Neurophysiological and kinematic correlates of improved motor-function in complex therapy movements in chronic stroke

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Abstract

The most common outcome post-stroke is motor impairment which is typically assessed using clinical tools mainly based on categorical and subjective scoring. This thesis investigated longitudinal changes using quantitative measures of muscle activation and movement kinematics to understand therapy-induced improvements of motor-function in chronic stroke. Electromyography (EMG) and tri-axial accelerometry were recorded from 6 sensors on the more-affected upper body of 24 patients during early- and late-therapy of an intensive 14-day program of Wii-based Movement Therapy, and for a subset of 13 patients at 6-month follow-up. Patients were classified according to residual voluntary motor capacity with low, moderate or high motor-function. Clinical motor-function was assessed pre- and post-therapy and at follow-up. Neurophysiological parameters including EMG area under the curve and muscle synergies, and movement kinematics were measured to investigate the improved motor-function. Finally, the correlates and potential predictors of therapy-induced and longitudinal changes were investigated using a multivariate model. Clinical assessments showed improved motor-function and independence in everyday life over time. The pattern of EMG change by late-therapy was variable within and between classifications of motor-function. Muscle synergy analysis revealed fewer synergies for patients with low compared to those with high motor-function at early-therapy, with a pattern of increased synergies by late-therapy. Movement acceleration magnitude increased over time but was significant only at proximal sensors; there was an effect of motor-function on acceleration at distal sensors. The multivariate model demonstrated that depression scores could predict 31% of improved motor-function, while baseline muscle synergy counts predicted 33% of the increase in acceleration magnitude. Different patterns of EMG and kinematic changes were observed according to motor-function level despite heterogeneity within each level that was not evident with clinical assessments. The combination of EMG and kinematic changes suggest improved motor control which was reflected in significantly greater independence in everyday life. This thesis demonstrates that patients in chronic stroke have the capacity to improve, and that there is no one pattern of improvement. The different patterns of improvement can be revealed by quantitative neurophysiological and kinematic measures but not clinical tools. Pooling data may obscure the changes in chronic stroke.

Table of contents

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List of abbreviations

ADL	Activities of Daily Living
AIHW	Australian Institute of Health and Welfare
APOE	Apolipoprotein E
ARAT	Action Research Arm Test
BB	Biceps brachii
BBT	Box and Block Test
BDNF	Brain-derived neurotrophic factor
CIMT	Constraint-induced Movement Therapy
DM	Deltoid medius
ECR	Extensor carpi radialis
EMG	Electromyography
FCR	Flexor carpi radialis
FDI	First dorsal interosseous
FMA	Fugl-Meyer Assessment
MADRS	Montgomery-Åsberg Depression Rating Scale
MALQOM	Motor Activity Quality of Movement
MEP	Motor evoked potential
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NMF	Non-negative matrix factorisation
NSF	National Stroke Foundation
PCA	Principal Component Analysis
SD	Standard deviation
SE	Standard error
tDCS	Transcranial direct current stimulation
TIA	Transient ischaemic attack
TMS	Transcranial magnetic stimulation
rTMS	Repetitive transcranial magnetic stimulation
VAF	Variability accounted for
WMFT	Wolf Motor Function Test
WMT	Wii-based Movement Therapy

List of figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

List of tables

Chapter 2

Chapter 4

Chapter 5

Introduction

Chapter **1**

Stroke

A stroke occurs when the blood supply to brain is disrupted through either a blockage or rupture in a blood vessel (NSF, 2013). The interrupted delivery of oxygen and nutrition to the brain results in cell death and rapid impairment of neurological function (AIHW, 2016). Stroke is a heterogeneous disease; the disruption of brain function can be widely diverse depending on the severity and duration of the infarction or haemorrhage, and the size and location of the lesion (Flynn *et al.*, 2008). If post-stroke impairment persists for more than 24 hours (Sacco *et al.*, 2013) multiple domains may be affected that influence motor function, sensation, cognition, mood, and speech (Flynn *et al.*, 2008).

Incidence and prevalence

Globally, 16 million people have a stroke each year (Davis & Norrving, 2013). Stroke is a major cause of chronic disability worldwide (Sacco *et al.*, 2013); 50%-83% of stroke survivors live with persistent motor disability (Paul *et al.*, 2007). In Australia, over 420,000 survivors were living with the effects of stroke in 2012. Approximately, 65% of whom had substantial disability and needed assistance in activities of daily living (Deloitte, 2013). There was an estimated 34,300 new or recurrent strokes in Australia in 2013, almost 100 every day (AIHW, 2016).

Although the incidence of stroke is expected to rise with the aging population (Paul *et al.*, 2007; Davis & Norrving, 2013), recent incidence studies identified an emerging crisis in the increasing number of young adults (<65 years) affected by stroke (Feigin *et al.*, 2014). While age, gender and family history are non-modifiable risks of stroke; the biomedical and behavioural factors (AIHW, 2014) such as hypertension (Kannel, 1996), high blood cholesterol, obesity (O'Donnell *et al.*, 2010), physical inactivity (Do Lee *et al.*, 2003), smoking (Wolf *et al.*, 1988; Shinton & Beevers, 1989), excessive alcohol consumption (Reynolds *et al.*, 2003), poor diet, stress (O'Donnell *et al.*, 2010), and recreational drug use (Westover *et al.*, 2007) are modifiable and lifestyle-related.

Stroke subtypes

Ischaemic stroke

The most common type of stroke is caused by a blood vessel blockage (80%-85%) (Flynn *et al.*, 2008) and is known as ischaemic stroke. Ischaemic stroke can occur by one of two major mechanisms: 1) embolic stroke in which a blood clot formed elsewhere in the body travels via the bloodstream into the brain where it reduces or blocks blood flow; 2) thrombotic stroke when an artery supplying blood to brain is narrowed or blocked by a clot formed locally, such as that built up over time from cholesterol-laden 'plaques'.

Haemorrhagic stroke

The second main type of stroke is haemorrhagic (15%-20%) (Flynn *et al.*, 2008) and occurs when there is a bleeding in the brain. A haemorrhage can be caused by many factors including prolonged hypertension, cerebral aneurysm, and arteriovenous malformations; usually a congenital abnormality between the arterial and venous vascular beds. Haemorrhagic stroke is subdivided according to location in the brain as intracerebral haemorrhage, and subarachnoid haemorrhage which although not a true stroke, presents with similar signs, symptoms and requires similar treatment (Sacco *et al.*, 2013).

Silent stroke

Stroke survivors are at risk of "silent stroke" when small infarcts occur in the brain without obvious symptoms. There may be some evidence of impairment (Sacco *et al.*, 2013) and lesions which can be detected by neuroimaging (Deloitte, 2013).

Transient Ischaemic Attack (TIA)

Transient ischaemic attack (TIA) is a brief and transient episode of neurological dysfunction caused by an ischaemic blockage (Easton *et al.*, 2009) lasting less than 24 hours (Levy, 1988). This older definition is focused on duration and symptoms whereas the more recent definition is based on negative brain imaging (Easton *et al.*, 2009; Sacco *et al.*, 2013). Magnetic resonance imaging (MRI), in particular

diffusion-weighted MRI, provides new insight into TIA pathophysiology (Pavlovic *et al.*, 2010; Kvistad *et al.*, 2013; Brazzelli *et al.*, 2014). TIA is a high risk factor for subsequent stroke (Sacco, 2004).

Post-stroke outcomes

Stroke can affect multiple domains including motor ability, cognition, mood, sensation, speech, and vision (Flynn *et al.*, 2008; Brainin *et al.*, 2011). Fatigue, neuropathic pain, and increased risk of seizure, epilepsy, falls, and dementia (Flynn *et al.*, 2008) may also arise after stroke. However, the most common post-stroke outcome is motor impairment (Deloitte, 2013; Norrving & Kissela, 2013; Andrew *et al.*, 2014) which affects up to 83% of patients (Paul *et al.*, 2007).

Motor impairment

Many factors contribute to or influence motor impairment. The predominant manifestation of motor impairment is usually attributed to hemiparesis (Bourbonnais & Noven, 1989; Colebatch & Gandevia, 1989; Ada *et al.*, 1996), or muscle weakness on the side of the body contralateral to the stroke lesion. Because a number of corticomotor neurons project ipsilaterally (Graziadio *et al.*, 2012), there may be minor impairments on the side ipsilateral to the lesion (Colebatch & Gandevia, 1989). For this reason the contralesional side of the body will be referred to as the more-affected side and the ipsilesional as the less-affected side.

Hemiparesis may develop over months as a consequence of reduced corticospinal drive to muscles (Kamper *et al.*, 2006; Puig *et al.*, 2013) and may be aggravated by disuse muscle atrophy (Hafer-Macko *et al.*, 2008; Ramsay *et al.*, 2011). Peripheral changes including decreased motor unit numbers, loss of functioning motor units and changes to motor unit firing rates and recruitment patterns may compound the effects of hemiparesis (Lukacs *et al.*, 2008; Chou *et al.*, 2013; Mottram *et al.*, 2014). Motor impairment is also seen as abnormal voluntary motor control (Lukács, 2005; Mottram *et al.*, 2009), impaired muscle co-ordination (Clark *et al.*, 2010; Cheung *et al.*, 2012; Roh *et al.*, 2013), and spasticity (O'dwyer *et al.*, 1996; Ada *et al.*, 2006).

Motor impairment can be categorised as either positive or negative. Negative impairments are those that represent a loss, while positive impairments result in additional signs and symptoms (Ada *et al.*, 2006). The major contributors to physical disability after stroke are considered to be the negative signs and symptoms including the loss of dexterity (defined as loss of the ability to control the performance of motor tasks involving hand and fingers) and strength (seen as weakness) (Canning *et al.*, 2004). Abnormal postures, increased cutaneous and/or proprioceptive reflexes (hyperreflexia) are considered positive post-stroke impairments. Spasticity, a velocity-dependent increase in muscle tone is an example of hyperreflexia (Ada *et al.*, 2006).

The brain damage arising from stroke results in impairments that may resolve over time; consequently secondary impairments arise as adaptations to the primary impairments. Contracture is one such secondary impairment that occurs as a consequence of spasticity or weakness. Contracture occurs when the limb is maintained in a shortened position that alters the passive tension properties of the muscle resulting in decreased range of motion over time (Ada *et al.*, 2006; de Jong *et al.*, 2006; Dudek & Trudel, 2008; Smania *et al.*, 2010).

In summary, motor impairment can readily be seen as weakness, spasticity (O'dwyer *et al.*, 1996; Ada *et al.*, 2006), and abnormal muscle co-ordination (Clark *et al.*, 2010; Cheung *et al.*, 2012; Roh *et al.*, 2013). These can in turn affect range of motion, endpoint precision, velocity and movement trajectory (Knaut *et al.*, 2009). Multifactorial contributions to impaired upper-limb motor-function are more common than in the lower-limb (Song *et al.*, 2008; Lee *et al.*, 2011). Due to its impact on the degree of independence in activities of daily living (Uswatte *et al.*, 2005), it is critical to focus on upper-limb movement restoration during rehabilitation. This may be slower and more complicated than that of the lower-limb, given that upper-limb tasks are typically more complex involving more degrees of freedom across multi-joint movements (Levin *et al.*, 2009; Aprile *et al.*, 2014).

Level of motor impairment

Classification of stroke patients is important to ensure a balanced cohort in clinical studies; yet, there is no standard approach. Motor deficits have broadly been categorised as mild, moderate or severe in clinical reports mainly in acute phase of stroke. Commonly used tests including the Functional Independence Measure (Granger *et al.*, 1993), Barthel Index (Granger *et al.*, 1979), modified Rankin Scale (Sulter *et al.*, 1999), and National Institutes of Health Stroke Scale (Goldstein & Samsa, 1997) were designed for this purpose. None of these tests specifically quantify upper-limb motor disability. More specific methods such as Fugl-Meyer Assessment (FMA) (Fugl-Meyer *et al.*, 1974) and Wolf Motor Function Test (WMFT) (Wolf *et al.*, 2001) focused on upper-limb assessment but do not address all aspects of upper-limb movement or the spectrum of post-stroke residual voluntary motor capacity. The FMA is more sensitive for patients with lower motor-function but has a ceiling effect for patients with high motor-function whereby patients achieve the highest possible score and cannot show improvements using this assessment tool (Gladstone *et al.*, 2002). The WMFT is sensitive for patients with higher motor-function but cannot discriminate between patients with the lowest possible score and those unable to complete any task, i.e. demonstrating a floor effect (Morris *et al.*, 2001).

Thompson-Butel and colleagues (2014) developed a classification scheme for upper-limb motor-function in stroke patients using two tests of manual dexterity (Fig. 1-1). Gross and fine manual dexterity were assessed using the Box and Block Test (BBT) (Mathiowetz *et al.*, 1985b) and grooved pegboard test (Kløve, 1963), respectively. Patients unable to move >1 block in BBT were classified with low motor-function. Those able to move >1 block in BBT but unable to complete the pegboard test were classified with moderate motor-function and those able to complete the grooved pegboard test were classified with high motor-function (see Fig. 1-1). This simple, quick assessment was congruent with clinical observations (Thompson-Butel *et al.*, 2014).

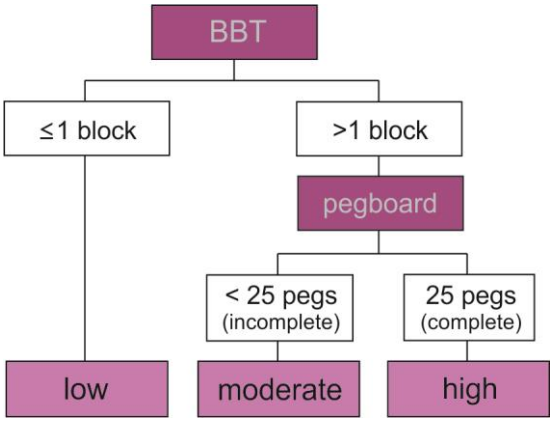

Figure 1-1. Stroke patient classification scheme, showing progression through testing (Thompson-Butel *et al.*, 2014).

Motor recovery

Post-stroke motor recovery occurs through a combination of natural recovery, neurological mechanisms, and compensation (Langhorne *et al.*, 2011; Buma *et al.*, 2013; Zeiler & Krakauer, 2013; Bernhardt *et al.*, 2017). These improvements are referred to as recovery but distinguishing the difference between them is important (Murphy & Corbett, 2009). Spontaneous or natural recovery occurs early after stroke and may occur without treatment. Natural recovery is seen when patients regain almost the same level of motor skill as pre-stroke and this may be referred to as true or neurological recovery. In contrast, neurophysiological recovery may include neuronal rewiring and the resolution of diaschisis (see below), while relearning alternative strategies to perform motor tasks is referred to as compensation (Levin *et al.*, 2009; Langhorne *et al.*, 2011; Buma *et al.*, 2013; Bernhardt *et al.*, 2017). In all types of recovery, patients are able to accomplish the motor task but the manner in which the task is performed may differ in terms of quality of movement (Buma *et al.*, 2013).

The mechanisms underlying true motor recovery and compensation are not well understood. In the following sections, two of the most important mechanisms that might impact on the recovery and development of compensatory strategies are addressed.

Diaschisis

Brain areas distant from the stroke lesion are affected and have an effect on motor deficit and recovery (Seitz *et al.*, 1999). The term diaschisis is used to describe the changes in remote brain areas induced by the removal of inputs that would otherwise originate from the area of the focal lesion (for review see (Andrews, 1991; Carrera & Tononi, 2014)). These changes might reduce metabolism, increase or decrease brain activation, cortical, or interhemispheric connectivity which are referred to respectively as diaschisis at rest, functional diaschisis, connectional diaschisis, and connectomal diaschisis (Carrera & Tononi, 2014).

Diaschisis is mainly associated with ischaemic stroke (Carrera & Tononi, 2014); although it has also been reported following haemorrhage stroke (Hausen *et al.*, 1997). The severity of post-stroke motor impairment may be affected by diaschisis which can also be a potential factor influencing the relationship between the lesion location and motor recovery (de Nap Shelton & Reding, 2001). The inhibitory or excitatory effect of diaschisis is related to the stroke lesion. It is important to distinguish the neurophysiological changes induced by diaschisis from those due to neuroplasticity (Carrera & Tononi, 2014). The resolution of diaschisis explains a proportion of natural recovery post-stroke (Carmichael *et al.*, 2004).

Neuroplasticity

Neuroplasticity describes the potential organisation and reorganisation of neural pathways in the brain during an individual's life (Alia *et al.*, 2017). All neural changes during aging, learning and adaptation can be attributed to brain plasticity. Moreover, it has been demonstrated that after an event of brain damage such as stroke, spontaneous reorganisation occurs within the penumbra of the stroke lesion, and this reorganisation is thought to be a response allowing adaption and compensation for the area of defect (Witte *et al.*, 2000). The term penumbra is used to describe the area of brain around the lesion in which the infarct damage is potentially reversible if sufficient blood flow is restored. However, the typical pattern is for the lesion to extend into the penumbra area over time (Dirnagl *et al.*, 1999).

The evidence for neuroplasticity favours compensation rather than true recovery which would only be possible by either full recovery or replacement of the infarcted neurons (Levin *et al.*, 2009). The capacity for neuroplasticity suggests that motor recovery can continue into the chronic phase by targeted therapies (Wolf *et al.*, 2006; Page *et al.*, 2008). However, this requires that post-stroke interventions involve purposeful, task-oriented, intense, and repetitive upper-limb movements to be effective (Jang *et al.*, 2003; Kleim & Jones, 2008).

Timeline of motor recovery

Almost all patients show some degree of neural repair (Langhorne *et al.*, 2011) in the first weeks after stroke onset and benefit from rehabilitative intervention in this period (Langhorne *et al.*, 2009; van Kordelaar *et al.*, 2013). It is thought that true recovery occurs only up to 4-10 weeks after stroke (Krakauer, 2006; Kwakkel *et al.*, 2006) or reaches a plateau over 3 (Stinear & Byblow, 2014) to 6 months (Krakauer, 2006) (see Fig. 1-2). It is commonly considered that learning-dependant mechanisms are operative in interact with therapeutic interventions only during the neurological recovery (Krakauer, 2006; Kwakkel & Kollen, 2013; Zeiler & Krakauer, 2013).

Figure 1-2. Pattern of post-stroke recovery, postulated by Langhorne and colleagues (2011).

While a great many researchers have focused on patients in the acute and subacute phases post-stroke and report that motor recovery reaches a plateau 3-6 months post-stroke, a comprehensive survey in Australia (Andrew *et al.*, 2014) studied the long-term unmet needs of community-dwelling stroke survivors. The results demonstrated that 89% of survivors received hospital care for 1-2 weeks (i.e. acute phase), one third of who were transferred to a rehabilitation facility for 3-4 more weeks (i.e. subacute phase). After this, access to facilities was not easy and dependent on non-standardised criteria. Nearly all (84%) participants had ongoing unmet needs, 82% of which were associated with movement ability and 79% with psychological wellbeing, multiple unmet needs were common. This study highlighted the substantial need for evidenced-based ongoing rehabilitation in chronic stroke.

The recent Stroke Recovery and Rehabilitation Roundtable agreed on a definition for acute, subacute, and chronic periods post-stroke (Bernhardt *et al.*, 2017). The period ≤ 24 hours from stroke onset has been classified as hyperacute stroke, and from 1-7 days as acute in which few trials have examined motor rehabilitation ((Stinear *et al.*, 2013); but see (Bernhardt *et al.*, 2015)). From the first week to 3 months post-stroke has been defined as early subacute and recognised as the crucial time to utilise neuroplasticity by targeted therapy. The period between 3 to 6 months has been termed late subacute, while >6 month is now referred to as the chronic phase. Unlike many previous studies (Stinear & Byblow, 2014; van Kordelaar *et al.*, 2014; Krakauer & Marshall, 2015), the Roundtable recognised the possibility of improvement during this period (Bernhardt *et al.*, 2017). Substantial improvements are possible in chronic stroke, but motor-function in this period requires intensive and targeted rehabilitation for continued improvements (Teasell *et al.*, 2014; McNulty *et al.*, 2015b; Ramos-Murguialday *et al.*, 2015).

