<td></td>
<td></td>
<td>No sensory, cognitive, ataxic or autonomic symptoms</td>
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<td></td>
<td>Type A mean FAC score 4.06 ± 0.68</td>
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<td></td>
<td></td>
<td>Type B mean FAC score 2.39 ± 1.27</td>
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<td></td>
<td></td>
<td></td>
<td>Type C mean FAC score 2.17 ± 1.11</td>
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<tr>
<td>Study</td>
<td>N</td>
<td>Type of Infarct or Haemorrhage</td>
<td>FAC</td>
<td>Clinical at Time of Admission</td>
<td>DTT:</td>
<td>Fac</td>
<td>After 4 Weeks of Rehab</td>
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<tr>
<td>Kim <em>et al</em>. (2016)</td>
<td>43</td>
<td>MCA infarct or haemorrhage</td>
<td>FAC</td>
<td>Clinical at time of admission (not specified)</td>
<td>DTT: DTT+ CST intact</td>
<td>FAC = 0</td>
<td>FAC = 1-3 FAC ≥ 4</td>
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<tr>
<td></td>
<td></td>
<td>First stroke</td>
<td>DTT- CST disrupted</td>
<td>Lesion volume</td>
<td>(TMS see Table 5.4)</td>
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<tr>
<td></td>
<td></td>
<td>MRI 39 days (3 – 8 weeks)</td>
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</table>

Abbreviations: ICH = intracerebral haemorrhage; MCA = middle cerebral artery; CST = corticospinal tract; FAC = Functional Ambulation Categories; MRC = Medical Research Council grade; FM = Fugl-Meyer scale; BI = Barthel Index; MRI = magnetic resonance imaging; DTT = diffusion tensor tractography; DTT+ = CST intact; DTT- = CST disrupted; TMS = transcranial magnetic stimulation; M1 = primary motor cortex; FA = fractional anisotropy.
MRI predictors for independent walking

Despite the abundance of research into MRI measures as predictors for recovery and outcomes in the upper limb after stroke, only three studies, all from the same research group, were found to have used MRI within one month of stroke to predict independent walking (Table 5.3). A fourth study with MRI measures obtained at 39 days (Kim et al., 2016) is also included in the discussion due to the limited studies available, and because this study used both MRI and neurophysiological testing as potential predictors for independent walking.

All four studies used diffusion tensor tractography (DTT) to categorise patients into groups based on the extent of CST disruption early after stroke, and investigated the relationship between early CST disruption and independent walking measured with the FAC score at six months post-stroke (Cho et al., 2007b; Jang et al., 2008; Kim et al., 2013) or after four weeks of rehabilitation (Kim et al., 2016). The three studies conducted early after stroke used DTT to split the patients into different categories. However, the criteria and number of DTT categories selected, stroke type, stroke location, and sample size varied between studies, making comparison difficult (Cho et al., 2007b; Jang et al., 2008; Kim et al., 2013). Nonetheless, the results of these studies are in general agreement, showing that patients with less disruption to the CST were more likely to have better walking outcomes 6 months post-stroke.

Although all the patients in these three studies who did not have CST damage achieved independent walking by six months, results for those with CST damage varied. Jang et al. (2008) reported that all patients with or without complete CST disruption achieved independent walking, and CST disruption only differentiated between those who walked independently indoors (FAC ≥ 4) and those who could walk outdoors (FAC ≥ 5) at six months. In contrast, the other two studies reported that patients with a completely disrupted
CST were less likely to walk independently by six months post-stroke (Cho et al., 2007b; Kim et al., 2013). Unfortunately, Kim et al. (2013) did not report percentages of patients in each group who achieved independent walking, probably because their primary outcome measure was change in FAC score rather than final FAC score. Possible contributions to the better walking outcomes in the study by Jang et al. (2008) are the location of the lesion in the pons, and that potential participants were excluded if they had sensory loss, ataxia or cognitive deficits. The combined findings of these three studies indicate that DTT predicts independent walking for those patients with no CST damage but it is less useful as a predictor for those with CST damage. It is not clear whether accurate predictions can be made for individual patients as sensitivity and specificity were not reported.

The third study by this group was the only one to include other MRI measures (FA ratio and lesion volume) as potential predictors for independent walking by six months post-stroke (Kim et al., 2013). A moderate positive correlation was found between baseline FA ratio (affected CST FA divided by unaffected CST FA) and six month FAC score, indicating that participants with more symmetrical FA values early after stroke achieved higher six month FAC scores. A weak negative correlation was found between baseline lesion volume and six month FAC scores, indicating that, as a group, participants with a larger stroke had worse walking outcomes at six months (Kim et al., 2013). These findings suggest that FA ratio is more strongly correlated with six month FAC scores than lesion volume. However no algorithm or predictive tool that could be used in clinical practice was developed from these findings.

These three studies all share the same limitations of different sample types and size; the use of whole group reporting of outcomes as means and standard deviations; no reporting of positive and negative predictive values; and no analysis to form a prospective prediction model or clinical algorithm. Two of these authors suggest that further investigation is
required in a larger sample, and combining DTT with transcranial magnetic stimulation (TMS) may be useful (Jang et al., 2008; Kim et al., 2013).

The final study in Table 5.3 (Kim et al., 2016) is discussed separately as it has substantial methodological differences from the other three studies that mean comparisons are not possible. The main differences are the inclusion of neurophysiology measures, recruitment of participants on admission to rehabilitation (up to eight weeks post-stroke), and a primary endpoint after four weeks of rehabilitation rather than at a fixed time of six months. This study included TMS to assess the functional integrity of the CST. The TMS findings are discussed in full in the next section. Based on the DTT findings alone, only half of the participants with an intact CST achieved independent walking, and no patients with complete CST disruption achieved independent walking after four weeks of rehabilitation. These poor outcomes are in contrast to the previous three studies that reported all participants with intact CST walked independently, and many of the participants with CST disruption achieved independent walking too. These different findings may be due to the much earlier primary end point in this study.

The strengths of this study are: including both MCA infarct and haemorrhage; reporting the numbers of patients achieving each FAC score in each group; and the use of more than one type of predictor (imaging and neurophysiology). However, this study has some substantial limitations including: sample selection (unclear whether some patients were already independent); relatively late recruitment after stroke onset; and the timing of the primary endpoint at four weeks after recruitment to the study. These limitations mean findings need to be interpreted with caution.

Although only a few studies have investigated MRI biomarkers for predicting walking recovery and outcomes after stroke, and their results are inconsistent in parts, the strong
correlations of both FA asymmetry and lesion load with upper limb recovery indicate that this is still an area worth investigating further in the lower limb. Several possible reasons exist for the weaker predictive value of CST damage in lower limb than in upper limb studies. The CST is involved in walking, but it may not be essential (Chapter 2), as it is possible to walk with complete disruption to the CST (Ahn et al., 2006; Cho et al., 2012). This suggests that other descending motor pathways may be more important for the recovery of independent walking, and because these techniques have been modelled on upper limb studies, they might not capture these pathways (Jones et al., 2016).

One of the main limitations of MRI is that although it can provide very detailed information about the structure of the white matter tracts, it is not able to provide information about whether the surviving neurons in these tracts are capable of transmitting a motor command to the spinal cord. TMS can be used to test the function of some descending motor pathways and will be discussed in the next section.

5.2.3 Neurophysiological predictors for independent walking

TMS is a non-invasive and painless technique for examining the functional integrity of the corticomotor pathway. A coil is held against the scalp over the location of the primary motor cortex. The brief magnetic pulse activates neurons in the motor cortex, and pyramidal neurons produce descending volleys to the spinal cord via the CST (Barker et al., 1985). When the summation of these descending volleys depolarises spinal motoneurons to their firing threshold, a motor evoked potential (MEP) is produced in muscles of the contralateral limb (Terao et al., 1994; Di Lazzaro et al., 1998a; Terao and Ugawa, 2002).
TMS has been established as an important tool for predicting the recovery from impairment and functional outcomes in the upper limb after stroke, discussed in detail in Appendix 1. Patients in whom it is possible to elicit a MEP (MEP+) exhibit proportional recovery from impairment and experience good functional outcomes in the upper limb after stroke (Heald et al., 1993; Rapisarda et al., 1996; Pizzi et al., 2009; Stinear et al., 2012; Byblow et al., 2015; Stinear et al., 2017a; Stinear et al., 2017b). MEP status is a robust biomarker for upper limb recovery, and therefore TMS may play an important role in baseline stratification of patients in upper limb stroke studies (Smith and Stinear, 2016) (Appendix 1). The usefulness of TMS as a prognostic tool in the lower limb is much less clear due to a paucity of literature and wide variation in how the studies have been conducted.

Two large systematic reviews have been conducted on the use of TMS for predicting motor outcomes after stroke (Hendricks et al., 2002b; Bembenek et al., 2012). Only Hendricks et al. (2002b) included both upper and lower limb studies. Five studies met their criteria for critical review, of which only two recorded lower limb MEPs (Escudero et al., 1998; Palliyath, 2000). Neither of these included lower limb MEP data in their final analyses.

Four studies were found that attempted to use lower limb MEPs to predict recovery of independent walking early after stroke (Hendricks et al., 2003; Piron et al., 2005; Chang et al., 2015; Kim et al., 2016) (Table 5.4). All four studies recorded MEPs from the tibialis anterior muscle of the affected leg, and one also recorded MEPs from the vastus medialis muscle (Hendricks et al., 2003). Three of the studies recruited participants within one month of stroke and had a primary endpoint of around six months post-stroke (Hendricks et al., 2003; Piron et al., 2005; Chang et al., 2015), and one study recruited participants up to two months after stroke and had a primary endpoint four weeks later (Kim et al., 2016). Chang et al. (2015) reported that all participants with MEPs (MEP+) recovered independent walking
by six months, while all participants with absent MEPs (MEP-) remained dependent. In contrast, two other studies reported that MEP- status more strongly predicted dependent walking than MEP+ status predicted independent walking (Piron et al., 2005; Kim et al., 2016). The fourth study reported no relationship between MEP status and subsequent independent walking, but tibialis anterior MEPs might predict the likelihood of regaining the ability to transfer independently (Hendricks et al., 2003). Only Chang et al. (2015) reported the results in the form of sensitivity, specificity, positive and negative predictive values.

More complex MEP data were analysed by Piron et al. (2005) in an attempt to distinguish between those MEP+ participants who did and did not achieve independent walking. They described MEP amplitudes for those participants who were MEP+ as a ratio of MEP/MEPmax. MEPmax was determined by the maximal motor response of the target muscle to supramaximal peripheral nerve stimulation (Piron et al., 2005). All nine participants who generated a MEP amplitude of at least 8% of their MEPmax walked independently by seven months. MEP/MEPmax ratio was not a predictor of walking outcome for the participants with MEPs of less than 8% MEPmax (Piron et al., 2005). Although generating MEP/MEPmax ratios slightly improved the prediction capabilities for those participants who were MEP+, the increased complexity of the testing means this is unlikely to be practical as a technique for all patients with stroke in a clinical setting. This study was also limited by the selection of the primary outcome measure (Hemiplegic Stroke Score), which does not define whether “independent walking” is with or without supervision and is therefore open to individual interpretation. They also had a small sample size (n = 20) and completed baseline and TMS assessments at one month after stroke which is too late to be relevant in a clinical setting.
### Table 5.4 TMS studies for prediction of independent walking

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Stroke type</th>
<th>Baseline clinical</th>
<th>TMS</th>
<th>Outcome measure</th>
<th>Follow-up time</th>
<th>Results for independent walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendricks et al. (2003)</td>
<td>38</td>
<td>Ischaemic Paralysis</td>
<td>LL FM (subsets) FAC BI</td>
<td>Time from onset: 3 – 7 days</td>
<td>MEPS present</td>
<td>2,3,6,12, weeks</td>
<td>3/7 MEP+ independent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe paresis</td>
<td></td>
<td>Muscle: VM TA Facilitation: Yes</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>? walking or not</td>
<td></td>
<td>Coil type: Circular 80, 100% MSO</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensity: Amplitude 200 µV – 2 responses</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MEP measure: LL FM subsets FAC ≥ 4 BI transfers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piron et al. (2005)</td>
<td>20</td>
<td>MCA infarct “Almost” complete paralysis</td>
<td>HSS motor and walking scores</td>
<td>Time from onset: 1 month</td>
<td></td>
<td>7 months</td>
<td>10/13 MEP+ independent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not walking</td>
<td></td>
<td>Muscle: TA Facilitation: Yes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coil type: Double cone 100% MSO</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensity: Amplitude 50 µV – 4 responses</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MEP measure: HSS walking score ≤ 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al. (2015)</td>
<td>14</td>
<td>ACA infarct</td>
<td>FAC</td>
<td>Time from onset: 17 days Clinical at 24 hours</td>
<td></td>
<td>6 months</td>
<td>7/7 MEP+ independent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe proximal weakness and distal paralysis</td>
<td></td>
<td>Muscle: TA Facilitation: No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not walking</td>
<td></td>
<td>Coil type: Circular RMT + 20% MSO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensity: Amplitude ≥ 50 µV on 2 out of 4 trials</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MEP measure: FAC ≥ 3</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MRI measures (DTT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. (2016)</td>
<td>43</td>
<td>MCA infarct or haemorrhage</td>
<td>FAC</td>
<td>Time from onset: 39 days (3 – 8 weeks)</td>
<td></td>
<td>After 4 weeks of rehab</td>
<td>11/33 MEP + independent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>? walking or not</td>
<td></td>
<td>Muscle: TA Facilitation: No</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coil type: Circular RMT + 20% MSO</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensity: Amplitude ≥ 50 µV on 5 out of 10</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MEP measure: FAC=0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MRI measures (DTT)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Abbreviations:** MCA = middle cerebral artery; ACA = anterior cerebral artery; HSS = Hemiplegic Stroke Scale; BI = Barthel Index; LL FM = lower limb Fugl-Meyer scale; MI = Motricity Index; FAC = Functional Ambulation Categories; TA = tibialis anterior muscle; VM = vastus medialis muscle; MSO = maximum stimulator output; MEP = motor evoked potential; MRI = magnetic resonance imaging; DTT = diffusion tensor tractography; MEP+ = MEPS present; MEP- = MEPS absent
Hendricks et al. (2003) had the second largest sample size of 38 participants, and was the only study of the four to report that MEP status was not a predictor for independent walking. This study recorded MEPs from both vastus medialis and tibialis anterior. They also measured motor recovery which they defined as a score that changed from zero at baseline to greater than zero at six months on the proximal or distal lower limb strength items on the Fugl-Meyer assessment. Vastus medialis MEPs had no predictive value either for recovery from motor impairment or achieving independent walking, suggesting that recovery of proximal leg muscle strength may not be reliant on CST function (Hendricks et al., 2003). In contrast, a significant relationship was found between the presence of TA MEPs at baseline and the recovery of distal leg strength at six months post-stroke. The presence of TA MEPs also predicted the ability to manage independent transfers at six months, but there was no relationship between the presence of TA MEPs and independent walking (Hendricks et al., 2003).

The strengths of this study are the larger sample size, early inclusion period of less than one week post-stroke, multiple assessment points, a fixed primary endpoint, and the inclusion of participants with severe hemiparesis or complete paralysis (Hendricks et al., 2003). It is these severely affected patients who present the greatest challenge to clinicians predicting walking outcomes. Limitations are the use of the non-validated subset scores of the Fugl-Meyer to score lower limb motor recovery, and the TMS criterion used to determine the presence or absence of MEPs. In this study, a MEP was considered to be present if a response with minimum peak-to-peak amplitude of 200 µV was generated, whereas in the other three studies the criterion for the presence of a MEP was a peak-to-peak amplitude of 50 µV, consistent with international guidelines (Piron et al., 2005; Chang et al., 2015; Rossini et al., 2015; Kim et al., 2016).
The findings of the study by Chang et al. (2015) appear promising, with all MEP+ participants achieving independent walking and all MEP- patients remaining dependent. This study included patients with severe hemiplegia or paralysis of the leg, completed clinical assessment within 24 hrs and TMS within 2.5 weeks, and had a fixed primary endpoint of FAC at six months post-stroke. However, the sample size is very small at only 14 participants, meaning at best this can be considered a preliminary study with interesting findings. The other significant limitation is that the FAC is incorrectly dichotomised for independent walking at ≥ 3. This makes comparing results with other studies difficult. Because the sample was so small, the authors were able to report the individual FAC scores at six months and only one MEP+ participant scored three points on the FAC at this time, while the other MEP+ participants score FAC ≥ 4. If the classification of this participant is corrected to dependent, 6/7 MEP+ participants achieved independent walking by six months. This study stands out due to the clear distinction between walking outcomes for MEP+ and MEP- patients. One possible reason for this is that the participants all had anterior cerebral artery infarcts which directly affect the leg area of the motor cortex, whereas the other studies included only middle cerebral artery infarcts (Piron et al., 2005; Kim et al., 2016) or a range of cortical, subcortical and brainstem strokes (Hendricks et al., 2003).

The final study in Table 5.4 differs from the other three in that it has late participant recruitment (up to two months post-stroke) and the primary outcome is only four weeks later (Kim et al., 2016), which means it cannot be compared with the studies with a primary endpoint of six months. As discussed in Section 5.2.2, Kim et al. (2016) used MRI (DTT) in combination with TMS to predict independent walking. Participants were classified as DTT+ if the CST was intact and DTT- if the CST was completely disrupted. Participants were then grouped according to the potential combinations of DTT and MEP status. All participants who were MEP- also had complete disruption to their CST (DTT-), however nine participants
who were DTT- still had MEPs (Kim et al., 2016). This suggests that patients can still have a functioning CST despite apparently severe damage according to imaging measures. In this study, participants who were both DTT+ and MEP+ were more likely to walk independently, while none of those who were DTT-, regardless of MEP status, walked independently (Kim et al., 2016). Both TMS and DTT had stronger negative predictive value than positive predictive value.

The results of this study need to be treated with caution due to several significant limitations. Firstly, the late timing of baseline variables and early primary endpoint placed some participants near the end of the spontaneous recovery process at follow up, while others were potentially only midway. The short time from baseline assessment to endpoint also limits the predictive value of these findings, as participants who did not achieve independent walking may well have achieved it at a later time point; this may particularly apply to the more severely impaired participants. The third major limitation is that it is unclear whether some participants were already walking independently at recruitment. This means some of the MEP+/DTT+ participants who were “predicted” to walk independently may have already achieved this, which artificially inflates the predictive value of the measure.

Despite some similarities between these four studies, the differences are substantive, making comparison difficult. Three studies recruited participants with moderate or severe leg paresis (Hendricks et al., 2003; Piron et al., 2005; Chang et al., 2015), while one didn’t report inclusion criteria relating to motor impairment or walking function (Kim et al., 2016). Two studies completed baseline measures within two weeks (Hendricks et al., 2003; Chang et al., 2015), one at a month (Piron et al., 2005) and one at up to two months post-stroke (Kim et al., 2016). Three studies used FAC to measure independent walking, but one dichotomised incorrectly at FAC ≥ 3 (Chang et al., 2015), and another study used the Hemiplegic Stroke Score dichotomised at ≤ 3, which may or may not allow supervision for walking (Piron et al.,
2005). All four studies used different techniques to determine MEP status. None of the studies meet the criteria for a high quality prediction study (Hendricks et al., 2002a).

There are not enough studies on using TMS for prediction of independent walking after stroke to draw any firm conclusions. However some of the groundwork has been done in studies investigating the relationship between CST integrity and walking at the chronic stage of stroke (Chapter 2). This early research, and the established role of TMS in the prediction of upper limb motor recovery and outcomes, provides some promising signs that TMS may be a useful prognostic tool for predicting independent walking after stroke. Yet the presence of alternative motor pathways and the ability to compensate for lower limb weakness during walking means that the role of the CST in walking may be less crucial than it is in the upper limb. This might mean that TMS needs to be used in combination with clinical or neuroimaging measures, which may capture the potential for compensatory mechanisms, in order to predict independent walking after stroke. There is little agreement in the literature on the most effective method for lower limb TMS with most studies using different protocols. More research is required to develop an effective protocol for using TMS to test the MEP status of the paretic lower limb in patients with sub-acute stroke.
5.3. Clinical applicability of prediction studies

Almost every prediction study begins and ends with a statement that predicting walking outcome will assist patients and clinicians after stroke. Yet few of these studies’ findings are ever implemented in clinical practice. The assessment tools are often inaccessible, the timing of the assessments or the type of outcome measure is not meaningful for clinicians and patients, and more often than not the prediction “tool” cannot make a clear prognosis for an individual patient.

One of the contributing factors to this is the method of analysis used in prediction studies. The established statistical approach for clinical prediction studies is multivariate logistic regression analysis (Kwakkel et al., 1996; Veerbeek et al., 2011a). However, it only provides probabilities based on group outcomes and averages, which is difficult to apply to an individual patient. Another limitation is that, with the exception of two studies (Veerbeek et al., 2011b; Bland et al., 2012), probabilities for recovery or outcomes are reported along a continuum, or as an explanation of variance within a sample. For example: a higher Barthel index score on admission, or a higher Motricity Index score, correlates with a higher probability of recovering independent walking. This information is useful in that it indicates which baseline measures may provide predictive information. However without a specific value for each predictor score and a clear expectation of how that translates into actual walking function, this is not able to be used in the clinical setting. The same issues of a lack of specific cut-off values for predictors and poor translatability also exist in imaging and neurophysiological studies. Some studies provide a regression equation to calculate the probability of a patient achieving independent walking (Table 5.5), however these are all different, and are not useful or practical for a clinician attempting to provide information to their patient. Specific guidelines on how to apply the predictive model in clinical practice were only provided by one study that predicted likelihood of achieving community
ambulation, and therefore was not specifically within the scope of this thesis (Bland et al., 2012).

**Table 5.5** Regression equations for the recovery of independent walking

<table>
<thead>
<tr>
<th>Equation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$72 \text{ hrs: } P = \frac{1}{1 + (\exp(-0.982 + 2.691 \times \text{TCT-s} + 2.083 \times \text{MI leg}))}$</td>
<td>Veerbeek et al., 2011b</td>
</tr>
<tr>
<td>$5 \text{ days: } P = \frac{1}{1 + (\exp(-1.236 + 2.815 \times \text{TCT-s} + 1.609 \times \text{MI leg}))}$</td>
<td></td>
</tr>
<tr>
<td>$9 \text{ days: } P = \frac{1}{1 + (\exp(-2.226 + 3.629 \times \text{TCT-s} + 1.854 \times \text{MI leg}))}$</td>
<td></td>
</tr>
<tr>
<td>$p = \frac{1}{1 + (\exp((\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n)))}$</td>
<td>Sánchez-Blanco et al., 1999</td>
</tr>
<tr>
<td>$P (\text{“non-independent gait” / TCT}) = \frac{e(3.13 - 0.081 \times \text{TCT})}{1 + e(3.13 - 0.081 \times \text{TCT})}$</td>
<td>Duarte et al., 2010</td>
</tr>
<tr>
<td>Walking (BI) score $= 0.38 + 0.78 \times (\text{balanced sitting+walking [MMAS]+bowel control scores})$</td>
<td>Loewen and Anderson, 1990</td>
</tr>
</tbody>
</table>

An alternative approach to regression analysis is the use of Classification and Regression Tree analysis (CART). The CART analysis independently selects and dichotomises variables in order to achieve the least overlap between resulting subgroups (Muller and Mockel, 2008). At each branch of the tree, the same process is repeated, producing a decision tree or prediction algorithm. The benefit of using CART analysis is that it provides a step-by-step approach to achieve a clear prediction for an individual patient in a format which is easily accessible to a clinician. CART analysis has recently been used in an upper limb stroke prediction study (Stinear et al., 2017a).

Clinical predictors are easily accessible and inexpensive, allowing relatively straight forward translation to clinical practice, but MRI and TMS are not. MRI scans are accessible in that most hospitals have an MRI scanner and clinicians are familiar and comfortable with their use. However, they are costly to run and not used for every patient immediately after stroke. The MRI protocols used in research take longer to run than routine CT or MRI, which means they cannot replace admission CT scans due to the delaying effect on door to
needle time, which is important in acute medical interventions such as thrombolysis and clot retrieval. Therefore, MRI scans for prediction of motor recovery and outcomes are likely to require an extra scan administered after admission. Identification of a subgroup of patients that benefit from MRI (Stinear et al., 2017a) would reduce the cost burden by only requiring scans for some patients. Other limitations of MRI are the software and technical expertise required for complex processing of MRI measures, and contraindications limiting patient eligibility.

TMS also requires specialist equipment and expertise, although a recent study reported successfully teaching physiotherapists to use TMS to determine upper limb MEP status in patients in an acute hospital (Stinear et al., 2017a). TMS machines are not common in the hospital setting, which affects accessibility and means that clinicians are often unfamiliar with TMS and its potential uses. TMS also has specific contraindications which affect patient eligibility. Therefore, there needs to be clear evidence that TMS is a robust biomarker for predicting lower limb motor recovery and walking to justify its use in a clinical setting, and this has not yet been achieved.

5.4. Summary

Several studies have investigated the predictive value of either clinical, TMS or MRI measures for independent walking after stroke. However, they are lacking in quality and consistency, making it difficult to draw firm conclusions from them. Most prediction studies provide broad generalisations for groups of patients, often producing models that are complex and lack the accuracy required to be of practical use in the clinical setting. Studies are usually observational, often without attempting to translate the findings into a format that may be of use in a clinical setting. Despite these challenges, it appears that clinical variables such as trunk control, lower limb impairment, age, initial activities of daily living function,
initial walking ability, sensory loss and hemianopia are important to include in future prediction studies. The presence of tibialis anterior MEPs and the use of MRI measures as prognostic indicators are inconclusive due to the small number of studies investigating these potential prediction tools and their widely varying methods. However the strength of these tools as predictors of upper limb recovery makes them worth investigating further.

Further research is required to identify variables that may be of prognostic value for individual patients, and in particular how to translate these predictions into clinical practice. Integrity of the CST appears to have some influence on walking after stroke, but may not be a robust predictor in isolation. Most studies use a single type of predictor (clinical, imaging, neurophysiology). Using a combination of clinical, imaging and neurophysiological measures may be the key to producing an accurate prediction model or algorithm.

**Challenges associated with lower limb TMS studies early after stroke**

One of the reasons few lower limb TMS studies have been conducted is that the technique can be difficult. This may also explain some of the conflicting results. Higher stimulation intensities are usually required for lower limb TMS than upper limb. Motor thresholds are typically raised as a result of the stroke, which increases the likelihood of false negative results (Chapter 6). In chronic stroke, a double cone coil is used to enable a deeper and stronger TMS pulse to target the lower limb motor area, however Madhavan et al. (2010) reported high levels of discomfort when using the double cone coil at high intensities. This is problematic early after stroke as patients have limited tolerance for high stimulus intensities due to being fatigued and less medically stable. Probably for this reason, there was only one study that used the double cone coil in patients sub-acutely at one month after stroke (Piron et al., 2005) and a figure 8 or circular coil is often used instead. The next chapter (Chapter 6) presents my first experiment investigating the effects of leg activation, current direction, and
limb dominance on lower limb motor thresholds in healthy adults. The purpose of this experiment was to design a TMS protocol that would optimise the determination of MEP status while minimising discomfort. This TMS protocol was then used to assess MEP status in patients within one week of stroke in Chapters 7 and 8.
Chapter 6. Optimising transcranial magnetic stimulation technique for the lower limb

This experiment has been reported in Brain Research


6.1. Abstract

Transcranial magnetic stimulation (TMS) is used to examine corticospinal tract integrity after stroke, however, generating motor-evoked potentials (MEPs) in the lower limb (LL) can be difficult. Previous studies have used activation of the target leg to facilitate MEPs in the LL but this may not be possible after stroke due to hemiplegia. The dominance of the target limb may also be important, however the neurophysiological effects of LL dominance are not known. We investigated whether voluntary activation of the non-target leg combined with optimal TMS coil orientation increases corticomotor excitability in healthy adults, and whether limb dominance influences these results. TMS was delivered to induce a posterior-anterior (PA) and a medial-lateral (ML) cortical current in 22 healthy adults. MEPs were recorded in tibialis anterior (TA) with the participant at rest and when activating the non-target leg. We found that non-target leg activation increased corticomotor excitability in the target leg (reduced rest motor threshold (RMT) and MEP latency, and increased recruitment curve slope). ML cortical current also reduced RMT and MEP latency. The degree of footedness correlated with the degree of RMT asymmetry, with a PA but not ML cortical current direction. In summary, cross-facilitation by activating the non-target leg in a task requiring postural stabilisation and inducing ML current increase corticomotor excitability regardless of limb dominance. This protocol may have practical application in testing CST integrity after stroke when paretic limb thresholds are high, by increasing the likelihood of eliciting a MEP.
6.2. Introduction

Recovery of independent ambulation is the most common therapy goal after stroke (Bohannon et al., 1988). The corticospinal tract (CST) plays a role during gait in healthy adults (Schubert et al., 1997; Capaday et al., 1999; Bonnard et al., 2002). After stroke, the integrity of the CST can be examined using transcranial magnetic stimulation (TMS). The presence of a motor evoked potential (MEP) in the target muscle indicates that the CST is functionally intact (Petersen et al., 2003; Talelli et al., 2006; Stinear et al., 2012). Gaining this information in the first week after stroke may help guide expectations for upper limb (UL) recovery (Stinear, 2010a). However, few studies have investigated CST integrity in the lower limb (LL) early after stroke.