Post-stroke therapy

With little efficient medical treatment for stroke after the first 48 hours (with the exception of specialist Stroke Unit care), the burden of care remains on therapeutic interventions (Langhorne *et al.*, 2009), particularly for chronic patients who are rarely

considered for ongoing rehabilitation. Rehabilitation after stroke is considered to be a learning-dependant process (Langhorne *et al.*, 2011). Post-stroke motor learning is task-specific and should be defined as the optimal selection of actions and improved execution of these actions to achieve a particular task (Zeiler & Krakauer, 2013).

With no rehabilitation, patients frequently stop using the more-affected side (Ding *et al.*, 2013; Rand *et al.*, 2014), especially in the upper limbs. This neglect of the impaired upper-limb is referred to as 'learned non-use' and arises as patients find it easier, quicker, more successful, and less frustrating to use the less-affected hand, further compounding the impairment of the more-affected limb (Taub, 1976). The potential to improve motor-function is significantly reduced due to learned non-use (Wu *et al.*, 2007a; Davis *et al.*, 2013) and the cortical area representing the more-affected upper-limb may be reduced (Ding *et al.*, 2013).

There is almost no standardised approach for post-stroke rehabilitative therapy. The most widely used standardised method for upper-limb rehabilitation is Constraint-induced Movement Therapy (Taub *et al.*, 2006a; Wolf *et al.*, 2008) but newer, more engaging modes include robotics therapy, virtual reality, and video games. In addition, non-invasive brain stimulation methods can be applied for therapeutic purposes. The most commonly reported methods of therapy are outlined below.

Non-invasive brain stimulation

Transcranial direct current stimulation (tDCS) is a non-invasive cortical stimulation method that has been used in stroke studies as a therapeutic intervention (for review see (Kang *et al.*, 2015)). There are three modes of tDCS used: anodal stimulation which typically increases cortical excitability, cathodal stimulation that typically decreases cortical excitability, and bihemispheric stimulation that has differential effects on both hemispheres. Although anodal, cathodal and bilateral stimulation can be effective, there is a paucity of supporting evidence as to which method is superior or for which patients (for review see (Marquez *et al.*, 2015)).

The effect of multiple sessions of stimulation in conjunction with conventional therapy has been evaluated in sham-controlled studies. Patients in the subacute phase who received cathodal tDCS showed significantly increased FMA scores compared to the sham group at 6-month follow-up (Kim *et al.*, 2010). In contrast, the improvement in clinical upper-limb and lower-limb motor-function after combined cathodal tDCS and conventional therapy was not superior to the sham condition in ischaemic subacute stroke at discharge, i.e. up to 3 months post-stroke (Fusco *et al.*, 2014). Similarly, anodal tDCS was safe but did not improve the clinical motor-function more than the sham group for patients with acute stroke (Rossi *et al.*, 2013). Bihemispheric tDCS in addition to standard physiotherapy improved motor-function in ischaemic chronic stroke compared to the sham group measured using the FMA at one week post-therapy (Lindenberg *et al.*, 2010). A time-dependent effect has been suggested whereby patients in the chronic phase and/or those with mild-to-moderate impairment may benefit more from tDCS (Marquez *et al.*, 2015).

Different methods of tDCS have been demonstrated to facilitate motor recovery and long-term motor learning (Schlaug *et al.*, 2008; Kang *et al.*, 2015). Although tDCS is easy to apply while the patient receives conventional therapy compared to other non-invasive methods of stimulation, it is limited by non-specificity of anatomical targets while the safety of prolonged periods of stimulation has not been fully demonstrated (Schlaug *et al.*, 2008). The optimal number and duration of tDCS sessions with maximal benefits needs further investigation (Marquez *et al.*, 2015). Finally, approximately 50% of people have limited or no response to tDCS (Wiethoff *et al.*, 2014), the reasons for which have not been fully elucidated. This is an important factor not always acknowledged, particularly when advocating the potential use of tDCS as a therapeutic tool.

The other important and well-known method of non-invasive brain stimulation is transcranial magnetic stimulation (TMS) which has been used with repetitive discharges as a rehabilitation tool, known as repetitive TMS (rTMS) (for review see (Lefaucheur, 2006; Le *et al.*, 2014)). Repetitive TMS has been applied to either ipsilesional and contralesional hemispheres to either increase (facilitate) or

decrease (inhibit) excitability, respectively. In acute ischaemic stroke, adjunct facilitatory rTMS with normal physical and drug therapies was applied over 10 consecutive days and identified as more effective in clinical motor-function outcomes than standard treatment alone (Khedr *et al.*, 2005). In chronic stroke, facilitatory rTMS improved motor learning of the more-affected hand (Kim *et al.*, 2006), while a single-session inhibitory rTMS had the same effect immediately after therapy but the response was diminished one week later (Takeuchi *et al.*, 2008). A 5-day course of inhibitory rTMS improved motor performance of the more-affected hand and this effect lasted for two weeks (Fregni *et al.*, 2006). Coupling bilateral inhibitory-facilitatory rTMS with an extended treatment timeframe showed more profound effects in motor performance than unilateral single-course rTMS in chronic stroke (Sung *et al.*, 2013).

Not all patients respond to rTMS, it has been shown that facilitatory rTMS improved movement kinematics of the more-affected hand in patients with subcortical stroke, but not those for whom the lesion extended into cortical areas. Some patients with a cortical lesion showed some deterioration in motor performance with facilitatory rTMS (Ameli *et al.*, 2009). Patients with aphasia improved less in motor-function from facilitatory rTMS compared to those with no aphasia (Lee *et al.*, 2015). However, since all patients with aphasia in Lee and colleagues (2015) study had subcortical and cortical stroke, it might emphasise the results of Ameli and colleagues (2009). It has been suggested that rTMS may be effective only for patients with exclusive subcortical stroke (Ameli *et al.*, 2009; Emara *et al.*, 2009), motor evoked potential response, or only mild motor impairment (Lee *et al.*, 2015).

Constraint-induced Movement Therapy

The primary objective of Constraint-induced Movement Therapy (CIMT) is to induce increased use of more-affected upper-limb (Taub *et al.*, 1998; Taub & Morris, 2001). CIMT is an intensive rehabilitation protocol initially implemented with patients in the subacute and chronic post-stroke period to overcome learned non-use (Wolf *et al.*, 1989; Taub *et al.*, 2006b). It involves restricting use of the less-affected arm for up to 90% of walking hours (other than for safety and water-related activities) each day for

2-3 weeks, in combination with task-specific training of the more-affected arm for 6 hours a day in one-on-one therapy (Taub *et al.*, 2002; Taub *et al.*, 2006a). The activities of CIMT are completed seated and include time trials of manipulating objects such as stacking cups and blocks, grasping and moving objects to increase either movement speed or the number of repetitions in a given time, and moving objects across progressively increasing distances (Wolf, 2007).

The largest multisite randomised controlled trial of CIMT was the Extremity Constraint Induced Therapy Evaluation (EXCITE) study which was designed to systematically test CIMT as a neurorehabilitation therapy for patients with mild to moderate impairment who were 3-9 months post-stroke. Two-hundred and twenty two patients were randomised to receive either CIMT or usual and customary care. CIMT demonstrated significant and substantial improvements in the more-affected arm motor-function that persisted for one (Wolf *et al.*, 2006) and two years (Wolf *et al.*, 2008) after the 2-week program. Wolf and colleagues (2010) compared the outcomes of CIMT delivered early, i.e. 3-9 months post-stroke, or late, 15-21 months post-stroke, and found similar outcomes in upper-limb motor-function after therapy.

Despite the proven success of this approach (Wolf *et al.*, 2006; Wolf *et al.*, 2008), it is often considered unacceptable by both patients and clinicians. The most common reasons are frustration, insufficient motivation, safety, and the additional disability imposed by restriction of the less-affected limb (Page *et al.*, 2002; Sterr *et al.*, 2006).

To address the concerns of patients and clinicians, CIMT is often modified by either reducing the intensity and duration of therapy, or reducing the restriction of the less-affected limb. For example, one model of modified CIMT (mCIMT) reduced the hours of clinical therapy to half an hour a day, three times a week for 10 weeks, while the less-affected arm and hand were constrained 5 days a week for 5 hours each day (Page *et al.*, 2001; Page *et al.*, 2004). mCIMT has been compared with time-matched exercise programs and no-therapy control groups in randomised controlled trials (Page *et al.*, 2004; Page *et al.*, 2008) and was shown to have

improvements in more-affected arm use and function of chronic patients that favoured mCIMT (for review see (Fleet *et al.*, 2014)).

A large number of studies (Lin *et al.*, 2007; Wu *et al.*, 2007a; Wu *et al.*, 2007b; Caimmi *et al.*, 2008; Corbetta *et al.*, 2015; Kwakkel *et al.*, 2015) have investigated the efficacy of different methods of CIMT using clinical motor-function measures and kinematic parameters (see the O*utcome Measures* section for details). One randomised controlled trial comparing CIMT with traditional therapy included a diverse range of patients from the acute to chronic phase of 3 weeks to 37 months (Wu *et al.*, 2007a). After therapy, the CIMT group showed more improvement in motor-function measures and better performance in reaching movement (measured as kinematic variables) compared to the control group. A recent review (Kwakkel *et al.*, 2015) stated that although the original and modified CIMT have long-term beneficial effects on motor-function, the type, timing and intensity of CIMT do not affect patient outcomes. Another recent review (Corbetta *et al.*, 2015, 2016) concluded that CIMT was associated with limited long-term motor-function effects.

CIMT is currently considered best practice for upper-limb rehabilitation in Australia (NSF, 2012) and the most effective approach for rehabilitation of upper-limb in chronic stroke. In contrast to the functional and clinical efficacy of CIMT, the compliance and acceptance of this therapy by patients and therapists is low (Ploughman & Corbett, 2004; Sterr *et al.*, 2006). In addition, the cost of ≤6 hours per day one-on-one therapy precludes implementation during times of health sector budget cuts (Secretariat & Ontario, 2011).

Robotic therapy

Robotic devices provide an alternative to CIMT and have often been used in upper-limb motor rehabilitation and to provide safe, intense, repetitive, task-specific and interactive therapy for stroke patients (Prange *et al.*, 2006; Brewer *et al.*, 2007). Robot-assisted therapy can now be more readily implemented independently by patients (Mehrholz *et al.*, 2012). It increases patients' motivation and compliance

(Kwakkel *et al.*, 2007) and also provides objective means to monitor their progress via the inbuilt sensors of the devices (Prange *et al.*, 2006).

A large study examined subacute and chronic patients receiving upper-limb robotic therapy (Dipietro *et al.*, 2012). Subacute patients completed standard inpatient therapy in addition to 18-session of 1-hour robotic therapy. Kinematic parameters were assessed for all patients during trained point-to-point and untrained circle drawing movements. While the pattern of changes with therapy was similar for trained and untrained movements, the chronic group indicated smaller changes in kinematic parameters compared to the subacute patients.

Despite several studies showing the effect of robot-assisted therapy on upper-limb motor-function (Lum *et al.*, 2002), skill improvement (Kitago *et al.*, 2015) and generic activities of daily living (Mehrholz *et al.*, 2012), no consistent influence on motor-function measures was found (Kitago *et al.*, 2015), particularly for patients with chronic stroke (Mehrholz *et al.*, 2015). It is unlikely that robotic therapy induced better results than dose-matched conventional therapy (Kwakkel *et al.*, 2007; Conroy *et al.*, 2011; Masiero *et al.*, 2014). A recent systematic review and meta-analysis stated that the effects of robotic therapy on motor control was specific to the targeted joints and there was no generalisation to the upper-limb capacity and activities of daily living (Veerbeek *et al.*, 2017).

There are some deficiencies with robotic systems: complicated devices with poor portability; and lack of precise real-time control of patient's joint angle and speed. Although robotic therapy increased patient motivation compared to CIMT, many training paradigms involve simplistic games that lack engagement. In addition to the comfort and safety of robotic systems, the biomechanics and human-computer interface of many systems need to improve (Maciejasz *et al.*, 2014; Zhang *et al.*, 2017).

Virtual reality

A novel approach in post-stroke interventions is virtual reality in which users interact with a multi-sensory simulated environment and receive immediate and continuous performance-related feedback (for review see (LeBlanc *et al.*, 2013; Laver *et al.*, 2015)). Both immersive (highest interaction) and non-immersive (least interaction) systems of virtual reality (LeBlanc *et al.*, 2013) have the ability to motivate patients and develop the motor skills using a range of task-based techniques (Mouawad *et al.*, 2011).

A number of trials have compared virtual reality training with conventional therapy for post-stroke rehabilitation. These studies have mostly assessed clinical motor-function measures (Piron *et al.*, 2009) and kinematics parameters (Kiper *et al.*, 2014). Turolla and colleagues (2013) recruited a large population (n=376) with mild to severe impairment from less than 3 months to more than a year post-stroke. They concluded that the combined non-immersive virtual reality and conventional therapy was more effective than conventional therapy alone. However, studies in chronic stroke have indicated that not all patients benefit from virtual reality interventions (Subramanian *et al.*, 2013; Kiper *et al.*, 2014). The evidence for the efficacy of virtual reality as a tool for post-stroke upper-limb rehabilitation and for long-term recovery is limited (for review see (Henderson *et al.*, 2007; Laver *et al.*, 2015)).

Virtual reality has the capacity and flexibility to improve as a post-stroke rehabilitation tool. However, further developments are needed to resolve ongoing issues and reduce the operational demands (Man, 2010). The customised programs and games of many virtual reality systems often require specialist operation staff and the learning of non-intuitive game structure and rules.

Video games

Commercial video games have largely overcome the poor portability of immersive virtual reality and robotic systems through engaging and motivational programs. Video games such as the EyeToy (Sony, Japan) (for review see (Taylor *et al.*, 2011)) and Kinect (Xbox, USA) (for review see (Webster & Celik, 2014)) have been

used as cost-effective and home-based alternatives to robotic and virtual reality in post-stroke rehabilitation. However, this type of intervention has not been standardised in terms of motor-function demands, intensity, progression, and modification.

The EyeToy gaming system was enjoyable, and sensitive to the differences in performance between healthy participants and those with stroke (Rand *et al.*, 2008). The EyeToy games for 30 minutes a day, 5 days a week for 4 weeks, combined with the conventional therapy for 2-5 hours a day, 5 days a week for 4 weeks, has the potential to improve upper-limb motor-function in patients with subacute stroke compared to the control group (Yavuzer *et al.*, 2008). The level of difficulty cannot be customised in the EyeToy games. Thus, its use is limited for stroke patients with severe impairment (Rand *et al.*, 2008). The Kinect system has been used in a randomised control trial for patients in chronic stroke with moderate to severe impairment (Sin & Lee, 2013). The patients in the experimental group received 30 minutes of conventional therapy in addition to Kinect games for 30 minutes 3 times a week for 6 weeks, compared to a conventional therapy alone control group. After 6 weeks both groups had significantly improved on the FMA and BBT, with significantly greater improvements for the Kinect group.

Nintendo Wii

One of the most commonly employed off-the-shelf video game systems used in post-stroke rehabilitation is the Wii (Nintendo, Japan). The interest and engagement in therapy promoted by this system provides a potentially motivational tool for rehabilitation (Lewis *et al.*, 2011). The Wii system was available in 73% of public and 92% of private hospitals in Australia (NSF, 2012), but there was little evidence of structured programs to optimise their use.

Previously, the Wii was used in unstructured upper-limb activities as part of a multi-disciplinary program for subacute patients with mild to moderate (Joo *et al.*, 2010; Saposnik *et al.*, 2010) or moderate to severe (Celinder & Peoples, 2012) impairment. The Wii was identified as a feasible adjunctive device to enhance the

traditional therapy for a cohort of subacute patients with moderate impairment (Joo *et al.*, 2010). However, some studies found no significant differences in clinical motor-function assessments between the game-based therapy using the Wii and conventional or recreational therapy in subacute patients with mild to moderate (Saposnik *et al.*, 2016) and moderate to severe (Choi *et al.*, 2014) impairment.

Later, studies used the Wii for patients with chronic stroke. A randomised controlled trial compared the Wii with dose-matched traditional therapy (one-hour session two times a week for 3 months) for patients in chronic phase with mild to severe impairment (Rand *et al.*, 2014). The results demonstrated higher repetitions of purposeful movements and higher movement acceleration using the Wii compared to traditional therapy. Another study with 16 sessions of Wii use for 15 minutes twice a week, showed significant improvements in fine and gross manual ability and activities of daily living from pre- to post-therapy for patients in chronic stroke with mild to moderate impairment (Paquin *et al.*, 2015).

Wii-based Movement Therapy

Wii-based Movement Therapy (WMT) uses the Wii and Wii-Sports games (Nintendo, Japan) of golf, baseball, bowling, tennis and boxing as a rehabilitation tool in a structured protocol that can be individually tailored to the level of motor-function and progress of each patient. WMT is a standardised 14-day program (Fig. 1-3) which primarily focuses on movement quality of the more-affected upper-limb and independent use of that limb in everyday activities (Mouawad et al., 2011; McNulty, 2012; McNulty et al., 2013a; McNulty et al., 2015b). It consists of 1-hour formal therapy sessions on 10 consecutive weekdays administered by an Accredited Exercise Physiologist and augmented by home practice starting with 15 min on day 2 and progressively increasing each day throughout the program to 180 min by day 14. This provides up to 22.5 hours of home practice in addition to 10 hours of supervised formal therapy. The content and duration of home practice were prescribed by the therapist in consultations with each patient based on individual needs, ability, and progress. All patients are encouraged to carry out their activities

of daily living with the more-affected side, when possible and even when the therapy period is over.

The movements required in Wii-Sports are modified according to the capacity, range of motion, strength and needs of each patient. Patients use only the more-affected upper-limb during therapy activities. When unavoidable, assistance is provided either with the less-affected hand or by the therapist. Clinical motor-function assessments are measured immediately before and after therapy, while neurophysiological measures are recorded at early- (day 2-3) and late- (between days 12-14) therapy. Game performance is also recorded during formal sessions but the scores are used only for motivational purposes and are not the focus of therapy.

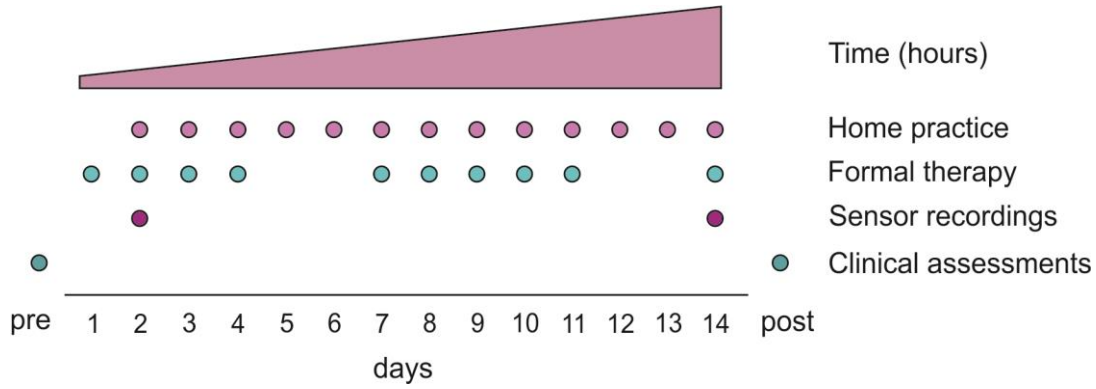

Figure 1-3. Schematic of the standardised 14-day program of Wii-based Movement Therapy. There is homework but no formal therapy on weekends. A single rest day is provided between the end of therapy and the post-therapy clinical assessments.

WMT has only been implemented in chronic stroke. This therapy was as effective as dose-matched mCIMT, demonstrated in a randomised controlled trial (McNulty et al., 2015b). There was no difference between WMT and mCIMT in motor-function improvements assessed by clinical tests, suggesting that dose-matched WMT was as effective on every measure as the current best-practice therapy, mCIMT. Patients reported high self-perceived improvement and satisfaction scores, increased independence, and improved mood in both groups, but lifestyle outcomes at 6-months were better after WMT than mCIMT. Home practice and compliance were also monitored. The average scheduled home practice was 19.8 hours for WMT and 19.9 hours for mCIMT; with a compliance median of 105.7% (range 93.6-114.7%)

for WMT and 101.0% (range 87.6-108.1%) for mCIMT (McNulty et al., 2015b). This suggests that most patients performed more home practice than was required.

The clinical assessment tools used to quantify the efficacy of WMT (such as the WMFT, FMA, and BBT) contain items that are unrelated to the content of therapy, which was not the case for CIMT and most other upper-limb therapies (McNulty et al., 2015b). As described previously, CIMT activities include stacking objects, moving objects across the workspace, and manipulating objects while patients are seated and using only the more-affected upper-limb (Trinh *et al.*, 2016a). In contrast, WMT is undertaken standing unless patients are unable to stand or remain standing due to insufficient strength, balance or lower-limb function (Trinh et al., 2016b). The movements in WMT replicate the real-world movements of the Wii-sports played, ranging from small and well-controlled golf putts to large and powerful tennis forehand swings (Thompson-Butel et al., 2013). In addition, WMT improves motor ability even in patients with very low motor-function as the therapy can be readily tailored for patients with minimal voluntary movement post-stroke (McNulty *et al.*, 2013a). Cardiovascular fitness (Trinh *et al.*, 2016a) and lower-limb symmetry (Trinh *et al.*, 2016b) were ancillary improvements during WMT trials despite the focus of this therapy on the upper-limb quality of movement.

Unlike other Wii studies, WMT uses rehabilitation principles in a structured way to promote motivation and feedback, rather than simply allowing patients to play the games. It is a targeted therapy focusing on the more-affected upper-limb in an engaging environment where patients report that the hard work of therapy is no longer a chore (McNulty *et al.*, 2013a). WMT trials were the first to use the Wii as a rehabilitation tool in chronic stroke and showed that the Wii-Sports can facilitate repetitive purposeful movements and improve motor-function (Mouawad *et al.*, 2011; McNulty, 2012).

Outcome measures

The outcomes after stroke are heterogeneous both in severity and the number of physiological systems that are affected. Although the focus of this thesis is motor

impairment, it is well known that impairment in other domains such as sensation (Bowden *et al.*, 2014a; Meyer *et al.*, 2014), mood (Srivastava *et al.*, 2010; Matsuzaki *et al.*, 2015) and cognition (Mullick *et al.*, 2015) impact movement ability and the capacity for improvement. The manner in which stroke outcomes are assessed varies according to the setting, facilities, and training of health professionals (Luker *et al.*, 2017). Most clinical assessment tools rely on categorical and/or subjective scoring. Chapters 2-4 specifically address the need for more objective and quantitative measures which are crucial when investigating the mechanisms of post-stroke impairment and suggesting an optimal therapeutic approach.

Demographic characteristics

Patient demographics may affect the level of motor impairment and recovery; these may include age, sex, time post-stroke, stroke subtype (ischaemic/haemorrhagic), and whether the more-affected side was the pre-stroke dominant side. Age has a small but significant effect on motor-function outcome; although, advanced age had no effect on changes in motor-function (Bagg *et al.*, 2002). Sex-dependent differences in brain excitability have been demonstrated to exist in the acute phase of stroke. Males had higher excitability in the contralesional hemisphere and higher inter-hemispheric asymmetry than females (Di Lazzaro *et al.*, 2016). Time post-stroke is commonly thought to influence motor recovery (see *Timeline of motor recovery s*ection). Patients with haemorrhagic stroke generally have lower motor-function compared to those with ischaemic stroke (Katrak *et al.*, 2009; Persson *et al.*, 2016). However, they had greater motor improvement with therapy measured using the clinical tools from 1 to 3 months (Persson *et al.*, 2016) and faster improvements in independence in activities of daily living from 12 to 26 weeks post-stroke (Schepers *et al.*, 2008). Motor recovery of the more-affected upper-limb may be determined by the dominance of the affected hemisphere (but see (Bajaj *et al.*, 2016)). While the more-affected dominant side had poorer recovery, rTMS improved the dexterity of more-affected dominant hand but not for the patients with non-dominant hemisphere (Lüdemann-Podubecká *et al.*, 2015).

Brain imaging and non-invasive stimulation

Brain imaging via MRI (Chalela *et al.*, 2007), diffusion-weighted MRI (Makin *et al.*, 2015), and computed tomography have been used to diagnose and identify the location and extent of the stroke lesion. Functional brain imaging including functional MRI (Askim *et al.*, 2009), positron-emission tomography (Sahathevan *et al.*, 2016), and electromagnetic tomography (Semenov *et al.*, 2015) are effective tools to map brain regions and visualise activated areas during motor tasks. Non-invasive brain stimulation methods have been used to understand motor recovery mechanisms including TMS (McDonnell & Stinear, 2017) and tDCS (Schlaug *et al.*, 2008). These tools have also been used in therapeutic protocols to target motor-function (see *Post-stroke therapy* section). These tools provide detailed information but are expensive, and have strict screening criteria that exclude many patients in research studies. Despite this, the presence or absence of a motor evoked potential (MEP) in forearm muscles in response to TMS is commonly used as a predictor of recovery in subacute stroke (Stinear *et al.*, 2012; Boyd *et al.*, 2017) (see *Multimodal assessment* section).

Genotype

There are many genetic factors that might be related to post-stroke motor outcomes, recovery and response to therapy (Cramer, 2008; Juth *et al.*, 2016). The absence or presence of two common genetic polymorphisms: the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and the *apolipoprotein E* (APOE) ε4 allele have been investigated in stroke genetics studies (Kim *et al.*, 2016; Shiner *et al.*, 2016). There is evidence that these polymorphisms are related to neuroplasticity and neural repair, and might affect patient responsiveness to therapy (Stewart & Cramer, 2017). BDNF Val66Met was related to motor learning and the severity of impairment in the acute phase after stroke (McHughen *et al.*, 2009) with an interaction between motor-function and response to therapy in the chronic phase, with reduced improvement for carriers with moderate and high motor-function and greater improvement for carriers with low motor-function (Shiner *et al.*, 2016). The APOE-ε4 allele is less common but is thought to contribute to motor outcome variability, while its presence was associated with poorer recovery in acute stroke

(Cramer & Procaccio, 2012). The study by Shiner and colleagues (2016) considered the BDNF Val66Met and APOE-ε4 alleles in the same cohort of patients and reported that both carriers and non-carriers of BDNF-Val66Met and APOE-ε4 retained the capacity for improved motor-function with intensive and targeted Wii-based Movement Therapy.

Cognition

Cognitive impairment is an important consequence of stroke, with a prevalence between 20%-80% (for review see (Sun *et al.*, 2014)). The prevalence varies with differences in age, ethnicity, and socioeconomic status (Douiri *et al.*, 2013). Impaired cognition has an impact on upper-limb motor recovery (Mullick *et al.*, 2015), and as a consequence, on stroke survivors' independence and quality of life (Cumming *et al.*, 2014). There is evidence that increased physical activity after stroke enhances cognition (Cumming *et al.*, 2012). The Mini Mental State Examination (MMSE) (Tombaugh & McIntyre, 1992) is commonly used to assess the cognitive deficit in stroke patients, in which scores ≥24 (from a maximum of 30) define cognitive competency in research studies. Another commonly used scale for cognition is Montreal Cognitive Assessment which is more sensitive but less specific than MMSE (Cumming *et al.*, 2013). MMSE was used in this thesis as a pre-screening tool to exclude patients with cognitive impairment during recruitment to therapy studies.

Mood status

Mood changes after stroke can be related to lesion factors including size and location (Mitchell *et al.*, 2017) and motor impairment (Parikh *et al.*, 1987; Karakus *et al.*, 2017). Major or minor depression is very common in acute stroke and continues into the chronic phase. The prevalence of any form of depression has been reported at 33.5% in a recent meta-analysis of patients from 2 days to 7 years post-stroke (Mitchell *et al.*, 2017), similar to previous studies (Hackett *et al.*, 2005; Srivastava *et al.*, 2010). Time post-stroke has been both implicated (Aström *et al.*, 1993) and refuted (Mitchell *et al.*, 2017) as a risk factor for post-stroke mood disorders. It has been suggested that early-onset depression is related to motor disability in acute

(Karakus *et al.*, 2017), but not chronic (Srivastava *et al.*, 2010) stroke. The persistence of a relationship between motor impairment and depression might reflect the effect of depression in sustaining or slowing down motor recovery (Parikh *et al.*, 1987; Srivastava *et al.*, 2010). In this thesis, the severity of depression was assessed using Montgomery-Åsberg Depression Rating Scale (MADRS) which is a ten-item questionnaire with scores ranging from 0 to 60 in which 0-6 is considered not depressed, 7-18 as mild, 19-34 as moderate, and ≥35 as severe depression (Müller *et al.*, 2000). There are other screening scales for post-stroke depression including the Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale, 9-item patient health questionnaire, and 15-item Geriatric Depression Scale. For screening depression, MADRS is slightly better than HADS (Sagen *et al.*, 2009) but generally there are no substantial differences in screening abilities between all these scales (Kang *et al.*, 2013). Self-reporting questionnaire tools suffer from similar problems in which patients with mild cognitive impairment and/or those with language impairments (either expressive or receptive) are not able to fully comprehend the questions and/or appropriately express their desired answers (van Dijk *et al.*, 2016).

Clinical motor-function measures

Clinical motor rehabilitation studies typically rely on standardised clinical assessment tools. Such scales are commonly based on task completion with limited assessment of movement quality (Aprile *et al.*, 2014) both after stroke and with rehabilitation. Even when scores of movement quality are included (for example in WMFT Functional Ability Scale (Wolf *et al.*, 2001)), scoring usually requires qualitative, subjective and categorical methods (de los Reyes-Guzmán *et al.*, 2014). This may increase the incidence of ceiling and floor effects (Thompson-Butel *et al.*, 2015).

Commonly used upper-limb outcome measures in post-stroke studies include the WMFT, the upper-limb motor section of the FMA, Action Research Arm Test (ARAT), BBT, grooved pegboard test, and Motor Activity Log (MAL) particularly the Quality of Movement scale (MALQOM). The WMFT (Wolf *et al.*, 2001) quantifies

upper-limb motor ability using timed functional tasks and two strength-based tasks. It is unusual in that the timed-tasks are scored purely on the amount of time taken to complete each task. The 15 tasks become progressively more complex and functional as the test progresses and each task has a maximum possible time of 120 s. The WMFT has a recognised floor effect for patients with low motor-function but provides a sensitive tool for patients with moderate and high motor-function (Thompson-Butel *et al.*, 2015). The motor FMA (Fugl-Meyer *et al.*, 1974) measures motor ability, active range-of-motion and the ability to move in and out of synergy. It is scored using a 3-point categorical score from 0 to 2. The items were initially ordered to reflect the order of recovered function post-stroke (Fugl-Meyer *et al.*, 1974). The ARAT (Van der Lee *et al.*, 2001) measures the ability to handle objects of different sizes, weights and shapes over different distances. The BBT (Mathiowetz *et al.*, 1985b) is a measure of unilateral gross manual dexterity, while the grooved pegboard (Kløve, 1963) assesses fine manual dexterity. The MALQOM scale (Uswatte *et al.*, 2005) is a self-reported questionnaire which assesses independence of the more-affected arm in 30 common daily activities.

Few traditional clinical assessments quantify how well a task is performed using objective and continuous measures. Changes in movement characteristics, muscle activation and muscle co-ordination can be better discriminated via objective and quantitative methods. Quantitative measures of movement quality are essential for assessing therapy-induced changes and neurorehabilitation outcomes after stroke to help understanding the underlying mechanisms (de los Reyes-Guzmán *et al.*, 2014). More objective and quantitative measures are possible through the examination of electromyography, muscle activation patterns and movement kinematics. However, when these tools are implemented, most upper-limb studies investigate simple tracking tasks (Hughes *et al.*, 2010; Song & Tong, 2013; Sin *et al.*, 2014) or reaching movements (Lum *et al.*, 2004; Silva *et al.*, 2014; van Kordelaar *et al.*, 2014) that are constrained in time and space.

Muscle activation parameters

Post-stroke muscle weakness (Bourbonnais & Noven, 1989; Ada *et al.*, 1996) is a consequence of many factors including reduced corticospinal drive (Werring *et al.*, 2000), disuse muscle atrophy (Hafer-Macko *et al.*, 2008; Ramsay *et al.*, 2011), and spasticity (O'dwyer *et al.*, 1996; Ryu *et al.*, 2015). These factors, either in isolation or combination, result in abnormal muscle activation during voluntary movements (Dewald *et al.*, 1995; Canning *et al.*, 2000; Ramos-Murguialday *et al.*, 2015).

Surface electromyography (EMG) can be used to identify impaired muscle activation such as tonic muscle activity in which ongoing muscle activity is unrelated to the motor task (McNulty *et al.*, 2014); profuse single motor unit activity that becomes compound muscle activity with improved motor-function (Li *et al.*, 2015); and abnormal co-contraction (Hughes *et al.*, 2010; Silva *et al.*, 2014). Post-stroke upper-limb EMG is commonly recorded during simple stereotypical tasks (Castilho *et al.*, 2012; Sin *et al.*, 2014), reaching (Lum *et al.*, 2004; Cesqui *et al.*, 2013), gripping (Lee *et al.*, 2011), and tracking (Hughes *et al.*, 2010; Song & Tong, 2013) movements while fully supported or restricted in two-dimensional planes of movement.

Muscle activation patterns are typically compared either with control groups, or from pre- to post-intervention performance. Many EMG studies focus on parameters including movement time, EMG peak amplitude, co-activation between muscles, maximum voluntary contraction (MVC), and total EMG activity (Wagner *et al.*, 2007; Hughes *et al.*, 2010; Silva *et al.*, 2014; Sin *et al.*, 2014). Differences in the muscle onset time and relative activation (%MVC) during a reaching task was found between acute stroke patients and a healthy control group (Wagner *et al.*, 2007). Improvements were observed from the acute to the subacute phase. The timing and amplitude of peak EMG from different upper-limb muscles during multiple tracking tasks also varied between patients in chronic stroke and healthy subjects (Hughes *et al.*, 2010). Comparing pre- to post-intervention EMG showed changes towards healthy patterns in patients with chronic stroke, while the co-activation between

biceps and triceps decreased after therapy. Increased co-activation between muscle pairs is evident in stroke (Hughes *et al.*, 2010; Silva *et al.*, 2014).

The relation between weakness, spasticity, and force variability for patients in chronic stroke demonstrated that voluntary force control is impaired by muscle weakness but not spasticity during submaximal isometric force (Chang *et al.*, 2013). This confirms previous reports of abnormal EMG-force relationship after stroke (Tang & Rymer, 1981; Zhou *et al.*, 2013) and suggests post-stroke therapy should target muscle strength on the more-affected side.

Patients with chronic stroke may retain some residual corticomuscular drive that enables the activation of any voluntary muscle capacity. The contribution of each muscle in simple movements was identified based on test items in the FMA scale (Ramos-Murguialday *et al.*, 2015). The level of residual voluntary muscle activation can be measured in rehabilitative studies as an indicator of improved muscle activity.

Although EMG from individual muscles can elucidate the effects of altered net synaptic drive (the sum of all neural inputs to the muscle), it cannot address the changes from single motor unit activity to compound motor unit activity (McNulty *et al.*, 2014), changes in phenotype (Scherbakov *et al.*, 2013), or those arising from disuse atrophy (Triandafilou & Kamper, 2012). To provide some insight into the complex co-ordination of multiple muscles that is required to generate a purposeful movement, muscle synergies can be investigated (Hesam-Shariati *et al.*, 2017b).

Muscle synergies

Fine motor control of the upper-limb is achieved through the co-ordinated activation of groups of muscles, known as "muscle synergies". Muscle synergies have been extracted from EMG recordings in animals (Tresch *et al.*, 1999; Cheung *et al.*, 2005; Torres-Oviedo *et al.*, 2006; Chvatal *et al.*, 2013), and in humans defining a wide range of movements including gait (Clark *et al.*, 2010; Coscia *et al.*, 2015), arm

movements (Cheung *et al.*, 2012; d'Avella & Lacquaniti, 2013) and isometric force production (Roh *et al.*, 2012; Borzelli *et al.*, 2013).

Muscle synergy analysis can detect post-stroke abnormalities in the number, structure and recruitment profile of muscle synergies. Muscle synergies have been investigated in acute, subacute (Hidler *et al.*, 2007; Gizzi *et al.*, 2011; Tropea *et al.*, 2013) and chronic stroke (Dipietro *et al.*, 2007; Clark *et al.*, 2010; Cheung *et al.*, 2012) showing abnormalities compared to healthy people (Roh *et al.*, 2013; Coscia *et al.*, 2015; Li *et al.*, 2016). In contrast, few studies have examined the changes in post-stroke muscle synergies with rehabilitation (but see (Tropea *et al.*, 2013)). Muscle synergy analysis can be used as a neurophysiological indicator to distinguish the level of impairment and the effect of therapy on co-ordinated muscle activation. It cannot be used to investigate recovery mechanisms occurring within the brain (Casadio *et al.*, 2013).

Multiple factorisation methods have been used to identify muscle synergies. Principal component analysis (PCA), factor analysis (FA), independent component analysis (ICA), and non-negative matrix factorisation (NMF) are the most commonly used. Each of these algorithms has specific and different assumptions the activation co-efficient and the noise in the data. PCA and FA assume the distribution of activation/noise as Gaussian and ICA as non-Gaussian (Attias, 2000; Hyvärinen & Oja, 2000), while NMF has no explicit assumption on distribution, only the non-negativity of the muscle activations (Donoho & Stodden, 2004). To achieve this muscle activation is root mean square processed using a defined sliding window to become non-negative. PCA, ICA and NMF assume that the variance of the noise approaches zero, only FA assumes that the data has non-zero noise. Overall, NMF has a relatively robust performance compared to other methods. This robustness is a result of the non-negativity condition. Tresch and colleagues (2006) evaluated a number of factorisation algorithms and concluded that these algorithms determine co-ordinated muscle activation in similar ways. The consistency between the muscle synergies extracted using PCA, ICA and NMF methods demonstrated that these algorithms detect the basic characteristics of muscle activation patterns.

Kinematic parameters

Three-dimensional kinematics, including acceleration, velocity, and displacement, can quantify and define movement in space and time without reference to the forces involved (Aprile *et al.*, 2014). Post-stroke upper-limb kinematics have been measured to quantify important characteristics of movement, including smoothness, duration, displacement, speed and acceleration. This type of analysis has been used to evaluate performance in tracking or pointing movements (Knaut *et al.*, 2009; Kitago *et al.*, 2012), reach-and-grasp tasks (Caimmi *et al.*, 2008; Lum *et al.*, 2009), and activities of daily living (Alt Murphy *et al.*, 2011; Aprile *et al.*, 2014; Kim *et al.*, 2014; Bailey *et al.*, 2015). Moreover, the movements studied have predominantly been experimentally-restricted, rather than goal-oriented tasks reflecting real-world situations (for review see (Alt Murphy & Häger, 2015)).