The majority of studies using TMS in the LL have been conducted in healthy adults (Terao et al., 2000; Di Lazzaro et al., 2001; Richter et al., 2013) or in patients at least six months after stroke (Forrester et al., 2006; Cacchio et al., 2011; Madhavan et al., 2011). High TMS stimulus intensities are required to generate MEPs in the LL due to the deep location of the cortical leg representation within the interhemispheric fissure (Terao et al., 1998; Terao and Ugawa, 2002; Groppa et al., 2012). Furthermore, compared to the UL the LL has larger and less dextrous muscle groups, with a greater proportion of motor units driven by large alpha motoneurons with a higher activation threshold (Henneman et al., 1965; Brasil-Neto et al., 1992b). These factors mean high TMS intensities are required to generate MEPs in the LL, relative to the UL.

The excitability of motor neurons is compromised early after stroke by permanent tissue loss affecting both grey and white matter, and by temporary physiological effects on surviving tissue including oedema, diaschisis, metabolic dysfunction and tonic inhibition (Xing et al., 2012; Zeiler and Krakauer, 2013). These combined effects may result in an
increase in motor threshold in the ipsilesional motor cortex. At the same time, patients are less medically stable, have high fatigue levels and limited tolerance for high TMS stimulus intensities. Developing a technique that optimises TMS delivery to the LL motor cortex by reducing motor thresholds may increase patient tolerance and be useful for delivering TMS early after stroke.

Activating the target muscle is an established method of decreasing motor threshold (Hess et al., 1986; Di Lazzaro et al., 1998b). Voluntary muscle contraction increases the excitability of the motoneuron pool, reducing the stimulus intensity required to bring the neurons to firing threshold, and increasing the number and size of descending volleys evoked by TMS (Di Lazzaro et al., 1998b; Di Lazzaro et al., 1999; Ortu et al., 2008). For these reasons, previous LL studies have routinely been conducted with the target leg active (Terao et al., 2000; Cacchio et al., 2011; Jayaram et al., 2012). However, for many patients early after stroke, activation of the paretic (target) leg is not possible. Therefore alternative methods of reducing motor threshold, with the target leg at rest, are required for investigating CST integrity in this group.

In healthy adults, MEPs recorded from the resting target UL are facilitated by activation of homologous muscles in the non-target UL (Muellbacher et al., 2000; Stinear et al., 2001; Ibey and Staines, 2013). This is mediated by an “overflow” effect resulting in modulation of interhemispheric inhibition and a reduction in short latency intracortical inhibition in the resting UL (Perez and Cohen, 2008). This overflow effect requires a high level of force production by the homologous non-target UL muscles (Perez and Cohen, 2009). Chiou et al. (2013) investigated cross-facilitation of MEPs recorded in LL muscles by voluntary activation of either the homologous muscle, or a heterologous muscle. Participants were in a recumbent, fully supported position, with no postural demands. They reported an increase in recruitment curve slope, but did not report any effects on rest motor threshold (Chiou et al.,
The present study is the first to investigate cross-facilitation of MEPs in the resting LL by a task that required combined activation of homologous and heterologous non-target LL muscles. This task also required trunk muscle activation to maintain postural stability in a seated position. This approach capitalises on the expected homologous cross-facilitation as observed in the UL, and the potential influence of trunk and postural control mechanisms.

Another important factor affecting motor threshold is cortical current direction. The direction of the current induced in the cortex by TMS influences both the efficacy of stimulation (reducing the stimulus intensity required to bring corticospinal neurons to firing threshold) and also affects the combination of cortical elements that are stimulated (Brasil-Neto et al., 1992a; Werhahn et al., 1994; Di Lazzaro et al., 1998a). TMS generates a descending volley of waves in the corticospinal tract by direct stimulation of pyramidal neuron axons (D waves) and indirect stimulation via intracortical circuits (I waves) (Day et al., 1989; Di Lazzaro et al., 2012). Cortical current direction affects the relative contributions of D and I waves to the descending volley, and its susceptibility to intracortical inhibition and facilitation.

Cortical current directions that produce the lowest motor threshold differ between the upper and lower limb. For the UL, posterior to anterior current flow perpendicular to the central sulcus produces the lowest motor thresholds (Brasil-Neto et al., 1992a; Groppa et al., 2012; Rossini et al., 2015; Volz et al., 2015). In contrast, for the LL, medial to lateral current produces the lowest motor thresholds, as the cortical current flows parallel to the neuronal axons as they traverse into the interhemispheric fissure (Priori et al., 1993; Terao et al., 2000; Di Lazzaro et al., 2001; Groppa et al., 2012; Richter et al., 2013; Rossini et al., 2015).

While it is clear that contralateral muscle activation and cortical current direction separately affect corticomotor excitability, it is unclear whether these factors interact. Motor
threshold may be affected by the interaction between the intracortical and interhemispheric mechanisms of cross-facilitation, and the composition of the descending volley produced by different cortical current directions. In patients with stroke, where LL thresholds are even higher than in healthy adults, it may be important to select an optimal combination of cross-facilitation and cortical current direction to reduce motor threshold.

Limb dominance may also affect motor threshold. There is some evidence of a relationship between neurophysiological asymmetry and hemisphere dominance in the UL (Triggs et al., 1997; Brouwer et al., 2001; Daligadu et al., 2013). To the best of our knowledge, the effect of hemisphere dominance on corticomotor excitability has not been investigated previously in the LL. Understanding this relationship in healthy adults may provide context for the interpretation of asymmetries within the corticomotor system of patients after stroke.

The aim of this study was to investigate the effects and interactions between two different motor tasks (both legs at rest or non-target leg active), two cortical current directions (posterior-anterior (PA) or medial-lateral (ML)) and hemisphere dominance on LL corticomotor excitability in healthy adults, in order to develop a protocol for patients early after stroke.

We hypothesised that 1) activation of the non-target leg and induction of an ML cortical current will independently increase the excitability of the LL corticomotor representation; 2) the effects of non-target leg activation and cortical current direction on corticomotor excitability may interact; 3) corticomotor excitability will be higher in the dominant hemisphere; 4) the degree of hemispheric asymmetry in corticomotor excitability will correlate with the degree of footedness.
6.3. Materials and methods

6.3.1 Participants

Twenty-two healthy adults participated in this experiment (11 males, 11 females, mean age 30 years, range 19 – 47 years). Participants had no neurological lower limb deficits, and were screened for contraindications to TMS by a neurologist (PAB). Written informed consent was obtained, the protocol was approved by the University of Auckland Human Participants Ethics Committee, and the study was conducted in accordance with the Declaration of Helsinki.

6.3.2 Experimental design

Hand and foot dominance were determined for each participant. TMS was delivered to each motor cortex (M1) while EMG data were collected bilaterally during all test conditions. For the purpose of this study, the “target” leg refers to the leg contralateral to the stimulated M1. The “non-target” leg refers to the leg ipsilateral to the stimulated M1. Four test conditions were used in each hemisphere (Figure 6.1)
Figure 6.1 Experimental design

The centre of the figure-8 coil was placed 1 cm posterior to the vertex and 1-2 cm laterally on the target hemisphere (target foot shaded). The coil was then orientated to generate either a posterior-anterior (PA) current (A and B), or a medial-lateral (ML) current (C and D) in the primary motor cortex (M1). Both hemispheres were tested: A. PA current, both legs at rest; B. PA current, non-target leg active; C. ML current, both legs at rest; D. ML current, non-target leg active. MEPs were recorded from the tibialis anterior (TA) muscle in both legs.
6.3.3 Hand and foot dominance

All participants were assessed for hand dominance using the Edinburgh Handedness Inventory (Oldfield, 1971). Participants were then asked to complete an inventory of ten physical tasks to determine foot preference (Table 6.1). Although most LL activities are bipedal, many tasks require a combination of “non-skilled” stabilising function (non-dominant leg) and “skilled” manipulation function (dominant leg) such as kicking a ball or picking up a marble with the toes (Kalaycioglu et al., 2008; Schneiders et al., 2010). Tasks were selected to include both skilled manipulation tasks and non-skilled tasks (Schneiders et al., 2010).

Table 6.1 Footedness assessment

<table>
<thead>
<tr>
<th>Footedness assessment</th>
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<tbody>
<tr>
<td>1. Digging with a spade</td>
</tr>
<tr>
<td>2. Stamping out a simulated fire</td>
</tr>
<tr>
<td>3. Kicking a ball towards a target</td>
</tr>
<tr>
<td>4. Picking up a marble using toes</td>
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<tr>
<td>5. Tracing three shapes with the big toe</td>
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<tr>
<td>6. Hopping on one leg 5 times</td>
</tr>
<tr>
<td>7. Stepping forward up a step</td>
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<tr>
<td>8. Stepping forward down a step</td>
</tr>
<tr>
<td>9. Initiation of tandem walking</td>
</tr>
<tr>
<td>10. Stepping response to perturbation</td>
</tr>
</tbody>
</table>

Each participant performed all tasks. The leg chosen to initiate the task was considered the dominant foot for each task.
To avoid bias, participants were informed that the tasks were being used as a measure of their balance and coordination and were unaware that the purpose of the tasks was to determine foot preference. The starting position for each task was standardised. Participants were asked to stand with their feet hip width apart and hands resting at their side. Any items used during the tasks were placed in a midline position between the feet. The foot used to initiate the movement for each task was documented. The number of tasks initiated with the right foot and the number of tasks initiated with the left foot were entered into the following formula to determine a laterality quotient for foot preference:

\[
\text{Foot lateralisation} = \frac{(R-L)}{(R+L)}
\]

A foot lateralisation score > 0 reflects right footedness and a score < 0 reflects left footedness.

6.3.4 Electromyography (EMG)

Surface EMG was recorded from TA of both legs using pairs of electrodes (Red Dot, 3M Health Care) placed on each muscle belly 3 cm apart, following standard skin preparation techniques. A ground surface electrode (Red Dot, 3M Health Care) was placed on the skin over each patella. EMG signals were amplified by 1000 gain (CED 1902; Cambridge Electronic Design (CED); Cambridge, United Kingdom), bandpass-filtered (20 - 1000 Hz), and sampled at 2 kHz (CED 1401). EMG signals were displayed and stored for offline analysis using Signal software (CED).
6.3.5 **Transcranial Magnetic Stimulation (TMS)**

Single pulse TMS was delivered to each M1 using a 70 mm figure-of-eight coil connected to a Magstim 200 unit (Magstim company, Dyfed, Wales). To induce a PA current, the coil was placed 1 cm posterior to the vertex and 1 - 2 cm laterally to the left or right to stimulate the corresponding motor cortex. The coil handle was pointing posteriorly in the sagittal plane (figure 1). The coil position was adjusted for each individual to the site that elicited maximal amplitude motor evoked potentials (MEPs) in the resting target TA muscle. A tight fitting cap was worn by the participant, allowing markings to be drawn to ensure consistency of coil placement and orientation throughout the protocol.

To induce an ML current, the centre of the coil was placed in the same position on the head as for PA but with the handle pointing medially towards the non-target hemisphere (figure 1). The handle was then rotated up to 30° posteriorly to elicit the greatest MEP amplitude in the target TA (Richter *et al.*, 2013).

Rest motor threshold (RMT) of each M1 was determined as the minimum stimulus intensity required to elicit a MEP of > 50 µV peak-to-peak amplitude in at least five out of ten consecutive trials in the target TA (Rossi *et al.*, 2009). RMT was measured for each of the four test conditions.

TMS was used to construct a stimulus-response recruitment curve for each of the four test conditions for each M1. Stimulus intensities were relative to RMT, with the weakest at 5% maximum stimulator output (MSO) below RMT, and rising in 10% MSO increments. A maximum of five different intensities were delivered unless the maximum stimulator output was reached. Stimuli were delivered in blocks of 12, with the order of intensity randomised for each test condition. Pre-trigger EMG was collected for 100 ms prior to each stimulus.
6.3.6 **Testing Position**

Each participant was seated with their hips and knees at 90° angles and feet on the floor. For the resting position, the participant was instructed to keep both legs relaxed. For the active position, the participant was instructed to lift the non-target leg off the floor with the hip in 100° flexion (thigh off the chair), the knee in 45° flexion and the ankle in full dorsiflexion. The participant was also instructed to keep the target leg completely at rest. Due to the stabilising role of the resting lower limb in this position, a low level of muscle activity in the target limb was expected.

6.3.7 **Data processing**

Each trace was rectified and then a waveform average was created for each stimulus intensity and within each test condition, prior to calculation of the variables below.

*MEP latency*

MEP latency was calculated from a waveform average of the highest stimulus intensity delivered to each participant, in each test condition. This method was selected to ensure consistency between participants. MEP latency was defined as the time (ms) from stimulus to MEP onset. MEP onset was determined by a rise of 3 standard deviations above the mean pre-trigger root mean squared (rms) EMG.

*MEP area*

MEP area was measured in a 20 ms window from MEP onset. This was calculated from a waveform average of each intensity, in each test condition. A stimulus-response curve was then constructed for MEP area in each test condition. The steepest slope of the linear component of the recruitment curve in each test condition was calculated and used in subsequent analyses.
Neurophysiological lateralisation

Neurophysiological lateralisation was described in terms of right TA (RTA) and left TA (LTA), not left and right hemisphere, in order to be able to calculate correlations with footedness. Neurophysiological lateralisation was calculated for RMT, recruitment curve slope and latency. The asymmetry between RMT and latency in RTA and LTA was determined with an equation:

Neurophysiological lateralisation = (RTA-LTA)/(RTA+LTA)

The further the neurophysiological lateralisation value is from zero, the greater the lateralisation to either the right side (RTA) or left side (LTA). For RMT, a negative value indicates lateralisation towards the right side (RMT is lower in RTA), whereas a positive value indicates lateralisation towards the left side. For latency, a negative value also indicates lateralisation towards the right side (latency is shorter for RTA).

Asymmetry of the recruitment curve slope was calculated using the same equation. However, for recruitment curve slope, a positive value indicates lateralisation towards the right side (the slope is steeper in RTA), and a negative value indicates lateralisation towards the left side.

6.3.8 Statistical Analysis

RMT, recruitment curve slope, and MEP latency for the target TA were separately examined using three-way repeated measures analyses of variance (rmANOVA) with factors Current (PA, ML), Task (rest, active) and Hemisphere (dominant, non-dominant).

A three-way rmANOVA was used to examine pre-trigger rmsEMG during the resting protocols with factors Current (PA, ML), Hemisphere (dominant, non-dominant) and Leg (target, non-target). A second three-way rmANOVA examined pre-trigger rmsEMG of the
target leg during both resting and active protocols with factors Current (PA, ML), Task (rest, active) and Hemisphere (dominant, non-dominant). This three-way rmANOVA was repeated for the target leg. Paired t-tests were used to explore interactions and main effects.

Correlations were examined between the degree of neurophysiological lateralisation (both RMT and recruitment curve slope) and the degree of foot lateralisation using Pearson’s correlation coefficient. Linear regression modeling was then conducted using a best subsets model in SPSS (V21, Chicago) with corrected Akaike Information Criterion (AICc) as criteria for entry and removal. The dependent variable was foot lateralisation. Neurophysiological lateralisation scores for each of the test conditions were entered into the regression analysis as predictors of the degree of foot lateralisation. Data were transformed and one outlier was trimmed from the analysis with a Cooks distance of 0.24. The β coefficient was calculated with a 95% confidence interval and goodness of fit (adjusted R²) was calculated. Statistical significance was set at p < 0.05 and multiple comparisons were corrected with a modified Bonferroni procedure (Rom, 1990). Data are reported as mean ± standard error (SE).

6.4. Results

6.4.1 Hand and foot preference

Fourteen participants were right (R) hand, R foot dominant. Three participants were left (L) hand, L foot dominant. Three participants were R hand, L foot dominant, and two were L hand, R foot dominant. Mean handedness scores: right handed 0.70 ± 0.31, left handed -0.70 ± 0.18. Mean footedness scores: right footed 0.63 ± 0.24, left footed -0.43 ± 0.20.
6.4.2 **Resting motor threshold (RMT)**

RMT was lower with an ML current and with the non-target leg active (Figure 6.2).

RMT was examined using three-way repeated measures analyses of variance (rmANOVA) with factors Current (PA, ML), Task (rest, active) and Hemisphere (dominant, non-dominant). There was a main effect of Current on RMT (PA 70.1 ± 2.9% MSO, ML 62.8 ± 2.3% MSO, $F_{1,21} = 27.57$, $p < 0.001$, mean difference 7.3% MSO, 95% CI 4.4 - 10.2% MSO). There was also an effect of Task as RMT was lower with the non-target leg active (rest 67.4 ± 2.5% MSO, active 65.5 ± 2.6% MSO, $F_{1,21} = 7.65$, $p = 0.012$, mean difference 2% MSO, 95% CI 0.5 - 3.4 % MSO). These results indicate that both an ML current and activating the non-target leg reduced RMT. There was no effect of Hemisphere ($p = 0.508$) indicating that foot dominance did not affect RMT. There were no significant interactions between Current, Task, and Hemisphere (all $p > 0.06$).

![Image](122x204 to 419x397)

**Figure 6.2** Rest motor threshold (RMT).

RMT was lower with an ML current ($p < 0.001$), and with activation of the non-target leg ($p = 0.012$). PA = posterior-anterior current; ML = medial-lateral current. * $p < 0.05$, *** $p < 0.001$
6.4.3 Recruitment curve slope

The slope of the recruitment curve was steeper while the non-target leg was active (Figure 6.3). A steeper recruitment curve slope indicates an increase in corticomotor excitability. There was a main effect of Task on recruitment curve slope (rest 24.4 ± 3.5 μV/% MSO, active 44.7 ± 7.5 μV/% MSO, F$_{1,21}$ = 17.37, p < 0.001, mean difference 20.4 μV/% MSO, 95% CI 10.20 - 30.5μV/% MSO). The effect of Current approached significance (PA 31.7 ± 6.2 μV/% MSO, ML 37.3 ± 4.7 μV/% MSO, F$_{1,21}$ = 3.73, p = 0.068) but there was no effect of Hemisphere (p = 0.498), indicating that current direction and foot dominance do not affect corticomotor excitability. There were no significant interactions between Current, Task and Hemisphere (all p > 0.07).

**Figure 6.3 Recruitment curve slope.**

Recruitment curve slope was steeper during activation of the non-target leg (p = 0.001). PA = posterior-anterior current; ML = medial-lateral current. ** p < 0.01
6.4.4 MEP latency

Activating the non-target leg and using an ML current reduced MEP latency (Figure 6.4). There was a main effect of Task (rest 29.2 ± 0.6 ms, active 28.5 ± 0.6 ms, $F_{1,21} = 16.56$, $p = 0.001$, mean difference 0.7 ms, 95% CI 0.3 – 1.1 ms) and Current (PA 29.1 ± 0.6 ms, ML 28.6 ± 0.6 ms, $F_{1,21} = 5.55$, $p = 0.028$, mean difference 0.5 ms, 95% CI 0.1 – 1.0 ms) on MEP latency. There was no effect of Hemisphere on latency ($p = 0.996$). There were no significant interactions between Current, Task and Hemisphere (all $p > 0.06$).

**Figure 6.4 MEP latency**

MEP latency was shorter when using an ML current ($p = 0.028$), and when the non-target leg was active ($p = 0.001$). PA = posterior-anterior current; ML = medial-lateral current. * $p < 0.05$. ** $p < 0.01$
Table 6.2 Results

<table>
<thead>
<tr>
<th></th>
<th>PA rest</th>
<th>PA active</th>
<th>ML rest</th>
<th>ML active</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RMT (% MSO)</strong></td>
<td>71.2</td>
<td>69.1</td>
<td>63.7</td>
<td>61.9</td>
</tr>
<tr>
<td><strong>Slope (µV/%MSO)</strong></td>
<td>20.6</td>
<td>42.9</td>
<td>28.1</td>
<td>46.6</td>
</tr>
<tr>
<td><strong>Latency (ms)</strong></td>
<td>29.4</td>
<td>28.8</td>
<td>29.0</td>
<td>28.2</td>
</tr>
</tbody>
</table>

RMT and MEP latency were reduced, and the slope of the recruitment curve was increased, with ML current and activating the non-target leg. PA = posterior-anterior current; ML = medial-lateral current; RMT = rest motor threshold

6.4.5 Pre-trigger rmsEMG

Pre-trigger rmsEMG at rest had no effects of Current (p = 0.413), Hemisphere (p = 0.091) or Leg (p = 0.518). There was a weak interaction between Hemisphere and Leg (non-dominant target leg 0.008 ± 0.002 mV, dominant target leg 0.008 ± 0.001 mV, non-dominant non-target leg 0.007 ± 0.001 mV, dominant non-target leg 0.009 ± 0.002 mV, F1,21 = 4.77, p = 0.041). These data indicate that there were small but systematic variations of resting rmsEMG around the grand mean rmsEMG of 0.008 ± 0.001 mV, which may have arisen due to DC offset in the amplifiers used for recording.

There was a large effect of Task on rmsEMG in the non-target leg (rest 0.008 ± 0.001 mV, active 0.236 ± 0.036 mV, F1,21 = 41.43, p < 0.001, mean difference 0.228 mV, 95% CI 0.154 – 0.302 mV). There was also an effect of Task on rmsEMG in the target leg with a small but consistent increase in rmsEMG in the resting target leg when the non-target leg was active (rest 0.008 ± 0.002 mV, active 0.010 ± 0.002 mV, F1,21 = 21.58, p < 0.001, mean difference 0.002, 95% CI 0.001 – 0.002).
6.4.6 Correlations

The relationship between footedness and the lateralisation of neurophysiological variables was explored. There was a moderate relationship between the degree of footedness and the asymmetry of RMT measured with the PA current while the non-target leg was active (p = 0.017, r = -0.504) but not when the participant was at rest (p = 0.285, r = -0.238). The RMT of right tibialis anterior (RTA) was relatively lower than the RMT of left tibialis anterior (LTA) in more strongly right footed participants i.e. the more strongly right footed the participant was, the greater the difference between RMT of the dominant (RTA) and non-dominant (LTA) hemisphere (Figure 6.5). There was no relationship between footedness and the asymmetry of RMT measured with the ML current or between footedness and the slope of the recruitment curve.

In linear regression modelling, the only significant predictor of foot lateralisation was RMT with PA current and the non-target leg active. The intercept was 0.336 (p = 0.003) and β coefficient was -4.401 (p = 0.017). An R² value of 0.216 indicates that the degree of asymmetry of the RMT between dominant and non-dominant hemisphere explains 21.6% of the variance in the degree of foot lateralisation.
There was a significant correlation between the degree of foot dominance (y axis) and the asymmetry of the RMT (x axis) using a PA coil orientation while the non-target leg was active ($p = 0.017, r = -0.504$). Participants with a stronger negative neurophysiological lateralisation score (RMT of the RTA was relatively lower than the RMT of the LTA) were more strongly right footed. PA = posterior-anterior coil orientation; RMT = rest motor threshold; M1 = primary motor cortex; RTA = right tibialis anterior muscle; LTA = left tibialis anterior muscle

6.5. Discussion

This study found that activating a combination of homologous and heterologous muscles in the non-target leg reduced RMT and MEP latency and increased the slope of the recruitment curve, as predicted by our first hypothesis. In addition, using an ML current reduced RMT and MEP latency in the target TA muscle compared with a PA current, also as predicted. In contrast to our second hypothesis, there was no interaction between cross-facilitation and cortical current direction. However, combining activation of the non-target leg with the ML current produced the greatest reduction in RMT and MEP latency and greatest increase in recruitment curve slope, which may be useful when testing patients soon after stroke.
In contrast to our third hypothesis, there was no evidence of greater corticomotor excitability in the dominant hemisphere, with no difference between hemispheres for RMT, MEP latency, or the slope of the recruitment curve. However, a novel observation was made of a relationship between the degree of lateralisation of RMT and the degree of foot lateralisation. Our fourth hypothesis was supported by a significant correlation between asymmetry of the RMT of the dominant and non-dominant hemispheres and lateralisation of foot preference.

6.5.1 Non-target leg active

Activating the non-target lower limb increased recruitment curve slope in the target TA, and reduced RMT and MEP latency, as predicted. The slope of the recruitment curve almost doubled from 24.4 to 44.8 μV/% MSO, RMT reduced by 2% MSO and mean MEP latency reduced from 29.2 ms to 28.5 ms. The small reduction of RMT and MEP latency, although statistically significant, may have little clinical significance in the healthy adult. However the effects of cross-facilitation may be greater in a patient with stroke, where thresholds are pathologically high. This may assist in generating a MEP in the paretic LL before maximum stimulator output is reached.

The findings from this study build on previous work (Muellbacher et al., 2000; Stinear et al., 2001; Chiou et al., 2013; Ibey and Staines, 2013), demonstrating for the first time that activating a combination of muscles in the non-target leg facilitates MEP responses in the target leg.

Participants attempted to keep the target leg at rest during the active task. However, an increase in mean rmsEMG of 0.002 mV was observed in the target leg. Due to a possible influence on recruitment curve slope, we re-processed the data for MEP area, correcting for baseline EMG by subtracting a 20 ms window of baseline EMG area from the MEP area.
Correcting the data for baseline EMG did not affect results and so the results from uncorrected data are reported.

Chiou et al. (2013) used a recumbent position to investigate cross-facilitation of the LL. However, when seated and attempting to lift one leg, a postural adjustment occurs at the trunk and hips to shift more weight onto the non-elevated, resting (target) leg in order to enable the non-target leg to leave the ground. This anticipatory postural adjustment is involuntary and via alternative motor pathways such as the reticulospinal and vestibulospinal tracts, rather than the CST which plays a greater role in voluntary control (Shumway-Cook and Woollacott, 2007; Sousa et al., 2012). The facilitatory effect of this anticipatory postural adjustment may be of benefit when attempting to generate MEPs in the lower limb after stroke. Although the patient may be unable to voluntarily activate their paretic leg, lifting the unaffected leg may result in a postural adjustment and facilitation of MEPs in the paretic leg.

6.5.2 Current direction

The reduction in RMT and MEP latency when using an ML current is likely due to optimising the direction of current flow in relation to the anatomical structure of the brain (Priori et al., 1993), and activation of different populations of cortical neurons/axons than the PA current (Di Lazzaro and Ziemann, 2013). Terao et al. (2000) demonstrated that stimulation with a figure-8 coil elicits predominantly I waves but the proportion of D waves increases at higher stimulus intensities. The MEPs produced with both ML and PA currents were found to have a higher proportion of D and early I waves than less optimal current directions such as anterior-posterior (AP) and lateral-medial (LM) (Terao et al., 2000). In the current study, MEP latency was shorter with the ML current than the PA current. This may be due to a higher proportion of early I waves, and the increased recruitment of D waves with an
ML current, particularly as latency was calculated at the highest stimulus intensity delivered for each participant.

In previous studies, large adjustments of coil orientation between 45 and 180 degrees were used to investigate optimal cortical current direction for the lower limb (Priori et al., 1993; Terao et al., 2000). The effects of small adjustments to current direction using a figure-8 coil and MRI cortical mapping have recently been investigated (Richter et al., 2013). The optimal orientation for generating MEPs in abductor hallucis muscle was found to be with the coil handle rotated 30 degrees posterior to the coil orientation used to induce a pure ML current direction.