Many movements are composed of sub-movements, smooth movements are those with continuous and closely linked sub-movements (Balasubramanian *et al.*, 2012). Movement smoothness is a characteristic of post-stroke motor recovery (Bosecker *et al.*, 2010; Dipietro *et al.*, 2012), motor learning (Franklin *et al.*, 2008), and spatiotemporal co-ordination (Balasubramanian *et al.*, 2015). The analysis of movement smoothness requires robust dimensionless measures (Rohrer *et al.*, 2002; Balasubramanian *et al.*, 2012). Different measures have been proposed to quantify smoothness, including normalised jerk (Rohrer *et al.*, 2002; van Kordelaar *et al.*, 2014), velocity peak count (Rohrer *et al.*, 2002; Cirstea *et al.*, 2003; Dipietro *et al.*, 2012), and sub-movement count (Cirstea *et al.*, 2003; Kitago *et al.*, 2012; Aprile *et al.*, 2014). Jerk-based measures appear most frequently in the literature as the dimensionless measure of normalised jerk (for review see (Balasubramanian *et al.*, 2015)).

The technology of wearable, sensor-based devices is a rapidly developing field. Hybrid body-worn sensors have the ability to record surface EMG and accelerometry concurrently. These sensors have been used to identify tremor and dyskinesia in patients with Parkinson's disease (Roy *et al.*, 2013; Cole *et al.*, 2014),

and to monitor stroke patients with mild to moderate impairment (Roy *et al.*, 2009) during activities of daily living (ADL). The EMG and tri-axial accelerometry data used in this thesis were recorded from the same sensors during the WMT program (see Chapters 2-5). The newer versions of these sensors include gyroscope and magnetometer, in addition to accelerometer which enable the reconstruction of movement trajectories, and the more accurate quantification of displacement and velocity (Howard *et al.*, 2016).

Multimodal assessments

Stroke outcomes are complex and heterogeneous which result in substantial variability in recovery patterns and response to therapy. Inter-patient variation after stroke complicates the classification of patients (Cramer, 2010), prediction of recovery, and as a consequence, the development of assessment and rehabilitation methods (Stinear, 2010; Burke & Cramer, 2013).

The severity of the initial motor deficit has been negatively related to the reduction of motor impairment over time (Stinear, 2010; Zarahn *et al.*, 2011). However, the inter-patient variability makes the prediction of motor outcomes and recovery difficult (Kwakkel & Kollen, 2007). Most often, the motor impairment in the acute and early subacute stroke has been used to predict the motor recovery in late subacute and chronic phase (Beebe & Lang, 2009; Groisser *et al.*, 2014; Stinear *et al.*, 2014; Byblow *et al.*, 2015). Many studies have included acute patients with mild to moderate upper-limb deficits and showed that the motor recovery can be predicted by clinical measures such as FMA (Feys *et al.*, 2000; Prabhakaran *et al.*, 2008; Winters *et al.*, 2015). The shoulder abduction-finger extension score (more commonly referred to as the SAFE score) was used to suggest a proportional recovery after stroke. Yet, this method was not readily able to predict the motor recovery of patients with severe impairment (Prabhakaran *et al.*, 2008; Zarahn *et al.*, 2011). Thus, clinical measures alone are not able to predict motor recovery for all patients (Byblow *et al.*, 2015). The functional integrity of the ipsilesional corticomotor tract might help the prediction of upper-limb motor recovery for patients with severe impairment (Stinear *et al.*, 2014). A recent systematic review specifically included

patients with severe impairment (mostly >6 months post-stroke) to investigate brain biomarkers (Hayward *et al.*, 2017). In this review, the presence of an MEP was identified as the only predictor associated with motor outcome measured by upper-limb motor FMA.

The impact of age (Bagg *et al.*, 2002), stroke subtype (Burke Quinlan *et al.*, 2015), genotypes (Cramer & Procaccio, 2012), neural function (Burke Quinlan *et al.*, 2015), brain injury (Groisser *et al.*, 2014), cognitive status (Burke *et al.*, 2014), active range of motion (Beebe & Lang, 2009) and neurophysiology (Byblow *et al.*, 2015) have been investigated to predict motor recovery although the best approach remains unknown. Thus, a multimodal model that includes multiple measures using a variety of modes has the potential to advance our understanding of the variability of motor recovery and identify the most critical measures (Stinear *et al.*, 2012; Burke Quinlan *et al.*, 2015).

A multimodal algorithm was suggested by Stinear and colleagues (Stinear *et al.*, 2012; Stinear *et al.*, 2014) to predict the potential for upper-limb motor recovery by 3 months post-stroke. The PREP algorithm is a sequential combination of a clinical assessment, neurophysiological and neuroimaging measures. Shoulder abduction and finger extension strength are assessed on a 10 point scale within 3 days of the infarct. Patients with a score ≥8 are classified with the potential to recover almost completely, while those scoring <8 progress to TMS over the primary motor cortex within 7 days. If the MEP response to TMS, is present in the wrist extensor muscles, the patient is classified with the potential for a notable recovery; if not, diffusion-weighted MRI on or before day 14 post-infarct is used to assess damage to corticospinal tract, the primary corticomuscular pathway. In this test the posterior limb of the internal capsule in both hemispheres is compared. Patients with an asymmetry index <0.15 are classified as limited potential and those with >0.15 index are described as “beyond the point of no return” with no potential for upper-limb recovery.

Two more recent multimodal studies have focused on patients 3 to 6 months post-stroke with moderate to severe impairment. The best predictors of poorer motor outcome was identified to be lower corticospinal tract integrity and the absence of a motor response to TMS, known as MEP (Burke *et al.*, 2014), while smaller corticospinal tract injury combined with greater functional connectivity were best predictors of therapy-induced improvements (Burke Quinlan *et al.*, 2015).

In the recent Stroke Recovery and Rehabilitation Roundtable, the biomarkers and predictors of motor outcome and recovery were reviewed (Boyd *et al.*, 2017). They reported that in the acute phase of stroke the following corticospinal tract measures were identified as predictors of motor outcome: the extent of injury, white matter integrity, and tract fibre numbers. In the chronic phase the asymmetry index between the ipsilesional and contralesional tracts, and the extent of corticospinal tract had the ability to predict therapy-induced motor recovery while the presence of an MEP in response to TMS in the acute phase predicted a good motor outcome. Patients who had an MEP were more likely to follow the proportional recovery rule (Prabhakaran *et al.*, 2008) and benefit from physical therapy.

A previous preliminary analysis in chronic stroke from our group demonstrated that the absence of an MEP is correlated with poorer motor-function at baseline but with greater therapy gains. These results suggested that baseline impairment does not predict therapy-induced motor recovery and that patients with low motor-function can improve with therapy (Shiner, 2015).

Conclusion

The studies in this thesis were designed to investigate the hypothesis that there is no one pattern of improvement across the chronic stroke population. Furthermore, these studies investigated whether neurophysiological and kinematic data would reveal more subtle details of changes than can be detected using clinical assessment tools alone.

Summary of chapters

In the studies of this thesis, motor-function was measured using WMFT-timed tasks (WMFT-tt), upper-limb motor FMA, MALQOM, BBT and grooved pegboard test, while the modified Ashworth Scale was used to assess muscle resistance to passive movement (Lee *et al.*, 1989) as it is frequently used clinically as a surrogate test of spasticity despite containing no velocity-dependent component (Fleuren *et al.*, 2010). In addition, the motor control and neurophysiological mechanisms responsible for the improved motor-function were investigated using muscle activation and muscle synergies (from EMG recordings), and kinematics aspects of movement (from tri-axial accelerometry data). Finally, a multimodal assessment was performed to investigate the relationship between these different measures and whether the improvements could be predicted by patient characteristics and baseline measures.

When these studies were planned and implemented there were no standardised terms to describe time periods post-stroke. Thus, patients were recruited who were ≥3 months post-stroke as at the time this was considered to be chronic stroke. The recent Stroke Recovery and Rehabilitation Roundtable has now defined these periods as: 1-7 days, acute; 7 days-3 months, early subacute; 3-6 months, late subacute; and >6 months, chronic (Bernhardt *et al.*, 2017). The same group of 24 patients was used in each study of this thesis (Chapters 2-5). Twenty-one of these patients would now be classified with chronic stroke (i.e. >6 months post-stroke) while the remaining 3 would be classified as late sub-acute. Two of these patients (one with moderate motor-function at 5 months post-stroke, and one with high motor-function at 3 months post-stroke) were tested using the FMA, WMFT-tt and MALQOM two weeks prior to baseline testing and were found to have stable motor-function prior to WMT (McNulty *et al.*, 2015b). The third patient was 6 months post-stroke with high motor-function and presumably had similarly stable motor-function.

Chapter 2 aimed to examine changes in muscle activation as a consequence of a 14-day program of Wii-based Movement Therapy to investigate the mechanisms underlying therapy-induced motor improvements. Muscle activation was measured

during therapy sessions via body-worn EMG sensors. The stability of motor-function improvements and changes in EMG during therapy was assessed via a longitudinal comparison to 6-month follow-up. The hypothesis tested was that there would be distinct patterns of change in EMG, and that these would correlate with the level of residual voluntary motor-function. EMG area under the curve was measured as the product of movement duration and EMG amplitude during largely unconstraint movements of Wii-golf putting, Wii-baseball swing, and Wii-tennis forehand and backhand to provide quantitative measures of therapy outcomes in chronic stroke.

Chapter 3 aimed to extract muscle synergies from the EMG recordings used in Chapter 2 during the complex movement of a Wii-baseball swing to investigate changes in the number of synergies used, and the timing profile and muscle weight structure of those synergies. The hypotheses tested was that there would be distinct differences in muscle synergy counts between patients with low, moderate and high motor-function, and that synergy counts would change with therapy. Muscle synergies were extracted from EMG signals of the Wii-baseball swing using the NMF algorithm. NMF is a robust optimisation method which has commonly been used to quantify muscle synergies in stroke patients (Clark *et al.*, 2010; Frère & Hug, 2012; Roh *et al.*, 2012; Chiovetto *et al.*, 2013). Muscle synergy counts were determined based on higher values of the variable *variability accounted for* while minimising the mean square error.

Chapter 4 investigated kinematic measures to assess therapy-induced and longitudinal changes while patients with chronic stroke completed the complex movement of a Wii-baseball swing. The data were recorded concurrently with the EMG used in Chapters 2 and 3. Kinematic parameters were derived from tri-axial accelerometry data to examine the mechanisms underlying the improvements in motor-function with Wii-based Movement Therapy measured using clinical assessment tools. The hypotheses were that there would be improvements from early- to late-therapy in kinematic parameters and that these would be sustained at 6-month follow-up; the secondary hypothesis was that correlations would be found between the improvement in clinical assessments and changes in kinematic

parameters during therapy. The mean values for acceleration magnitude, normalised velocity, normalised jerk, and peak acceleration and deceleration (for 3 axes) were measured to provide objective and quantitative measures.

Chapter 5 aimed to investigate if patient characteristics and baseline measures could predict therapy-induced and longitudinal improvements in both motor-function and acceleration magnitude in chronic stroke. Potential relationships between patient characteristics and baseline motor-function and acceleration were also investigated. The hypothesis was that baseline clinical motor-function measures and the level of residual voluntary motor-function could predict the magnitude of therapy-induced and longitudinal changes.

Heterogeneous changes in muscle activation despite consistent improvements in clinical assessments

Chapter **2**

Abstract

Post-stroke weakness on the more-affected side may arise from reduced corticospinal drive, disuse muscle atrophy, spasticity, and abnormal co-ordination. This study investigated changes in muscle activation patterns to understand therapy-induced improvements in motor-function in chronic stroke compared to clinical assessments, and to identify the effect of motor-function level on muscle activation changes.

Electromyography (EMG) was recorded from 5 upper-limb muscles on the more-affected side of 24 patients during early- and late-therapy sessions of an intensive 14-day program of Wii-based Movement Therapy, and for a subset of 13 patients at 6-month follow-up. Patients were classified according to residual voluntary motor capacity with low, moderate or high motor-function. The area under the curve was calculated from EMG amplitude and movement duration. Clinical assessments of upper-limb motor-function pre- and post-therapy included the Wolf Motor Function Test, Fugl-Meyer Assessment and Motor Activity Log Quality of Movement scale.

Clinical assessments improved over time ($p<0.01$) with an effect of motor-function level ($p<0.001$). The pattern of EMG change by late-therapy was complex and variable, with differences between patients with low compared to moderate or high motor-function. The area under the curve ($p=0.028$) and peak amplitude ($p=0.043$) during Wii-tennis backhand increased for patients with low motor-function whereas EMG decreased for patients with moderate and high motor-function. The reductions included: movement duration during Wii-golf ($p=0.048$, moderate; $p=0.026$, high), and Wii-tennis backhand ($p=0.046$, moderate; $p=0.023$, high) and forehand ($p=0.009$, high); and the area under the curve during Wii-golf ($p=0.018$, moderate) and Wii-baseball ($p=0.036$, moderate). For the pooled data over time there was an effect of motor-function ($p=0.016$) and an interaction between time and motor-function ($p=0.009$) for Wii-golf movement duration. Wii-baseball movement duration decreased as a function of time ($p=0.022$). There was an effect on Wii-tennis forehand duration for time ($p=0.002$), an interaction of time and motor-function ($p=0.005$), and an effect of motor-function level on the area under the curve ($p=0.034$) for Wii-golf.

This study demonstrated different patterns of EMG changes according to residual voluntary motor-function levels despite heterogeneity within each level that was not evident following clinical assessments alone. Thus, rehabilitation efficacy might be underestimated by analyses of pooled data.

Introduction

Motor impairment is the most common outcome after stroke (Langhorne *et al.*, 2009; Deloitte, 2013; Norrving & Kissela, 2013; Andrew *et al.*, 2014) and is predominately attributed to muscle weakness (Bourbonnais & Noven, 1989; Ada *et al.*, 1996; Canning *et al.*, 2004) as a consequence of reduced corticospinal drive (Werring *et al.*, 2000), disuse muscle atrophy (Hafer-Macko *et al.*, 2008; Ramsay *et al.*, 2011), impaired voluntary control of muscles (Lukács, 2005; Mottram *et al.*, 2009), spasticity (O'dwyer *et al.*, 1996; Ada *et al.*, 2006; Brainin, 2013; Ryu *et al.*, 2015) and impaired muscle coordination (Clark *et al.*, 2010; Cheung *et al.*, 2012; Roh *et al.*, 2015). These factors, either in isolation or combination, result in abnormal muscle activation during voluntary movements (Dewald *et al.*, 1995; Canning *et al.*, 2000; Ramos-Murguialday *et al.*, 2015). Multifactorial contributions to impaired upper-limb motor-function are more common than in the lower-limb (Song *et al.*, 2008; Lee *et al.*, 2011) and a more important focus for improving independence in activities of daily living (Uswatte *et al.*, 2005; Trinh *et al.*, 2016b). Post-stroke upper-limb recovery may be slower and more complicated than that of the lower-limb, given that upper-limb tasks are typically more complex involving more degrees of freedom in multi-joint movements (Levin *et al.*, 2009; Aprile *et al.*, 2014).

Recovery after stroke is a complex combination of spontaneous neurological mechanisms and relearning processes (Levin *et al.*, 2009; Langhorne *et al.*, 2011; Buma *et al.*, 2013). It is commonly thought that learning-dependant mechanisms are only operative during natural recovery and interact with therapeutic interventions (Krakauer, 2006; Kwakkel & Kollen, 2013). Furthermore, true recovery is thought to be complete between 4-10 weeks post-stroke (Krakauer, 2006; Kwakkel *et al.*, 2006) or reaches a plateau over 6 months (Krakauer, 2006; Langhorne *et al.*, 2011; Kwakkel & Kollen, 2013; van Kordelaar *et al.*, 2014). It has been speculated that any improvement in the chronic period is not true improvement but rather a restitution of therapy gains made earlier and lost over time (Stinear, 2016). Despite this, significant improvements are possible in chronic stroke, but motor-function in this

period needs intensive rehabilitation for continued improvements (Andrew *et al.*, 2014; Teasell *et al.*, 2014; Ramos-Murguialday *et al.*, 2015).

Clinical motor assessment both after stroke and with rehabilitation is traditionally based on task completion with limited assessment of movement quality (Fugl-Meyer *et al.*, 1974; Mathiowetz *et al.*, 1985a; Wolf *et al.*, 1989; Uswatte *et al.*, 2005). Most assessments are qualitative with subjective and categorical scoring, and many suffer from ceiling and floor effects (Thompson-Butel *et al.*, 2015). To provide more objective and quantitative measures, recent studies have examined muscle activation and joint kinematics to evaluate post-stroke motor outcomes; yet most upper-limb studies consist of simple tracking tasks (Hughes *et al.*, 2010; Song & Tong, 2013; Sin *et al.*, 2014) or reaching movements (Lum *et al.*, 2004; Aprile *et al.*, 2014; Silva *et al.*, 2014; van Kordelaar *et al.*, 2014) constrained in time and space.

In this study electromyography (EMG) analysis was used in addition to clinical assessments to provide quantitative measures of outcomes with therapy in chronic stroke. The aim of this study was to examine changes in muscle activation (EMG) with an intensive 14-day program of Wii-based Movement Therapy (WMT) to investigate the mechanisms underlying therapy-induced motor improvements. WMT is the equivalent of current best practice in upper-limb stroke rehabilitation, Constraint-induced Movement Therapy (McNulty *et al.*, 2015b). The stability of motor-function improvements and changes in EMG during therapy was assessed via a longitudinal comparison to 6-month follow-up. We hypothesised there would be distinct patterns of change in EMG and that these would vary according to the level of residual voluntary motor capacity, and correlate with improvements in motor-function quantified using clinical assessments.

Methods

Participants

The data from thirty patients with chronic stroke (i.e. ≥ 3 months post-stroke) were included in this study from those previously recorded from patients consecutively recruited from St Vincent's and Prince of Wales Hospitals, Sydney for concurrent

studies of WMT (Fig. 2-1). The level of residual voluntary motor-function was classified pre-therapy for each patient as low, moderate or high based on performance of the Box and Block Test of gross manual dexterity and the grooved pegboard test of fine manual dexterity; patients unable to move >1 block in Box and Block Test were classified with low motor-function, those able to move >1 block but unable to complete the pegboard test were classified with moderate motor-function, and those who could complete the pegboard test were classified with high motor-function (Thompson-Butel *et al.*, 2014). Thirteen patients were classified with low, 9 with moderate, and 8 with high motor-function. To ensure balanced groups, the data for all 8 patients with high motor-function were included, and data for 8 patients were randomly selected using a computer-generated algorithm from each group of patients with low and moderate motor-function. The data analysis reported here has not been published previously although the clinical assessment data for all patients have been. Twenty patients were included in other WMT trials investigating cardiovascular fitness (Trinh *et al.*, 2016a), lower limb symmetry (Trinh *et al.*, 2016b), and motor-function measures (Thompson-Butel *et al.*, 2015); 9 in a randomised-controlled trial comparing WMT and modified Constraint-induced Movement Therapy (McNulty *et al.*, 2015b); and 20 were also included in a genotype study (Shiner *et al.*, 2016). The inclusion criteria for this study were: unilateral stroke with a contralesional upper-limb deficit; ≥3 months post-stroke; English communication; ≥10˚ of voluntary movement in at least one digit of the more-affected hand; age ≥18; medically stable; carer available during home practice; and cognitive competency measured as a Mini-Mental State Examination score ≥24. Exclusion criteria included: co-morbidities significantly affecting upper-limb sensorimotor function; unstable blood pressure; frail skin that prevented sensor placement and adhesion during recordings; and concurrent formal upper-limb therapy. Demographics and baseline characteristics are shown in Table 2-1. All patients gave signed informed consent to the studies which were approved by St Vincent's Hospital Human Research Ethics Committee, Sydney and conducted in accordance with the Declaration of Helsinki. All patients were enrolled in a standardised 14-day program of WMT. No attempt was made to control for activities after this period and prior to the 6-month follow-up, although suggestions were made

to each patient on how they might best maintain therapy-induced gains. A follow-up session was conducted for all available patients, i.e. a subset of 13 patients at 6-months post-therapy (3 low, 5 moderate, and 5 high motor-function). As stated in Figure 2-1, ten patients were unavailable, one returned to work, 4 had moved interstate or overseas, 2 had unrelated health problems, 3 insufficient time for neurophysiological recordings, and the data for one patient was lost due to technical issues.

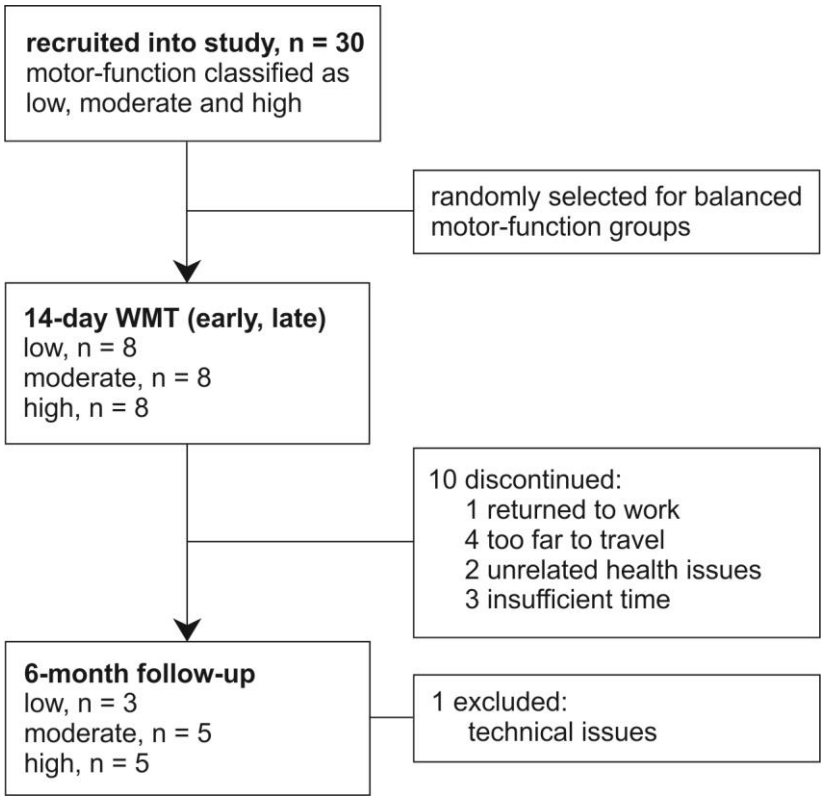

Figure 2-1. Flow of patients in this thesis. Patients were recruited for concurrent studies of Wii-based Movement Therapy.

Table 2-1. Baseline patient characteristics. Age is reported as mean±SD, remaining data are reported as mean±SE. More-affected dominant indicates that the more-affected side is the dominant side. Isch, ischaemic; haem, haemorrhage; WMFT-tt, mean time for the Wolf Motor Function-timed tasks where a lower time indicates better motor-function; FMA, upper-limb motor Fugl-Meyer Assessment; MALQOM, Motor Activity Log Quality of Movement scale.

	Low	**Moderate**	**High**	**all**	range
N	8	8	8	24	
Age	59.1±13.9	55.1±11.3	59.4±12.2	57.9±12.1	37-80
Sex (f/m)	4/4	2/6	2/6	8/16	
More-affected dominant (y/n)	1/7	3/5	3/5	7/17	
Stroke type (isch/haem)	3/5	7/1	6/2	16/8	
Time post-stroke (months)	33.3±9.4	27.3±8.0	19.6±4.5	26.7±4.3	3-88
Baseline WMFT-tt (/120 s)	81.6±6.9	26.5±10.4	6.3±2.6	38.1±7.8	
Baseline FMA (/66)	25.0±3.4	53.1±3.0	61.6±1.5	46.6±3.6	
Baseline MALQOM (/150)	18.9±5.8	60.0±9.0	101.5±11.7	60.1±8.7	

Therapy

The standardised 14-day WMT program targeted movement quality of the more-affected arm, and independence in everyday activities (Mouawad *et al.*, 2011; McNulty *et al.*, 2015b). Therapy consists of 1-hour formal sessions with an Accredited Exercise Physiologist on 10 consecutive weekdays with increasing prescribed home practice starting on day 2 (see Fig. 1-3). WMT uses the Nintendo Wii and Wii-Sports games (Nintendo, Japan) of golf, baseball, bowling, tennis and boxing as a rehabilitation tool in a structured protocol that can be individually tailored to the level of motor-function and progress of each patient (Thompson-Butel *et al.*, 2013; McNulty *et al.*, 2015b). Patients used only the more-affected upper-limb during therapy activities. When unavoidable, assistance was provided either with the less-affected hand or by the therapist. Game performance was recorded during formal sessions but the scores were used only for motivational purposes and were not the focus of therapy.

EMG recording

Surface EMG data were recorded during formal WMT sessions at two time-points *during* therapy, i.e. at early- (day 2-3) and late- (between days 12-14) therapy; and

for a subset of patients at 6-month follow-up. The EMG was not recorded on day one to avoid overwhelming patients as they became familiar with the therapy, the device and the therapist. Recordings were made using wireless telemetry sensors (Trigno, Delsys, USA) placed on the following muscles of the more-affected upper-limb: deltoid medius, biceps brachii, flexor carpi radialis (FCR), extensor carpi radialis (ECR), and first dorsal interosseus (FDI). Each sensor employs 4 silver bar electrodes in 2 pairs with an interelectrode pair distance of 10 mm. Each sensor is optimised for detecting the maximum EMG signal in an orientation perpendicular to the muscle fibres. The small inter-electrode distance helps to minimise crosstalk from adjacent muscles. EMG signals were filtered between 20-450 Hz, amplified 300 times and sampled at 2 kHz at the source in EMGworks (Delsys, USA) and then analysed using custom scripts in Spike2 software (CED, UK).

To maximise consistency across patients and sessions, the sensors were placed on the most prominent portion of the muscle belly based on manual palpation during a weak voluntary contraction. Each recording session was preceded by a calibration sequence that consisted of three conditions each held for at least 3 s with the limb segment: 1) supported at rest, 2) unsupported against gravity, and 3) unsupported with the addition of a 1 kg weight placed across the distal joint (Thompson-Butel *et al.*, 2013).

Primary outcome measures

EMG data were analysed for movement duration, averaged peak amplitude and the area under the curve for stereotypical movements of each activity using custom scripts in Spike2 software (CED, UK). Movement duration, peak amplitude and area under the curve were averaged for 10 consecutive swings of Wii-golf, -baseball, -tennis forehand and -tennis backhand of each patient at early- and late-therapy and for a subset of patients at 6-month follow-up. Wii-tennis forehand and backhand swings were analysed separately due to the need for distinctly different movement patterns. Wii-bowling data were not analysed as patients with low motor-function could not co-ordinate the necessary button press, and the speed of Wii-boxing movements particularly for patients with high motor-function, was too fast to enable

unambiguous movement identification. Therapy was completed standing for all patients except one (moderate) during Wii-tennis at early-therapy due to fatigue.

Secondary outcome measures

Upper-limb motor-function was assessed using the Wolf Motor Function Test-timed tasks (WMFT-tt) (Wolf *et al.*, 1989) and the upper-limb motor Fugl-Meyer Assessment (FMA) (Fugl-Meyer *et al.*, 1974). The Motor Activity Log Quality of Movement scale (MALQOM) (Uswatte *et al.*, 2005) was used to assess the independence in activities of daily life. Additionally, the modified Ashworth Scale (Lee *et al.*, 1989) was used as a clinical measure of muscle resistance at the shoulder, elbow (Bohannon & Smith, 1987), and wrist (Bodin & Morris, 1991). These clinical tests were measured for all patients immediately pre- (baseline) and post-therapy and for a subset of 13 patients at 6-month follow-up. The clinical assessments were unrelated to the content of therapy.

Although the primary goal of therapy was quality of movement and not game performance; the scores of Wii-golf, -baseball and -tennis games were recorded during therapy. In Wii-golf, the aim was to successfully land the ball in the hole and each success was noted, while Wii-baseball and -tennis swings were scored when the ball was hit, regardless of whether the hit was successful or not according to the rules of each game.

Data analysis

Data analysis for this study was conducted by an independent assessor who was not involved in clinical assessments or therapy delivery. We have used the terms early-therapy and late-therapy to refer to EMG data recorded during formal therapy sessions, and pre- and post-therapy to refer to assessments made using clinical tools prior to and following the therapy protocol.

The EMG data were detrended (DC removed) and root mean square (RMS) processed using a sliding 50 ms window. The mean baseline EMG was measured over 2-3 s prior to the commencement of each activity at rest and then subtracted

from the EMG signal. High definition video recordings were used to match the EMG signal to therapy movements. Due to the heterogeneous patterns of motor control and impairment between patients and sports, EMG analysis was targeted to the dominant EMG signal for each patient. Proximal muscles (deltoid medius/biceps brachii) were primarily analysed. However if proximal muscles were silent or tonically active with no phasic activity, and clear task related activity was evident in a distal muscle (FDI, ECR or FCR), the distal muscle was used. For example, proximal muscle signals were analysed in Wii-golf and -tennis except for three and two patients, respectively. In Wii-baseball, the distal muscle signals were more distinct compared to proximal muscles in most patients. For consistency, distal muscle signals were analysed in Wii-baseball where possible. The same muscle was analysed for each patient at each time-point.

To identify the onset and offset of therapy movements, a threshold level was set at 5 standard deviations above the mean baseline EMG for each activity of each patient. The movement duration was measured as the interval between the onset and offset of movement; the peak amplitude of each movement was averaged over a 50 ms interval around the absolute peak EMG; and the area under the curve was defined as the area above the baseline level between the onset and offset of the RMS-processed EMG. Both peak amplitude and area under the curve were normalised to the *weighted* condition of the calibration sequence to enable comparison between patients.

Statistical analysis

Data were compared for each motor-function group (low, moderate, high) from early- to late-therapy (EMG analysis), or pre- to post-therapy (clinical measures) using paired t-test for normally distributed data, and reported as mean and standard error (SE); otherwise using Wilcoxon signed-rank test, reported as median and interquartile range (IQR).

Longitudinal data were analysed using mixed models of repeated measures with factors of motor-function (low, moderate, high) and time (pre-therapy/early-therapy,

post-therapy/late-therapy, 6-month follow-up). Linear mixed models provide unbiased estimates for the missing data (Ashbeck & Bell, 2016) at 6-month follow-up and are more powerful and flexible (Krueger & Tian, 2004; Bernal-Rusiel *et al.*, 2013) than repeated measures ANOVA in the presence of multiple missing data points because of the emphasis on the pattern of change rather than the quantitative difference (Krueger & Tian, 2004).

The relationship between the change in area under the curve and clinical assessments was investigated using Spearman's rank-order correlation with Bonferroni corrections for multiple comparisons. Statistical analyses were conducted in SPSS 23 software (IBM, USA), and differences were considered significant when $p<0.05$.

Results

All patients completed all formal therapy sessions, home practice and clinical assessments, ten were unavailable for 6-month follow-up (Fig. 2-1). Data are reported at early- and late-therapy for Wii-golf putting (n = 23), -baseball swing (n = 24) and -tennis forehand and backhand (n = 23). The same activities at follow-up are reported for 12, 13, and 12 patients, respectively. Data could not be analysed during therapy for Wii-golf for one patient (with moderate motor-function) due to tonic muscle activity, and during Wii-tennis for another patient (low motor-function) with limited shoulder movement that prevented this activity. No adverse events were reported, either minor or major.

Changes in EMG as a consequence of therapy (early- to late-therapy)

Changes in the area under the curve, movement duration and peak amplitude of muscle activation from early- to late-therapy for different Wii-activities are shown in Table 2-2 and illustrated in Figure 2-2. For Wii-golf putting, the movement duration decreased significantly for patients with moderate ($p=0.048$) and high motor-function ($p=0.026$); area under the curve was also reduced for patients with moderate motor-function ($p=0.018$). The movement duration of Wii-baseball swings showed a trend towards decreasing for patients with low motor-function ($p=0.050$), while there was a

reduction in the area under the curve for the patients with moderate motor-function (p=0.036). The movement duration of Wii-tennis forehand (p=0.009) and backhand (p=0.023) decreased for patients with high motor-function by late-therapy. Moreover, the movement duration of Wii-tennis backhand decreased (p=0.046) for patients with moderate motor-function. The area under the curve (p=0.028) and peak amplitude (p=0.043) increased for patients with low motor-function during backhand swings, while the area under the curve (p=0.050) showed a reduction trend for patients with high motor-function.

Changes in EMG over time (early-therapy, late-therapy, and follow-up)

Linear mixed models demonstrated an effect of motor-function during Wii-golf (p=0.009) and an interaction between time and motor-function (p=0.016) for movement duration. Wii-baseball movement duration changed as a function of time (p=0.022). Wii-tennis forehand swing movement duration demonstrated an effect of time (p=0.002) and an interaction of time and motor-function (p=0.005). In addition, the pattern of change for Wii-tennis backhand movement duration over time showed a non-significant trend (p=0.059). For Wii-golf area under the curve there was an effect of the level of motor-function (p=0.034), with a non-significant trend for an interaction between time and motor-function (p=0.072). Finally, there was a non-significant trend for the effect of time on Wii-baseball area under the curve (p=0.070).

Table 2-2. Therapy-induced EMG changes from early- to late-therapy for patients with low, moderate and high motor-function. EMG area under the curve and peak amplitude are reported as median, IQR, and movement duration as mean±SE. Significant Changes are highlighted in bold, and trends in italics. Mod: moderate; early: early-therapy; late: late-therapy.

	Low early	**Low late**	***p***	**Mod early**	**Mod late**	***p***	**High early**	**High late**	***p***
Wii-golf putting	**n = 8**	**n = 8**		**n = 7**	**n = 7**		**n = 8**	**n = 8**	
Area under the curve (mV.s/mV)	2.2 (1.8-5.0)	3.3 (2.0-7.3)	0.401	2.4 (1.8-7.0)	1.7 (0.6-2.0)	**0.018**	2.1 (1.3-3.1)	1.5 (1.0-1.9)	0.161
Movement duration (s)	3.32±0.39	3.83±1.02	0.600	3.08±0.47	2.18±0.47	**0.048**	2.23±0.26	1.89±0.19	**0.026**
Peak amplitude (mV/mV)	1.5 (1.2-3.9)	2.0 (1.2-7.1)	0.674	1.8 (1.3-3.6)	2.0 (1.3-2.2)	0.612	2.3 (1.3-3.1)	1.7 (1.3-2.7)	0.327
Wii-baseball swing	**n = 8**	**n = 8**		**n = 8**	**n = 8**		**n = 8**	**n = 8**	
Area under the curve (mV.s/mV)	1.4 (1.3-1.8)	1.4 (1.3-1.7)	1.000	3.1 (1.3-8.9)	1.8 (0.9-3.3)	**0.036**	1.9 (0.8-4.8)	2.1 (0.5-4.2)	0.123
Movement duration (s)	0.8 (0.6-1.1)	0.7 (0.6-0.8)	*0.050*	1.31±0.26	1.01±0.17	*0.095*	0.75±0.15	0.73±0.11	0.662
Peak amplitude (mV/mV)	1.5 (1.4-1.5)	1.4 (1.3-1.5)	0.263	6.2 (1.9-12.4)	4.8 (2.2-12.2)	0.575	5.5 (3.6-15.6)	5.7 (2.2-12.4)	0.123
Wii-tennis forehand	**n = 7**	**n = 7**		**n = 8**	**n = 8**		**n = 8**	**n = 8**	
Area under the curve (mV.s/mV)	2.7 (2.2-3.6)	3.9 (2.5-5.0)	*0.091*	2.6 (1.9-4.2)	3.5 (2.1-5.1)	*0.093*	2.1 (1.5-3.8)	2.0 (1.3-3.0)	0.123
Movement duration (s)	1.81±0.25	1.90±0.34	0.869	1.85±0.18	1.94±0.20	0.682	2.03±0.23	1.55±0.20	**0.009**
Peak amplitude (mV/mV)	3.9 (2.3-5.4)	4.1 (3.0-6.6)	0.128	2.5 (1.7-4.5)	4.2 (2.9-9.2)	*0.093*	2.7 (2.1-5.8)	3.0 (1.7-7.2)	0.401
Wii-tennis backhand	**n = 7**	**n = 7**		**n = 8**	**n = 8**		**n = 8**	**n = 8**	
Area under the curve (mV.s/mV)	1.7 (1.4-3.1)	3.3 (2.3-5.2)	**0.028**	3.3 (1.8-5.4)	3.4 (1.5-5.7)	0.575	3.3 (2.2-6.1)	2.6 (2.1-3.8)	*0.050*
Movement duration (s)	1.54±0.25	1.65±0.19	0.862	1.87±0.15	1.64±0.09	**0.046**	1.76±0.13	1.48±0.15	**0.023**
Peak amplitude (mV/mV)	2.6 (1.7-5.3)	4.3 (2.7-7.1)	**0.043**	3.7 (3.0-5.4)	5.3 (4.0-10.1)	*0.069*	4.5 (4.0-13.2)	4.9 (3.4-5.7)	0.123

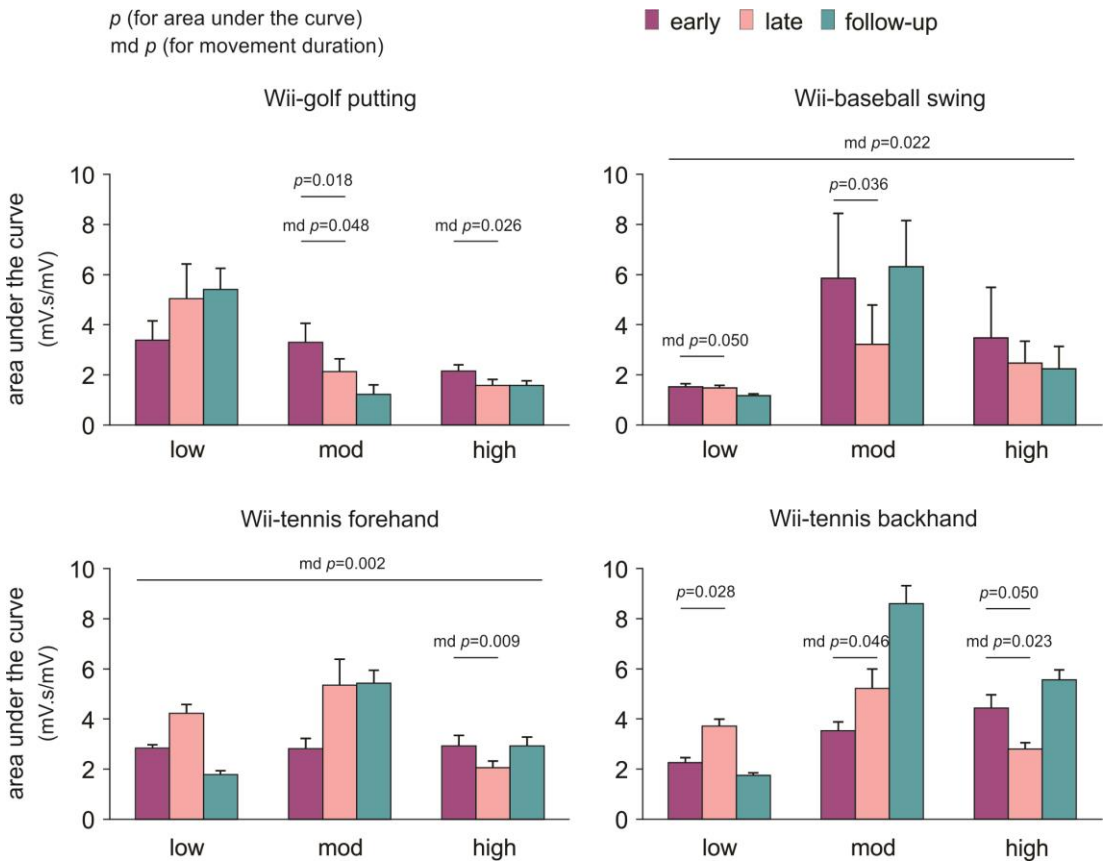

Figure 2-2. Changes in EMG over time, pooled data across levels of motor-function. Changes are presented as mean±SE for the area under the curve according to the level of post-stroke motor-function. Significant changes in movement duration (md) are also indicated.