In this study the degree of coil rotation for the ML current was determined on an individual basis via “hot-spotting”. It has been argued that varying the angle of the coil between participants may affect the consistency of some results and take longer to complete the hot-spotting and thresholding components of the TMS protocol (Richter et al., 2013). However, we found that starting from a pure ML current direction and making a slight adjustment in coil rotation took only a few additional stimuli and had very little impact on the time to complete the overall study. Selecting the optimal cortical current direction rather than using a standardised coil orientation takes into account inter-individual differences in the shape of the LL cortex in the medial wall of the precentral gyrus.

6.5.3 Foot dominance

A moderate negative correlation was found between the degree of foot dominance and asymmetry of RMT, in keeping with previous studies of the upper limb (Macdonell et al., 1991; Civardi et al., 2000; Brouwer et al., 2001; De Gennaro et al., 2004). The greater the difference between RMT in the dominant and non-dominant hemispheres, the stronger the preference to use a particular foot. This novel finding was only demonstrated when using PA
cortical current. The absence of this effect when using ML cortical current may be explained by considering the more direct activation of the cortical neurons (i.e. D waves) and short latency I waves produced by the ML current. Later I waves produced by the PA cortical current may be more sensitive to intracortical inputs that underlie functional asymmetries, such as footedness. Thus, the use of ML cortical current rather than PA may eliminate the need to consider the effects of prior footedness in stroke research. In contrast, a PA cortical current should be used during future investigation into the relationship between foot dominance and neurophysiological lateralisation.

6.5.4 Limitations

More participants are required to investigate the effects of foot dominance found in this study. Another limitation is the omission of a condition where the target TA muscle was activated. This would have allowed a direct comparison between excitatory effects of activating the non-target or the target leg. An interaction between cross-facilitation and cortical current direction requires further investigation with AP and LM directions. These cortical current directions were not tested here, as they produce higher RMTs which are counter to our objective of selecting a combination of factors to lower RMT in patients with stroke. The study was conducted in healthy adults and using the protocol in patients with stroke will further assess its feasibility and usefulness.

6.6. Conclusions

Activating the non-target leg with a task that requires postural control of the trunk, and using an ML cortical current, effectively reduce RMT and MEP latency and increase recruitment curve slope in healthy adults. This may be a useful protocol to consider using in people with stroke where the stimulus intensity required to generate MEPs is higher than in healthy adults. There was a relationship between the degree of foot dominance and RMT,
and this novel finding warrants further investigation. This relationship was only present when using the PA current, which supports the use of the ML current in situations where the effects of foot dominance need to be avoided.
Chapter 7. Proportional recovery from lower limb motor impairment after stroke

This experiment has been reported in Stroke


7.1. Abstract

Background and Purpose: In people with preserved corticospinal tract (CST) function after stroke, upper limb (UL) impairment resolves by approximately 70% within 3 months. This is known as the proportional recovery rule. Patients without CST function do not fit this rule and have worse UL outcomes. This study investigated resolution of motor impairment in the lower limb (LL).

Methods: Patients with stroke and LL weakness were assessed 3 days and 3 months after stroke with the LL Fugl-Meyer (FM). CST integrity was determined in a subset of patients using transcranial magnetic stimulation to test for LL motor-evoked potentials (MEPs) and MRI to measure CST lesion load. Linear regression analyses were conducted to predict resolution of motor impairment (∆FM) including factors initial impairment, MEP status, CST lesion load and LL therapy dose.

Results: 32 patients completed 3-month follow-up and recovered 74% (95% CI 60-88%) of initial LL motor impairment. Initial impairment was the only significant predictor of resolution of motor impairment. There was no identifiable cluster of patients who did not fit the proportional recovery rule. Measures of CST integrity did not predict proportional LL recovery.

Conclusions: Lower limb impairment resolves by approximately 70% within 3 months after stroke. The absence of a non-fitter group may be due to differences in the neuroanatomical
organisation of descending motor tracts to the UL and LL. Proportional recovery of the LL is not influenced by therapy dose providing further evidence that it reflects a fundamental biological process.

7.2. Introduction

The resolution of impairment and recovery of function are both important components of motor recovery following stroke (Levin et al., 2009). Greater residual impairment requires more compensation to recover function. Most patients resolve ≈70% of their initial upper limb impairment within 3 – 6 months after stroke, which has been called the proportional recovery rule (Prabhakaran et al., 2008; Zarahn et al., 2011; Byblow et al., 2015; Feng et al., 2015; Winters et al., 2015; Buch et al., 2016). Proportional recovery occurs regardless of stroke type (haemorrhage or ischemic) (Stinear et al., 2017b), previous stroke (Stinear et al., 2017b), or therapy dose (Byblow et al., 2015; Stinear et al., 2017b). Patients with functionally (Byblow et al., 2015; Stinear et al., 2017b) and structurally (Feng et al., 2015; Buch et al., 2016) intact descending motor pathways from the ipsilesional primary motor cortex follow the rule, while for those without recovery tends to be poor. Proportional recovery of aphasia has also been observed, indicating that it may occur across different domains (Lazar et al., 2010). These findings suggest proportional recovery reflects a fundamental biological process (Krakauer et al., 2012; Byblow et al., 2015; Krakauer and Marshall, 2015; Winters et al., 2015; Buch et al., 2016).

No studies investigating proportional recovery of lower limb (LL) impairment have been previously reported. The aim of this study was to investigate resolution of impairment in the LL, and to determine whether CST integrity was required for proportional recovery.
7.3. Materials and Methods

Patients aged 18 years or older with new LL weakness (< 100 on LL Motricity Index) after ischemic or haemorrhagic stroke were eligible for the study. Previous stroke and treatment with stroke thrombolysis and endovascular clot retrieval were allowed. Patients with cerebellar stroke, contraindications to TMS or MRI, or inability to consent to research participation were excluded. Written informed consent was gained from each participant and the study was approved by the regional ethics committee.

Baseline demographic and clinical information was recorded for each participant including age, gender, stroke severity (NIHSS), and LL strength (Motricity Index). The LL component of the Fugl-Meyer (FM) scale was administered 3 days and 3 months after stroke. Lower limb physical therapy dose was recorded in minutes during inpatient rehabilitation. Assessors were blinded to all aspects of patient care. Resolution of motor impairment was calculated as the difference between FM scores at baseline and 3 months (ΔFM). Initial motor impairment (FMii) was calculated as maximum LL FM score (34) minus baseline FM score.

The integrity of the descending motor pathways were determined in a subset of patients using transcranial magnetic stimulation (TMS) on day 5–7 and MRI on day 7–10 post-stroke. These time-points are consistent with previous studies (Byblow et al., 2015b, a; Feng et al., 2015; Buch et al., 2016) and intended to reduce false negatives for MEP status and the effects of edema on MRI measures. For TMS a flat figure-8 coil was placed over the scalp, oriented to generate a medial-lateral current flow in the LL motor cortex. MEPs were recorded from the paretic tibialis anterior muscle. If no MEPs were elicited at rest, patients were instructed to activate the paretic leg, or the contralateral leg if unable to activate the paretic side (Smith et al., 2017). Participants were considered MEP+ if a MEP of any amplitude was consistently observed with the leg either active or at rest.
T1-weighted MRI was used to calculate CST lesion load. A template CST was constructed from diffusion-weighted images acquired from 85 patients with stroke, between the contralesional primary motor cortex and inferior border of the pons. Lesion masks were hand drawn on individual patients’ T1 images by one researcher and independently verified by two others. Lesion load was calculated as the percentage of CST template voxels overlapped by the stroke lesion mask (Stinear et al., 2017b).

Bivariate correlations were used to examine relationships between resolution of impairment (∆FM) and initial motor impairment (FMii), MEP status (present or absent), lesion load, age, gender, previous stroke, stroke type (ischemic, haemorrhage), comorbidities (Charlson Comorbidity index), LL therapy dose (total minutes of inpatient rehabilitation targeting the lower limb and walking), and LL therapy intensity (minutes per day). Variables with p<0.1 were entered into multivariable linear regression with ∆FM as the dependent variable and the intercept set to the origin. Further regression analyses were completed with the subsets of patients who underwent TMS and MRI.

7.4. Results

Of the 41 patients recruited, 32 completed the 3 month assessment (Table 7.1). Four patients died, two were withdrawn due to the development of new medical issues and three were lost to follow-up. MEP status was determined for 22 patients and lesion load was calculated for 23 patients. Most patients were non-ambulatory at baseline (59%), half scored >7 on NIHSS, and five patients had no affected LL movement at baseline (Motricity Index score of zero).
Table 7.1  Participant characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>Median age (range) 71 (39 - 96)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Female 17 (53%)</td>
</tr>
<tr>
<td><strong>Stroke risk factors</strong></td>
</tr>
<tr>
<td>Smoker 4 (13%)</td>
</tr>
<tr>
<td>Ex-smoker 7 (22%)</td>
</tr>
<tr>
<td>Diabetes mellitus 11 (34%)</td>
</tr>
<tr>
<td>Hypertension 20 (63%)</td>
</tr>
<tr>
<td>Dyslipidaemia 13 (41%)</td>
</tr>
<tr>
<td>Atrial fibrillation 9 (28%)</td>
</tr>
<tr>
<td>Previous cardiac history 9 (28%)</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
</tr>
<tr>
<td>Charlson Comorbidity index median (range) 1 (1 - 3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First stroke</strong> yes 28 (87%)</td>
</tr>
<tr>
<td><strong>Stroke type (Oxfordshire classification)</strong></td>
</tr>
<tr>
<td>Total anterior circulation infarct 3 (9%)</td>
</tr>
<tr>
<td>Partial anterior circulation infarct 14 (44%)</td>
</tr>
<tr>
<td>Lacunar infarct 9 (28%)</td>
</tr>
<tr>
<td>Posterior circulation infarct (excluding cerebellar) 2 (6%)</td>
</tr>
<tr>
<td>Intracerebral haemorrhage 4 (13%)</td>
</tr>
<tr>
<td><strong>Hemisphere</strong></td>
</tr>
<tr>
<td>Right 15 (47%)</td>
</tr>
<tr>
<td><strong>Alteplase</strong> yes 5 (16%)</td>
</tr>
<tr>
<td><strong>Endovascular clot retrieval</strong> yes 1 (3%)</td>
</tr>
<tr>
<td><strong>Stroke severity</strong></td>
</tr>
<tr>
<td>NIHSS median (range) 7 (0-18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical lower limb measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAC score</strong></td>
</tr>
<tr>
<td>Non-ambulatory (FAC=0) 19 (59%)</td>
</tr>
<tr>
<td>Dependent ambulation FAC (1,2,3) 12 (38%)</td>
</tr>
<tr>
<td>Independent ambulation (FAC≥4) 1 (3%)</td>
</tr>
<tr>
<td><strong>Lower Limb impairment</strong></td>
</tr>
<tr>
<td>Fugl-Meyer score out of 34, median score (range) 19 (7 - 33)</td>
</tr>
<tr>
<td>3 days 19 (7 - 33)</td>
</tr>
<tr>
<td>3 months 32 (19 - 34)</td>
</tr>
<tr>
<td>Motricity Index, median (range) 53.5 (0 - 92)</td>
</tr>
<tr>
<td><strong>Lower limb therapy dose median hours (range)</strong> 11 (0 - 43)</td>
</tr>
<tr>
<td><strong>Lower limb therapy intensity minutes per day (range)</strong> 17 (9 – 116)</td>
</tr>
<tr>
<td>Length of inpatient stay median days (range) 32 (2 – 82)</td>
</tr>
<tr>
<td>LL MEP present (subset n=22) 14 (64%)</td>
</tr>
<tr>
<td>Lesion load (subset n=23) % overlap median (range) 15 (0 - 52)</td>
</tr>
</tbody>
</table>
Initial motor impairment ($FM_{ii}$) and therapy dose were entered into linear regression analysis of the full dataset with resolution of impairment ($\Delta FM$) as the dependent variable. $FM_{ii}$, therapy dose and either MEP status or lesion load were entered into regression analyses for the TMS and MRI subsets respectively. Age, sex, stroke type, previous stroke, comorbidities and therapy intensity were excluded as they did not correlate with $\Delta FM$ ($p>0.1$).

Initial motor impairment ($FM_{ii}$) predicted recovery from impairment (Table 7.2), as patients resolved 74% (95% CI 60-88%) of initial impairment. Patients whose $\Delta FM$ differed from predicted $\Delta FM$ by $\geq 4$ points were classified as outliers, but there was no identifiable cluster of non-fitters (Figure 7.1). Therapy dose and lesion load were not predictors of $\Delta FM$ (Table 7.2). In the subset with TMS data, $\Delta FM$ was 3 points lower in patients without MEPs ($p=0.06$).

**Table 7.2** Linear regression statistics for predictors of $\Delta FM$

<table>
<thead>
<tr>
<th>predictor</th>
<th>Complete cohort (n=32)</th>
<th>TMS (n=22)</th>
<th>MRI (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$\beta$ 95%CI</td>
<td>Adj $R^2$</td>
</tr>
<tr>
<td>$FM_{ii}$</td>
<td>0.74</td>
<td>0.60-0.88</td>
<td>0.93</td>
</tr>
<tr>
<td>Therapy dose (min)</td>
<td>-0.001</td>
<td>-0.003-0.002</td>
<td>0.569</td>
</tr>
<tr>
<td>$FM_{ii}$</td>
<td>0.81</td>
<td>0.63-0.99</td>
<td>0.94</td>
</tr>
<tr>
<td>MEP (1=MEP-)</td>
<td>-3.38</td>
<td>-6.97-0.202</td>
<td>0.063</td>
</tr>
<tr>
<td>Therapy dose (min)</td>
<td>0.000</td>
<td>-0.003-0.003</td>
<td>0.96</td>
</tr>
<tr>
<td>$FM_{ii}$</td>
<td>0.71</td>
<td>0.533-0.891</td>
<td>0.93</td>
</tr>
<tr>
<td>Lesion load</td>
<td>0.051</td>
<td>-0.056-0.158</td>
<td>0.33</td>
</tr>
<tr>
<td>Therapy dose (min)</td>
<td>-0.001</td>
<td>-0.005-0.002</td>
<td>0.41</td>
</tr>
</tbody>
</table>
Figure 7.1

A. Resolution of lower limb motor impairment (ΔFM) is proportional to initial impairment (FMii) regardless of MEP status. Circle=MEP+; Square=MEP-; Triangle=No TMS data; Open symbols=outlier ≥4 points outside predicted ΔFM. B. Resolution of impairment is also proportional in patients with haemorrhagic stroke and previous stroke. Black=first ischemic stroke; Dark grey=haemorrhagic stroke; Light grey=previous stroke. C. Resolution of impairment is not proportional to lower limb therapy dose. Regression lines have 95% confidence intervals.
7.5. Discussion

This is the first report of proportional recovery from LL motor impairment after stroke. Patients recover around 70% of their available improvement as previously demonstrated in the UL (Prabhakaran et al., 2008; Zarahn et al., 2011; Byblow et al., 2015; Feng et al., 2015; Winters et al., 2015; Buch et al., 2016) and in speech (Figure 1) (Lazar et al., 2010). This study showed that people with previous stroke and ICH can also recover proportionally as reported in the UL (Stinear et al., 2017b) (Figure 1) although a larger sample is required to explore this finding for the LL. In keeping with reports for the UL (Byblow et al., 2015; Stinear et al., 2017b), therapy dose was not a predictor of recovery from LL motor impairment, which supports the theory that proportional recovery reflects a fundamental biological process (Krakauer and Marshall, 2015).

Approximately 30% of patients do not resolve UL impairment proportionally (Prabhakaran et al., 2008; Byblow et al., 2015; Winters et al., 2015; Buch et al., 2016). If the same were true for LL impairment, nine patients would have been expected to not fit the rule and exhibit poor recovery. However, there was no identifiable cluster of non-fitters and even more severely impaired patients recovered proportionally. While it is possible that the four patients who died may not have fit the rule (median NIHSS 11), it appears that almost all patients demonstrate proportional recovery from LL impairment. This may be due to greater redundancy in the form of alternate descending pathways to the LL, such as the reticulospinal tract and projections from the contralesional cortex (Jang et al., 2013a). The potential contribution of uncrossed descending pathways did not increase the proportion of recovery above 70%.
As there was no cluster of non-fitters, measures of CST integrity were not useful for identifying which patients would recover proportionally. Patients without LL MEPs still recovered proportionally although there was a trend towards less recovery. This may be related to the technical challenges of stimulating LL motor cortex with TMS, resulting in false negatives. Other limitations were that MEP status and lesion load were collected only for a subset of patients, and lower limb sensory loss was not recorded. The findings in this report are preliminary and larger samples are needed to explore the relationships between CST integrity and LL proportional recovery.

7.6. Summary

Lower limb impairment resolves by approximately 70% within 3 months after stroke. The absence of an identifiable group of non-fitters indicates that proportional recovery from LL impairment is achievable for most patients, in contrast to the UL where a functional CST is required. This may mean that measures of CST integrity are not needed to predict proportional resolution of LL impairment. Measuring proportional recovery may be a useful tool in future trials for determining whether interventions in the subacute stage are interacting with the neurobiological mechanisms of recovery.
Chapter 8. The TWIST algorithm predicts Time to Walking Independently after Stroke

This experiment has been reported in Neurorehabilitation and Neural Repair


8.1. Abstract

Background and Objective: The likelihood of regaining independent walking after stroke is of concern to patients and their families and influences hospital discharge planning. The objective of this study was to explore factors that could be combined in an algorithm for predicting whether and when a patient will walk independently after stroke.

Methods: Adults with new lower limb weakness were recruited within three days of having a stroke. Clinical assessment, transcranial magnetic stimulation and magnetic resonance imaging were completed 1-2 weeks post-stroke. Classification and regression tree (CART) analysis was used to identify factors that predicted whether a patient achieved independent walking by 6 or 12 weeks, or remained dependent at 12 weeks.

Results: We recruited 41 patients (24 women; median age 72 years, range 43-96 years). The CART analysis results were used to create the Time to Walking Independently after Stroke (TWIST) algorithm, which made accurate predictions for 95% of patients. Patients with a trunk control test score >40 at one week walked independently within six weeks. Patients with a trunk control test score <40 only achieved independent walking by 12 weeks if they also had hip extension strength of Medical Research Council grade 3 or more. Neurophysiological and neuroimaging measures did not predict independent walking after stroke.
Conclusion: In this exploratory study, the TWIST algorithm accurately predicted whether and when an individual patient walked independently after stroke using simple bedside measures one week post-stroke. Further work is required to develop and validate this algorithm in a larger study.

8.2. Introduction

The ability to walk independently is the most common rehabilitation goal after stroke (Bohannon et al., 1988). While up to 85% of all stroke survivors are able to walk independently by six months (Friedman, 1990), only 40 to 60% of those who require assistance to walk early after stroke regain independent walking (Friedman, 1990; Jorgensen et al., 1995; Kollen et al., 2006). Whether a patient is expected to achieve independent walking influences decisions about the type and duration of rehabilitation and likely discharge destination (Kollen et al., 2006). Several factors in the first two weeks post-stroke predict walking outcomes, including age, lower limb weakness, sensory loss, hemianopia, sitting balance and trunk control (Sánchez-Blanco et al., 1999; Patel et al., 2000; Duarte et al., 2002; Kollen et al., 2005; Kollen et al., 2006; Masiero et al., 2007; Verheyden et al., 2007; Veerbeek et al., 2011b). Previous studies have typically predicted walking outcome at a single time point (Sánchez-Blanco et al., 1999; Hendricks et al., 2003; Veerbeek et al., 2011b; Kim et al., 2013), using group data to produce regression equations that are not easily implemented in clinical practice (Sánchez-Blanco et al., 1999; Patel et al., 2000; Masiero et al., 2007). While clinicians may be able to predict whether a patient will regain independent walking ability, predicting when this will occur is even more difficult (Kwakkel et al., 2000), as motor recovery is a non-linear process (Friedman, 1990; Jorgensen et al., 1995; Sánchez-Blanco et al., 1999; Verheyden et al., 2008; Shum et al., 2014). Predicting when a patient will become independently mobile could be clinically useful and allow early anticipation of the level and duration of support required after discharge from hospital.
Neurophysiological and neuroimaging biomarkers can be useful for predicting motor outcomes in the upper limb, particularly for patients with severe initial impairment (Bembenek et al., 2012; Coupar et al., 2012; Kim and Weinstein, 2017). Transcranial magnetic stimulation (TMS) and magnetic resonance imaging (MRI) can be used to examine the integrity of descending motor pathways (Puig et al., 2011; Bembenek et al., 2012; Stinear et al., 2012; Kim and Weinstein, 2017). Few studies have investigated TMS or MRI as predictors for recovery of walking (Hendricks et al., 2003; Piron et al., 2005; Cho et al., 2007a; Cho et al., 2007b; Kim et al., 2013; Chang et al., 2015; Kim et al., 2016) and none have used these biomarkers to predict when a patient will walk independently.

The aim of this exploratory study was to identify predictors of whether and when an individual patient will regain independent walking after stroke, and to combine these in an algorithm that could be used in clinical practice.

8.3. Methods

8.3.1 Participants

Patients aged over 18 years and presenting within three days of stroke (ischemic or intracerebral hemorrhage) were eligible if they had new lower limb weakness (< 100 on lower limb Motricity Index score) and required supervision or assistance for walking. Patients with previous stroke and those who were treated with intravenous thrombolysis and endovascular thrombectomy could be enrolled. Exclusion criteria included the requirement for supervision or assistance to walk prior to admission, cerebellar or bilateral stroke, not expected to survive for the duration of the study, communication or cognitive deficits precluding informed consent, and contraindications to TMS or MRI. Written informed consent was obtained from all patients. This study was approved by the national ethics committee.
8.3.2 Clinical assessments

Demographic and stroke characteristics were recorded at day three post-stroke (Table 1). Neurologic impairment was assessed with the National Institutes of Health Stroke Scale (NIHSS) (Adams et al., 1999). NIHSS sub-scores for items 4 (hemianopia), 8 (sensory), and 11 (inattention) were used to categorise stroke type as either motor (M), motor-sensory (MS), or motor-sensory-hemianopia (MSH) for analysis (Sánchez-Blanco et al., 1999). Walking ability was graded with the Functional Ambulation Category (FAC) scale (Mehrholz et al., 2007). FAC is a six point scale with a score of 0 indicating the patient is non-ambulatory or requires the assistance of at least two people to walk. An FAC score of 1-3 indicates either assistance or supervision from one person is required to walk. An FAC score of 4 indicates that the patient is able to walk indoors on level surfaces without hands-on assistance or supervision, and a score of 5 indicates that the patient is able to walk up and down stairs, slopes and outdoors without assistance or supervision. Independent walking was defined as an FAC score of 4 or 5. Patients were allowed to use walking aids such as a stick, quad stick or an ankle support. FAC scores for each participant were obtained on day three, and again at 1, 4, 6 and 12 weeks post-stroke. FAC scores were dichotomized at each time point to classify participants as being able to walk independently (FAC ≥ 4) or as dependent (FAC < 4) (Kollen et al., 2006; Veerbeek et al., 2011b). The primary outcome was the time post-stroke at which the participant achieved independent walking (FAC ≥ 4).

All participants completed full clinical assessments one week after stroke (Table 2). These included: walking ability (FAC); trunk control [Trunk Control Test (TCT)]; lower limb power (Motricity Index); and lower limb muscle strength graded with the Medical Research Council (MRC) grades for hip flexion, extension and abduction, knee flexion and extension, ankle dorsiflexion and plantarflexion. The Trunk Control Test (TCT) is a validated 4-item scale measuring both static and dynamic trunk control (Collin and Wade, 1990; Franchignoni
Rolling to each side in bed, moving from lying to sitting, and sitting unsupported for 30 seconds, are each scored out of 25, totalling 100 points. Clinical assessments were conducted by an experienced research physiotherapist trained in the assessments, and not involved in patient care.

8.3.3 Neurophysiological and imaging measures

TMS was used to evaluate the functional integrity of descending motor pathways in a subset of participants. The presence or absence of motor evoked potentials (MEPs) in the paretic tibialis anterior was evaluated one week after stroke. Tibialis anterior has a relatively large cortical representation, resulting in larger and more easily elicited MEPs than proximal leg muscles or muscles in the foot (Brouwer and Ashby, 1992; Petersen et al., 2003). The presence of MEPs in tibialis anterior has some predictive value for the recovery of walking (Hendricks et al., 2003; Piron et al., 2005; Chang et al., 2015; Kim et al., 2016). MEPs were recorded with surface electromyography (EMG) from the tibialis anterior muscle with a reference electrode placed over the patella. EMG signals were sampled at 2 kHz, amplified (1000 gain), filtered (20 – 1000Hz), and stored for offline analysis using Signal software (CED). Magnetic stimuli were delivered using a flat figure-8 coil attached to a MagStim 200 unit. The coil was placed over the scalp and oriented to generate a medial-lateral current flow in the affected LL motor cortex (Smith et al., 2017). Participants were tested while seated in a chair if able, or in a half-sitting position in bed. The stimulus intensity was increased up to 100% maximal stimulator output if required. If no MEP was observed in the paretic tibialis anterior at rest, the participant was instructed to activate the paretic leg if able, or to activate the non-paretic leg if severe hemiparesis prevented activation of the paretic leg (Smith et al., 2017). The participant was considered MEP positive (MEP+) when a MEP of any amplitude was consistently observed for over half of consecutive trials with the leg at rest or active (Stinear et al., 2017a).
Three MRI measures [Fractional Anisotropy (FA) asymmetry, corticospinal tract (CST) lesion load and sensorimotor tract (SMT) lesion load] were used to examine the structural integrity of white matter pathways in a subset of participants, with MRI scans obtained 7-14 days after stroke. T1-weighted and diffusion-weighted images were acquired with a Siemens 1.5T Avanto scanner. Axial T1-weighted images had 1.0 x 1.0 x 1.0 mm voxels, a 256 mm field of view, TR = 11 ms, and TE = 4.94 ms. Diffusion-weighted images (DWI) had 1.8 x 1.8 x 3.0 mm voxels, a 230 mm field of view, b = 2000 s.mm², and TR = 6,700 ms, TE = 101 ms, 30 gradient directions and two averages. DWI were pre-processed with motion and eddy current correction, skull stripping, estimation and fitting of diffusion parameters, and modelling of crossing fibres (Behrens et al., 2003a). FA maps were registered to the participant’s T1-weighted image and overlaid by a standard template of the voxels of interest (VOI) for the posterior limb of the internal capsules (PLIC). PLIC templates were manually edited if the PLIC template VOI encroached on basal ganglia structures or ventricles (Petoe et al., 2014). FA asymmetry was calculated as \( \frac{\text{FA}_{\text{contralesional}} - \text{FA}_{\text{ipsilesional}}}{\text{FA}_{\text{contralesional}} + \text{FA}_{\text{ipsilesional}}} \). A positive FA value indicates relatively reduced FA in the ipsilesional CST at the level of the PLIC.

A template CST was constructed from DWI obtained from the contralesional hemisphere of 85 patients with stroke from an earlier study (Stinear et al., 2017b), extending from the primary motor cortex to the inferior border of the pons. The template sensorimotor tract was a combination of the CST and sensory tracts extending from the primary sensory cortex to the medial lemniscus at the inferior border of the pons. Tractography was conducted with a curvature threshold of 0.2 and step-length of 0.5. The template tracts were thresholded at 75% probability to ensure that only fibres at each tract’s core were used for calculation of lesion load. Lesion masks were hand-drawn on the T1 images of individual participants. The percentage of the CST template voxels that were overlapped by the stroke lesion mask was
calculated to determine CST lesion load (Stinear et al., 2017a). This process was repeated for sensorimotor tract (SMT) lesion load.

8.3.4 **Therapy dose**

Therapists were blinded to the results of the assessments and continued making decisions regarding therapy type and dose for each patient based on their clinical judgement and service capacity. Lower limb therapy dose was defined as total time spent in active rehabilitation of the lower limb, trunk, balance or walking, and was recorded by the treating therapist immediately after each therapy session. Therapy dose was recorded for all inpatient therapy sessions from admission until discharge from hospital, and therefore included therapy completed in the acute stroke unit and during inpatient rehabilitation. Length of inpatient stay was recorded for all participants, and therapy intensity was calculated as minutes of targeted inpatient lower limb therapy received per day of inpatient stay. Total lower limb therapy dose and the amount of targeted lower limb therapy per day for each participant (therapy intensity) were used for subsequent analyses.

8.3.5 **Statistical analysis**

Participants with FAC < 4 at one week were included in the analysis. They were initially classified into four categories according to the time they achieved independent walking; 4 weeks, 6 weeks, 12 weeks, or dependent at 12 weeks. The analysis was conducted in two stages. Logistic regression was used to identify potential predictors of category membership. The demographic and stroke characteristic variables entered into the logistic regression analyses were age (years), sex (M,F), stroke classification (Oxford stroke classification), stroke severity (NIHSS), stroke type (M, MS, MSH), and comorbidities (Charlson comorbidity index binarised to mild 0-1 or severe ≥2). Less than 20% of participants had thrombolysis, thrombectomy or previous stroke, so these variables were not included in the
analysis. The one week clinical assessment variables entered were: FAC (out of 5); MRC grades (out of 5) for hip flexion, extension and abduction, knee flexion and extension and ankle dorsiflexion and plantarflexion; lower limb Motricity Index (out of 100) and TCT (out of 100). Therapy dose (min) and therapy intensity (min per day) were also entered. Separate logistic regressions were conducted for each variable. Variables with p < 0.05 were then entered into a Classification and Regression Tree (CART) analysis. The strict cut-off for inclusion in the CART analysis was used to minimise the number of variables for the relatively small sample size.

CART analysis was conducted to select, in a hierarchical order, the variables that best predicted each participant’s category membership. CART analysis independently dichotomizes and selects variables that achieve the least overlap between resulting subgroups and the most homogeneity within each subgroup, creating a decision tree or prediction algorithm (Muller and Mockel, 2008). CART was conducted using “gini” with a maximum tree depth of three, minimum of four cases in a terminal node and automatic pruning to reduce overfitting.

For the subsets of participants who completed TMS and MRI assessments, separate logistic regression analyses were conducted for MEP status (+/-) and MRI measures (FA asymmetry, CST Lesion load, SMT lesion load). The relationships between outcome at 12 weeks (independently walking or not) and MEP status and MRI measures were explored with Chi-square and two-sample two-tailed t-tests, respectively.

The results of the CART analysis were used to create an algorithm for predicting time to walking independently after stroke. Sensitivity and specificity of the algorithm were calculated for each category.
8.4. Results

There were forty-one participants (median age 72 (43 – 96); 59% female) included in the analysis (Figure 8.1, Tables 8.1 and 8.2). Most participants were not able to walk (FAC = 0, n = 33, 80%) at day three. Clinical assessments were completed for all participants. A subset of 25 participants had TMS at day 5-7 and 30 participants had MRI at day 7-14 post-stroke. The remaining participants were unable to have TMS or MRI as they were too unwell or had been moved to another rehabilitation centre at the time of testing. Three participants died before 12 weeks and last observations were carried forward, as FAC scores were zero at all prior time points.

Only five participants achieved independent walking between four and six weeks, therefore these two categories were combined. Although the number of participants in the 12 week category was also small (n = 15, 12%), they form a functionally distinct group from those participants walking independently by six weeks (n = 21, 51%), or not walking independently at 12 weeks (n = 15, 37%).
Figure 8.1 Study flowchart

713 Patients screened over 2 years

513 Unsuitable for TWIST Study
   317 No new lower limb weakness
   71 Unwell or palliative
   59 Cerebellar stroke
   24 Poor previous mobility, orthopaedic or neurological condition
   24 TMS contraindication
   14 Late presentation
   4 Bilateral stroke

152 Unsuitable for research
   59 Unable to consent
   56 Out of area
   24 Other study
   13 Declined

48 Patients consented

7 Patients FAC ≥ 4 by 1 week

41 Patients included in analysis at 3 months
   (3 Patients died before 3 months, last observations carried forward)
### Table 8.1 Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics (n = 41)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>72 (43–96)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (59%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>27 (66%)</td>
</tr>
<tr>
<td>Maori</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Pacific</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (7%)</td>
</tr>
<tr>
<td><strong>Stroke risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (66%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>17 (41%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14 (34%)</td>
</tr>
<tr>
<td>Previous Cardiac history</td>
<td>11 (27%)</td>
</tr>
<tr>
<td><strong>Co-morbidities (Charlson Comorbidity index)</strong></td>
<td></td>
</tr>
<tr>
<td>Low (Charlson&lt;2)</td>
<td>32 (78%)</td>
</tr>
<tr>
<td>High (Charlson≥2)</td>
<td>9 (22%)</td>
</tr>
<tr>
<td><strong>Stroke characteristics</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hemisphere</strong></td>
<td>Right</td>
</tr>
<tr>
<td><strong>Stroke type (Oxfordshire stroke classification)</strong></td>
<td>20 (49%)</td>
</tr>
<tr>
<td>Total anterior circulation infarct (TACI)</td>
<td>9 (22%)</td>
</tr>
<tr>
<td>Partial anterior circulation infarct (PACI)</td>
<td>14 (34%)</td>
</tr>
<tr>
<td>Lacunar infarct (LACI)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Posterior circulation infarct (POCI excluding cerebellar)</td>
<td>2 (5%)</td>
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<tr>
<td>Intracerebral haemorrhage</td>
<td>6 (15%)</td>
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<tr>
<td><strong>Thrombolysis</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Thrombectomy</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Previous stroke</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Stroke Severity (NIHSS)</strong></td>
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<tr>
<td>NIHSS median (range)</td>
<td>8 (1–21)</td>
</tr>
<tr>
<td>Mild (NIHSS&lt;5)</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Mod-Severe (NIHSS≥5)</td>
<td>34 (83%)</td>
</tr>
<tr>
<td><strong>Stroke Type</strong></td>
<td></td>
</tr>
<tr>
<td>Motor (M)</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>Motor-Sensory (MS)</td>
<td>19 (46%)</td>
</tr>
<tr>
<td>Motor-Sensory-Hemianopia (MSH)</td>
<td>9 (22%)</td>
</tr>
<tr>
<td><strong>Baseline FAC score (0-5)</strong></td>
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<td>Median FAC (range)</td>
<td>0 (0–2)</td>
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<tr>
<td>Non-ambulatory (FAC=0)</td>
<td>33 (80%)</td>
</tr>
<tr>
<td>Dependent ambulation FAC (1,2,3)</td>
<td>8 (20%)</td>
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Table 8.2 One week clinical, neurophysiological and MRI measures

<table>
<thead>
<tr>
<th>Time by which independent walking was achieved</th>
<th>Clinical measures</th>
<th>All participants</th>
<th>6 weeks</th>
<th>12 weeks</th>
<th>Dependent (12 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n = 41</td>
<td>n = 21</td>
<td>n = 5</td>
<td>n = 15</td>
</tr>
<tr>
<td></td>
<td>FAc 1 week (0 - 5)</td>
<td>Median FAC (range)</td>
<td>0 (0 – 3)</td>
<td>2 (0 – 3)</td>
<td>0 (0 – 2)</td>
</tr>
<tr>
<td></td>
<td>Trunk control test 1 week (0 - 100)</td>
<td>Median TCT (range)</td>
<td>49 (0 – 100)</td>
<td>62 (48 – 100)</td>
<td>24 (0 – 49)</td>
</tr>
<tr>
<td></td>
<td>LL Motricity Index 1 week (0 - 100)</td>
<td>Median LL Motricity Index (range)</td>
<td>48 (0 – 92)</td>
<td>65 (0 – 92)</td>
<td>48 (0 – 84)</td>
</tr>
<tr>
<td></td>
<td>MRC muscle strength 1 week (0 - 5)</td>
<td>Median (range)</td>
<td>Hip flexion</td>
<td>3 (0 – 4)</td>
<td>3 (0 – 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hip extension</td>
<td>2 (0 – 5)</td>
<td>3 (0 – 5)</td>
<td>3 (2 – 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hip abduction</td>
<td>2 (0 – 5)</td>
<td>3 (0 – 5)</td>
<td>2 (0 – 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Knee flexion</td>
<td>2 (0 – 5)</td>
<td>4 (0 – 5)</td>
<td>2 (0 – 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Knee extension</td>
<td>3 (0 – 5)</td>
<td>4 (0 – 5)</td>
<td>3 (1 – 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ankle dorsiflexion</td>
<td>2 (0 – 5)</td>
<td>3 (0 – 5)</td>
<td>2 (0 – 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ankle plantarflexion</td>
<td>3 (0 – 5)</td>
<td>4 (0 – 5)</td>
<td>3 (0 – 4)</td>
</tr>
<tr>
<td></td>
<td>Therapy dose (hrs)</td>
<td>Median dose (range)</td>
<td>11 (1 – 43)</td>
<td>11 (3 – 37)</td>
<td>24 (9 – 43)</td>
</tr>
<tr>
<td></td>
<td>Therapy intensity (min per day)</td>
<td>Median intensity (range)</td>
<td>18 (2 – 116)</td>
<td>21 (11 – 34)</td>
<td>18 (13 – 116)</td>
</tr>
<tr>
<td></td>
<td>Median length of inpatient stay (days)</td>
<td>Median days (range)</td>
<td>32 (13 – 82)</td>
<td>28 (13 – 65)</td>
<td>50 (41 – 82)</td>
</tr>
<tr>
<td></td>
<td>Neurophysiological and imaging</td>
<td></td>
<td>TMS</td>
<td>n = 25</td>
<td>n = 13</td>
</tr>
<tr>
<td></td>
<td>MEP present</td>
<td>10 (40%)</td>
<td>7 (54%)</td>
<td>1 (50%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>n = 30</td>
<td>n = 15</td>
<td>n = 4</td>
<td>n = 11</td>
</tr>
<tr>
<td></td>
<td>Mean FAAI (sd)</td>
<td>0.142 (0.139)</td>
<td>0.108 (0.141)</td>
<td>0.228 (0.233)</td>
<td>0.154 (0.085)</td>
</tr>
<tr>
<td></td>
<td>Mean % CST lesion load (sd)</td>
<td>21.14 (15.31)</td>
<td>19.06 (18.19)</td>
<td>22.63 (15.91)</td>
<td>23.44 (11.26)</td>
</tr>
<tr>
<td></td>
<td>Mean % SMT lesion load (sd)</td>
<td>16.78 (12.47)</td>
<td>15.56 (15.63)</td>
<td>16.91 (11.73)</td>
<td>18.39 (7.93)</td>
</tr>
</tbody>
</table>
Figure 8.2 CART analysis

CART analysis identified factors that predict time taken to walk independently after stroke (6 weeks or 12 weeks, or dependent at 12 weeks). TCT = trunk control test. MRC = Medical Research Council strength score.

The CART analysis is presented in Figure 8.2. Age, therapy intensity (minutes per day), therapy dose (total therapy time), FAC at one week (out of 5), TCT at one week (out of 100) and MRC grades at one week (out of 5) for hip flexion and extension, knee flexion and extension and ankle plantarflexion were entered into the CART analysis. The only predictors of the time by which participants regained independent walking were the trunk control test (TCT) score and MRC grade for hip extension strength. Most participants (91%) with TCT > 37 (21/23, 91%) achieved independent walking within six weeks of stroke. All participants
with TCT ≤ 37 achieved independent walking between six and 12 weeks post-stroke provided hip extension MRC grade was ≥ 3 (n = 4); otherwise they remained dependent at 12 weeks (n = 14). The logistic regression and CART analyses did not identify any other predictors from age; sex; stroke classification; stroke severity; stroke type (M,MS, MSH); comorbidities; one week FAC; MRC grades for hip flexion and abduction, knee flexion and extension, ankle dorsiflexion and plantarflexion; lower limb Motricity Index; therapy dose and intensity.

Regression analyses were also conducted with the subsets of participants who had TMS and MRI. TMS and MRI measures were not found to have predictive value and therefore not included in CART analysis. Of the 25 participants with TMS data, 10 (40%) were MEP+ and 15 (60%) were MEP- (Table 2). MEP+ participants had better outcomes with 8/10 independently walking at 12 weeks compared with 7/15 MEP- participants, however this finding was not significant ($P = 0.10$). Of the 13 participants who achieved independent walking by six weeks, only 7 (54%) were MEP+. MRI data for 30 participants were included in the regression analysis. No MRI measures were identified as predictors of outcome. There were no differences in MRI measures between participants who walked independently by 12 weeks and those who did not (all $P > 0.5$).

The CART analysis results were used to create the Time to Walking Independently after STroke (TWIST) algorithm for use with patients who are not yet walking independently one week post-stroke (Figure 8.3). For ease of clinical use, the dichotomized TCT score was rounded from 37 to 40 as this is easier to remember, and this change does not affect the decision tree as it is not possible to score between 37 and 40. The TWIST algorithm correctly predicted time to walking independently after stroke for 39/41 (95%) of participants. Accuracy, positive and negative predictive values, sensitivity, and specificity are reported in Table 8.3.
Figure 8.3. TWIST algorithm

The TWIST algorithm predicts time taken to walk independently after stroke (6 weeks, 12 weeks or dependent at 12 weeks). All assessments are at 1 week post-stroke. Each outcome category is colour-coded. The coloured dots indicate the actual category outcome of patients as a proportion of the total patients predicted for each category e.g. 5% of patients predicted to walk independently by 6 weeks actually walked by 12 weeks and 5% were dependent at 12 weeks. All patients predicted to walk by 12 weeks or to be dependent at 12 weeks achieved their predicted outcome. FAC = Functional Ambulation category. TCT = Trunk control test (out of 100). Hip extension = MRC grade for hip extension strength (out of 5).
Table 8.3 Sensitivity and specificity of TWIST algorithm

<table>
<thead>
<tr>
<th></th>
<th>Independent by 6 weeks</th>
<th>Independent by 12 weeks</th>
<th>Dependent at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>100% (84 – 100%)</td>
<td>80% (28 – 99%)</td>
<td>93% (68 – 100%)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>90% (68 – 99%)</td>
<td>100% (90 – 100%)</td>
<td>100% (87 – 100%)</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>91% (73 – 98%)</td>
<td>100% (40 – 100%)</td>
<td>100% (77 – 100%)</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>100% (100 – 100%)</td>
<td>97% (86 – 100%)</td>
<td>96% (81 – 100%)</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>95%</td>
<td>91% (21/23)</td>
<td>100% (4/4)</td>
</tr>
</tbody>
</table>

Positive predictive value (PPV) is the probability that a participant predicted to walk independently by a certain time point did so. Negative predictive value (NPV) is the probability that a participant predicted to not walk independently by a certain time point did not do so.

8.5. Discussion

This is the first study to identify predictors of both whether and when an individual patient will walk independently after stroke. Using simple bedside assessments at one week following stroke, the TWIST algorithm based on the CART analysis predicted with 95% accuracy the time taken to walk independently. The first step of the algorithm is to assess trunk control. Most participants with good trunk control (TCT > 40) at one week post-stroke walked independently by six weeks post-stroke. Participants with poor trunk control (TCT < 40) only achieved independent walking by 12 weeks post-stroke if they had hip extension of MRC grade 3 or more. Those with poor trunk control (TCT < 40) and hip extension of MRC grade 2 or less at one week post-stroke were predicted to be dependent at 12 weeks post-stroke (Figure 8.2).
The ability to predict whether and when a patient will regain independent walking may give a patient and their family realistic expectations of the level and duration of support they will need after discharge and allow clinicians to begin discharge planning earlier (Bland et al., 2012). The TWIST algorithm predicts walking independence, rather than the quality of walking, walking speed, or community ambulation. Walking speed is often the target of prediction studies due to the relationship between walking speed, community ambulation, and falls (Friedman, 1990; Bland et al., 2012; Jones et al., 2016). However, the ability to walk indoors without another person present (FAC ≥ 4), is more likely to influence the timing and destination of discharge from hospital than walking speed or community ambulation. It may also influence the level of support required after discharge. It is important to note that while the TWIST algorithm predicts that some patients will not be walking independently by 12 weeks post-stroke, they may be able to do so at a later time point.

These findings support previous work identifying trunk control and lower limb strength as predictors for the return of independent walking (Veerbeek et al., 2011b), with trunk control being the stronger predictor of the two (Kollen et al., 2005). In contrast to previous studies which used the Motricity Index as the sole measure of lower limb strength (Sánchez-Blanco et al., 1999; Veerbeek et al., 2011b), MRC grades for individual muscles were also included in this analysis. This allowed for muscles that are not included in the Motricity Index to be considered as potential predictors. The Motricity Index combines the scores of hip flexion, knee extension and ankle dorsiflexion. These muscles, along with ankle plantarflexion, are important for walking performance (Nakamura et al., 1985; Lin et al., 2006; Peterson et al., 2010a; Hall et al., 2011; Dorsch et al., 2012). It may therefore seem counterintuitive that the strength of these muscles was not identified as a predictor in the present study. This may be because the main outcome of this study is the ability to walk independently, rather than walking performance in terms of quality or speed. Provided the
patient has good trunk control, compensatory strategies involving the trunk, such as shifting weight away from the paretic side or using a walking aid, enable walking even with little voluntary control of the lower limb (Kollen et al., 2005). To achieve independent walking, it is possible to: compensate for poor hip flexor strength with lateral flexion and rotation of the trunk combined with circumduction of the hip to initiate swing; compensate for poor knee extensor strength with hyperextension of the knee or the use of a stick during stance; and compensate for poor ankle dorsiflexor strength by either high-stepping or using an ankle splint. The findings from the CART analysis suggest that the presence of hip extension may provide compensatory proximal stability for those patients with poor trunk control.

Several potential clinical predictors were not included in this exploratory study and would benefit from further investigation in a larger study. These include the presence of increased tone, proprioception, visuospatial inattention, cognition, mood and previous stroke. More sensitive measures of somatosensory and vision impairment than provided by the NIHSS could also be investigated.

Total therapy dose and therapy intensity (minutes per day) did not predict when a participant achieved independent walking. This may be due to the large separation between the outcome categories (6 and 12 weeks) and the relatively consistent amount of therapy that participants received per day regardless of their outcome category (Table 8.2). Participants in this study were provided with standard care for this centre and lower limb therapy intensity was relatively low (median 18 minutes per day of inpatient stay, range 2 – 116 minutes), and could have been over-estimated (Kaur et al., 2013). Further research is needed in different rehabilitation centres to establish whether therapy provided at higher intensities influences the time taken to walk independently.
Neurophysiological and imaging measures were not predictors of whether or when participants would regain independent walking, which is in contrast to studies of recovery in the upper limb (Stinear, 2010b; Stinear et al., 2012; Kim and Winstein, 2017). Participants with tibialis anterior MEPs generally had better walking outcomes than those without MEPs. However, almost half of the participants without MEPs still walked independently by 12 weeks, and MEP status did not predict when a participant would walk independently. In a study of 41 patients with chronic stroke, over half of the participants with absent tibialis anterior MEPs and disruption of CST on diffusion tensor imaging (complete corticospinal tract injury) were able to walk independently or with supervision (Cho et al., 2012). This suggests that the role of the corticospinal tract may be less important for the lower limb than the upper limb (Dawes et al., 2008; Cho et al., 2012; Jang et al., 2013a). Neuroanatomical control of the lower limb and walking differs from the upper limb, with the presence of bilateral and alternative descending pathways providing more redundancy (Dawes et al., 2008; Jang et al., 2013a). The finding that trunk control strongly predicts recovery of independent walking may reflect the contribution of medial descending pathways such as the reticulospinal tract and vestibulospinal tract (Shinoda et al., 2006). TMS specifically targeting the trunk muscles (O'Connell et al., 2007), and MRI measures of the projections from the cerebellum to the reticular and vestibular nuclei, were not assessed in this study and could be considered in future studies.

These findings do not align with the few previous studies reporting that MEP status of lower limb muscles may be a predictor for recovery of walking (Hendricks et al., 2003; Piron et al., 2005; Chang et al., 2015; Kim et al., 2016). However, it is difficult to draw conclusions from these studies due to small sample sizes and variations in selected outcome measures, timing of assessment, and TMS technique. Although previous MRI studies report that patients with less corticospinal tract damage achieve better overall lower limb strength
and gait outcomes, they do not specifically predict recovery of independent walking for an individual (Cho et al., 2007b; Jang et al., 2008; Jang et al., 2013b; Jones et al., 2016). The sample size in this study was small for the subsets of participants with TMS and MRI data, therefore firm conclusions cannot be drawn from these neurophysiological and imaging results and further investigation is warranted.

This study has several strengths. The clinical measures used in the TWIST algorithm are simple and quick to administer at bedside. Clinicians routinely assess trunk control and lower limb strength at several time points after stroke, making this algorithm practical and straightforward to complete. Clinical experience identifies sitting balance and lower limb strength as important in walking recovery. The TWIST algorithm provides a structured approach to combining these assessments to make predictions for individual patients. These features support the potential translation of the TWIST algorithm to clinical practice.

This exploratory study has several limitations. The sample size is small and not all participants had TMS and MRI. The small number of participants who walked independently between 4-6 and 6-12 weeks reflects the non-linear recovery timeline, with most participants recovering independent walking early after stroke or not at all (Jorgensen et al., 1995). This necessitated merging of the outcome categories for participants who achieved independent walking by four weeks and six weeks. The small sample size also has potential effects on the results of the CART analysis if a large number of variables are included. This was partly mitigated by the use of logistic regression analyses to select the variables for the CART analysis. It is possible that the TMS technique used here produced false negatives, due to the deep location of the lower limb motor cortex. Also TMS and MRI measures did not target alternative or un-crossed descending pathways controlling the trunk. The study did not differentiate between participants who were non-ambulatory at 12 weeks and those who
could walk with assistance from one person. These two groups of patients may have quite different support needs on hospital discharge.

Larger independent samples are required to refine and validate the TWIST algorithm to ensure that results are generalizable, to further investigate the potential roles of TMS and MRI, and to assess patients at later time points.

8.6. Conclusions

In conclusion, this exploratory study has identified a simple algorithm based on two clinical measures made at the bedside one week post-stroke that may predict whether and when a patient will walk independently within 12 weeks after stroke. Further work is needed to develop and validate the algorithm with a larger sample of patients and further investigate the role of TMS and MRI as predictors for independent walking.
Chapter 9. The effects of unilateral step training and conventional treadmill training on gait asymmetry in patients with chronic stroke.

This chapter describes the final experiment of this thesis. Background information on gait asymmetry and potential interventions are discussed, followed by details of the experiment and a concluding discussion.

9.1. Introduction

Approximately 60 – 70% of patients regain the ability to walk independently after stroke but many patients are left with a slower, more asymmetrical gait pattern (Nadeau et al., 1999; Lin et al., 2006; Allen et al., 2011). Gait asymmetry refers to the spatiotemporal differences between each leg during walking. Healthy adults have a largely symmetrical gait with less than 6% inter-limb difference in spatiotemporal gait parameters (Titianova and Tarkka, 1995; Kim and Eng, 2003; Patterson et al., 2010b). Patients with more severe motor impairment after stroke often exhibit greater gait asymmetry (Balasubramanian et al., 2007; Patterson et al., 2008a) and this may contribute to lower daily walking activity and poor outcomes (Hall et al., 2012). Asymmetrical gait may also contribute to poor balance; higher metabolic cost of walking; long term musculoskeletal injury due to asymmetrical limb and trunk loading; loss of bone mass density in the femoral neck of the paretic limb; and reduced physical activity levels (Patterson et al., 2012; Finley et al., 2013). Targeting interventions to address gait asymmetry may improve walking outcomes after stroke (Hall et al., 2012).

Improving gait asymmetry may also increase walking speed (Titianova and Tarkka, 1995; Lin et al., 2006; Peterson et al., 2010b; Allen et al., 2011) as propulsion and the ability to initiate swing phase with the paretic leg play an important role both in gait symmetry and in determining self-selected walking speed (Olney et al., 1994; Peterson et al., 2010b).
However, increased walking speed may be due to both true recovery (walking with a normal walking pattern), or compensation (walking with an altered walking pattern) (Allen et al., 2011; Wonsetler and Bowden, 2017). Some patients with asymmetrical gait can increase walking speed through compensation with the non-paretic leg and increased cadence without improving gait symmetry (Balasubramanian et al., 2007; Allen et al., 2011). This means interventions that improve both walking asymmetry and walking speed may have the greatest effect on walking outcomes (Awad et al., 2015b).

Improving gait symmetry may also reduce falls risk; reduce secondary musculoskeletal injury; improve the aesthetics of the walking pattern which may increase patients’ social confidence; and increase endurance and daily walking activity by reducing the metabolic cost of walking (Malone and Bastian, 2014).

9.1.1 Spatial or temporal asymmetry

After stroke, walking may be asymmetrical spatially (step length or joint angles), temporally (swing time, stance time), or both. Over half of patients with chronic stroke exhibit temporal asymmetry while a third exhibit spatial asymmetry (Patterson et al., 2008a).

Temporal asymmetry reflects a preference for weight bearing through the non-paretic leg. The degree of temporal asymmetry varies widely between individuals but the direction of asymmetry is almost always the same (Wall and Turnbull, 1986; Patterson et al., 2008a). Patients typically exhibit longer swing duration and shorter single limb support times in the paretic leg compared with the non-paretic leg (Brandstater et al., 1983; Wall and Turnbull, 1986; Titianova and Tarkka, 1995; Kim and Eng, 2003; Patterson et al., 2008a; Helm and Reisman, 2015).

Spatial asymmetry most commonly refers to step-length asymmetry, which might be particularly important for safe functional ambulation and contribute to self-selected walking
speed (Helm and Reisman, 2015). Step-length asymmetry is more likely to occur in patients with greater temporal asymmetry (Balasubramanian et al., 2007). Step-length asymmetry is often characterised by a longer step with the paretic leg than the non-paretic leg (PARETIClong) (Kahn and Hornby, 2009; Allen et al., 2011; Finley et al., 2015), but it can also be present in the opposite direction (PARETICshort) (Kim and Eng, 2003; Patterson et al., 2010b; Malone and Bastian, 2014).

Spatial and temporal parameters do not necessarily relate to each other (Patterson et al., 2008a; Finley et al., 2015). For example, although patients are likely to have temporal asymmetry in the same direction, with shorter single-support and longer swing time in the paretic leg, some take a longer step with the paretic leg (in relation to the non-paretic leg), while others take a shorter step with the paretic leg. Likewise, the degree of temporal and spatial asymmetry may differ within patients. A patient may have significant temporal asymmetry with minimal step length asymmetry, while another patient with substantial step length asymmetry may have only a small temporal asymmetry (Finley et al., 2015).

9.1.2 Biomechanical contributors to asymmetrical walking patterns

Although the biomechanical contributions to gait asymmetry are not directly investigated in this experiment, it is important to be aware of potential biomechanical contributors in order to understand how different patient groups may respond differently to the interventions described in Section 9.2.

Temporal asymmetry may be the result of minimising single limb support with the paretic limb due to poor paretic leg stability (Wall and Turnbull, 1986). Single limb support time of the paretic leg is equal to the swing time of the non-paretic leg. This means reduced single-support time on the paretic leg results in a short non-paretic swing duration and therefore a relatively longer paretic swing duration (Patterson et al., 2008a). Other factors
that can contribute to an increase in paretic swing duration include: an inability to generate 

enough force to initiate swing with the paretic leg; reduced paretic knee flexion; reduced 

paretic ankle dorsiflexion; and the use of paretic hip circumduction, resulting in a longer, 

slower swing (Wall and Turnbull, 1986; Patterson et al., 2008a).

In turn, a longer swing time with the paretic leg can contribute to step-length asymmetry, 
as the paretic leg has more time to take a longer step (Balasubramanian et al., 2007). 
However, this cannot be the whole reason for step-length asymmetry as the direction of 
spatial asymmetry varies between patients despite increased paretic swing duration. Other 
likely contributors to step length asymmetry are the ability to generate propulsive force in the 
paretic plantar flexors during late stance, and the ability to generate sufficient force in the 
paretic hip flexors to initiate swing (Kim and Eng, 2003; Balasubramanian et al., 2007; 
Peterson et al., 2010b; Allen et al., 2011; Finley et al., 2015).