Changes in clinical assessments with therapy (pre- to post-therapy)

Clinical assessment data showed improvements from pre- to post-therapy for the pooled data (n=24) for WMFT-tt (p=0.004), FMA (p=0.001) and MALQOM (p<0.001). There were no changes in Ashworth scores at wrist (p=0.355), elbow (p=0.796), or shoulder (p=0.592) at post-therapy. The detailed results for each level of motor-function are presented in Figure 2-3.

Changes in clinical assessments over time

(pre-therapy, post-therapy, and follow-up)

Linear mixed models demonstrated improvement over time for WMFT-tt (p=0.008), FMA (p=0.001) and MALQOM (p<0.001). There was an effect of the level of motor-function for the WMFT-tt, FMA and MALQOM (p<0.001 for all).

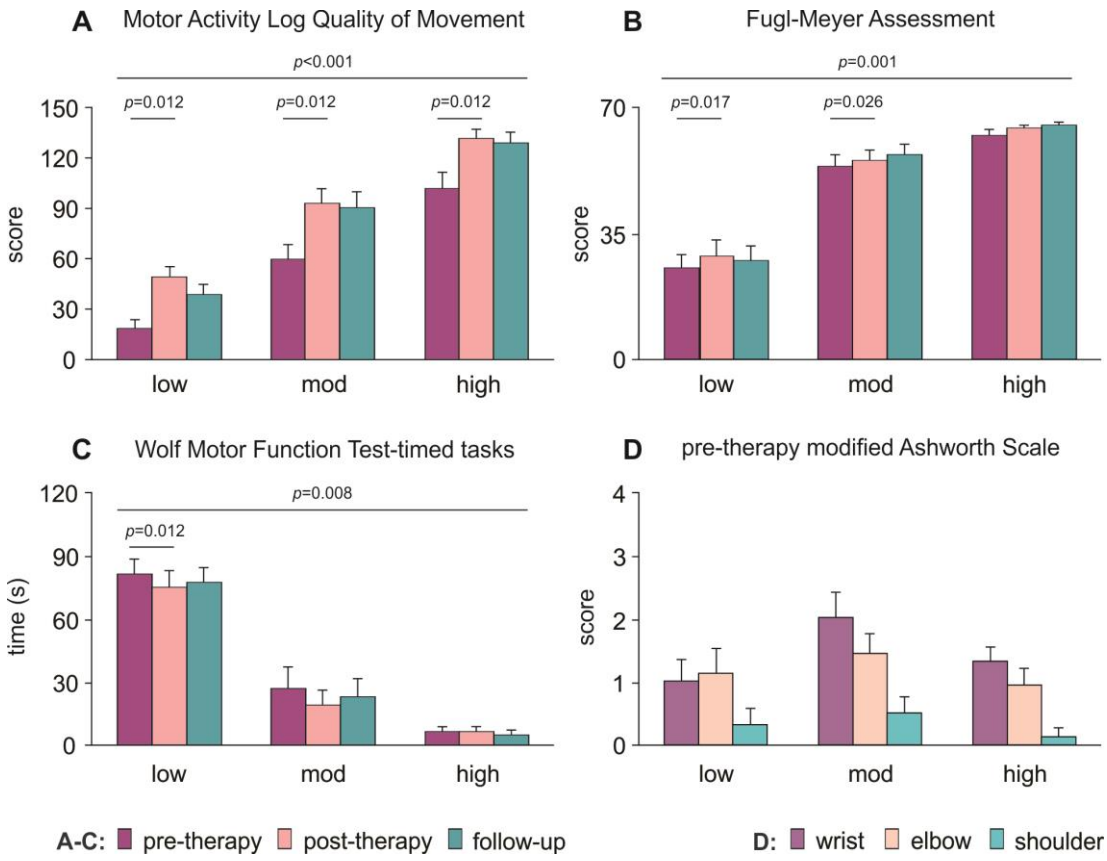

Figure 2-3. Changes in clinical assessments over time. Significant changes are evident for Motor Activity Log Quality of Movement scale, upper-limb motor Fugl-Meyer Assessment and Wolf Motor Function Test-timed tasks (note a decrease in time reflects improved performance). Modified Ashworth Scale pre-therapy (baseline) data are presented as there were no changes over time. All data are presented as mean±SE.

Game performance

Game performance improved from early- to late-therapy. The successful Wii-golf swings (landing the ball in the hole) increased by 30.7% (p=0.004). The number of Wii-baseball hits increased by 51.5% (p<0.001), while the combined Wii-tennis forehand and backhand hits increased by 91.5% (p=0.012). The increase in game

scores was sustained at 6-month follow-up with significant improvements over time for Wii-golf (p=0.004), -baseball (p<0.001) and -tennis (p=0.022).

Qualitative EMG observations

As detailed above, EMG data demonstrated therapy-induced changes particularly for patients with low motor-function. Qualitative observations included: that the EMG signal from muscles with prolific single motor unit activity became more compound by late-therapy indicating increased motor unit recruitment; tonic activity became more phasic; and there were more distinct and task-related bursts of EMG in more muscles (see Fig. 2-4).

Figure 2-4. Single patient raw EMG at early- and late-therapy for a 68-year old female, 46 months post-stroke with low motor-function during Wii-tennis. FDI: first dorsal interosseous, ECR: extensor carpi radialis, FCR: flexor carpi radialis, BB: biceps brachii, DM: deltoid medius.

Relationship between changes in EMG and clinical assessments

The correlation between therapy-induced changes in clinical motor assessments (WMFT-tt, FMA, and MALQOM) and the changes in EMG parameters (of Wii-golf, -baseball, -forehand, and -backhand) were examined. For the pooled data, there was

no relationship between the change in the clinical assessments and the change in area under the curve of each activity ($r<0.39$, $p>0.18$ for all comparisons) and the change in movement duration of the same activities ($r<0.20$, $p>0.90$ for all comparisons). Furthermore, within each level of motor-function, no relationship was found either for area under the curve (low: $r<0.45$, $p>0.78$; moderate: $r<0.71$, $p>0.14$; high: $r<0.54$, $p>0.50$), or movement duration (low: $r<0.73$, $p>0.12$; moderate: $r<0.62$, $p>0.30$), with the single exception of a significant correlation that was found between the change in Wii-baseball movement duration and clinical assessments in patients with high motor-function ($r=-0.81$, $p=0.048$).

Discussion

In this study we investigated changes in upper-limb muscle activation to gain greater insight into the neurophysiological mechanisms of improved motor-function in a heterogeneous stroke cohort from early- to late-therapy and with a subset of patients at 6-month follow-up. To the best of our knowledge this study is the first longitudinal analysis of upper-limb EMG *during* therapy in chronic stroke. Moreover, the movements we studied were largely unconstrained in time and space with no experimentally pre-defined start- or end-points. Although all patients made significant improvements on clinical assessments, and muscle activation changed with therapy, contrary to our hypothesis, there was no consistent pattern of change in EMG in the pooled data or within any motor-function group (see Fig. 2-5). Qualitatively, there were more discrete bursts of EMG, less tonic activity and less co-contraction (see Fig. 2-4). These findings demonstrate that there is no one pattern of improvement regardless of the level of motor-function, that task-related EMG demands may increase or decrease, and that both are associated with improved therapy (game) performance and independence in everyday tasks.

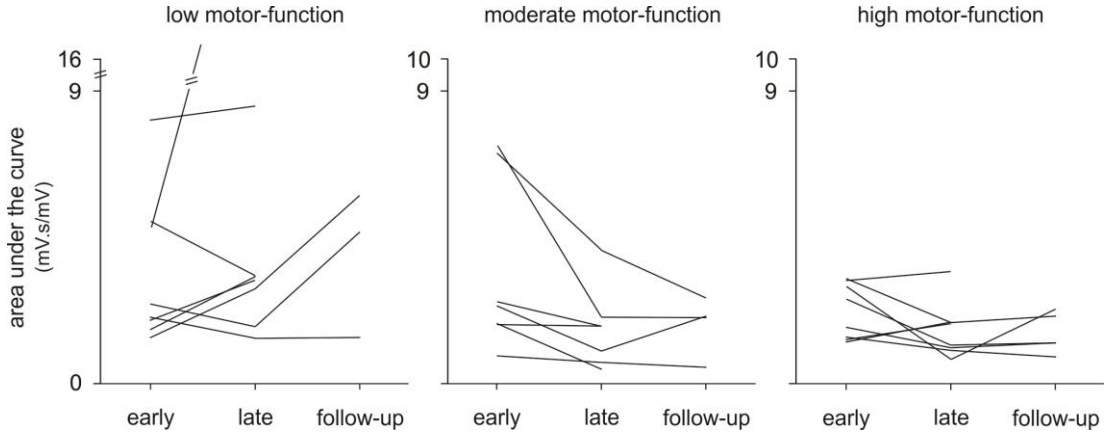

Figure 2-5. Changes in EMG over time, individual patient data. The mean area under the curve is shown for each patient (n=24) with low, moderate and high motor-function at early- and late-therapy and for a subset of patients (n=13) at 6-month follow-up during Wii-golf.

One of the two primary objectives of WMT is movement quality, rather than EMG activity or game scores. Thus, therapy activities were not modified in any way to enhance the recorded EMG signals (Thompson-Butel *et al.*, 2013; Trinh *et al.*, 2016a; Trinh *et al.*, 2016b). Wii-activities provide a wide range of movement demands. For example, the self-paced Wii-golf putting requires movements that are smaller and more controlled compared to the externally-timed Wii-baseball and -tennis swings that can be used to target movement speed, range, power and co-ordination (Deutsch *et al.*, 2011).

The pattern of change in the EMG signals by late-therapy was complex and variable. There were distinct differences between patients with low motor-function and those with moderate and high motor-function (Cramer & Bastings, 2000; Shiner *et al.*, 2015; Shiner *et al.*, 2016). The pattern of change in the area under the curve showed an increase for patients with low motor-function from early- to late-therapy for all activities except Wii-baseball in which there was no change. This pattern was reversed for patients with high motor-function, while those with moderate motor-function had a reduction in Wii-golf putting and -baseball swings and an increase in Wii-tennis forehand and backhand hits. In contrast, clinical motor assessments with the exception of the modified Ashworth Scale, improved for the pooled cohort. The

differences between the levels of motor-function arise as a consequence of the limitation of each assessment tool, particularly for the modified Ashworth Scale (Fleuren *et al.*, 2010; Thompson-Butel *et al.*, 2014; McNulty *et al.*, 2015b). These data emphasise differences in the level of residual voluntary motor capacity in chronic stroke. Although patients with low motor-function retain the capacity to improve, the level of impairment may limit their ability to participate fully in each activity and hence circumscribe the potential for improvement. Those with moderate motor-function have the greatest capacity for improvement whereas patients with high motor-function are the most likely to show improvements (van Kordelaar *et al.*, 2014). Regardless of changes in EMG and movement ability, the MALQOM data demonstrate that every patient became more independent in activities of daily living (McNulty *et al.*, 2013a; McNulty *et al.*, 2015b).

Muscle activation after stroke is typically analysed during simple single-joint tasks (Canning *et al.*, 2000; Song & Tong, 2013; Ramos-Murguialday *et al.*, 2015), or during experimentally constrained movements (Hughes *et al.*, 2010; Cesqui *et al.*, 2013; Silva *et al.*, 2014). Our analysis focused on the area under the curve because it is the product of EMG amplitude and the movement duration and so provides a more holistic view of the movement. While changes in movement duration were larger, there were fewer changes in peak amplitude. In this study, the movements were largely unconstrained, in that patients chose their own starting position within a task-dependent framework and the end position predominantly reflected movement capacity. When essential, positioning assistance was provided either with the less-affected arm, or by the therapist. Wii-golf was self-paced, Wii-baseball was paced by the game but required the development of fine response timing, while the timing of Wii-tennis was variable from swing to swing. Thus, these activities provide a better reflection of upper-limb use in everyday life than more constrained experimental tasks and are more likely to reflect the neurophysiology underlying functionally relevant changes in post-stroke motor-function.

Despite monotonic improvements in clinical assessments, there were heterogeneous changes in muscle activation patterns during therapy. Patients in

each level of motor-function used different strategies to perform a task according to their specific neuromuscular limitations. Wii activities target various muscles and movements (Deutsch *et al.*, 2011) and differences in residual voluntary muscle activation alter the goals of therapy for each patient and result in movement patterns that differ from those of healthy control subjects (Mouawad *et al.*, 2011; McNulty *et al.*, 2015b). These differences precluded analysis based on a single pre-determined muscle for all patients. Single muscle analysis provides some information about corticomotor changes in motor control but little about the co-ordination of muscles in the production of a complex movement. For this reason these data were further analysed to investigate the neuromuscular co-ordination of a complex movement (see (Hesam-Shariati *et al.*, 2017b)).

Clinical implications

Although all patients completed a standardised protocol of WMT and improved on clinical assessments, the pattern of change in EMG differed. Each motor-function group had a dominant pattern, yet there was a large amount of variation within each group (see Fig. 2-5). Regardless of the pattern of improvement in EMG, therapy-induced changes were reflected in improvements in independence (MALQOM) and quality of movement in activities of daily living that were unrelated to the content of therapy (see Fig. 2-3). These data suggest that WMT tasks can target different aspects of motor control. For example, the area under the curve in Wii-golf putting increased over time for patients with low motor-function showing that these patients were able to perform longer and stronger movement after therapy. Therefore, Wii-golf can be used to focus on slower and more-controlled movements with a sustained position at the end of the swing to target positional stability. Patients with moderate and high motor-function had a reduction in area under the curve over time indicating more co-ordinated and smaller movements, confirmed by video recordings. The increased area under the curve during Wii-tennis for patients with low and moderate motor-function suggests a greater ability to move from one side of the body to the other so that fuller "strokes" were played for both forehand and backhand as seen in video recordings. In contrast, the reduced area under the curve for patients with high motor-function suggests more efficient movements that can be

used to target the difference between making one movement and preparing for the next movement. An ancillary benefit of these changes is that Wii-tennis also promotes greater stepping (see (Trinh *et al.*, 2016b)) which we hypothesise will also improve standing balance.

Game scores indicated that patients improved in terms of game performance; however game scores do not necessarily reflect performance. Task difficulty is increased during therapy based on patient progress (Thompson-Butel *et al.*, 2013; Trinh *et al.*, 2016b). The increased difficulty typically lowers game scores resulting in a pattern of oscillating scores with a trend of improvement over time.

EMG analysis provides a means of demonstrating neurophysiological changes in chronic stroke underlying significant improvements in clinical assessments, suggesting that ongoing rehabilitation is effective. Preliminary data from our group (McNulty *et al.*, 2015a) emphasise that a continuous trajectory of improvement in clinical measures is possible when additional periods of therapy are provided in the chronic phase of stroke.

Study limitations

In this study, the sample size within each level of motor-function is small. Yet, the pooled sample size is comparable to published studies of post-stroke EMG (Wagner *et al.*, 2007; Zhang & Zhou, 2012; Chang *et al.*, 2013; Li *et al.*, 2015). A wide range of post-stroke motor impairment is included in this study based on clinical assessment data. Patients with low motor-function are not typically recruited in most neurophysiological studies due to methodological challenges. These patients need special care during assessment and therapy sessions due to pain, limited mobility and fatigue. Significant upper-limb motor heterogeneity, together with the largely unconstrained movements during therapy and EMG acquisition from a variety of muscles increase the complexity of EMG analysis and interpretation.

The absence of healthy control subjects is a limitation to this study. Given that therapy focuses on the quality of movements and increasing the use of more-

affected upper-limb in everyday activities, the instructions given to stroke patients are different from those given to healthy subjects performing the same Wii activities. Initially movements may be fractionated into their constituent parts for practice using the principles of shaping (Taub *et al.*, 1994). By the end of therapy most patients are able to perform the necessary reconstituted whole movements with game performance and scores used only as a motivational tool (McNulty *et al.*, 2015b). In contrast, healthy subjects playing the same games used more modified movements than the real-world equivalent, and despite skill acquisition during Wii-Sports, showed no change in clinical assessments of motor-function (Mouawad *et al.*, 2011). Thus, these differences in movement patterns may limit the utility of comparisons between healthy subjects and patients. This study also lacks comparison with a control therapy group. However, the movements used in WMT are designed to replicate movement patterns of real-world sporting activities, despite all activity being targeted as far as possible, to use of the more-affected upper-limb alone. As discussed above, the movements in this study were largely unconstrained with no pre-defined start- or end-points; while most upper-limb stroke studies on the analysis of muscle activation only include simple tracking or restricted tasks (Hughes *et al.*, 2010; Song & Tong, 2013; Ramos-Murguialday *et al.*, 2015). We are therefore unaware of any viable comparator therapy.

Although patients were drawn from several concurrent WMT studies, all received the standardised protocol and we have seen very little variation in therapy outcomes across trials (Mouawad *et al.*, 2011; McNulty *et al.*, 2013a; McNulty *et al.*, 2015b). The patients were instructed to perform the same task-dependent movements; however the variability in movement strategies, tonic muscle activity, level of impairment, and the ability to voluntarily relax muscles after each movement prevented the use of single muscle for all analyses. This approach adds complexity to the analysis but was preferable to attempting to ensure all patients activated a given muscle as this was either not possible for some patients, or would have produced extraneous or counterproductive movements. To enable comparisons between patients and between multiple time-points, EMG data were normalised to a standardised condition even though it has been suggested that EMG normalisation

in post-stroke data might lead to higher variability (Silva *et al.*, 2014). An unsupported weighted condition was used for normalisation as this was considered more reliable for stroke survivors than a maximal voluntary contraction that might be restricted due to pain (Halaki & Ginn, 2012). Such variability is an inherent problem of longitudinal post-stroke therapy studies when the aim of therapy is to change the muscles themselves, in addition to changing the neuromuscular control of those muscles.

Conclusion

This study demonstrates the magnitude of the variability in post-stroke response to therapy, and that WMT induced changes in upper-limb EMG in chronic stroke. The absence of correlations between EMG activity, game performance and clinical assessments highlight the complexity and heterogeneity that are characteristic of stroke, even in the chronic period. Despite the absence of readily identifiable patterns across the pooled EMG data, the pattern of changes in EMG was associated with the level of residual voluntary motor capacity. The heterogeneity within each level shown in this EMG study was not evident using clinical assessments of motor-function, although improved independence in everyday activities was evident for all patients. These data emphasise the importance of examining individual patient responses to therapy using multiple tools, as rehabilitation efficacy will be underestimated when data are pooled.

Changes in co-ordinated muscle activation of a complex therapy movement in chronic stroke

Chapter 3

Abstract

Fine motor control is achieved through the co-ordinated activation of groups of muscles, or "muscle synergies". Muscle synergies change after stroke as a consequence of the motor deficit. We investigated the pattern and longitudinal changes in upper-limb muscle synergies during therapy in a largely unconstrained movement in patients with a broad spectrum of post-stroke residual voluntary motor capacity.