Balasubramanian et al. (2007) conducted a study with 49 patients with chronic stroke and 
identified two groups of patients. PARETIClong patients had poor paretic plantar flexor 
propulsive force in late stance, resulting in a short step with their non-paretic leg. These 
patients then compensated with increased propulsive force on the non-paretic leg, increasing 
forward movement of the trunk, and therefore facilitating a longer step forward with the 
paretic leg (PARETIClong) (Balasubramanian et al., 2007). In other words, patients who 
produce poor paretic propulsion end up taking a longer step with their paretic leg than the 
non-paretic leg. This compensation may take place in order for the patient to maintain their 
self-selected walking speed. In contrast, PARETICshort patients generated greater 
propulsion with their paretic leg than their non-paretic leg, and also greater than that 
produced by the PARETIClong patients. Only 4/49 patients in this study had a shorter 
paretic step length, so conclusions about these patients should be treated with caution.
Allen et al. (2011) built on the findings by Balasubramanian et al. (2007) in a study of 55 patients with chronic stroke and identified three groups of patients: 29 PARETIClong, 17 symmetrical, 9 PARETICshort. They reported that of the three groups, PARETIClong patients had the lowest paretic leg propulsion in late stance. They compensated in the non-paretic leg with: greater propulsive force by the plantar flexors; greater hip flexor moments; and greater knee extensor moments compared with PARETICshort, symmetrical walkers, and healthy controls (Allen et al., 2011). These findings confirm that propulsion of the paretic limb during terminal stance is an important contributor to step length asymmetry in PARETIClong patients. Poor paretic propulsion is likely due to weakness of the paretic plantar flexors. In addition to this weakness, an inability to achieve adequate hip and knee extension in the trailing limb may limit the generation of propulsive forces at the end of stance phase (Balasubramanian et al., 2007; Peterson et al., 2010a; Awad et al., 2015a; Finley et al., 2015).

The biomechanical contributions to walking with a shorter paretic step are less clear. PARETICshort patients generated more paretic plantar flexor propulsion than PARETIClong patients and patients who walked symmetrically (Allen et al., 2011). These patients did not utilise the same compensatory strategies with the non-paretic leg that the PARETIClong patients did. They did not generate greater non-paretic hip flexion or knee extension in late stance, nor did they increase propulsion in the non-paretic leg. In fact, the propulsion in the non-paretic leg was lower than the paretic leg and lower than PARETIClong, symmetrical, or healthy controls (Allen et al., 2011). A greater limitation than lack of forward propulsion in PARETICshort patients may the inability to generate enough hip flexor power to initiate swing (Balasubramanian et al., 2007; Allen et al., 2011). This delay in initiating swing may require the non-paretic leg to reduce forward momentum by generating less propulsive
power. The lack of forward momentum of the trunk, combined with poor forward swing of the leg may result in a shorter step with the paretic leg.

People who walk symmetrically after stroke also differ biomechanically from healthy controls. These people use compensatory strategies to achieve step-length symmetry such as increased hip flexor activity to accelerate each leg forward during swing and increased non-paretic leg plantar flexor activity (Allen et al., 2011). These findings support earlier reports suggesting that increased hip flexor activity may compensate for reduced paretic plantar flexor propulsion (Olney and Richards, 1996; Nadeau et al., 1999).

It is worth noting that it is not just patients with severe hemiparesis who walk asymmetrically, but some patients with mild motor impairment also walk asymmetrically (Balasubramanian et al., 2007). This suggests that although motor impairment and compensatory strategies may contribute to gait asymmetry, there are likely to be other contributors which have not yet been identified (Patterson et al., 2010a). It is also unclear whether the direction of spatial asymmetry is determined by the degree and type of motor impairment or whether there are other drivers determining which compensatory mechanisms are adopted, such as the type of early rehabilitation training, spasticity, or sensory impairments. Further investigation into the specific biomechanical and compensatory mechanisms contributing to the direction of spatial asymmetry would be of benefit.

The following sections describe two treadmill training interventions that specifically target step-length asymmetry after stroke.
9.1.3 **Split-belt treadmill training**

Treadmill training after stroke enables high repetitions of task-specific walking practice (Awad *et al.*, 2015a) and is commonly used as an intervention to improve comfortable walking speed and endurance (Dean *et al.*, 2010; Dean *et al.*, 2014). While conventional treadmill training may increase gait symmetry during the training (Chen *et al.*, 2005; Brouwer *et al.*, 2009; Tyrell *et al.*, 2011), these effects typically do not transfer to overground walking (Patterson *et al.*, 2008b).

One rehabilitation intervention targeting step-length asymmetry is split-belt treadmill training. A split-belt treadmill consists of two belts that can either be tied together (functioning as a standard treadmill), or can move independently at different speeds. The person is required to make rapid adaptive adjustments by stepping the leg on the fast-moving belt more quickly than the slow belt in order to maintain their position on the treadmill. This walking is initially spatially and temporally asymmetrical but becomes more symmetrical through trial-and error practice (Reisman *et al.*, 2010; Malone and Bastian, 2014).

Split-belt training induces a form of error-based motor learning called locomotor adaptation and this plays an important role in rapid adjustments for walking in different environments (Morton and Bastian, 2006; Reisman *et al.*, 2010). The different belt speeds force one leg to move twice as fast as the other leg, creating a perturbation of the pre-learned locomotor pattern. This perturbation creates a mismatch between what is expected and what actually occurs, resulting in significant movement errors (Tyrell *et al.*, 2015). With practice, feed-forward adjustments are made to the motor plan and accuracy improves so that walking becomes more symmetrical. When the belts are tied together again, further errors occur, resulting in asymmetry in the opposite direction in healthy adults or an improved symmetry in patients with chronic stroke (essentially creating a rebound effect or negative after-effect) (Helm and Reisman, 2015). These after-effects provide evidence that the new locomotor
pattern was learned and stored, and have been demonstrated in healthy participants and patients with stroke (Reisman et al., 2009; Reisman et al., 2010; Tyrell et al., 2015).

De-adaptation back to baseline symmetry in healthy adults after training suggests that humans naturally favour symmetrical conditions (Tyrell et al., 2015). However, after stroke, the asymmetrical walking pattern may have become the new “normal” symmetry which doesn’t trigger the nervous system to respond with correction (Reisman et al., 2010). Exaggerating the asymmetry with split-belt training creates a perturbation large enough to generate a neural corrective response with after-effects of a more symmetrical walking pattern (Reisman et al., 2010; Reisman et al., 2013; Malone and Bastian, 2014). During split-belt training the leg on the fast belt takes a shorter step relative to the leg on the slow belt. This means in order to exaggerate asymmetry, PARETICshort patients should be trained with the paretic leg on the fast belt, and PARETIClong patients should be trained with the paretic leg on slow belt (Reisman et al., 2007; Malone and Bastian, 2014). Split-belt training may seem like an ideal opportunity to provide patients with the experience of practising symmetrical walking by training them towards symmetry. However, participants do not maintain this symmetrical walking pattern during training and instead respond by adapting back towards their baseline asymmetry so that the after-effects then worsen the asymmetry (Malone and Bastian, 2014). This suggests that error-augmentation training may be more effective than training towards symmetry.

The error-based learning component of locomotor adaptation relies on the cerebellum. In a study by Morton and Bastian (2006), nine participants with cerebellar damage and age matched healthy controls completed a single session of split-belt training. Participants with cerebellar injury were able to respond reactively to the split-belt perturbation by adjusting stance time and stride length at a similar speed and magnitude to the controls, creating an asymmetrical walking pattern. In contrast to the control group, participants with cerebellar
damage did not then make feed-forward adaptations to improve symmetry during the split-belt training, nor did they display after-effects once the belts were tied together again (Morton and Bastian, 2006). These findings suggest that predictive or feedforward adaptations are dependent on intact cerebellar function while feedback driven reactive locomotor adaptations are more likely to be mediated by non-cerebellar systems such as spinal reflexes, central pattern generators (CPG) and brainstem mechanisms (Chapter 2) (Morton and Bastian, 2006).

In healthy adults, participants provided with visual and auditory cues (to support conscious learning) adapted more quickly to split-belt training than those who were actively distracted from the task, or a control group (Malone and Bastian, 2010). In contrast, the group who were distracted were slower to adapt but displayed after-effects for longer than those in the conscious learning group. This means that participants who use conscious correction make changes more rapidly but these changes are transient, while participants completing dual-task training may retain the learning for longer. These learning types only affected spatial asymmetry measures suggesting that conscious correction processes may access spatial control but temporal control is more strongly influenced by different neural circuits, such as the CPG (Malone and Bastian, 2010). The implication of these findings is that if adaptation training is not reliant on conscious correction it may be useful in patients with limited ability to consciously correct their walking pattern after stroke.

Initial studies in split-belt training were conducted in healthy adults (Prokop et al., 1995; Jensen et al., 1998; Reisman et al., 2005). Studies in patients with chronic stroke have demonstrated that provided the cerebellum is intact, patients with stroke retain the capacity for locomotor adaptation (Reisman et al., 2007) albeit with a slower rate of adaptation (Savin et al., 2013; Malone and Bastian, 2014). A slower adaptation rate in those with stroke suggests that spatial walking adaptation is not only influenced by the cerebellum but also by
cerebellar-cerebral connections which may have been affected by the stroke (Malone and Bastian, 2014).

Split-belt training studies have consistently demonstrated that patients with chronic stroke improve step-length symmetry for a short period immediately after training. This occurs by increasing the length of the shorter step, rather than reducing the length of the longer step, which is important for functional walking speed (Reisman et al., 2013). The effects of a single session of split-belt training are relatively short lived (Reisman et al., 2007). One study evaluated the effects of repeated split-belt training over a four week period in patients with chronic stroke (Reisman et al., 2013). For those participants who responded, the improvement in step length asymmetry was retained up to three months later. This study made the important observation that not all people with stroke responded to split-belt training. The non-responders did not differ from the responder group in terms of lower limb impairment, degree of asymmetry, walking speed, proprioceptive or sensory loss. However the participants who had the greatest response to training were those who reported greatest exertion during walking prior to training. This might mean that patients after stroke who walk in the least economical pattern may make the greatest improvement in step-length symmetry (Reisman et al., 2013). This is the only study to consider differences between responders and non-responders and the small sample size of 12 patients means the interpretation of these findings is speculative.

The strengths of these studies are consistent study design making comparisons between studies relatively straight forward, and the use of healthy controls for all studies involving patients with stroke. A limitation of the split-belt training studies is that they do not report the magnitude of change in step-length asymmetry, nor do they discuss whether the improvement is clinically significant. These studies instead focus more on using split-belt training to understand the motor learning involved in locomotor adaptation. Sample sizes
tend to be small and only two studies evaluated the effect of split-belt training on overground walking, reporting that the effects of training only partially transfer to overground walking (Reisman et al., 2009; Reisman et al., 2013). The biomechanics of walking on a treadmill differ to those required for overground walking, particularly relating to propulsive effort and hip flexion (Alton et al., 1998; Brouwer et al., 2009). Although the assertion from all of these studies is that split-belt training is superior to conventional treadmill training, no studies were conducted to compare treadmill training and split-belt training in the same group of patients.

In summary, split-belt treadmill training may be an effective intervention for improving step-length asymmetry after stroke through error-dependent locomotor adaptation, although the magnitude of the benefit and its clinical relevance are unclear. Although it appears that the effects transfer to overground walking and are sustained after repeated sessions, very little research has been conducted into these clinically important aspects of split-belt training. It is not clear whether the effects of split-belt training are superior to conventional treadmill training as no studies have been conducted to compare the two in the same patient sample. One final limitation of split-belt training in stroke rehabilitation is the limited access to a split-belt treadmill in a clinical setting.
9.1.4 Unilateral step training

Kahn and Hornby (2009) described a novel method of symmetry training called unilateral step training (UST), which attempted to replicate the effects of split-belt training using a standard motorised treadmill. The participants stood with the paretic leg on the side of the treadmill while stepping with the non-paretic leg on the moving treadmill belt. This movement mimics split-belt treadmill training in that the participant has the paretic leg on the “slower” (in this case stationary) belt and the non-paretic leg on the “faster” belt.

Kahn and Hornby (2009) included 10 PARETIClong participants with chronic stroke who exhibited a step-length asymmetry of more than 20% to investigate the effects of a single session and repeated sessions of UST. A single session of UST produced an improvement in step-length asymmetry of 9 – 13%, 10 minutes after training. But this effect was only seen when the participant walked at their fastest pace overground and not at their self-selected pace. As with split-belt training (Reisman et al., 2013), the improved step-length asymmetry was a result of the participant taking a longer step with the non-paretic limb, rather than a decrease in step-length of the paretic limb (Kahn and Hornby, 2009). This effect was retained but reduced at 24 hours. Repeated sessions produced improved step-length asymmetry in both self-selected and fast overground walking, with effects retained two weeks after training (Kahn and Hornby, 2009).

These results indicate that UST training promoted improved step-length asymmetry and this was successfully transferred to fast-paced overground walking. The authors suggest the results may be due to similar adaptation mechanisms to split-belt training but describe the intervention as training towards symmetry by practising taking longer steps on the treadmill with the non-paretic (short stepping) leg in order to keep up with the treadmill (Kahn and Hornby, 2009). This is in fact the opposite to the approach of split-belt training which trains towards asymmetry and relies on the after-effect of training to produce symmetrical gait.
(Reisman et al., 2010). The authors expected that the extended period of time in single leg stance on the paretic leg during training may have contributed to increased stability in weight bearing and therefore a longer step with the non-paretic leg. This hypothesis was not supported by the results as the stance time asymmetry did not improve after UST training (Kahn and Hornby, 2009). This lack of effect on temporal asymmetry is similar to results from split-belt training studies, confirming that both UST and split-belt training specifically target spatial asymmetry (Kahn and Hornby, 2009; Malone and Bastian, 2010; Reisman et al., 2013; Helm and Reisman, 2015).

Huynh et al. (2014) included 18 healthy adults in a study comparing split-belt training with UST and included kinematic data in the analysis. Both training methods produced after-effects of step-length asymmetry but the split-belt training had a greater effect. The after-effects of both types of training were characterised by increased hip flexion and reduced hip extension in the limb that was trained on the “fast” belt. However, the authors suggest that UST does not involve actual bipedal locomotion and therefore the mechanism for creating these effects in UST may be due to repetitive learning through use-dependent plasticity, not error-based adaptation (Huynh et al., 2014). This study had limitations in that three treadmill training protocols (split-belt, UST at a slow pace, and UST at a fast pace) were all completed in a single session. Participants only trained for 10 minutes for each intervention type and completed 10 overground gait mat walks in between. There is no description of the time between each training session, but the authors acknowledge that the effects of each intervention had not washed out before beginning the next 10 minute block (Huynh et al., 2014).

Another likely difference in mechanism between the two training types is that UST requires a greater degree of conscious correction than split-belt training. During split-belt training, the participant is required to adapt their pre-learned locomotor pattern, which is a
cerebellar dependent process. Whereas during UST they are required to interrupt their locomotor pattern and fix one leg stationary on the ground, effectively overriding the CPG. They are also required to actively shift weight between legs rather than simply keeping all of their weight on the stationary leg (Kahn and Hornby, 2009; Huynh et al., 2014).

These two studies provide preliminary data suggesting that UST may be a viable alternative to split-belt training for targeting step-length asymmetry in a rehabilitation setting. The protocol is simple and only requires the use of a motorised treadmill and a safety harness, which are both usually accessible in rehabilitation units. The presence of after-effects in healthy adults and patients with stroke suggests that UST does provide some degree of perturbation to the locomotor pattern, generating a response even in healthy adults who usually walk symmetrically. Whether that is through error-based learning or use-dependent plasticity is unclear. It is also unclear whether the different magnitude of effects reported between split-belt training and UST in healthy adults would be the same in patients with stroke, as patients with stroke transfer after-effects from treadmill walking to overground walking more effectively than healthy adults (Reisman et al., 2009).

The research to date has several limitations. Firstly, neither study included a control condition of conventional treadmill training. Secondly, only patients with marked step-length asymmetry have been studied so far. It is not known whether patients with a wide range of either step-length or step-time asymmetry would benefit from UST. And thirdly, only 10 patients with stroke have been studied, all of whom were PARETIClong patients who take a longer step with their paretic leg. Whether UST would be equally effective in patients with step-length asymmetry in the opposite direction has not been investigated. If the effects of UST are similar to split-belt training, during UST the PARETICshort patients would most likely benefit from training with the paretic leg on the moving belt (opposite to the PARETIClong patients). In this training set-up, if the driving mechanism for the after-effects
were the increased practise of single-leg stance on the paretic limb (Kahn and Hornby, 2009), it would be expected that PARETICshort patients would not benefit. If, however, the mechanisms contributing to the after-effects are related to the leg stepping on the treadmill, rather than stability of the supporting leg, then PARETICshort patients may benefit. Biomechanically it has been suggested that PARETIClong patients lack propulsive power, while PARETICshort patients lack swing initiation (Allen et al., 2011). These differences may be important in the response to UST.

The aims of this experiment were to investigate:

- whether UST had a greater effect on step-length asymmetry than conventional treadmill training after stroke
- whether UST improves asymmetry in patients with a range of asymmetry levels
- the effect of training the paretic or non-paretic leg on the moving belt during UST in relation to the direction of step-length asymmetry

We hypothesised that:

- UST would improve step-length asymmetry more than conventional treadmill training
- UST would improve step-length asymmetry for participants with a range of asymmetry levels
- step-length asymmetry would improve when PARETICshort patients completed UST with the paretic leg on the moving belt, and when PARETIClong patients completed UST with the non-paretic leg on the moving belt.
9.2. Methods

9.2.1 Participants

People over 18 years old, more than six months after first-ever ischaemic or haemorrhagic stroke, and with lower limb motor impairment (Fugl-Meyer score less than 34) were recruited from a research volunteer register. Potential participants were included if they demonstrated more than 6% step length or step time asymmetry (as 6% is the natural asymmetry variation observed in healthy adults (Kim and Eng, 2003)), while walking at a self-selected pace, and could walk for 20 minutes overground with no aid or with a stick. Potential participants were excluded if they had: cerebellar stroke; plantar flexor muscle contracture with < 10 degrees available ankle dorsiflexion; cardiac pacemaker; angina; severe respiratory disease; inability to consent to research participation; or were reliant on a walking frame. Potential participants were screened using a treadmill training screening questionnaire (Appendix 10) for medical contraindications to high intensity treadmill training prior to inclusion in the study. Written informed consent was obtained from each participant. The protocol was approved by the University of Auckland Human Participants Ethics Committee, and the study was conducted in accordance with the Declaration of Helsinki.

9.2.2 Experimental design:

Clinical and demographic information was obtained on inclusion to the study (Table 9.1). Participants completed clinical assessments at the beginning of the first training session: lower limb motor impairment measured with the lower limb Fugl-Meyer scale (LL FM) (Gladstone et al., 2002); muscle strength graded with the Motricity Index (Collin and Wade, 1990); plantar flexor muscle tone graded with the Modified Ashworth Scale (MAS)(Bohannon and Smith, 1987); type of walking aid normally used (stick, quad stick, no
aid, ankle foot orthosis); and self-selected walking speed measured with the 10 metre walk test (Flansbjer et al., 2005).

The study consisted of three sessions spaced at least 48 hours apart. Each session included baseline gait assessments, then 20 minutes of treadmill training, followed by repeated gait assessments immediately, 10 minutes and 30 minutes after completing the treadmill training (see Figure 9.1).

![Figure 9.1 Training session design](image)

Gait assessments included walking on a GAITRite® instrumented mat, and 10 metre walk test. Gait mat walking was tested before, immediately post, 10 minutes post and 30 minutes post treadmill training. 10 metre walk was tested before and 30 minutes after treadmill training.

Each session involved a different type of treadmill training: conventional treadmill training; unilateral step training with the paretic leg on the side of the treadmill and the non-paretic leg stepping on the treadmill (UST hemislow) (Kahn and Hornby, 2009); and unilateral step training with the non-paretic leg on the side of the treadmill and the paretic leg stepping on the treadmill (UST hemifast). The terms hemislow and hemifast were selected to identify whether the paretic limb was stationary (equivalent to slow belt in split belt training) or stepping (equivalent to fast belt in split belt training) (Huynh et al., 2014; Tyrell et al., 2015). All participants completed conventional treadmill training for the first session as the control intervention. Participants then completed either UST hemislow or UST hemifast in a randomised order for the second and third sessions.
Table 9.1 Clinical and demographic characteristics

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<th>Years post-stroke</th>
<th>Fugl-Meyer (LL)</th>
<th>Motricity Index (LL)</th>
<th>Modified Ashworth PF</th>
<th>Step length asymmetry (%)</th>
<th>Step time asymmetry (%)</th>
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<td>70</td>
<td>L</td>
<td>6.2</td>
<td>18</td>
<td>45</td>
<td>1</td>
<td>-45.1</td>
<td>37.2</td>
<td>0.48</td>
<td>S</td>
</tr>
<tr>
<td>19</td>
<td>short</td>
<td>73</td>
<td>R</td>
<td>10.6</td>
<td>31</td>
<td>92</td>
<td>0</td>
<td>-21.6</td>
<td>-13.5</td>
<td>0.65</td>
<td>N</td>
</tr>
<tr>
<td>mean (sd)</td>
<td>9 short</td>
<td>66 (9)</td>
<td>3 R</td>
<td>7.7 (4.7)</td>
<td>24 (5)</td>
<td>73 (19)</td>
<td>1.7 (1.0)</td>
<td>-21.1 (17.1)</td>
<td>16.6 (16.0)</td>
<td>0.70 (0.28)</td>
<td></td>
</tr>
<tr>
<td>Total mean (sd)</td>
<td>64 (11)</td>
<td>10 R</td>
<td>7.5 (5.5)</td>
<td>23 (5)</td>
<td>70 (15)</td>
<td>1.7 (1.0)</td>
<td>±17.7 (13.7)</td>
<td>20.7 (10.9)</td>
<td>0.79 (0.30)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: y = years; LL = lower limb; PF = plantar flexors; sd = standard deviation; AFO = ankle foot orthosis; S = standard walking stick; Quad = quad stick; N = no aid
### 9.2.3 Gait assessments

Gait assessments were completed at the beginning of each training session and repeated immediately, 10 minutes and 30 minutes afterwards (Figure 9.1). Participants were asked to walk without a walking aid for the 10 m walk and gait mat assessments. Participants who usually wear an AFO were allowed to do so during the study.

#### Spatiotemporal gait assessment

Spatiotemporal gait parameters were measured using the GAITRite® Electronic Walkway (CIR Systems Inc. US). The GAITRite mat is 427 cm in length and 61 cm wide with 48 x 336 sensors spaced 1.27 cm apart. As the participant steps on the mat, sensors are activated producing footfall data. The time of activation and distance between activated sensors provides spatiotemporal information about each footfall. Footfall data were sampled at 60 Hz. The GAITRite® software computed the spatiotemporal parameters for each walk along the mat, which were then stored for offline analysis using Excel software.

Participants were instructed to walk at a self-selected pace to the end of the gait mat. No feedback or correction was provided on walking pattern. Participants completed three walks at a self-selected pace and five walks at fastest pace. The parameters of interest were step length, step time, stance time (% stride time), single support time (% stride time), double support time (% stride time), velocity, and cadence (Table 9.2). Velocity recorded from the gait mat is more precise than 10 m walking speed and is therefore reported in cm/sec, while 10 m walk speed is reported in m/s.
Table 9.2 Gait parameters

<table>
<thead>
<tr>
<th>Gait parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step length (cm)</td>
<td>Distance from heel contact of one foot to heel contact of opposite foot</td>
</tr>
<tr>
<td>Step time (sec)</td>
<td>Time from first foot contact of one foot to first contact of the opposite foot</td>
</tr>
<tr>
<td>Stride time (sec)</td>
<td>Time between two consecutive footfalls of the same foot (time taken to step with both the right and left legs)</td>
</tr>
<tr>
<td>Stance time (% stride time)</td>
<td>Time from heel contact of one foot to toe off of the same foot (time in weight bearing) expressed as percentage of stride time</td>
</tr>
<tr>
<td>Single support time (% stride time)</td>
<td>Time during which only one leg is on the ground (equates to swing time of opposite leg) expressed as percentage of stride time</td>
</tr>
<tr>
<td>Double support time (% stride time)</td>
<td>Time when both feet are on the ground simultaneously (combination of initial double support and terminal double support time) expressed as percentage of stride time</td>
</tr>
<tr>
<td>Velocity (cm/sec)</td>
<td>Distance travelled divided by ambulation time</td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>Number of steps divided by ambulation time</td>
</tr>
</tbody>
</table>

Walking speed

Overground walking speed was assessed using the 10 m walk test. The 10 m walk test was included in addition to the velocity measures acquired from the gait mat as a walking distance of 10 metres is likely to be a more accurate indicator of actual overground walking speed. Participants were instructed to walk at a self-selected pace and the time taken to walk the middle 10 m of a 14 m walkway was recorded (Perera et al., 2006). The average of three 10 m walks was used in analysis. The 10 m walk was repeated with the patient walking at their fastest pace. The 10 m walk test was completed only at baseline and 30 minutes after training (Figure 9.1).
9.2.4 Treadmill training

Participants completed three treadmill training conditions: conventional, UST hemislow, and UST hemifast. The following procedure applied for all training conditions.

Participants were assisted onto a standard motorised treadmill and fitted with a safety harness. This harness served as a safety precaution and did not provide any body weight support. A horizontal support rail was placed in front of the participants at waist height and they were instructed to hold the rail as lightly as possible for balance. Regular feedback was given during the treadmill training to maintain only light support on the rail. All participants were required to wear the harness and place both hands on the rail for safety and consistency (Malone and Bastian, 2014).

The self-selected 10 m walk speed was used as the starting treadmill speed for all three training conditions. Treadmill speed was then adjusted as necessary to reach a comfortable start pace. Participants were asked to walk comfortably for three minutes on the treadmill at the beginning of each session to familiarise themselves and adjust treadmill speed. Participants were then given a short rest. Participants completed 5 minutes walking at the selected comfortable walking speed, with a 25% increase in speed every 5 minutes thereafter until they had completed 20 minutes (Kahn and Hornby, 2009). If a participant was unable to increase their speed this was documented and they continued at the highest speed they reached for the remainder of the 20 minutes. Participants were allowed to stop for a rest as required but did not disembark the treadmill. Heart rate was monitored for safety during training using a Polar® heart rate monitor around the chest.
**Conventional training**

For conventional treadmill training, participants were instructed to walk comfortably on the treadmill and warned when treadmill speed was due to increase. Verbal and visual cues were not provided about gait pattern.

**UST hemislow**

After the three minute warm-up to determine self-selected conventional treadmill walking pace, participants were instructed to stand with their paretic leg on the side of the treadmill. They were then asked to take steps on the treadmill with their non-paretic leg as the belt was moving, while keeping the paretic leg stationary (Kahn and Hornby, 2009; Huynh et al., 2014). Instructions and manual assistance were given during the first two minutes to ensure the participant was shifting weight between legs and stepping effectively on the treadmill. Further feedback was only provided if necessary to correct weight shift. The participants walked at self-selected pace for five minutes, and then speed was increased every five minutes as per the protocol for conventional training.

**UST hemifast**

The protocol for UST hemifast training was the same as UST hemislow, except participants stood with their non-paretic leg on the side of the treadmill and stepped with the paretic leg.

**9.2.5 Data processing – GAITRite**

Only the middle steps from each GAITRite walking trial were used for analysis to avoid the effects of acceleration and deceleration. Mean and standard deviation step length were calculated for the three self-selected speed walking trials. Steps that were more than 1.5 standard deviations from the mean and fell within the first or last three steps of each gait mat trial were removed. A step during the middle of the walk that was more than 1.5 standard
deviations from the mean was highlighted as an outlier but retained in the analysis as a reflection of natural variation in the participant’s gait.

The remaining steps of the three self-selected speed walking trials were combined to calculate mean and standard deviations for each of the following parameters: step length, step time, stance time, single support time, double support time, stride time, velocity and cadence. Stance time, single support time, and double support time were expressed as a percentage of the total stride time (Table 9.2). This process was repeated for each leg at each time point and for each walking pace.

Asymmetry measures

The primary outcome was change in step length asymmetry. Secondary asymmetry measures were step time asymmetry, stance time asymmetry and single support time asymmetry. Double support time was averaged across both legs instead of calculating an asymmetry value as few patients exhibited double support time asymmetry in accordance with previous work by Patterson et al. (2010b).

Several equations exist for calculating asymmetry of spatiotemporal gait parameters. There is no advantage in using one equation over the other in terms of accuracy or sensitivity but an asymmetry ratio (paretic limb/non-paretic limb) has been recommended simply for ease of interpretation (Patterson et al., 2010b). However, we have used the same equation as the original study investigating unilateral step training after stroke (Kahn and Hornby, 2009) for ease of comparison. Asymmetry values for each parameter were calculated using the following equation and expressed as a percentage:

\[
\text{Step-length asymmetry} = 100 - \left( \frac{\text{Non-paretic step length}}{\text{Paretic step length}} \right) \times 100
\]
A value of zero indicates no asymmetry, a positive value indicates that the paretic leg takes a longer step than the non-paretic leg (PARETIClong), and a negative value indicates that the paretic leg takes a shorter step than the non-paretic leg (PARETICshort).

9.2.6 Statistical Analysis

Data from the gait mat analyses were used to group the participants according to the direction of step length asymmetry; longer step on the paretic leg (PARETIClong) or a shorter step on the non-paretic leg (PARETICshort). Independent samples t-tests were used to compare baseline characteristics of participants in each group. Baseline comparisons for each spatiotemporal parameter were performed using one way rmANOVAs using a within subject factor of Session (conventional, UST hemislow, UST hemifast) and a between subject factor of Group (PARETIClong, PARETICshort). If Group was significant, separate rmANOVAs were performed for each group. Paired samples t-tests were used for post-hoc comparisons with correction for multiple comparisons (Rom, 1990). All statistical analyses were repeated for the parameters at self-selected speed and at fast speed. Baseline data are reported as mean ± standard error. Pearson correlation coefficients were calculated between baseline variables (Table 9.1) and: 1) absolute value step-length asymmetry at self-selected speed; 2) absolute value step timing asymmetry at self-selected speed; and 3) actual step-length asymmetry at self-selected speed, to identify any relationships between baseline variables and the direction of asymmetry.

Asymmetry parameters

For asymmetry parameters (step length, step time, single support time, and stance time), two way rmANOVAs were conducted using within-subject factors of Session (conventional, UST hemislow, UST hemifast) and Time (pre, post, post 10, post 30) and a between-subject
factor of Group (PARETIClong, PARETICshort). If Group was significant, separate
rmANOVAs were performed for each group. Greenhouse-Geisser correction was used when
the assumption of sphericity was violated. Paired samples t-tests were used to investigate
significant main effects or interactions, with Bonferroni correction for multiple comparisons
(Rom, 1990). Paired samples t-tests were also conducted with raw data for each limb to
identify the potential contributors to any effects on asymmetry. Effects of Session, Group or
Time are reported as mean difference with 95% confidence interval (CI).

Non-asymmetry parameters

For non-asymmetry parameters (Double support time, velocity, cadence, 10 metre walk
speed), two-way rmANOVAs were conducted with factors of Session (Conventional, UST
hemislow, UST hemifast) and Time (pre, post, post 10, post 30) and a between-subject factor
of Group (PARETIClong, PARETICshort). If Group was significant, separate rmANOVAs
were performed for each group. Paired samples t-tests were used for post hoc comparisons,
with Bonferroni correction for multiple comparisons (Rom, 1990). Effects of Session, Group
or Time are reported as mean difference with 95% confidence interval (CI).
9.3. Results

Twenty participants were recruited (16 male, median age 65 (range 43 – 80) years). Eleven participants took a longer step with their paretic leg relative to their non-paretic leg (PARETIClong), and nine participants took a shorter step with their paretic leg (PARETICshort). All but one of the PARETICshort participants had a slower step time with their paretic leg, confirming that spatial and temporal asymmetries do not necessarily relate to each other. All participants were able to complete the 10 m walk and GAITRite trials without a stick and with a mean self-selected walking speed of 0.79 m/s (Table 9.1). Baseline characteristics were similar between groups (Table 9.1) (all p > 0.05).

Four participants (two PARETIClong and two PARETICshort) had step-length asymmetry less than 6%. The step-length asymmetry analysis was carried out with and without these people included and the results were the same, so their data were retained in the analysis. There were no significant correlations between absolute step-length asymmetry or direction of asymmetry and any of the following: age; lower limb impairment (lower limb Fugl-Meyer (FM) and lower limb Motricity Index); 10 m walk speed; use of walking aid; or plantar flexor tone (all p > 0.2). Impairment (lower limb Motricity index, lower limb FM and NIHSS) was correlated with step-time asymmetry (lower limb Motricity index p = 0.001; lower limb FM p = 0.008; NIHSS p = 0.004) indicating that participants with more severe lower limb impairment, and more severe stroke, exhibited greater temporal asymmetry. Lower limb Motricity Index, lower limb FM and NIHSS are co-linear, therefore only lower limb FM is presented in Figure 9.2. No other baseline variables were correlated with temporal asymmetry.
Figure 9.2 Correlations between baseline lower limb motor impairment and baseline asymmetry.

A. Lower limb Fugl-Meyer (FM) scores are not correlated with absolute step length-asymmetry. B. Lower limb FM scores correlate with absolute step-time asymmetry as participants with more severe lower limb impairment exhibit greater step time asymmetry. C. The degree of lower limb impairment (lower limb FM) is not correlated with the direction of step-length asymmetry. Participants who took a shorter step with their paretic limb have asymmetry values below zero and participants who took a longer step with their paretic limb have step-length asymmetry values above zero.
9.3.1 Step length asymmetry

Baseline comparisons revealed that PARETICshort participants were more symmetrical at baseline in the UST hemislow session than the conventional session (conventional -21.1 ± 5.7%, UST hemislow -10.2 ± 3.1%, F2,18 = 4.82, p = 0.021; mean difference 10.89%, 95% CI 2.15 - 19.62%), but not UST hemifast sessions (all p > 0.06). There was no difference in step-length baseline symmetry between sessions for PARETIClong participants or for either group walking at a fast pace (all p > 0.08).

There was a significant interaction between Group, Session and Time (F6,14 = 3.34, p = 0.029) at self-selected walking speed. PARETICshort participants increased symmetry by 9.1% (95% CI 2.7 – 15.5%, p = 0.011) immediately after conventional training, maintained this at 10 minutes, with a small drop to 7.5% (95% CI 1.6 – 13.5%, p = 0.019) at 30 minutes (Figure 9.3). These participants took a longer step (mean difference 3.6 cm, 95% CI 2.0 – 5.3 cm, p = 0.001) with their paretic leg after conventional training, with no change in their non-paretic leg step length (Figure 9.3).

Immediately after UST hemifast training, PARETICshort participants increased symmetry by 11.6% (95% CI 5.3 – 17.9%, p = 0.003) but were not different from baseline at 10 minutes and 30 minutes after training. These participants took a shorter step (mean difference 5.9 cm, 95% CI 2.4 – 9.4 cm, p = 0.005) with their non-paretic leg after UST hemifast with no change to the step length of their paretic leg. There was no effect of UST hemislow training on step length asymmetry for either group (p > 0.06). There was no effect of any of the interventions on step length asymmetry for participants in the PARETIClong group or for any participants when walking at fastest pace (all p > 0.06).
Figure 9.3 Step length asymmetry – self-selected speed

A. PARETICshort patients significantly improved step-length asymmetry at all time points after conventional training (p < 0.05). B. PARETICshort participants took a longer step with their paretic leg after conventional treadmill training (p < 0.01). C. PARETICshort participants significantly improved step-length asymmetry immediately after UST hemifast training (p < 0.01). Effects were not present 10 minutes or 30 minutes after training. Although PARETIClong patients exhibited worse asymmetry after UST hemifast, this did not reach significance (p > 0.06) D. PARETICshort participants took a shorter step with their non-paretic leg immediately after hemifast training (p < 0.05).
These results indicate that for participants who take a shorter step with their paretic leg, conventional training increases symmetry by increasing the step length of the paretic leg during comfortable walking. In contrast, these participants increased symmetry during comfortable walking after UST hemifast by taking a shorter step with their non-paretic leg, while their paretic leg step length did not change. The effects of conventional training lasted for 30 minutes, whereas the effects of UST hemifast were gone by 10 minutes after training. UST hemislow was not an effective intervention for step length asymmetry for either group at a comfortable walking pace. Neither conventional, UST hemislow nor UST hemifast training was effective at altering step length asymmetry for PARETICshort participants during fast walking or for PARETIClong participants at either pace.

9.3.2 Step time asymmetry

There was no difference in step time asymmetry between sessions or groups at baseline (all \( p > 0.30 \)). There was no effect of training on step time asymmetry for either group after any of the three training sessions, at either self-selected or fast walking pace (all \( p > 0.20 \)). These results indicate that conventional, UST hemislow, and UST hemifast training do not affect step timing asymmetry at either a self-selected or fast walking pace.

9.3.3 Single support time asymmetry

There was no difference in single support time asymmetry between sessions or groups at baseline (all \( p > 0.40 \)). There was no effect of training on single support time asymmetry after any of the three training sessions, or at either self-selected or fast walking pace (all \( p > 0.05 \)). This means conventional, UST hemislow, and UST hemifast training do not affect single support time asymmetry at either a slow or fast pace.
9.3.4 *Stance time asymmetry*

There was no difference in stance time asymmetry between sessions or groups at baseline (all $p > 0.60$). At self-selected walking pace there was an interaction between Time and Group ($F_{3,17} = 2.89$, $p = 0.044$) for stance time asymmetry, but no interaction with Session. Paired t-tests with sessions pooled indicated that PARETICshort participants increased stance time asymmetry by 2.4% ($p = 0.013$) immediately after training, but were not different from baseline at 10 or 30 minutes after training. The paretic limb had a 1.1% increase in stance time after training, but this did not reach significance ($p = 0.068$). There was no effect of training on stance times for the non-paretic limb. Stance time asymmetry did not change for PARETIClong participants at self-selected pace or for either group at a fast pace.

These results indicate that conventional, UST hemislow and UST hemifast training equally improve stance time symmetry for PARETICshort participants walking at a self-selected pace. This small effect is short-lived and disappears by 10 minutes after training. None of the training sessions improved stance time asymmetry in PARETIClong participants or in either group at a fast pace.

9.3.5 *Double support time*

There was an effect of Session on baseline double support time when walking at a self-selected pace ($F_{2,18} = 3.4$, $p = 0.046$). Participants spent less time in double support for UST hemislow (34.0 ± 2.9%) than conventional training (36.2 ± 2.9%; mean difference 2.2%, 95% CI 1.2 – 3.3%, $p < 0.001$). There was also an effect of Session on baseline double support time when walking at a fast pace ($F_{2,18} = 4.32$, $p = 0.021$). Participants spent less time in double support for UST hemislow (31.05 ± 2.90%) and UST hemifast (30.67 ± 2.32%) compared to conventional (32.69 ± 2.69%; mean difference with UST hemislow 1.6%, 95% CI 0.2 – 2.9%, $p = 0.024$; mean difference with UST hemifast 2.1%, 95% CI 0.6 – 3.5%, $p = 0.024$).
There was no difference in baseline double support time between PARETICON and PARETICshort groups.

For double support time there was a significant interaction between Session and Time (F$_{6,14} = 3.05$, $p = 0.009$), but no effect of Group ($P > 0.90$) at self-selected walking speed. Participants increased double support time after UST hemislow by 1.7% (95% CI 0.8 – 2.6%, $p = 0.001$) and UST hemifast by 2.7% (95% CI 1.5 – 3.8%, $p < 0.001$). Double support time returned to baseline by 10 minutes post training. There was no effect of conventional training on double support time at a self-selected pace ($p > 0.10$).

There was no effect of any training type on double support time at fast walking speed (all $p > 0.06$).

9.3.6 Velocity

Participants walked faster at baseline in the second and third training sessions. There was a main effect of Session on baseline gait mat velocity at self-selected pace ($F_{2,18} = 7.7$, $p = 0.002$). Velocity was faster for UST hemislow (90.8 ± 7.3 cm/sec) and UST hemifast (86.9 ± 7.4 cm/sec) than Conventional (78.8 ± 7.2 cm/sec; mean difference with UST hemislow 11.9 cm/sec, 95% CI 4.4 – 19.5 cm/sec, $p = 0.004$; mean difference with UST hemifast 8.1 cm/sec, 95% CI 1.1 – 15.2 cm/sec, $p = 0.027$). There was also a main effect of Session on baseline gait mat velocity when walking at a fast pace ($F_{2,18} = 8.91$, $p = 0.001$). Velocity was faster for UST hemislow (117.9 ± 10.4 cm/sec) and UST hemifast (115.0 ± 10.1 cm/sec) than Conventional (103.8 ± 9.5 cm/sec; mean difference with UST hemislow 13.9 cm/sec, 95% CI 4.9 – 23.0 cm/sec, $p = 0.004$; mean difference with UST hemifast 11.5 cm/sec, 95% CI 3.9 – 19.0 cm/sec, $p = 0.005$).

There was no effect of training on velocity at self-selected walking speed (all $p > 0.05$).

At fastest pace, there was an effect of Session and Time ($F_{6,14} = 3.54$, $p = 0.003$) but no effect
of Group (p > 0.30). Participants walked 5.3 cm/sec more slowly immediately after UST hemislow training (95% CI 2.0 – 8.6 cm/sec, p = 0.003) and 5.7 cm/sec more slowly immediately after UST hemifast training (95% CI 1.0 – 10.4 cm/sec, p = 0.019), but returned to baseline walking speed within 10 minutes (Figure 9.4). There was no difference between PARETIClong or PARETICshort patients.

![Figure 9.4 Velocity – fast speed](image)

**Figure 9.4 Velocity – fast speed**

At fast pace, participants walked more slowly immediately after UST hemislow training (p < 0.01) and immediately after UST hemifast training (p < 0.05), but not after conventional training. Participants returned to baseline speed by 10 minutes post training.
9.3.7 Cadence

There was an effect of Session on baseline cadence at self-selected pace (F2,18 = 3.75, p = 0.033). Baseline cadence was higher for UST hemislow (100.8 ± 2.8 steps/min) than for Conventional (95.0 ± 3.0 steps/min, mean difference 5.5 steps/min, 95% CI 0.6 – 10.8 steps/min, p = 0.04). There was no difference between UST hemifast and conventional baseline cadence (p > 0.20). There was also an effect of Session on baseline cadence at fast pace (F2,18 = 10.50, p < 0.001). Baseline cadence was higher for UST hemislow (119.0 ± 4.5 steps/min) and UST hemifast (116.6 ± 4.0 steps/min) sessions than the conventional session (Conventional 110.1 ± 4.1 steps/min; mean difference with UST hemislow 8.5 steps/min, 95% CI 3.3 – 14.0 steps/min, p = 0.004; mean difference with UST hemifast 6.3 steps/min, 95% CI 2.6 – 10.0 steps/min, p = 0.002).

At self-selected walking speed there was a significant effect of Time (F3,17 = 12.01, p < 0.001), but no effect of Session or Group and no interactions (all p > 0.20). Participants reduced their cadence by 3.3 steps/min (95% CI 1.7 – 4.9 steps/min, p < 0.001) immediately after training, but returned to baseline cadence within 10 minutes (Figure 9.5). There was no difference between groups or training type. There was no effect on cadence at a fast walking pace.
Participants reduced cadence immediately after all training types when walking at a self-selected pace (p < 0.01) but returned to baseline cadence within 10 minutes.

9.3.8 10 metre walk speed

Participants walked faster at baseline in the second and third training sessions. There was a main effect of Session on baseline 10 m walk speed at self-selected pace (F\textsubscript{2,18} = 9.25, p = 0.001). Both UST hemislow (0.89 ± 0.07 m/s) and UST hemifast (0.87 ± 0.07 m/s) walking speeds were faster than Conventional (0.78 ± 0.07 m/s; mean difference with UST hemislow 0.11 m/s, 95% CI 0.04 – 0.17 m/s; p = 0.004, mean difference with UST hemifast 0.09 m/s, 95% CI 0.03 – 0.15 m/s, p = 0.005). There was also a main effect of Session on baseline 10 m walk speed at fast pace (F\textsubscript{2,18} = 8.18, p = 0.001). Both UST hemislow (1.17 ± 0.09 m/s) and UST hemifast (1.14 ± 0.1 m/s) walking speeds were faster than Conventional (1.03 ± 0.09 m/s; mean difference with UST hemislow 0.14 m/s, p = 0.004, 95% CI 0.05 – 0.22 m/s; p = 0.004 mean, difference with UST hemifast 0.11 m/s, 95% CI 0.03 – 0.20 m/s, p = 0.011).

At self-selected walking pace, there was a significant interaction between Session and Time (F\textsubscript{2,18} = 5.50, p = 0.008), but no effect of Group (p > 0.10). Although overground
walking speed was higher 30 minutes after all types of training, conventional training had the greatest effect, increasing walking speed by 0.14 m/s (95% CI 0.08 – 0.20 m/s, p < 0.001). Walking speed increased by 0.06 m/s (95% CI 0.01 – 0.12 m/s, p = 0.026) after UST hemislow, and by 0.08 m/s (95% CI 0.05 – 0.10 m/s, p < 0.001) after UST hemifast (Figure 9.6A).

At fast pace, there was a significant interaction of Session and Time (F_{2,18} = 4.59, p = 0.017), but no effect of Group (p > 0.70). Participants’ walking speed was 0.13 m/s faster 30 minutes after conventional training (95% CI 0.07 – 0.20 m/s, p < 0.001) (Figure 9.6B). There was no effect of UST hemislow or UST hemifast on fast walking speed.

**Figure 9.6 10 m walk speed**

A. Self-selected walking speed increased the most after conventional training (p < 0.01), but also increased after UST hemislow (p < 0.05) and UST hemifast training (p < 0.01). B. When walking at a fast pace, participants increased walking speed after conventional training (p < 0.01) but not after UST hemislow or UST hemifast training.
9.4. Discussion

This was the first study to investigate unilateral step training in participants with asymmetry in both directions, and to compare these results with conventional treadmill training. The main finding from this experiment was that both conventional and UST training improved step-length asymmetry during overground walking at a self-selected pace in those participants who took a shorter step with their paretic leg (PARETICshort). This did not support the first hypothesis that UST training would have a greater effect on step-length asymmetry than conventional treadmill training. The second hypothesis that participants with a wide range of step-length asymmetries would improve step-length asymmetry after UST training was supported in the PARETICshort group, but not the PARETIClong group. The third hypothesis was partially supported with PARETICshort participants improving step-length asymmetry when stepping with the paretic leg on the moving belt (hemifast), but PARETIClong participants did not improve step-length asymmetry after UST training with the non-paretic leg on the moving belt (UST hemislow). As the effects of training on asymmetry were predominantly demonstrated during self-selected walking, the discussion will focus on results relating to self-selected walking rather than fast paced walking.

PARETICshort and PARETIClong participants had similar baseline characteristics. Those with greater temporal asymmetry had greater lower limb motor impairment. None of the following baseline variables: age; stroke severity (NIHSS score), lower limb impairment (lower limb FM and lower limb Motricity Index); 10 m walk speed; use of walking aid; or plantar flexor tone, were significantly correlated with step-length asymmetry at baseline, or with the direction of step-length asymmetry. Both groups of participants exhibited training effects with higher baseline velocity, cadence and 10 metre walk speed in the second and third training sessions than in the first.
9.4.1 Symmetry effects

PARETICshort participants took a longer step with their paretic leg after conventional treadmill training, resulting in improved step-length asymmetry of 9.1% that was retained at 30 minutes after training. These participants also improved step-length asymmetry by 11.6% after UST hemifast training (with the paretic leg stepping on the moving belt). The improvements in step-length asymmetry after UST hemifast training were due to the participants taking a shorter step with their non-paretic leg, with no change in step length of the paretic leg. These effects were only transient, and participants had returned to baseline by 10 minutes after training. Although UST hemifast training produced the largest improvement in step-length asymmetry for this group of participants, conventional training produced more sustained effects. The magnitude of improvements in step-length asymmetry after both conventional and UST hemifast training were similar to those produced by UST hemislow training in the study by Kahn and Hornby (2009).

Although these findings partially support the previous UST studies reporting after-effects on step-length asymmetry (Kahn and Hornby, 2009; Huynh et al., 2014), there are four key differences between our findings and those of previous treadmill and UST studies. Firstly, conventional training improved step-length asymmetry. Previous treadmill training studies report improvements in symmetry during training (Chen et al., 2005; Brouwer et al., 2009; Tyrell et al., 2011) that does not transfer to overground walking (Patterson et al., 2008b). However the studies investigating transfer to overground walking did not differentiate between participants by direction of step-length asymmetry. The effects on step-length asymmetry in our experiment were only seen in PARETICshort participants. These participants represent a smaller proportion of the stroke population than PARETIClong participants (Balasubramanian et al., 2007; Allen et al., 2011), therefore any effects seen in this participant group may be missed in studies that do not group patients by direction of
asymmetry. The increased paretic step length produced by conventional training is consistent with previous treadmill studies that report overall increased step length, and may contribute to improved overground walking speed (Patterson et al., 2008b).

Secondly, and unexpectedly, there was no significant effect on step-length asymmetry for PARETIClong patients after any training type. PARETIClong participants in this study had a mean step-length asymmetry of 14.9% compared with the 45% asymmetry in the UST study by Kahn and Hornby (2009). It may be that UST hemislow training is only effective for PARETIClong participants with a marked step-length asymmetry. In this study, PARETICshort participants who had a mean step-length asymmetry of only 21.1% did respond to UST training (hemifast). They also exhibited a trend towards worsened step-length asymmetry after hemislow UST training (10% worse). These results did not reach statistical significance but indicate that these participants were more responsive to both directions of UST training than the PARETIClong participants. There were no significant differences between baseline characteristics of each group to explain the difference in response, nor was there a correlation between lower limb impairment and direction or degree of asymmetry. It is possible that a baseline characteristic not measured in this study such as perceived exertion may have differentiated between the responders and non-responders, as reported in a previous study where patients who walked with the greatest initial metabolic cost responded the most to training (Reisman et al., 2013).

A third difference with the previous UST study is that in this study the after-effects occurred during overground walking at a self-selected pace. In the previous UST study, after-effects were only demonstrated during fast overground walking. This may have been a limitation of their sample size (Kahn and Hornby, 2009). An effect demonstrated during walking at a self-selected walking pace is more relevant to participants after stroke than an
effect during fast walking, as the former is the walking pace they will usually select during their daily activities.

The final difference between these findings and the previous UST study is that the after-effects of UST hemifast training in PARETICshort participants were a result of a shorter step taken with the leg that was stationary during training (non-paretic leg). Kahn and Hornby (2009), reported that UST hemislow training for PARETIClong participants resulted in improved step-length asymmetry and this was due to an increased step-length in the leg which was stepping on the moving belt during training (also the non-paretic leg). If the same underlying mechanisms for improvement were occurring in both PARETICshort participants in this experiment and PARETIClong participants in the experiment by Kahn and Hornby (2009), and they were trained according to the direction of their asymmetry, it would be expected that both groups of participants would have the same after-effect of taking a longer step with the leg trained on the moving belt. PARETIClong participants would take a longer step with their non-paretic leg, and PARETICshort participants would take a longer step with their paretic leg, with both groups therefore improving symmetry. Instead, both groups responded with their non-paretic legs and in opposite directions. A closer look at our data indicates that although not all measures were statistically significant, UST training for both groups resulted in a trend toward either reduced or increased step-length of the stationary leg for both hemifast and hemislow conditions, regardless of the direction of asymmetry. This does not support the findings from the Kahn study but does support findings from the study by Huynh et al. (2014), which reported that asymmetry effects were driven by reduced step length of the leg on the “slow” belt.

These important differences with the three UST studies conducted to date make it difficult to draw conclusions about the effectiveness of, or the mechanisms contributing to, the effects of UST training. PARETICshort participants have difficulty initiating swing with
their paretic leg (Allen et al., 2011) but as they did not increase paretic step length in this study, improving swing initiation is unlikely to have contributed to the improvement in step-length asymmetry. PARETICshort patients contribute to step-length asymmetry with increased propulsion of their paretic leg compared with their non-paretic leg (Balasubramanian et al., 2007; Allen et al., 2011). Treadmill training requires less propulsion than overground walking (Alton et al., 1998; Lee and Hidler, 2008; Brouwer et al., 2009). This suggests that when these patients initially transferred to overground walking, they continued to produce less paretic propulsion from their paretic limb, resulting in a shorter non-paretic step until adjusting to the new requirements of overground walking by 10 minutes after training. Ground-reaction force analysis of the overground walking may be useful in future studies to identify whether altered paretic propulsion contributes to the training effects of UST hemifast in PARETICshort participants.

Another factor which may influence the response to UST training for PARETICshort and PARETIClong participants is the method by which they shift their weight from the stepping leg to the stationary leg (Huynh et al., 2014). PARETICshort participants may use the non-paretic stationary leg to “pull” their weight across to the stationary leg while PARETIClong participants may push their weight across with the non-paretic leg to the paretic stationary leg. Without motion-capture video analysis it is not possible to identify whether these different weight transfer techniques occur or if they have an effect on training outcomes. Further investigation may be beneficial in understanding the biomechanical changes that contribute to improved step-length asymmetry after UST hemifast training.

The improvements in step-length asymmetry for PARETICshort participants in this study were accompanied by a slight (2%), transient improvement in stance time asymmetry across all sessions that was not retained 10 minutes after training. As this improvement in stance time was very small and was not accompanied by a significant difference in stance time on
either the paretic or non-paretic leg, it is unlikely to be a meaningful difference or a contributor to the improvement in step-length asymmetry.

9.4.2 Training effects

Although only the PARETICshort group displayed improved symmetry with conventional and UST training, both groups demonstrated training effects across the three sessions. Participants had faster baseline walking velocity on the gait mat, higher cadence, and shorter double support times in the second and third sessions than in the first one. 10 m walk speed increased between each session and during each session for all training types, with the largest effect being an increase of 0.14 m/s after conventional training. As this finding was present in both groups, it is unlikely that improved step-length asymmetry contributed to improved walking speed. Instead, it is likely to be due to training at greater than comfortable walking pace during all training sessions, and possibly also demonstrates an improvement in fitness over the three sessions.

Immediately after UST training, both groups demonstrated increased double support time at self-selected pace but not fast pace. Cadence reduced immediately after all training types in both groups and both groups walked more slowly immediately after UST hemislow and UST hemifast training at a fast pace. All three parameters returned to baseline by 10 minutes. These effects suggest participants were fatigued after training and required more stability with increased double support time and slower cadence.

The findings from this study differ in several ways to the previous study by Kahn and Hornby (2009). This may be due to methodological differences. In this study, participants were required to hold the rail throughout the training, whereas in the previous study, participants were encouraged to walk without holding the rail; all participants wore a safety harness but were not provided with bodyweight support, whereas the previous study provided
mean bodyweight support of 8 kg (95% CI 2 – 14 kg); we included participants with less pronounced step length asymmetry as well as participants with marked asymmetry; we tested participants immediately after training, 10 and 30 minutes after rather than at 10 and 30 minutes.

9.4.3 Strengths and limitations

The strengths of this study were the inclusion of a control condition of conventional treadmill training that was conducted at increasing speed to match the UST conditions. This enabled, for the first time in either patients with stroke or healthy adults, a comparison between conventional treadmill training and asymmetry targeted treadmill training. A second strength is the separation of participants by direction of asymmetry as these participant groups are likely to have different biomechanical drivers for their gait patterns, despite being very similar in baseline characteristics. The UST training protocol closely matched that used by Kahn and Hornby (2009), which allowed comparisons to be made.

Limitations of this study include the fact that while the time period between training sessions was at least 48 hours, it is possible that training effects were still present after 48 hours. It was not possible to investigate the effects of session order due to the small sample size in each group but the impact of this was minimised by the randomisation of UST session order. The group sizes were small although the total sample size of 20 participants is comparable to previous studies. The removal of the first few steps on each gait mat trial may have meant that some transfer of effects to overground walking was missed due to rapid adaptation over the first few steps. Finally, this study did not use measures of ground reaction force or motion-video capture systems that may have provided more insight into the biomechanical contributions to the findings.
9.4.4 Summary

Step-length asymmetry improved after both conventional training and UST hemifast training in participants who walk with a shorter step with their paretic leg. Conventional training was more effective than UST hemifast as the effects of conventional training were retained for at least 30 minutes. Training was effective for participants with mild to marked step-length asymmetry. Conventional and UST training had no effect on temporal parameters. Conventional and UST training had no effect on step-length asymmetry in participants who took a longer step with their paretic leg. The reasons for the negative results for these participants are unclear but may be related to kinematic or fitness factors not tested in this study, or due to the relatively mild step-length asymmetry of the sample. Based on these findings, unilateral step training provides little benefit over conventional treadmill training for improving spatial asymmetry after stroke. Further investigation is required in a larger sample of participants, divided by baseline asymmetry direction, before considering using unilateral step training as a rehabilitation tool for spatial asymmetry after stroke.
Chapter 10. Discussion

10.1. Summary of research and implications for clinical practice

The impact of stroke on the lives of patients, families and health care services is substantial. Despite medical advances, the numbers of people living with the effects of stroke are expected to double by 2030 (Feigin et al., 2014a). Over 60% of people with stroke experience lower limb weakness and difficulty walking so that research investigating how to predict and improve their recovery and outcome is important. The first experiment in this thesis (Chapter 6) developed a technique for investigating the functional integrity of the corticospinal tract to the lower limb using transcranial magnetic stimulation (TMS) which was then used with patients in the subacute stage of stroke for the next two experiments. The following experiments provided the first evidence of proportional recovery from lower limb motor impairment (Chapter 7); generated an algorithm for predicting when a patient will achieve independent walking (Chapter 8); and, in patients with chronic stroke, investigated unilateral step training as an intervention to improve gait asymmetry (Chapter 9).