Electromyography (EMG) was recorded using wireless telemetry from 6 muscles acting on the more-affected upper body in 24 stroke patients at early- and late-therapy during formal Wii-based Movement Therapy sessions, and in a subset of 13 patients at 6-month follow-up. Patients were classified with low, moderate or high motor-function. The Wii-baseball swing was analysed using a non-negative matrix factorisation (NMF) algorithm to extract muscle synergies from EMG recordings based on the temporal activation of each synergy and the contribution of each muscle to a synergy. Motor-function was clinically assessed immediately pre- and post-therapy and at 6-month follow-up using the Wolf Motor Function Test, upper-limb motor Fugl-Meyer Assessment and Motor Activity Log Quality of Movement scale.

Clinical assessments and game performance demonstrated improved motor-function for all patients at post-therapy ($p<0.01$) and these improvements were sustained at 6-month follow-up ($p>0.05$). NMF analysis revealed fewer muscle synergies (mean±SE) for patients with low motor-function (3.38±0.2) than those with high motor-function (4.00±0.3) at early-therapy ($p=0.036$) with an association trend between the number of synergies and the level of motor-function. By late-therapy there was no significant change between groups, although there was a pattern of increase for those with low motor-function over time. The *variability accounted for* (VAF) demonstrated differences with motor-function level ($p<0.05$) but not time. Cluster analysis of the pooled synergies highlighted the therapy-induced change in muscle activation.

Muscle synergies could be identified for all patients during therapy activities. These results show less complexity and more co-activation in the muscle activation for patients with low motor-function as a higher number of muscle synergies reflects greater movement complexity and task-related phasic muscle activation. The increased number of synergies and changes within synergies by late-therapy suggests improved motor control and movement quality with more distinct phases of movement.

Introduction

Fine motor control of the upper-limb requires complex movements based on multiple degrees of freedom that permit movement variability and versatility (Cheung *et al.*, 2009; d'Avella & Lacquaniti, 2013). The central nervous system (CNS) controls such complex motor tasks by co-ordinated activation of groups of muscles, referred to as "muscle synergies" (Lee, 1984; Tresch *et al.*, 2002; d'Avella *et al.*, 2003; Bizzi *et al.*, 2008). The combination of the brain and spinal circuitry is essential for the simultaneous recruitment of multiple muscle synergies that explain a wide range of movement patterns (Safavynia *et al.*, 2011; Coscia *et al.*, 2014). Muscle synergies have been extracted from electromyography (EMG) recordings to define movements in both animals including frogs (Tresch *et al.*, 1999; Cheung *et al.*, 2005), rats (Kargo & Nitz, 2003), cats (Ting & Macpherson, 2005; Torres-Oviedo *et al.*, 2006; Chvatal *et al.*, 2013), and monkeys (Overduin et al., 2008); and in humans with reference to gait (Clark *et al.*, 2010; Chvatal & Ting, 2013; Coscia *et al.*, 2015), balance and posture (Torres-Oviedo & Ting, 2007; Chvatal *et al.*, 2011), hand function and posture (Ajiboye & Weir, 2009; Zariffa *et al.*, 2012), arm movements (Cheung *et al.*, 2012; d'Avella & Lacquaniti, 2013; Coscia *et al.*, 2014) and isometric force (Roh *et al.*, 2012; Borzelli *et al.*, 2013).

Multiple temporal synergy profiles are weighted and integrated to define co-ordinated muscle activation during a task (d'Avella & Lacquaniti, 2013). Muscle synergies can include any number of muscles and each muscle can contribute to multiple synergies (Safavynia et al., 2011). Muscle synergies have been investigated in acute, subacute (Hidler *et al.*, 2007; Gizzi *et al.*, 2011; Tropea *et al.*, 2013) and chronic stroke (Dipietro *et al.*, 2007; Clark *et al.*, 2010; Cheung *et al.*, 2012) showing abnormalities compared to healthy people (Roh *et al.*, 2013; Coscia *et al.*, 2015; Li *et al.*, 2016). Such changes reflect post-stroke motor impairment which can be attributed in large part to disorders in the neural pathway (Safavynia et al., 2011), reduced corticospinal drive (Werring et al., 2000), disuse atrophy (Ramsay et al., 2011), and loss of independent joint control and impaired motor co-ordination (Dipietro et al., 2007).

Muscle synergy analysis has detected post-stroke abnormalities in the number, structure, and recruitment profile of muscle synergies. For example, the number of muscle synergies recruited in the post-stroke gait cycle was reduced in patients with more severe impairment and in comparison to healthy subjects (Kautz & Brown, 1998; Clark *et al.*, 2010). This presumably reflects a change in the number of independent motor subtasks given the standard analysis of the gait cycle in four distinct phases and the use of four synergies for healthy subjects and patients with high motor-function.

Several analysis algorithms have been suggested for the decomposition of muscle activation profiles into muscle synergies. Tresch and colleagues (Tresch et al., 2006) evaluated and compared different matrix factorisation methods including factor analysis, independent component analysis alone and applied to principle component analysis (PCA), and non-negative matrix factorisation (NMF). The authors concluded that these methods identify muscle synergies very similar to one another. In this study we implemented NMF which has commonly been used to detect muscle synergies from EMG activation (Clark *et al.*, 2010; Frère & Hug, 2012; Roh *et al.*, 2012; Chiovetto *et al.*, 2013). NMF quantifies muscle synergies as a linear combination of the timing profile and a weighting assigned to each muscle involved in each synergy.

Few studies have examined the changes in post-stroke muscle synergies with rehabilitation, (but see (Tropea et al., 2013)). In this study, we extracted muscle synergies during a complex task to investigate the changes in muscle activation profiles (i.e. muscle synergies) in chronic stroke during an intensive 14-day protocol, in this case Wii-based Movement Therapy (Mouawad *et al.*, 2011; McNulty *et al.*, 2015b). This therapy is as effective as the current best practice in stroke rehabilitation, Constraint-induced Movement Therapy (McNulty *et al.*, 2015b; Trinh *et al.*, 2016a). The primary aim of this study was not the therapy itself, but to quantify post-stroke muscle synergies during therapy. Muscle synergy analysis cannot be used to investigate recovery mechanisms occurring in the brain but was

used here as a neurophysiological indication to distinguish the level of impairment and the effect of therapy on co-ordinated muscle activation (Casadio et al., 2013). To identify some of the neuromuscular mechanisms underpinning the improvement reported using clinical motor-function assessments (Mouawad *et al.*, 2011; McNulty *et al.*, 2015b), NMF was applied to the EMG recorded from 6 muscles of the more-affected arm and upper body during the Wii-baseball component of Wii-based Movement Therapy. This longitudinal study examined EMG at early- and late-therapy, and at 6-month follow-up for a subset of patients. We hypothesised that the number of muscle synergies would be correlated with the level of motor-function after stroke, and that the number of synergies would change with therapy.

Methods

Participants

Twenty four patients (16 males, 8 females) aged 37-80 years (57.9±12.1, mean±SD) and 3-88 months post-stroke (26.7±4.3, mean±SE) were randomly selected from a larger cohort who were consecutively recruited from St Vincent's and Prince of Wales' Hospitals, Sydney (the same patients as presented in Chapter 2, see Table 2-1 for a summary of baseline characteristics). All participants were hemiparetic following either an ischaemic or haemorrhagic stroke and were classified into three groups of low, moderate or high motor-function based on their ability to perform two tests of upper-limb manual dexterity (Thompson-Butel et al., 2014). The inclusion criteria were as before: ≥10˚ of voluntary movement in at least one digit of the more-affected hand; cognitive competency measured as a Mini-Mental State Examination score ≥24; suitable skin for sensor placement; and the ability to communicate in English. Exclusion criteria included: unstable blood pressure; comorbidities affecting upper-limb sensorimotor function; and engagement in any other formal upper-limb rehabilitation program. All participants gave signed informed consent to the study which was approved by the St Vincent's Hospital Human Research Ethics Committee, Sydney and conducted in accordance with the Declaration of Helsinki. Ten of the 24 patients could not attend the 6-month follow-up session for a range of reasons including: return to work, too far to travel, and unrelated health problems. The data for one patient was excluded for technical issues (see Chapter 2, Fig. 2-1).

As detailed in Chapter 2 (Hesam-Shariati *et al.*, 2017a), the clinical assessment results for all patients (but not NMF analyses) have been published previously (see (Shiner et al., 2016), n = 20; (McNulty *et al.*, 2015b), n = 9; and (Trinh *et al.*, 2016a), n = 8).

Therapy

Wii-based Movement Therapy is a standardised 14-day program focused on the more-affected upper-limb which consists of 1-hour of formal therapy on 10 consecutive weekdays delivered by an Accredited Exercise Physiologist, augmented by prescribed home practice starting on day 2 and increasing throughout the program (see Chapter 1, Fig. 1-3). This therapy uses the Nintendo Wii and Wii-Sports games (Nintendo, Japan) as a rehabilitation tool that targets movement quality and independence in activities of daily living (Mouawad *et al.*, 2011; McNulty *et al.*, 2015b). The movements required in Wii-Sports were modified according to the capacity, range of motion and strength of each patient. Although Wii-based Movement Therapy games include Wii-golf, -baseball, -tennis, -bowling, and -boxing, the analyses of this study were applied only to Wii-baseball swings. Each patient played two or three games of Wii-baseball during each session of therapy. This Wii-baseball movement was selected for analysis for several reasons. First, all patients were able to complete this game regardless of the level of residual voluntary motor-function. Second, the game determines the onset of each movement by pitching the ball. This allowed individual movements to be identified more clearly in the EMG signal. Finally, the nature of the game provided the most consistent task demands.

EMG recording

Surface electromyography (EMG) was recorded from 6 muscles of the upper body on the more-affected side: trapezius (middle portion), deltoid medius, biceps brachii, extensor carpi radialis (ECR), flexor carpi radialis (FCR), and first dorsal interosseus (FDI) using Trigno wireless sensors (Delsys, USA). The data were collected continuously during formal Wii-based Movement Therapy sessions at early- (day 2-3) and late- (between days 12-14) therapy, and in a subset of patients, again during

the 6-month follow-up session. Each EMG sensor contains 4 silver bar electrodes, arranged in two pairs with an interelectrode pair distance of 10mm. The sensor is designed to maximise the detection of muscle activation in a field perpendicular to the muscle fibres. Data were amplified 300 times, filtered between 20-450 Hz, and sampled at 2 kHz using EMGworks (Delsys, USA) as per intrinsic device settings.

Clinical motor-function assessments and game performance

The efficacy of Wii-based Movement Therapy was evaluated using clinical motor-function tests as described in Chapter 2 (Hesam-Shariati *et al.*, 2017a) including the Wolf Motor Function Test (WMFT) (Wolf *et al.*, 1989), upper-limb motor Fugl-Meyer Assessment (FMA) (Fugl-Meyer *et al.*, 1974) and the Motor Activity Log Quality of Movement scale (MALQOM) (Uswatte *et al.*, 2005). The Wii-baseball game performance was assessed as the number of hits, regardless of the outcome according to the rules of baseball and this was recorded during therapy. However the primary goal of therapy was movement quality and not game performance. The average duration of each swing for each trial was measured in seconds.

Data analysis

EMG pre-processing. EMG signals were DC removed, root mean square (RMS) processed using a sliding 50 ms window and demeaned using Spike2 software (CED, UK). Mean baseline EMG was measured over 1 s prior to the beginning of the Wii-baseball game while the muscles were at rest. The mean was subtracted from the signal of the same game for each patient. To enable comparison between patients, the EMG of each muscle was normalised to its peak amplitude, then averaged over 10 consecutive Wii-baseball swings for each patient at early- and late-therapy and at 6-month follow-up.

Non-negative matrix factorisation. Muscle synergies were extracted from the EMG signals using the non-negative matrix factorisation (NMF) method (Paatero & Tapper, 1994; Lee & Seung, 1999; d'Avella *et al.*, 2003; Tresch *et al.*, 2006). This optimisation method was applied to the EMG recordings of the 6 muscles using the in-built nnmf function in MATLAB R2014a (MathWorks, USA). Random initial values

were generated as the input for the multiplicative algorithm of the function, the output of which provided the initial values of the alternating least squares (ALS) algorithm (Berry et al., 2007). Then the ALS algorithm was used to characterise the EMG of the 6 recorded muscles (m=6) as a lower-rank combination of the relative weighting (W) of each muscle and the timing profile (H) of each synergy (equation below) in a complex movement (see Fig. 3-1).

$$\mathrm{EMG} \cong \sum_{k=1}^{m-1} \mathrm{W_k H_k(t)}$$

Number of muscle synergies. The number of muscle synergies needed to define co-ordinated muscle activation in a complex movement was determined using the term *variability accounted for* (VAF) (Torres-Oviedo *et al.*, 2006; Clark *et al.*, 2010) and the mean squared error term (MSE) (Cheung et al., 2005; Roh et al., 2015) according to the formula below. The VAF is defined as 100 times the squared correlation coefficient between the original EMG (EMG_o) and the reconstructed EMG (EMG_r) from the NMF algorithm (Cheung et al., 2012). The minimum number of synergies was identified when VAF increased by less than 2% when another synergy was added. VAF for the acceptable number of synergies was required to be greater than 97% while the MSE was less than $10x10^{-4}$.

$$\mathrm{VAF} = 100 \times (1 - \frac{\sum(\mathrm{EMG_o} - \mathrm{EMG_r})^2}{\sum(\mathrm{EMG_o} - \overline{\mathrm{EMG_o}})^2})$$

$$\mathrm{MSE} = \frac{1}{n} \sum_{1}^{n} (\mathrm{EMG_o} - \mathrm{EMG_r})^2$$

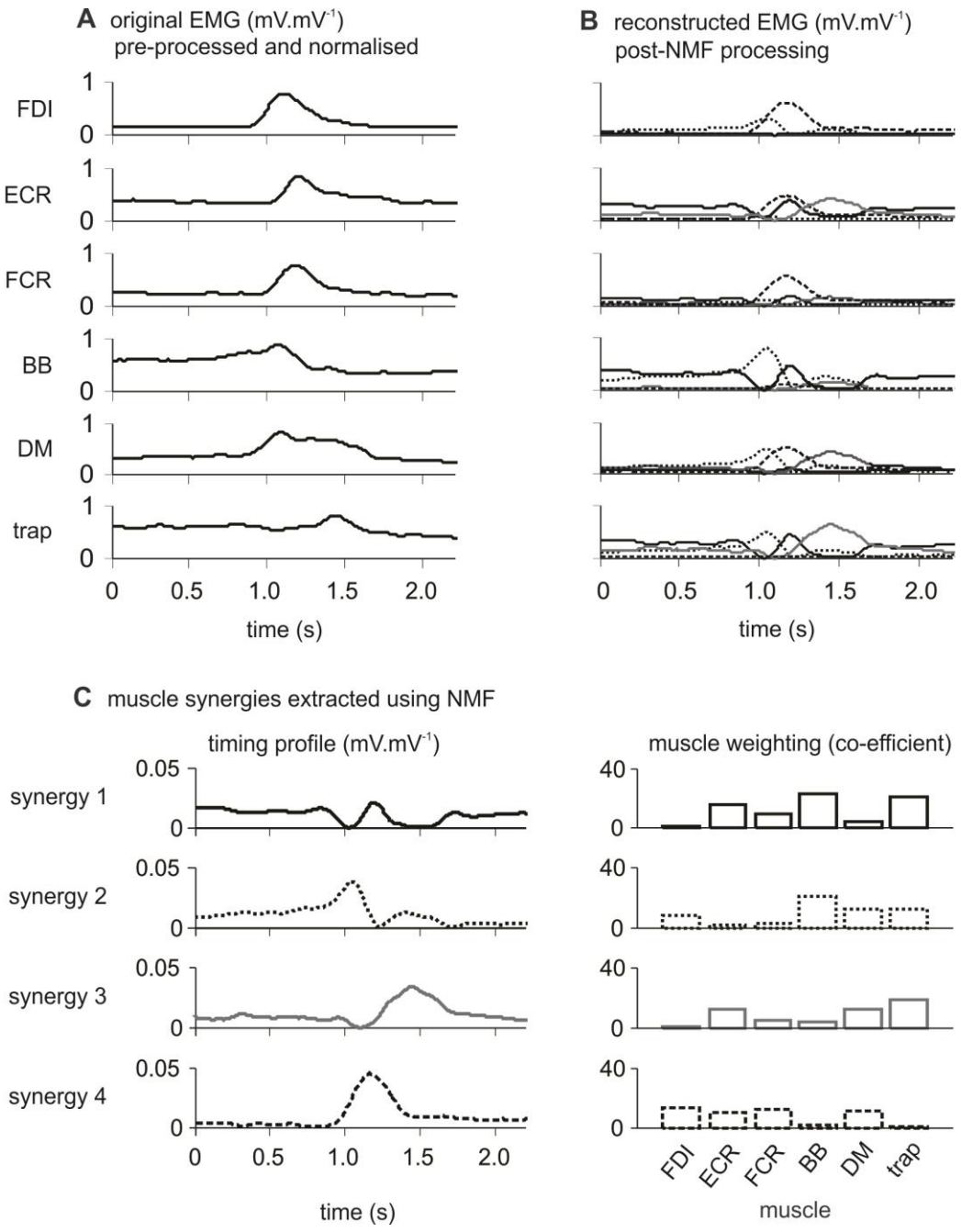

Figure 3-1. Single patient EMG data showing the progression through analysis using non-negative matrix factorisation (NMF). The 61-year old male patient with moderate motor-function was 5 months post-stroke. **A)** Pre-processed normalised EMG from 6 upper-body muscles on the more-affected side during Wii-baseball swings prior to processing by the NMF algorithm. **B)** Reconstructed EMG after processing by NMF as the integration of muscle synergies for each muscle. **C)** Each derived muscle synergy is a combination of the timing profile and muscle weightings. FDI: first dorsal interosseous, ECR: extensor carpi radialis, FCR: flexor carpi radialis, BB: biceps brachii, DM: deltoid medius, trap: trapezius (middle portion).

Similarity of synergy timing profiles. The similarity between individual synergy timing profiles from each subject on a group basis was quantified using the scalar product (Cheung et al., 2009; Roh et al., 2013). More than 50% of patients used four distinct synergies to account for the variability of muscle activation at early- and late-therapy and at 6-month follow-up. The analysis of similarity between timing profiles requires the same number of synergies from each patient to be entered in the analysis to enable the comparison of synergy profiles. Thus, regardless of the actual number of synergies, four synergies were extracted from the muscle activation of all patients. Then, one set of 4 synergies from one subject was randomly selected in each motor-function group and used as the template. The synergy timing profiles from all other subjects within the same motor-function group at each time-point were matched to provide the highest scalar product between two synergies. The scalar product (r-value) is a measure of the similarity in which one numerical vector is projected onto another, so that an r-value of 1 represents complete similarity and a value of 0 represents the absence of any similarity.

Clustering synergy structures. The muscle weightings of the actual synergies from all subjects were pooled to be categorised using cluster analysis (Cheung et al., 2012; Roh et al., 2015) at early- and late-therapy. This procedure was performed using the in-built functions from the MATLAB statistics toolbox. Euclidean distance was used to measure the similarity between pairs of muscle weightings. The minimum number of clusters was determined based on grouping synergies when there was no more than one synergy from a subject in each cluster. Cluster analysis requires the inclusion of all extracted synergies to avoid overlap and to merge the analysis to a limited and realistic number of clusters. This method avoids the inclusion of more than one synergy from each patient in each cluster.

Statistical analysis

A potential relationship between the number of muscle synergies and the level of motor-function was investigated using Pearson Chi-square test, Fisher's exact test and linear-by-linear association. If more than 20% of the cells had an expected

count <5, the p-value of Fisher's exact test was reported instead of Pearson Chi-square. In addition, linear-by-linear association was used to reveal trends in larger-than-2x2 tables. The same tests were used after the cluster analysis to evaluate the incidence of each cluster in each level of motor-function.