Considerable gains have been made in the last few years in understanding the timing and mechanisms of stroke recovery and how rehabilitation may interact with these. For many years, the focus of stroke recovery has been on use-dependent plasticity, leading to the development of task-oriented training as the gold-standard rehabilitation technique. This focus has been largely driven by animal studies and human stroke studies conducted with patients at the chronic stage. This is undoubtedly an important area of research and clinical practice, but it is becoming increasingly apparent that there is more to stroke recovery than use-dependent plasticity.

The distinction between recovery from impairment and achieving functional outcomes after stroke highlights that impairment and function represent different aspects of recovery
(true neurological recovery vs compensation). Furthermore, recovery from impairment and achieving functional outcomes occur over different time frames and are influenced differently by rehabilitation. Recovery from lower limb motor impairment is proportional to the degree of impairment at the time of stroke and does not appear to be influenced by current therapy practices (shown in Chapter 7 for the first time), as has been previously reported for the upper limb and aphasia. The absence of a group of outliers in this experiment suggests that lower limb proportional recovery is present for all patients, potentially due to the presence of alternate descending pathways. This experiment establishes that proportional recovery is not limited to the upper limb, but that the whole motor system recovers proportionally. The uniformity of proportional recovery across patients and the lack of interaction with therapy indicates that this large component of stroke recovery is a fundamentally biological process.

One implication of proportional recovery from motor impairment is that the functional gains made during rehabilitation are likely due to a combination of spontaneous recovery from impairment and therapy-induced compensation. In other words rehabilitation, in its current form, does not seem to increase true neuroplastic brain recovery from stroke, but teaches the patient to work with and around their impairment to achieve their functional goals. The wider implications of these findings may be disconcerting, but this growing understanding of proportional recovery from impairment is important for therapists to know. Firstly, a greater understanding about which aspects of stroke recovery are influenced by current therapy and the potential neurobiological mechanisms, can only improve clinical practice. Secondly, it provides a neurobiological explanation for the ceiling effect therapists encounter on a regular basis with patients of all levels of stroke severity. And thirdly, it identifies a whole area of untapped potential for greater recovery after stroke if any pharmacological, neurophysiological or rehabilitation strategies can be found to increase the proportion of recovery above the ceiling seen in this and other studies of approximately 70%.
It is likely that proportional recovery from lower limb impairment will not limit functional gains to the extent that it does for the upper limb, due to the bipedal nature of walking and the many compensatory strategies available for patients when learning to walk independently (Chapter 8). However, it is likely to have an impact on gait asymmetry as worse lower limb impairment is associated with greater step timing asymmetry (Chapter 9). This means that current therapy practice in the subacute stage after stroke might facilitate regaining independent walking, but probably has little influence on how symmetrical the walking pattern will be.

The symmetry of the walking pattern is of little importance if a patient still requires assistance to walk. The ability to walk independently is important for the patient’s sense of self-efficacy and for a safe discharge home from hospital. It is a difficult challenge for clinicians to not only predict whether a patient will achieve independent walking, but when this will be achieved. Early and accurate predictions may provide information that allows more informed rehabilitation planning and earlier, more comprehensive discharge planning. This provides families with the time needed to put in place the support networks necessary for a safe and effective discharge. We generated a prediction algorithm (TWIST) that is simple to use, easy to remember, and only requires information from baseline assessments that a therapist would routinely complete after stroke (Chapter 8). For these reasons, it is likely to be relatively straightforward to translate into routine clinical practice. This is the first time a study has attempted to predict when a patient will achieve independent walking after stroke. The clinical predictors selected by the analysis were trunk control and hip extension. These predictors align with what we know about the neural control of human walking. This is that the reticulospinal tract controlling muscles of the trunk and proximal muscles of the legs, and central pattern generators in the spinal cord, may have a greater role than the corticospinal tract in walking (Chapter 2). Also, the concept that a patient must be
able to sit by themselves in order to walk by themselves is intuitive for most clinicians and reflects what they see in clinical practice. Patients are able to use compensatory strategies to walk provided they have sufficient trunk control to support themselves in standing on the non-paretic leg.

The experiments in Chapter 7 and Chapter 8 differ from similar studies in the upper limb as neither proportional recovery nor achieving independent walking appeared to rely on an intact corticospinal tract measured by TMS and MRI. Only clinical measures were selected by the analysis, despite including a combination of clinical, neurophysiological and imaging measures as potential predictors for when a patient achieved independent walking. This doesn’t suggest that the other measures have no predictive power but that trunk control was a stronger predictor. It is possible that TMS and MRI will only be important predictors for those participants with poor trunk control. These participants have fewer compensatory options available to them and are likely to rely more heavily on any remaining lower limb movement. However, the number of participants in the experiment in Chapter 8 was too small to investigate TMS and MRI in this subgroup. Although it may be disappointing to find that established biomarkers for prediction of upper limb functional outcomes may be less useful for walking, it is good news for the clinician and the patient if they are not required to predict time taken to walk independently. The algorithm can be used for patients with contraindications to TMS or MRI and translation into clinical practice is likely to be more achievable without these more complex biomarkers.

For those patients who do achieve independent walking after stroke, how well they walk becomes important. Gait asymmetry increases the metabolic cost of walking and may limit community ambulation and participation. The fourth experiment (Chapter 9) investigated the effects of unilateral step training and conventional training on gait asymmetry. Both conventional training and unilateral step training improved step length asymmetry but only
for those participants who took a shorter step with their affected leg. This experiment highlighted that not all patients with stroke respond to the same training type.

Unilateral step training might have potential as a rehabilitation tool at the sub-acute stage of stroke, despite having modest effects in chronic stroke. It may provide an opportunity to work on specific aspects of walking such as stance or swing practice using much higher repetitions than is possible during overground walking practice. It may be suitable for participants who are not yet ready to participate in conventional treadmill training. By isolating one aspect of the walking pattern for practice, such as the swing phase or weight shift, unilateral step training becomes an impairment level therapy. Animal studies suggest that increasing recovery from impairment requires very high numbers of repetitions, but high therapy doses are not usually available for patients. Unilateral step training in sub-acute stroke may provide a rehabilitation tool that combines a weight bearing position with high repetition impairment level stepping practice, with the aim of increasing recovery from lower limb motor impairment and improving gait symmetry.

10.2. Future directions

Proportional recovery from lower limb motor impairment and the TWIST prediction algorithm need to be validated in larger samples and in separate cohorts of patients. The algorithm predicts the timing of achieving independent walking, and it is possible that different centres and different rehabilitation practices and environments may affect this timing. A multicentre trial is therefore planned to refine and validate the TWIST algorithm and will include measures of lower limb motor impairment to confirm whether proportional recovery exists in a different patient sample, and whether there is a subgroup of severely impaired patients who do not recover proportionally.
The multi-centre study will include more assessment time points, including a follow up at six months, which may increase the clinical usefulness of the algorithm. In the original TWIST experiment (Chapter 8), most participants achieved independent walking by six weeks or not at all. And most of those who achieved independent walking by six weeks actually achieved this within four weeks. The multi-centre study will need large numbers of patients to identify predictors for the small but clinically important group of patients who achieve independent walking between four and 12 weeks after stroke.

Two more potential clinical predictors will be included in the multi-centre study. These are cognition and visuospatial inattention. Both of these functions have important roles in walking (Chapter 2) and therefore may affect when a patient recovers walking after stroke, and whether a patient has more falls. This multicentre trial also presents an opportunity to determine how the TWIST algorithm performs compared with therapist predictions. At one week after stroke, the treating therapist will be asked to predict firstly, whether the patient will achieve independent walking, and secondly, when they will achieve this. They will also be asked how confident they are in their predictions. It is anticipated that TWIST will be more accurate than therapist predictions. However, if therapist predictions and the TWIST algorithm have similar prediction accuracy for time taken to achieve independent walking, further study would be useful to determine whether using the TWIST algorithm increases therapist confidence in their predictions, making it a useful clinical tool.

TMS and MRI were not significant predictors of either recovery from lower limb motor impairment or of time taken to achieve independent walking, which may be due to the small sample sizes of participants who underwent TMS and MRI during the experiments. For this reason, TMS and MRI will be included again in the multicentre trial in order to ascertain whether they emerge as predictors with a larger sample size and with a separate cohort of patients. In particular, we need to recruit larger numbers of patients with severe lower limb
motor impairment, and with poor trunk control. It is these patients for whom neurophysiological and imaging measures are most likely to be significant predictors of motor recovery and outcomes, based on findings in the upper limb. The MRI measures used in the experiments in this thesis examined the sensorimotor pathways between the primary sensorimotor cortex and the pons. More recently, a tractography template has been developed for sensorimotor pathways arising in other cortical regions including the dorsal premotor cortex, ventral premotor cortex, supplementary motor area, and the presupplementary motor area (Archer et al., 2017). Inclusion of these other contributing areas may be important in establishing the effect of white matter damage on walking outcomes as only 40% of corticospinal fibres arise from the primary motor cortex. Also, this template may enable investigation of corticobulbar pathways which contribute to the reticulospinal tract.

If the TWIST algorithm is validated in the multicentre trial, it will raise several important issues. The first is that having multiple centres will increase the generalisability of TWIST to the wider stroke population. However, because this is a timing-based algorithm, it is possible that therapist decisions may influence timing of achieving independent walking. Secondly, once therapists and patients are given information about when they are expected to achieve independent walking, this may provide “goal-posts” for either achieving or beating the target time. Further investigation of the effects of implementing the algorithm into clinical practice would be beneficial.

Thirdly, and most importantly, the TWIST algorithm is not intended to be used to determine whether a patient is entitled to a period of inpatient rehabilitation. Although the algorithm provides information about when a patient is likely to achieve independent walking, some patients may achieve this later than three months after stroke. TWIST only predicts whether and when a patient will achieve independent walking up to three months.
Independent walking is not the only goal of rehabilitation. A period of rehabilitation for patients who do not regain independent walking is still beneficial if they are able to, for example, learn to transfer from bed to chair without a mechanical hoist, or progress from bed to chair to walking with assistance.

The evidence in this thesis suggests that current therapy practice does not affect either recovery from lower limb motor impairment or the time taken to walk independently. It is important to continue measuring both therapy type and therapy dose in future studies. It is possible that current therapy practice simply does not include enough repetitions to influence recovery from impairment. Further research into very high repetitions at the subacute stage of stroke might be beneficial.

The focus of this thesis has been on motor impairment and walking outcomes. However, further research could be conducted in two related and important areas. Firstly, no studies to date have considered proportional recovery from sensory impairment. The sensory system is closely integrated with the motor system, and it is likely that it will also recover proportionally. Secondly, very little research has been conducted into outcomes after cerebellar stroke. Patients with cerebellar stroke typically have difficulty walking. They also experience difficulty with axial and proximal limb muscle control, which may mean that predictors for walking outcomes after cerebellar stroke are similar to those for non-cerebellar stroke, albeit probably for reasons of poor muscular control or ataxia than muscle weakness. The trajectory of cerebellar stroke recovery is not clear, so despite possibly having similar predictors to patients with cortical or subcortical stroke, the time frames for achieving independent walking may differ. For these reasons, it is worth considering including patients with cerebellar stroke as a subgroup in the multicentre trial to increase our knowledge of how these patients recover. Doing so could potentially increase the generalisability of the algorithm, or develop a similar algorithm for patients with cerebellar stroke.
10.3. Conclusion

In conclusion, this thesis addresses important gaps in the literature by shedding new light on recovery from impairment and predicting functional outcomes for the lower limb and walking after stroke. Conducting research early after stroke is challenging and time consuming, requiring a high level of flexibility with patient and clinician interactions, and working around the other medical and rehabilitation needs that a patient has in these early stages. Despite these challenges, the information that can be gained from research initiated early after stroke is invaluable for understanding stroke recovery. This thesis is comprehensive in its scope, as it covers recovery from impairment, functional outcomes, and an intervention; and includes patients at both the subacute and chronic stage. The novel findings of proportional recovery from lower limb impairment, and an algorithm to predict when a patient will walk independently after stroke, are highly clinically relevant and potentially transferrable to clinical practice. These findings should improve the patient journey after stroke by providing information that is beneficial both to them and their treating clinician.
Appendices

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Appendix 1: Transcranial magnetic stimulation in stroke

This appendix contains an abridged version of the full literature review published in the Journal of Clinical Neuroscience:


Abstract

The use of transcranial magnetic stimulation (TMS) in stroke research has increased dramatically over the last decade with two emerging and potentially useful functions identified. Firstly, the use of single pulse TMS as a tool for predicting recovery of motor function after stroke, and secondly, the use of repetitive TMS (rTMS) as a treatment adjunct aimed at modifying the excitability of the motor cortex in preparation for rehabilitation. This review discusses recent advances in the use of TMS in both prediction and treatment after stroke. Prediction of recovery after stroke is a complex process and the use of TMS alone is not sufficient to provide accurate prediction for an individual after stroke. However, when applied in conjunction with other tools such as clinical assessment and magnetic resonance imaging (MRI), accuracy of prediction using TMS is increased. Although gains have been made, further investigation is needed before these techniques can be applied in routine clinical care.
Introduction

TMS is a non-invasive and painless technique which, when applied over the primary motor cortex (M1), generates a descending volley in the corticospinal pathway, and elicits a motor evoked potential (MEP) in muscles of the contralateral limb (Barker et al., 1985). The presence or absence of MEPs early after stroke provides information about the functional integrity of the corticospinal tract (CST) (Talelli et al., 2006; Stinear et al., 2007). The amplitude and latency of the MEP are measures of the excitability of the corticomotor system.

The use of TMS in stroke research has increased dramatically in the last 20 years, although studies are primarily limited to patients at the chronic stage of stroke (> 6 months post-stroke) and recording MEPs from the upper limb. Few studies have used TMS to record MEPs from the lower limb after stroke. The purpose of this review is to describe recent advances in the use of TMS in predicting both the resolution of impairment and the recovery of motor function after stroke.

Prognosis

Recovery of motor function after stroke is a complex process (Murphy and Corbett, 2009) which is difficult to predict from clinical assessment alone (Nijland et al., 2013). Despite this, clinical assessment continues to be an important tool in providing an indication of prognosis. There is a strong relationship between the degree of early motor impairment and recovery of function in groups of patients (Wandel et al., 2000; Smania et al., 2007; Nijland et al., 2010; Veerbeek et al., 2011b). However, there is also large inter-individual variability, which makes prediction of recovery for each individual difficult (Patel et al., 2000; Beebe and Lang, 2009; Stinear, 2010a; Veerbeek et al., 2011b; Stinear et al., 2012). Nijland et al. (2013) asked experienced physiotherapists to predict the recovery of arm
function in 131 patients with stroke. Therapists predicted functional outcome based on the Action Research Arm Test (ARAT): 1) no recovery of hand function, (ARAT < 10/57); 2) recovery of some arm and hand function but not a full recovery (ARAT 10-56/57); or 3) full recovery of arm and hand function (ARAT = 57). Predictions made ≤ 72 hrs after stroke were only 60% accurate, with 20% too optimistic, and 20% too pessimistic. The number of years of clinical experience did not affect the accuracy of physiotherapists’ predictions (Nijland et al., 2013). This wide variation in recovery from similar baseline clinical presentations highlights the challenge that clinicians face in predicting recovery of motor function. TMS may provide additional information to explain individual variability and enable a more accurate prognosis.

TMS is used to test the functional integrity and excitability of the corticomotor pathway from the ipsilesional M1 to the affected limb (Talelli et al., 2006). The ability to elicit a MEP in the paretic upper limb indicates a functional CST, and is associated with greater potential for recovery (Rapisarda et al., 1996; Escudero et al., 1998; Cruz Martinez et al., 1999; Stinear et al., 2012). The use of TMS in the early prediction of motor recovery after stroke is a relatively new procedure and many questions remain about who this technique is suitable for, how soon after stroke is optimal for testing, whether it can be used equally effectively in both the lower limb and upper limb, and which other assessment tools can be used in conjunction with it to provide the most accurate prognosis.

A systematic review by Bembenek et al. (2012), found only 15 studies investigating the use of TMS within two weeks after stroke as a predictive tool for upper limb motor recovery, revealing a paucity of research in this area. However, 14 of these studies supported the use of TMS as a predictive tool within this time frame. Research in the lower limb is even more limited. We found only four studies investigating TMS as a predictor of walking conducted within one month of stroke (Hendricks et al., 2003; Piron et al., 2005; Chang et al., 2015;
Kim et al., 2016). This lack of research may be due to several factors such as difficulty accessing the lower limb motor cortex, resulting in higher stimulus intensities required than the upper limb (Terao and Ugawa, 2002), and because the importance of CST integrity in the recovery of ambulation after stroke remains unclear (Dawes et al., 2008). Due to the lack of literature, it is not possible to draw any conclusions at this stage on the use of TMS as a predictive tool for walking. Therefore, this section of the review will focus on prediction of upper limb functional outcomes and recovery from upper limb motor impairment.

As described in Chapter 3, by 3 – 6 months after stroke, most patients recover around 70% of the upper limb movement that they lost. Proportional recovery from upper limb impairment was first reported by Prabhakaran et al. (2008), who postulated that this almost fixed level of improvement must be due to a spontaneous biological process of neurological recovery, rather than external influences. Prabhakaran et al. (2008) found that a small group of participants with the lowest baseline upper limb FM score did not achieve proportional recovery. Several other studies have since replicated this work, with similar results (Marshall et al., 2009; Zarahn et al., 2011; Feng et al., 2015; Winters et al., 2015). Byblow et al. (2015) were the first to use TMS to differentiate between those who did, and those who did not experience proportional recovery from impairment. They demonstrated that the proportional recovery rule only applies to patients who had MEPs in their upper limb, regardless of baseline FM score. This confirms that the ipsilesional CST must be viable for the proportional rule to apply, and indicates that TMS may be useful soon after stroke to predict resolution of impairment.

Predicting recovery of function is important in stroke as it is functional recovery rather than impairment which dictates whether a patient with stroke is able to participate in their normal activities. Early studies (Rapisarda et al., 1996; Escudero et al., 1998; Cruz Martinez et al., 1999) made the observation that overall, patients with MEPs experienced a better
recovery of upper limb function than those without MEPs. However, TMS alone is not sufficient to provide an accurate prognosis for every patient.

Stinear (2010a) suggested that although clinical assessment, TMS, and MRI each have merits in the prediction of recovery early after stroke, none of them in isolation provide a sufficiently accurate individual prognosis. They proposed an algorithm for predicting the recovery of upper limb function using a combination of all three (PREP algorithm). This novel sequential approach means that not all patients require all assessments, and begins with the simplest and cheapest bedside assessment which can be completed by all clinicians.

Previous work by Nijland et al. (2010) found that clinical assessment of finger extension and shoulder abduction within 72 hours of stroke was a strong predictor for the return of some dexterity. However, they quantified “some dexterity” of the upper limb as an ARAT score of ≥ 10. An ARAT score ≥ 10 indicates that participants gained at least a flicker of hand movement by 6 months, and it was unclear how many were actually able to use the upper limb functionally in everyday activities. Stinear (2010a) built on this work and created a specific score called the SAFE score (SAFE=Shoulder Abduction, Finger Extension). This score is used in the PREP algorithm to make predictions for individual patients. Those who scored a sum of eight or more out of ten on the medical research council (MRC) scale for shoulder abduction and finger extension within 72 hours of stroke onset were predicted to have a complete recovery of upper limb function at 12 weeks (Stinear et al., 2012). TMS was used for patients with SAFE ≤ 7 to determine if they had MEPs. If MEPs were present, they were predicted to have a notable recovery of upper limb function by 12 weeks. If MEPs were absent, MRI was used to determine which patients have limited potential for recovery and which have none (Stinear, 2010a; Stinear et al., 2012)
Using the PREP algorithm, Stinear et al. (2012) reported that 60% of patients needed TMS and only 20% required MRI. This reflects a significant saving in expenditure compared with the use of MRI alone. TMS was not required for 40% of patients who could be given a prognosis with the SAFE score. As this was the first study of its kind, the algorithm requires further testing and refining before being used in a clinical setting. Questions remain, such as whether the motor impairment threshold for TMS testing ($\leq 7$ on MRC) is at the optimal level, whether therapy dose has an impact on reaching the predicted potential and whether these results in a relatively small sample of 40 participants can be extrapolated to the general stroke population. The authors acknowledge that there was only a small subset of severely impaired participants and more work needs to be done to refine the boundary between the categories of limited or no potential (Stinear et al., 2012).

The studies discussed here highlight two important and exciting uses of TMS in stroke with potential to influence clinical decision making and target rehabilitation to each individual patient: a) the use of TMS to check for the presence or absence of MEPs to predict proportional recovery of impairment, and b) the use of TMS in conjunction with clinical assessment and MRI to predict functional recovery.

These findings have implications for patient stratification in clinical trials (Byblow et al., 2015). It is becoming clear that matching groups on baseline clinical assessment alone (such as UL strength or function) is not sufficient to ensure that both groups have equal potential for subsequent recovery. We now know that the severity of impairment early after stroke does not necessarily reflect the functional outcome at six months, and that large variation in outcome may occur regardless of therapy input. Therefore, it may not be possible to attribute the changes in function to the research intervention, whether pharmacological or some form of physical therapy. For example, the researcher may unwittingly have several patients who are MEP negative in one group, while all patients in the second group are MEP positive. In
this situation, the second group will recover better than the first group with or without an intervention, skewing the results of the study. The risk is that researchers will exclude severely impaired patients as they are more likely to be MEP negative. However, there is no agreed clinical level at which MEPs are guaranteed to be absent, which means all patients without movement would likely be excluded. It would be unfortunate for this to occur, as within this group of patients with no movement early after stroke, there may be some who are actually MEP positive and may make remarkable gains with physical therapy or other interventions. The use of TMS to differentiate between severely impaired patients may open up opportunities for research into treatment modalities specifically suited to this patient population.

The advantages of TMS are that it is inexpensive, quick to deliver, safe, and a relatively straightforward way to test the functional integrity of the CST. However, TMS is contraindicated for some people, and even after testing, more information is required for some patients. There is still work to be done before TMS can be implemented into standard clinical practice as a prediction tool early after stroke. Some suggestions for future research are: Increased research into TMS as a predictor in the lower limb, using larger sample sizes of patients; research to be carried out within the clinical setting rather than in a laboratory; a cost-benefit analysis of the potential use in clinical practice; and assessing the feasibility of training clinical staff to perform this test.

Conclusion

There has been considerable progress in TMS research in stroke over the last few years. Of particular note are advances in the use of TMS as a prognostic tool early after stroke, indicating that TMS may play an important role in stratification of patients in future clinical trials.
Appendix 2. Participant information sheet for Chapter 6

PARTICIPANT INFORMATION SHEET

Project title: Assessing uncrossed motor pathways to the lower limb

Names of Researchers: Dr James Stinear (MSc, PhD), Dr Cathy Stinear (PhD), Jennifer Chi Yi Chin (BSc, PGDipSci), Marie-Claire Smith (BHScPhysiotherapy), Sheena Sharma (MSc), April Ren (MSc)

Researcher introduction

Dr James Stinear is a senior lecturer in the Department of Sport and Exercise Science at the University of Auckland. His research examines how the brain controls movement of the lower limbs, especially following brain injury and disease. Dr Cathy Stinear is a senior lecturer in the Department of Medicine at the University of Auckland. Jennifer Chi Yi Chin is a Masters student in the Movement Neuroscience Laboratory with an interest in lower limb motor recovery after brain injury and disease. Marie-Claire Smith is a PhD student in the Clinical Neuroscience Laboratory. Sheena Sharma is a PhD student in the Movement Neuroscience Laboratory. April Ren is a technician in the Movement Neuroscience Laboratory.

Project description and invitation

You are invited to participate in a study that aims to identify a method of detecting uncrossed motor pathways from brain to lower limb muscles, and to assess the role of these pathways in the control of the hip, knee and ankle joint. For the arm, these uncrossed pathways have been implicated in recovery of movement after stroke, but it is not known if these pathways play a positive or negative role in the recovery of walking after stroke. The study of these
pathways in healthy individuals will therefore assist the refinement of walking rehabilitation strategies.

You have been invited to participate in the study because you are a healthy adult between 18 and 50 years of age.

**Project Procedures**

As a participant you will be asked to attend up to two data collection sessions in the Movement Neuroscience Laboratory Building 731.134 at the Tamaki Innovation Campus, Glen Innes. Each session will last approximately 1½ to 2 hours and will be separated by at least 4 weeks. Your participation is entirely voluntary, and you can withdraw from the study at any time without providing a reason. If you are a student and you decline the invitation to participate in the study, or if you withdraw from the study at any stage, neither your grades nor academic relationships with the department or members of staff will be affected by your refusal or agreement to participate. Prior to accepting you into the study you will be asked to complete a safety questionnaire and give your consent to participate in writing. The safety questionnaire asks some health-related questions such as a history of injuries to the head, and medications that you take regularly.

During the first experimental session you will have sticky electrodes placed over your leg muscles to record their electrical activity. A small patch of hair may need to be shaved where the electrodes need to be placed and the skin will be cleaned with an alcohol swab. There is an extremely slight chance that these recordings could reveal an abnormality. If so, you will be informed and advised to seek medical advice. You may have a cloth cap tied firmly on your head and a plastic covered magnetic stimulator coil will be placed on top of your head. Magnetic stimulation is safe and painless. You will hear a click and may feel a brief twitch in the muscles of your scalp and face when the stimulator is activated. The twitching is like winking and typically participants do not feel any discomfort or concern. You will be offered disposable soft earplugs to wear to reduce the sound of the coil being activated. During magnetic stimulation you may be asked to weakly contract some of your leg muscles. Depending on the results of the first session you may be asked to participate in the second experimental session. If you agree to participate, you will have a device that measures movement placed around each ankle. You will be asked to watch a line being traced by a computer on a screen, and you will be asked to trace over the line by moving your foot up and down at the ankle joint. You will be asked to move either foot on its own or both feet together.
Should a medical emergency occur during data collection, first aid will be provided by certificated laboratory staff and medical assistance will be summoned by calling 111.

**Data storage/retention/destruction/future use**

Individual’s data will not be published. Data will be used for group analyses and may be published in a thesis, a peer-reviewed journal, or presented at a conference. Individuals will not be identifiable. Data will be stored for 6 years on password protected computers and locked filing cabinets located in the Movement Neuroscience Laboratory (Building 731.134) and then destroyed. Only authorised personnel have access to the laboratory which is secured at all times with an automatic electronic door lock. After 6 years data will be destroyed and all electronic data will be deleted. This will allow time for the study to be published and questions arising from its publication to be addressed through a review of data. You will be offered a summary of the study findings written in plain language at the end of the experiments.

**Right to Withdraw from Participation**

Participants have the right to withdraw from participation at any time without providing a reason. Participants may withdraw their data from the research any time during a period of three months from the date of collection.

**Anonymity and Confidentiality**

Your participation will be completely confidential. Participant’s data will be given a numerical identifier so that the individual cannot be identified in publications or presentations.

**Contact Details and Approval Wording**

For more information and queries please contact:

**Researcher:**

Marie-Claire Smith
Movement Neuroscience Laboratory
Tamaki Campus, Glen Innes
P: +64 9 3737599 extension 86887
F: +64 9 373 7043
m-c.smith@auckland.ac.nz

Principal Investigator:
James W. Stinear, PhD
Senior Lecturer
Academic Director, Exercise & Neurorehabilitation Programmes
Dept. Sport & Exercise Science
Tamaki Innovation Campus
University of Auckland
New Zealand
P: +64 9 373 7599 extension 82378
F: +64 9 373 7043
j.stinear@auckland.ac.nz

For any queries regarding ethical concerns you may contact the Chair:

The University of Auckland Human Participants Ethics Committee, The University of Auckland, Office of the Vice Chancellor, Private Bag 92019, Auckland 1142. Telephone 09 373-7599 extn. 83711.

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE ON 14th May, 2012 for 3 years, Reference Number 2012/8111
Appendix 3. Consent form for Chapter 6

CONSENT FORM

THIS FORM WILL BE HELD FOR A PERIOD OF 6 YEARS

Project title: Assessing uncrossed motor pathways to the lower limb

Names of Researchers: Dr James Stinear (MSc, PhD), Dr Cathy Stinear (PhD), Jennifer Chi Yi Chin (BSc, PGDipSci), Marie-Claire Smith (BHScPhysiotherapy), Sheena Sharma (MSc), April Ren (MSc).

I have read the Participant Information Sheet, have understood the nature of the research and why I have been selected. I have had the opportunity to ask questions and have them answered to my satisfaction.

- I agree to take part in this research
- I understand there are two experiments and I may or may not be requested to attend a second experiment.
- I understand each experiment may take up to 2 hours.
- I understand that my participation or non-participation will not influence my relationship with the researchers and if I feel this assurance has been breached I may contact Associate Professor Greg Anson, Head of Sport and Exercise Science.
- I understand that I am free to withdraw participation at any time, and to withdraw any data traceable to me up to three months from the date of collection.

- I wish / do not wish to receive the summary of findings.

- I understand that data may be published in a thesis, a peer-reviewed journal, or at a conference, and that data will not reveal my identity.

- I understand that data will be kept for 6 years and then destroyed.

Name ___________________________

Signature _________________________ Date _________________

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE ON 14th May, 2012 for 3 years, Reference Number 2012/8111
Appendix 4. Participant information sheet for Chapters 7 and 8

TRIO

Does Targeted Stroke Rehabilitation Improve Outcomes?

Participant Information Sheet

You are invited to take part in the TRIO study.
Please take your time to think about the information provided below, and feel free to discuss it with your whānau, family or other support people. Taking part is completely voluntary (your choice). If you decide not to take part, your health care will not be affected in any way.

What is the study about?

This study explores rehabilitation for arm and leg weakness, which are common after stroke. This study will include 240 adults who have weakness due to a recent stroke.

This study has two phases. You are invited to take part in Phase 1 / Phase 2.

Phase 1: Benchmarking
In this phase, we will observe how people recover movement during the 6 months after stroke.
- We will measure the effects of stroke on the area of the brain that controls movement.
- We will also record the amount of rehabilitation therapy each person completes. This phase will tell us how people with different kinds of stroke respond to rehabilitation therapy, and let us predict the optimal rehabilitation for people with different kinds of stroke.

Phase 2: Implementation
In this phase, we will measure the effects of the stroke on the movement areas of the brain and use this information to guide rehabilitation planning for each person.
- We will see whether individualised rehabilitation planning improves recovery.
This planning information will be shared with you, your family, and your therapy teams.

The results of this study will help us to plan rehabilitation for each patient, based on their individual stroke. This is expected to improve recovery after stroke, and increase patient satisfaction with the rehabilitation process.

Can I take part?

Department of Medicine
Room 12.065
Support Building
Telephone (09) 92 33 779

Dr Cathy Stinear
Dr Suzanne Ackerley
Marie-Claire Smith
Professor Alan Barber
Dr Samir Anwar
Anna McRae
A/P Rhema Vaithianathan
Professor Winston Byblow
You may be eligible to participate if you are
- at least 18 years old
- have experienced a stroke within the last 3 days
- have weakness on one side of your body

You may not be eligible to participate if
- you have a cardiac pacemaker, or other metal implants that prevent you from having an MRI scan
- you experience seizures
- take certain types of medication

You are not eligible to participate if
- the stroke has affected a part of your brain called the cerebellum
- the stroke has severely affected your ability to communicate or understand the study

What does the study involve?

The study involves a range of assessments. You will complete some or all of the assessments described below, depending on how the stroke has affected you.

Hand and arm strength
- Some participants will be asked to complete this assessment.
- You will be asked to raise your weak arm and straighten your weak fingers.
- You will also be asked to make some simple movements and perform some everyday tasks with your weak hand and arm.
- This assessment takes about half an hour, and will take place at the hospital.

Balance and walking
- Some participants will be asked to complete this assessment.
- You will be asked to sit up, and to make some simple movements with your weak leg and foot.
- This assessment takes about half an hour, and will take place at the hospital.
- This assessment will be repeated around 10 days after the stroke.

Transcranial Magnetic Stimulation (TMS)
- Some participants will be asked to complete this assessment.
- Transcranial magnetic stimulation (TMS) will be used to test the pathways from the brain to the weak muscles.
- TMS is a safe, painless, non-invasive technique.
- TMS briefly activates the pathway to the weak muscles, and the response is recorded with electrodes on the skin.
- A small area of skin on your weak arm and/or leg is first prepared by shaving hair and mild abrasion. This can result in a mild and transient irritation of the skin that does not require treatment.
- Occasionally, some people experience mild, transient scalp discomfort due to the activation of the scalp muscles by the stimulator.
- If you feel uncomfortable at any time, please notify the researcher.
- There are no other specific risks associated with the procedures and the equipment used in this assessment.
- This session will take around 45 minutes to complete, and you will be able to take breaks as required.
- This assessment will take place at the hospital, within 14 days of the stroke.
Neuroimaging
- Some participants will be asked to complete this assessment.
- Magnetic resonance imaging (MRI) will be used to see the pathways from the brain to the weak arm muscles.
- The scanner is quite noisy when it is running, so you will be wearing headphones. You will be able to hear the radiographer and also listen to music if you wish.
- You will be told when each scan is starting, and what to expect.
- If at any time you want to stop the scan, you can press a safety button, and the scanning will stop straight away.
- In the event that a condition which is assessed to be a clinical abnormality is detected through performing a scan on you, you will be informed of this and will be advised to consult your general practitioner.
- Because the images are not routinely reviewed by a radiologist we are unable to perform diagnostic scans for medical purposes of areas where you have known abnormalities.
- The scan will take about 20 minutes.
- This assessment will take place at the hospital, within 14 days of the stroke.

Clinical assessment 2 weeks after the stroke
- Some participants will be asked to complete this assessment.
- You will be given some brief memory and thinking tasks.
- You will also be asked to complete a questionnaire about how you are feeling.
- This assessment takes about 30 minutes, and will take place at the hospital.

Clinical assessment 12 weeks after the stroke
- All participants are asked to complete this assessment.
- You will be asked to make some simple movements with your weak arm and/or leg
- You may be asked to perform some everyday tasks with your weak hand and arm.
- We will also test the strength and reflexes in your weak arm and/or leg.
- This assessment takes about an hour, and will take place at a convenient location for you, such as your home or at the hospital.

Clinical assessment 6 months after the stroke
- All participants are asked to complete this assessment.
- A researcher will telephone you to ask you some questions about how the stroke might still be affecting you.
- They will also ask how satisfied you are with your recovery.
- This assessment takes up to an hour, and will be arranged at a time that suits you.

Clinical assessment 2 years after the stroke
- We may contact you again in 2 years' time, to ask whether you would like to complete a follow-up assessment.
- You can decide then whether or not to complete this assessment.
- Depending on the results of this assessment, you may be offered a home-based therapy programme for 1 month, for your hand and arm.

The information we collect as part of this research may be passed on to your rehabilitation team or doctor, if it is clinically significant.

What are the risks and benefits?
• During TMS, some people experience mild skin irritation where the recording electrodes are placed on their arms. This irritation is transient, and doesn’t require any treatment.
• Similarly, there is a risk of mild, transient scalp discomfort during TMS, due to activation of the scalp muscles, and this doesn’t require any treatment.
• There are no other specific risks associated with the assessments and equipment used in this study.
• There will be someone with you at all times during the assessments and the scans.
• Your medication will not be changed due to your participation in this study.
• Participation will not cost you anything, and you will receive no payment. However, you will be offered reimbursement for your travel expenses.
• You may withdraw from this study at any time without giving a reason. Your withdrawal will not affect your medical treatment.
• Participation in this study might benefit you indirectly by helping researchers better understand how to plan rehabilitation for individual patients.
• When you complete the study, you will be offered a written summary of your personal results.
• When the study is complete, you will be offered a written summary of the overall results of the study.

Participation

Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part this will not affect any future care or treatment.

In total, taking part requires up to 7 hours of your time, over 6 months. Most of the sessions take place at the hospital, and we can provide transport if you need help to return to the hospital.

If you volunteer for this study, you will be asked to complete two checklists to ensure that it is safe for you to participate in some assessments. One checklist relates to the TMS, and the other relates to the MRI scan.

If you do agree to take part, you are free to withdraw from the study at any time, without having to give a reason. This will in no way affect your future health care but you will follow the standard care schedule at that time.

Your agreement to participate in this project will be obtained in writing on a Consent Form. Your agreement to participate in the project will include your permission for the researchers to review your medical records, in order to measure how much rehabilitation you complete.

You can choose to have your general medical practitioner informed of your participation, by the researchers.

You are encouraged to have your friend, family or whanau help you understand the risks and/or benefits of this study and any other explanation you may need.

Confidentiality
No information that could personally identify you will be used in any reports on this study. The information and data collected from you will be stored securely, in locked cabinets and on secure computer networks. Only the investigators will have access to this information, and your data will be made anonymous by assigning a unique code to it.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. For more details, refer to http://www.acc.co.nz. If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this trial.

Summary of Your Rights

- Your participation is entirely voluntary.
- You may withdraw from the project at any time without providing a reason. This will not affect your future health care.
- You may have your data withdrawn from the study within three months of your participation.
- You may obtain results regarding the outcome of the project from the researchers upon completion of the study.
- You will be asked to sign a Consent Form. If you are unable to sign your name, there is a section of the Consent Form where another adult may sign on your behalf.
- Your identity will be kept strictly confidential, and no identification of you or your data will be made at any time during collection of the data or in subsequent publication of the research findings.
- Ongoing discomfort or incapacity have not been reported from any of the procedures that will be used in this project, however, if the procedures cause you concern, you may withdraw from the project at any time.
- You are encouraged to consult with your whanau/family, hapu or iwi regarding participation in this project.

Who should I contact if I have further questions?

If you have any further questions about the study, or would like to participate in this study, please contact one of the following people:

Lead Investigator: Dr Cathy Stinear
Telephone: 09 92 33 779
Email: c.stinear@auckland.ac.nz
1. If you have any questions or concerns about your rights as a participant in a research study, you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050  
Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)  
Email (NZ wide): advocacy@hdc.org.nz

For Maori health support, or to discuss any concerns or issues regarding this study, please contact Mata Forbes RGON, Maori Health Services Co-ordinator / Advisor, 5th Level, GM Suite, Auckland City Hospital. Telephone 307 4949 extn. 23939 or Mobile 021 348 432.

This study is funded by the Health Research Council of New Zealand.

This study has received ethical approval from the Northern X Regional Ethics Committee (Ref NTX 11/08/070).
Appendix 5. Consent form for Chapters 7 and 8

Does Targeted Stroke Rehabilitation Improve Outcomes?

Consent Form

REQUEST FOR INTERPRETER

<table>
<thead>
<tr>
<th>Language</th>
<th>Request</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaf</td>
<td>I wish to have a NZ sign language interpreter.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samoan</td>
<td>Oute mana’o ia iai se fa’amatala upu.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiema’u ha fakatonulea.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook Island</td>
<td>Ka inangaro au i tetai tangata uri reo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niuean</td>
<td>Fia manako au ke fakaaoaga e taha tagata fakahokohoko kupu.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

By signing this consent form, you are making the following statements:

1. I have read and I understand the information sheet dated 01/03/2014 for volunteers taking part in this study.
2. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
3. I have had sufficient time and the opportunity to discuss this project with Family/Whanau or a friend to help me ask questions and understand the study.
4. I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time.
5. I understand that my participation and my medical information used in this study is confidential and that no material that could identify me will be used in reports on this study.
6. I understand that the information obtained from my medical files will be used to measure my rehabilitation.
7. I understand that my participation will be stopped if it should appear harmful to me.
8. I understand the compensation provisions for this study.
9. I have had time to consider whether to take part.
10. I know whom to contact if I have any side effects to the study.
11. I know whom to contact if I have any questions about the study.
12. I understand that an interpreter will be available if necessary.

Please turn over.
The following statements are options, please circle either YES or NO.

13. I would like to take part in both the arm and leg parts of the study

........................................................................................................YES / NO

If No, which part would you like to take part in?

ARM  LEG

14. I would like the researcher to mail me a plain English summary of my results from this study, once I have finished it.................................YES / NO

15. I would like the researcher to let me know when the entire study is complete, and mail me a plain English summary of the overall results

........................................................................................................YES / NO

16. I agree to my GP being informed of my participation in this study of my participation in this study......................................................YES / NO

17. I would like the researcher to mail my GP a copy of my personal results from the study, once I have finished it......................................................YES / NO

I consent to take part in this study.

Signed: ______________________________________

Name (please print): ________________________________________________

Date : _______________________

Project explained by: ________________________________________________

Signature:  __________________________________

Date:  _______________________

This section is to be completed for patients who are unable to sign their name:

____________________________ is unable to sign their name.

Researcher’s signature: _______________________________ Date: _______________

I am not associated with the research project, or the researchers. I have witnessed the subject give their verbal consent to participation in this project, and have been authorised by the subject to sign this consent form on their behalf.

Witness name: _______________________________________________________

Witness signature: _______________________________ Date: _______________

(The witness may be any adult other than the researchers named in the Patient Information Sheet.)
Appendix 6. Participant information sheet for Chapter 9

Participant Information Sheet

Title of Project: Does unilateral step training improve walking after stroke?

Researchers:
Associate Professor Cathy Stinear
Dr James Stinear
Marie-Claire Smith (BHSc Physiotherapy, PhD Candidate, Department of Medicine)
April Ren (MSc)

You are invited to take part in the above-named study. Please take your time to consider the information provided below before deciding if you would like to participate. Participation is voluntary (your choice).

What is the study about?

The aim of the study is to examine how different types of treadmill walking affect the symmetry and speed of your walking. We will also examine the activity patterns of the muscles in your legs during the walking practice. This study will include up to 20 participants who have had a stroke at least 6 months ago and have some remaining leg weakness or altered walking patterns. Participants’ data will be grouped for statistical analysis and reporting in a scientific journal.

Am I eligible to participate?

You may be able to participate in this study if you:

- are aged over 18 years
- have experienced one stroke more than 6 months ago
- have weakness in one leg
- your walking has not returned to the level it was before the stroke (either slower or uneven walking)

You are not eligible to participate if you:

- have experienced more than one stroke
- have a cardiac pacemaker, angina or severe respiratory disease
- have severe tightness in your leg muscles
- require a walking frame to mobilise
Prior to inclusion in the study you will be asked to complete a checklist to ensure it is safe for you to participate.

What does the study involve?

The study is separated into six sessions over a two week period (every second day). Each session takes place at the Movement Neuroscience Laboratory at the Tamaki Campus, in Glen Innes. The first two sessions in each week (four in total) will take up to 2 hours and will include clinical assessments, and a 20 minute period of treadmill training. Sensors will record the muscle activity in your legs while you are walking. You will be provided with rest periods as required during the session. At the beginning of the first session, you will be asked to complete a handedness and footedness questionnaire, to determine which hand and foot you prefer to use. The third session in each week will be a short follow up session of approximately 30 minutes. This will involve clinical assessments (walking tests) only.

Clinical assessments:
The strength and movement of your legs will be assessed. You will also be asked to do some walking tests before and after the treadmill practice to measure how you are walking. This will involve walking at a comfortable speed over a 5 metre gait sensor mat and walking as fast as you can over 10 metres.

Treadmill training
After the clinical assessments, you will be asked to walk on a treadmill for up to 20 minutes. You will be fitted with a bodyweight support harness and will be closely supervised during treadmill training for your safety. The treadmill speed will be adjusted to suit your walking level. Once treadmill training is completed, your walking will be assessed again.

Surface Electromyography (EMG)
- Surface electromyography (EMG) will be used to record the activity of the muscles in your legs while you are completing the walking tests and for short periods while you are on the treadmill
- Sensors will be applied to both legs over the front and back of your thighs, your calf muscles and over your shins
- A small area of skin on your leg is first prepared by shaving hair and gentle abrasion. This can result in a mild irritation of the skin that does not require treatment.

What are the risks and benefits?

- Some people develop a mild skin irritation from the placement of the electrodes. This usually resolves quickly and doesn’t require any treatment.
- There is a risk of falling during treadmill training. This risk is minimised by the use of a harness to support your body-weight, and close supervision during all treadmill walking.
- There are no other specific risks associated with the assessments or treadmill training.

Participation

Participation in this study is voluntary (your choice). You have the right to withdraw at any time without giving a reason and at your request we will stop the experiment. You may withdraw your data from this study up to three months after you complete the study.
Withdrawal or non-participation will not affect your relationship with the University. Your agreement to participate will be obtained in writing on a Consent Form.

In total, taking part requires up to 10 hours of your time, over a two week period. The sessions will take place at the Movement Neuroscience Laboratory, Tamaki Campus. Taxi vouchers or petrol vouchers will be provided for transport to and from Tamaki Campus.

Confidentiality

Your data will be identified by a unique code. No information that could personally identify you will be used in any publications or presentations. Data will be stored in a locked cabinet and secure computer network for a period of six years. After six years, your consent form and related paperwork will be securely destroyed. Data may be kept for future use.

Summary of Your Rights

- Your participation is entirely voluntary.
- You may withdraw from the project at any time without providing a reason. This will not affect your future health care.
- You may have your data withdrawn from the study within three months of your participation.
- You may obtain results regarding the outcome of the project from the researchers upon completion of the study.
- Your identity will be kept strictly confidential, and no identification of you or your data will be made at any time during collection of the data or in subsequent publication of the research findings.
- Ongoing discomfort or incapacity have not been reported from any of the procedures that will be used in this project, however, if the procedures cause you concern, you may withdraw from the project at any time.
- You are encouraged to consult with your whanau/family, hapu or iwi regarding participation in this project.

Who should I contact if I have further questions?

If you have any further questions about the study, or would like to participate in this study, please contact one of the following people:

**Researcher:**
Marie-Claire Smith  
Clinical Neuroscience Laboratory  
Ph: 09 373 7599 extension 84897  
Mobile: 02102323351  
Email: m-c.smith@auckland.ac.nz

**Principal Investigator:**
Associate Professor Cathy Stinear  
Department of Medicine, University of Auckland  
Ph: 09 923 33 779  
Email: c.stinear@auckland.ac.nz

**Head of Department:**  
Professor Phillippa Poole  
Department of Medicine, University of Auckland  
Ph: 09 923 6440
Email: p.poole@auckland.ac.nz

For any concerns regarding ethical issues you may contact the Chair:
The University of Auckland Human Participants Ethics Committee, The University of Auckland, Research Office, Private Bag 92019, Auckland 1142.
Telephone 09 373-7599 extension 83711
Email: ro-ethics@auckland.ac.nz

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE ON 21 March 2014 for 3 years, Reference Number 2014/011285
Appendix 7. Consent form for Chapter 9

Consent Form
This form will be held for six years.

Title of Project: Does unilateral step training improve walking after stroke?

Researchers:
Associate Professor Cathy Stinear
Dr James Stinear
Marie-Claire Smith (BHSc Physiotherapy)
April Ren (MSc)

I have been given and understood the explanation of this research project and my role as a participant. I have had the opportunity to consult my whanau, hapu or iwi, or a family member/friend to help me ask questions. I have had time to consider whether to take part. I am satisfied with the answers I have been given. I know who to contact if I have any further questions about the study.

I understand that:

- I will attend the Movement Neuroscience Laboratory (Tamaki Campus) for four treadmill training sessions that may last for up to two hours each, and two follow-up sessions that may last up to 30 minutes each with a total time commitment of approximately 10 hours.
- In each training session, I will be asked to walk on a treadmill for 20 minutes, while wearing a bodyweight support harness.
- In each session, surface electromyography will be used to test the activity of the muscles in my legs.
- Recording sensors will be placed over the front and back of my thighs, over my calf muscles and over my shins, after shaving hair and preparing the skin over the muscles.
- My data will be combined with data from other participants for statistical analysis and reporting in a scientific journal.
- My participation is voluntary and that I may withdraw myself from the experiment at any time without giving a reason, and withdraw any information traceable to me from this study up to three months after I have completed it.
- After six years this consent form and all associated paperwork will be securely destroyed. Study data may be kept for future use.
- Confidentiality will be maintained by de-identifying my data, which will be securely stored, and in any reporting of this research.
I may obtain results regarding the outcome of this project from the named researcher upon completion of the study.

I agree to take part in this research.

Signed:___________________________________________________________

Name:________________________________________________________________
(Please print name in full)

Date:_________________________________________________________________

I would like the researchers to send me a summary of the study results  YES  NO

If YES: my address is _________________________________________________

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE ON 21 March 2014 for 3 years, Reference Number 2014/011285
Appendix 8. TMS participant screening checklist

PARTICIPANT CHECKLIST FOR USING TRANSCRANIAL MAGNETIC AND TRANSCRANIAL ELECTRICAL STIMULATION

Last name
First names
DOB
dd/mm/yyyy
Sex
Male  Female

Please take a moment to carefully answer all questions.

Question:

1. Do you suffer from epilepsy, or have you ever had an epileptic seizure?

2. Does anyone in your family suffer from epilepsy?

3. Do you have any metal implant(s) in any part of your body or head?
   (Excluding tooth fillings)

4. Do you have an implanted medication pump or any other implanted electronics?

5. Do you have a pacemaker or defibrillator?

6. Do you suffer from any form of heart disease or had heart surgery?

7. Do you suffer from recurring headaches?

8. Have you ever had a skull fracture or head injury?

9. Have you ever had any head or brain surgery?

10. Is there any chance you could be pregnant?

11. Do you take any medication?

12. Do you suffer from any neurological or other medical conditions?

Interview guidelines and medication screening checklist developed by Dr. Winston Byblow (PhD), Dr. Alan Barber (PhD, MBChB, FRACP Neurology) and Dr. Cathy Stenzer (PhD), for use in the Movement Neuroscience Laboratory, Clinical Neuroscience Laboratory, Visual Neuroscience Laboratory and Metabolic Neuroscience Laboratory. Updated: January 2011. Pharmacist review: February 2009.
Participant
Name: ____________________
Signature: ____________________
Date: ____________________

Researcher
Name: ____________________
Signature: ____________________
Date: ____________________

Type of experiment: 
- Single Pulse TMS
- Paired pulse TMS
- Repetitive TMS
- TDCS
- Other

Neurological condition: ____________________

Outcome
- Include
- Exclude

Consultation with study physician:
Name: ____________________
Signature: ____________________
Date: ____________________

Supervisor:
Name: ____________________
Signature: ____________________
Date: ____________________
Interview guidelines and medication screening checklist developed by Dr. Winston Byblow (PhD), Dr. Alan Barber (PhD, MBChB, FRACP Neurology) and Dr. Cathy Stinear (PhD), for use in the Movement Neuroscience Laboratory, Clinical Neuroscience Laboratory, Visual Neuroscience Laboratory and Metabolic Neuroscience Laboratory. Updated: January 2011. Pharmacist review: February 2009.
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Interview guidelines and medication screening checklist developed by Dr. Winston Byblow (PhD), Dr. Alan Barber (PhD, MBChB, FRACP Neurology) and Dr. Cathy Stinear (PhD), for use in the Movement Neuroscience Laboratory, Clinical Neuroscience Laboratory, Visual Neuroscience Laboratory and Metabolic Neuroscience Laboratory. Updated: January 2011. Pharmacist review: February 2009.
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MRI SAFETY AND CONSENT FORM

Name _______________________________ Scan # __________

Date of Birth _____/____/_____ NHI ______________

Weight __________ kg Height __________ cm

Magnetic Resonance Imaging involves the use of an extremely powerful magnet. For your safety please answer the following questions:

- Have you had a previous MRI scan? □ yes □ no
- Do you have or have you ever had a cardiac pacemaker? □ yes □ no
- Do you have any other electronic or magnetic implants? E.g. defibrillator, nerve stimulator, cochlear implant □ yes □ no Have you ever had an injury to the eye with a metallic object or fragment? □ yes □ no
-Have you had any previous surgery (operations)? □ yes □ no

Please list __________________________________________________________
________________________________________________________
________________________________________________________

- Do you have any of the following?: anaemia, blood disorders, seizures □ yes □ no
- Do you have any allergies to medications? □ yes □ no

Please list __________________________________________________________

- Do you have any of the following implants inside your body? (Please circle) □ yes □ no
  metallic stent, filter or coil; prosthesis or joint replacement; screws, plates or wires; shunt; vascular or drug access port or catheter; radiation seeds

- Do you have any of the following? (Please circle) □ yes □ no
  medication patches (nicotine or hormone); tattoo or permanent makeup; dentures or partial plate; body piercings; shrapnel, bullets or other metal; hearing aids

If you answer YES or are uncertain regarding any of the above, please contact us on (09) 303 5966 prior to your appointment.
FEMALE PATIENTS
Is there any chance that you could be pregnant? □ yes □ no
Are you currently breastfeeding? □ yes □ no

USE OF YOUR IMAGES
As a University it may be useful to use your images (without your name or other identifying details) for all or some of the following purposes -

- education and training by Centre for Advanced MRI staff
- scientific publications, reports and presentations
- University teaching
- publicity material for the Centre for Advanced MRI
- the Centre for Advanced MRI website and websites of organisations we collaborate with (e.g. Siemens the manufacturer of the machine)
- publicity materials for non-profit organisations
- television documentaries or other public interest media
- databases that may be published on the internet

I give consent for my images to be used for the above purposes provided that all details that could allow me to be identified have been removed □ yes □ no

I confirm that the information provided on this form is true and correct to the best of my knowledge.

Signature ____________________________ Date ___/___/____

Screening form checked by ____________________________

BEFORE ENTERING THE MR SCAN ROOM
You must remove all metallic objects, including jewellery, watches, keys, coins, credit cards, pens, cell phones, hearing aids, clothing with metallic zips and fasteners, metallic threads, or glitter finishes. You will be asked to change into a gown.

Owing to the loud noises emitted by the MR system, you will be given headphones or ear plugs to protect your hearing.
Appendix 10. Treadmill training safety questionnaire

Treadmill training screening questionnaire

Last name: __________________________

First name: __________________________

Please take a moment to carefully answer all questions:

1. Are you able to walk for 20 minutes outside without stopping? Yes No
   Comments: _______________________

2. Do you use a walking aid? Yes No
   Which type of walking aid?

3. Do you have a heart condition? Yes No
   Comments: _______________________

4. Do you get chest pain when exercising? Yes No
   Comments: _______________________

5. Do you get chest pain when you are resting? Yes No
   Comments: _______________________

6. Do you experience breathlessness when you are walking? Yes No
   Comments: _______________________

7. Have you ever fainted or experienced dizziness while exercising? Yes No
   Comments: _______________________

8. Do you have or have you ever had any of the following conditions?
   Angina Yes No
   Heart attack Yes No
   Heart surgery Yes No
   High blood pressure Yes No
   Asthma Yes No
   Emphysema Yes No
   Chronic Obstructive pulmonary disease Yes No
   Arthritis or joint pain Yes No
   Back pain Yes No
   Comments: _______________________

9. Do you take any medication? Yes No
10. Do you know of any reason why you should not partake in physical activity? Yes No

Comments:

Other comments:

Participant: 
Name ____________________________ 
Signature ____________________________ 
Date ________________

Researcher: 
Name ____________________________ 
Signature ____________________________ 
Date ________________

OUTCOME: 
INCLUDE EXCLUDE
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Dear Marie-Claire

Thank you for your request, you have the journal’s permission to do this. Please reference appropriately when doing so.

Kind regards

Leigh

LEIGH HALE • PROFESSOR AND DEAN
SCHOOL OF PHYSIOTHERAPY / TE KURA KOMIRI PAI • UNIVERSITY OF OTAGO
PO BOX 56, DUNEDIN 9054, NEW ZEALAND
T: 03 479 5425 | W: http://www.otago.ac.nz/physio
E: physio.dean@otago.ac.nz

Claire Angliss
Membership Administrator
Physiotherapy New Zealand
Tel: +64 4 801 6500
PO Box 27386, Wellington
Member website – pnz.org.nz
Public website – www.physiotherapy.org.nz

Marie-Claire Smith

I am seeking permission to re-use the following article published in the physiotherapy NZ journal in the literature review for my PhD thesis. I would like to abridge the article if possible, removing part of the introduction and part of the summary (which are not directly relevant to my thesis) rather than use the article in full.


Kind regards,

Marie-Claire Smith
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References


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