A mixed-effect model was implemented for any given number of synergies (range 1-5) to detect the effect of motor-function level (low, moderate, high) and time (early-therapy, late-therapy, follow-up) on VAF. This model is powerful and flexible with missing data (i.e. to account for n=13 at follow-up). Clinical assessments and game performance data were analysed using paired t-test (for parametric data) and Wilcoxon signed-rank test (for non-parametric data) to compare means between time-points. Statistical analyses were conducted in SPSS 23 software (IBM, USA) and the differences were considered significant when $p<0.05$.

Results

Number of muscle synergies extracted from Wii-baseball

Difference in the number of synergies across groups. The number of muscle synergies required to define the Wii-baseball movement is presented in Figure 3-2A for each level of motor-function at each time-point. At early-therapy, most patients with low motor-function used three synergies, while most patients with moderate and high motor-function used four synergies to define the movement. However, two patients with high motor-function used five synergies. As can be seen in Figure 3-2B at early-therapy, the number of synergies (mean±SE) for patients with low motor-function (3.38±0.18) was significantly less than for patients with high motor-function (4.00±0.27) ($p=0.036$). At early-therapy, Fisher's exact test showed no relationship between the number of muscle synergies and the level of motor-function ($p=0.217$), although linear-by-linear association indicated a trend ($p=0.045$).

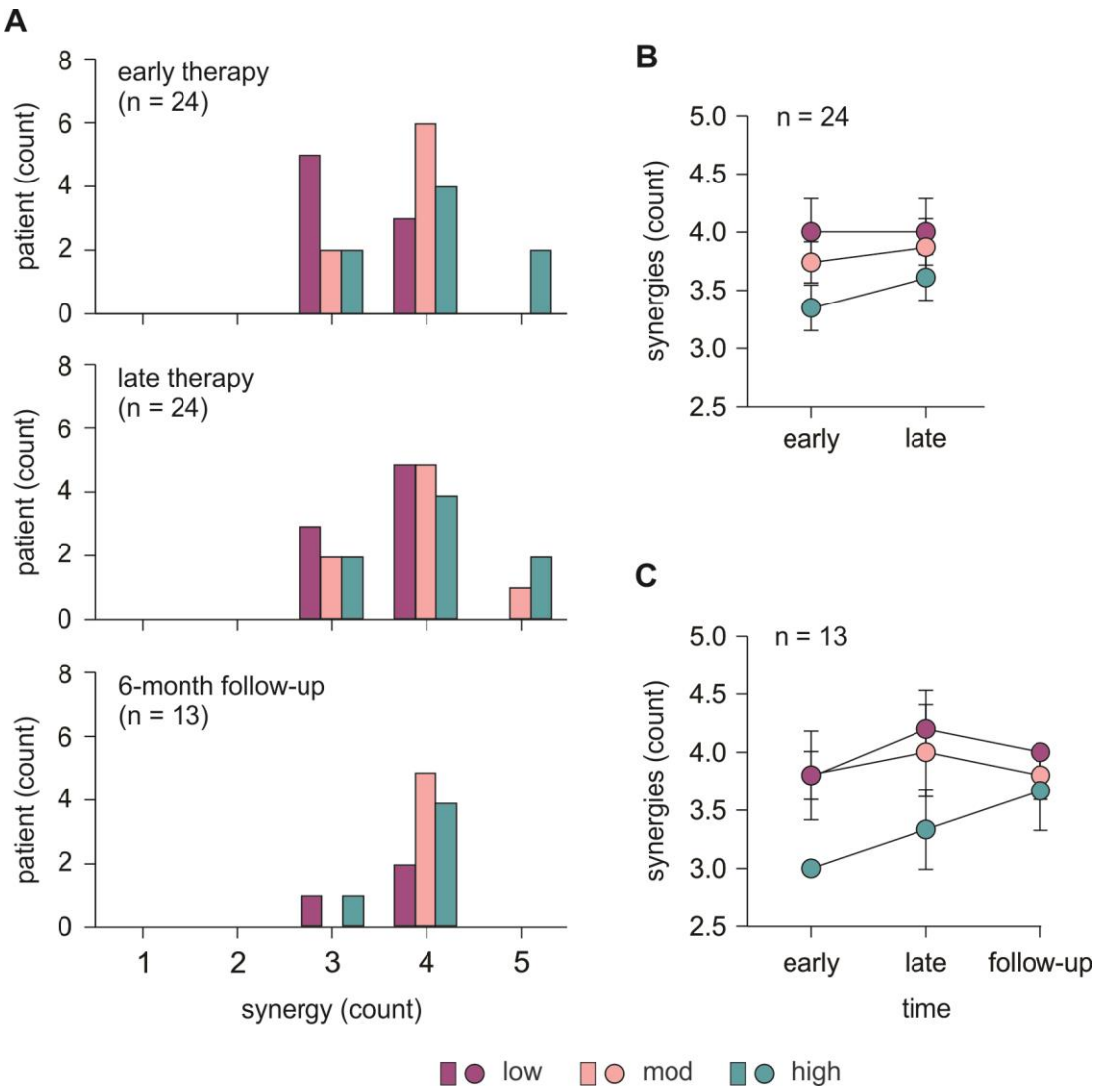

Figure 3-2. Number of synergies required to define Wii-baseball swing. A) Comparison of the number of synergies used for patients (n=24) with different levels of motor-function at early- and late-therapy and for a subset (n=13) at 6-month follow-up. **B)** The number of synergies for all patients (n=24) at early- and late-therapy (mean±SE). At early-therapy, there was a significant difference between patients with low and high motor-function. There was also a trend towards an increase in the number of synergies from early- to late-therapy for patients with low and moderate motor-function. **C)** The number of synergies for the subset of patients (n=13; 3 low, 5 moderate and 5 high motor-function) who completed 6-month follow-up assessments (mean±SE). There was no significant change over time.

Changes in the number of synergies over time. At late-therapy, an increase in the number of synergies was evident for patients with low and moderate motor-function, albeit not statistically significant (Fig. 3-2B). The number of synergies

(mean±SE) increased from 3.38±0.18 to 3.63±0.18 (p=0.317) for patients with low motor-function and from 3.75±0.16 to 3.88±0.23 (p=0.564) for patients with moderate motor-function from early- to late-therapy. There was no change for patients with high motor-function. For the subset of patients with 6-month follow-up data, the number of synergies over time is illustrated in Figure 3-2C. There were no significant changes over time for this subset of patients.

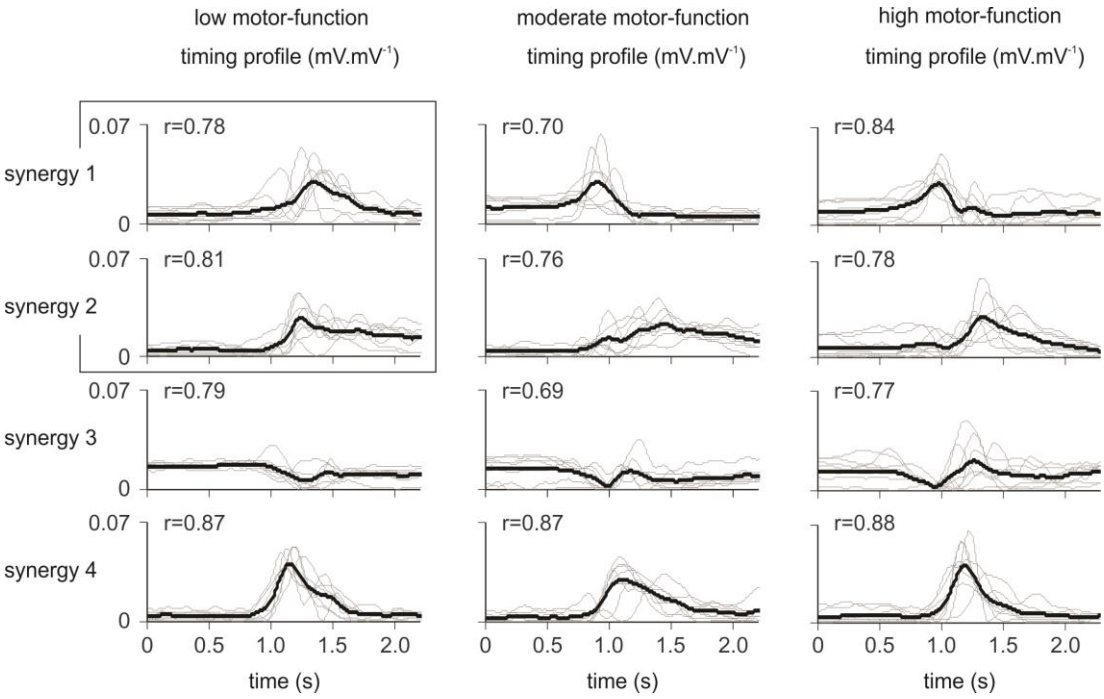

Figure 3-3. Synergy activation timing for patients according to the level of residual voluntary motor-function. Thin grey lines illustrate the synergy timing profile for each patient (mean of 10 trials), overlaid by the within-group mean (black line). Similar synergies are overlaid based on the scalar product between synergies. The r-value shown for each synergy indicates the group-averaged scalar product. For patients with low motor-function, the scalar product between mean synergy 1 and 2 indicated similarity (r=0.71). These two synergies were assumed to be one (as indicated by the overlaid box). Thus, patients with low motor-function used three distinct synergies to define the movement, while patients with moderate and high motor-function required four synergies.

Consistency of muscle synergy timing profiles within groups

The synergy timing profiles (Fig. 3-3) were similar for patients in each level of motor-function. The timing profile of muscle synergies in each group was matched based on the scalar product (r-value) between pairs of synergies from different patients in

each group. The within group mean r-value is shown for each synergy in Figure 3-3. Four distinct synergies demonstrated the profile of muscle synergies for patients with high and moderate motor-function. For patients with low motor-function, the between-synergy scalar product for synergy 1 and 2 (r=0.71) showed high similarity, suggesting a single synergy. Thus, three distinct synergies defined the movement in patients with low motor-function.

Variability (VAF) of muscle synergies across groups

VAF increased with a higher number of synergies (Fig. 3-4). A mixed-effect model revealed changes in VAF according to the level of motor-function over time for any given number of muscle synergies (range 1-5) for each patient. The level of motor-function, but not the time-point, had an effect on the VAF (for any given number of synergies $p<0.05$); although the VAF appears similar between groups in Figure 3-4, the variability within each group was large.

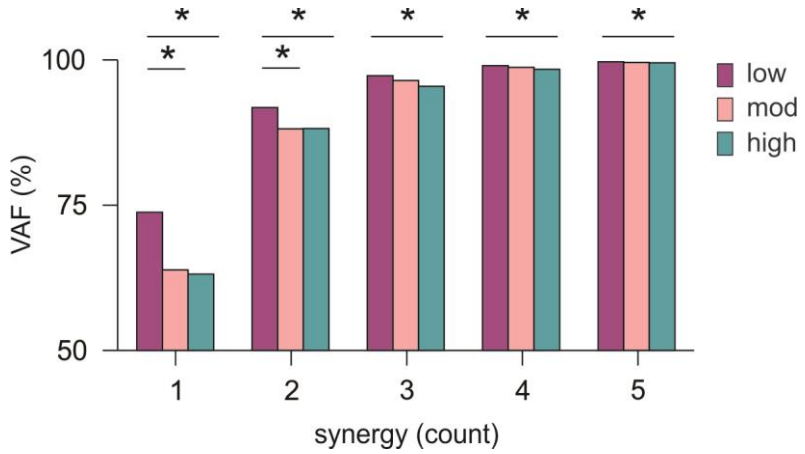

Figure 3-4. Variability accounted for (VAF) in muscle synergies. VAF changed little over time; the mean VAF was measured for any given number of synergies and compared between patients for the three levels of motor-function. For each number of synergies, patients with low motor-function had higher VAF compared to the other two groups ($p<0.05$). Lower VAF for patients with moderate and high motor-function indicated that the analysis is less able to account for variability of muscle activation because of more movement complexity.

Muscle synergy clusters

At early- and late-therapy, the muscle weightings of each synergy from all patients were pooled and then categorised into 10 and 11 clusters, respectively. Thus, all the synergy structures from all patients can be summarised into 10 or 11 distinct synergies (Fig. 3-5). At early-therapy there was no significant difference in the incidence of muscle synergies from different levels of patient motor-function in each cluster based on Fisher's exact test, except for cluster 2 (Fig. 3-6). However, a trend was observed in the incidence of cluster 3 and 9 using linear-by-linear association (see Fig. 3-6).

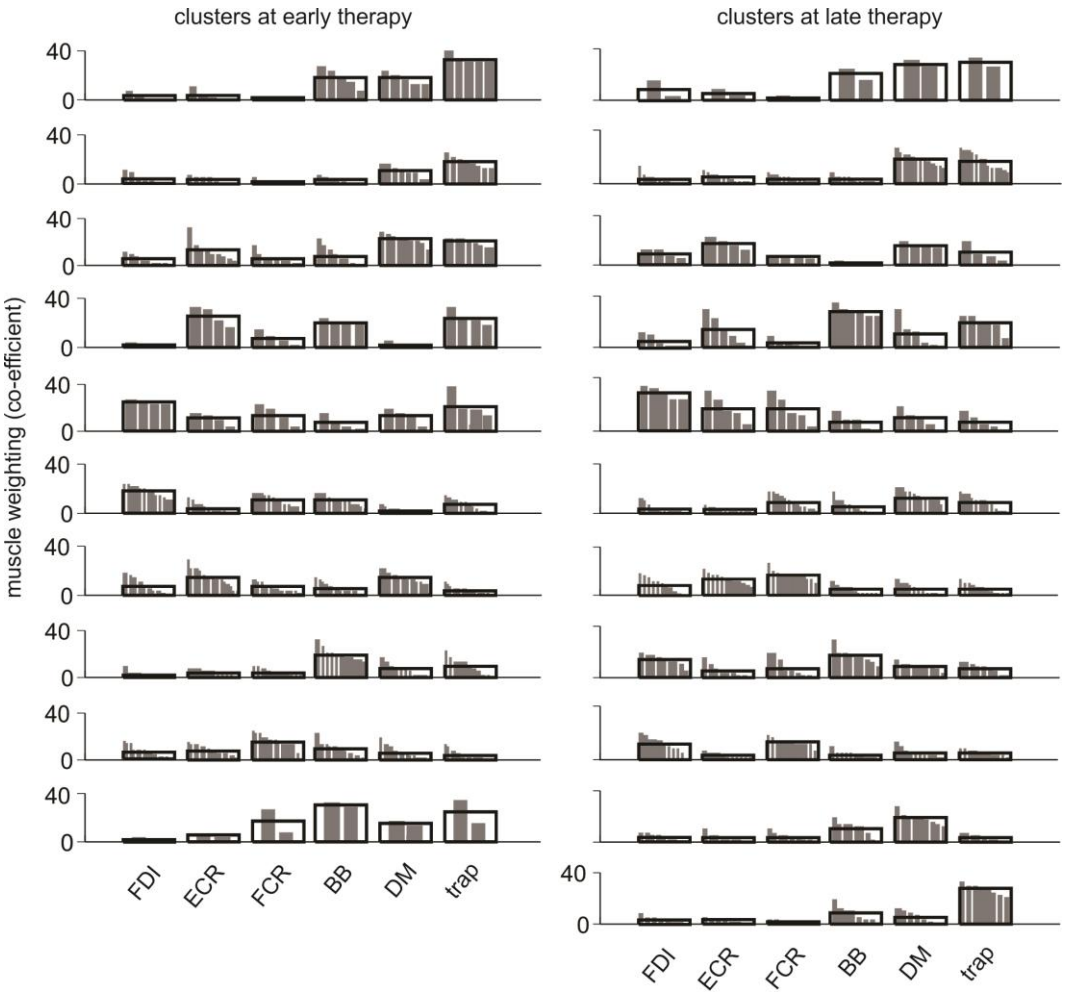

Figure 3-5. Composition of muscle synergies at early- and late-therapy. Synergy muscle weightings at early- and late-therapy were categorised into 10 and 11 clusters, respectively. For each cluster, the distribution of muscle weightings from different synergies is shown, overlaid by the group mean. The synergy clusters changed from early- to late-therapy except for the first four clusters.

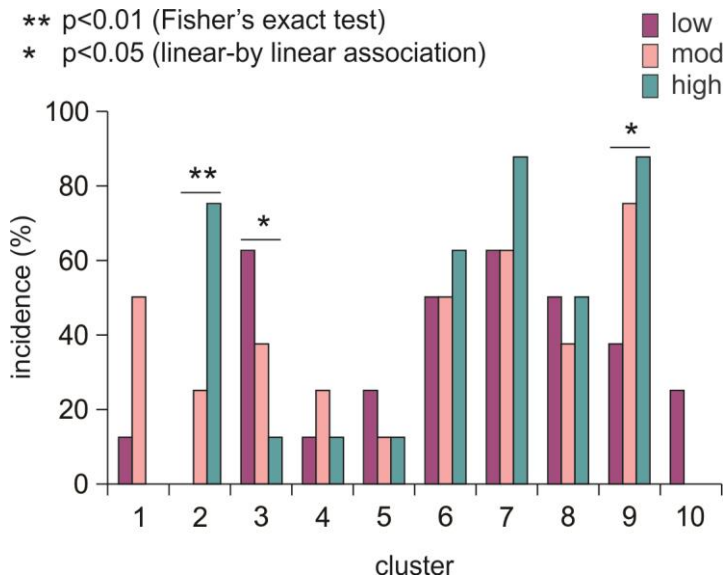

Figure 3-6. Incidence of muscle synergy clusters across groups at early-therapy. The incidence of muscle synergies did not differ with the level of motor-function except for cluster 2 ($p<0.01$). There was a trend between the incidence of muscle synergies and the level of motor-function in cluster 3 and 9 ($p<0.05$).

Wii-baseball game performance

The number of balls hit by patients was averaged for each recording session. The number of Wii-baseball hits increased ($p<0.001$) from early-therapy (4.42±0.63) to late-therapy (7.37±0.40) and was sustained at 6-month follow-up (6.33±0.65, $p=0.106$). There was no difference in the duration of the Wii-baseball swing between groups (low, 1.30±0.51 s; moderate, 1.37±0.24 s; high, 0.75±0.15 s; $p=0.379$), i.e. there was no effect of motor-function level.

Clinical motor-function assessments

The clinical motor-function measures showed significant improvements from pre- to post-therapy. WMFT task times for the pooled data reduced (improved) from 38.1±7.8 s to 33.6±7.2 s ($p=0.004$), FMA scores increased from 46.6±3.6 to 48.9±3.6 ($p=0.001$), and MALQOM scores of 60.1±8.7 increased to 91.3±8.1 ($p<0.001$). All improvements were sustained at 6-month follow-up so that changes from post-therapy to the follow-up assessments were not significant (WMFT, $p=0.917$; FMA, $p=0.107$; MALQOM, $p=0.454$).

Discussion

In this longitudinal study, we identified and quantified muscle synergies during formal therapy sessions for patients with chronic stroke and different levels of motor-function at early- and late-therapy, and for a subset of patients at 6-month follow-up. As far as we can ascertain, this is the first study to investigate changes in the co-ordinated activation of muscles in chronic stroke during rehabilitation activities, rather than during unrelated clinical assessment tasks or restricted experimental tasks. The novel aspects of this study include a broad spectrum of post-stroke residual voluntary motor-function; and the nature of the complex movement that was largely unconstrained, i.e. the start- and end-points were not experimentally pre-determined. Therapist-guided quality of movement was the primary objective of the task during which EMG was recorded, and not the recording per se or game performance. Despite this, we identified differences in the number of muscle synergies used by patients as a function of the level of motor deficit. Thus, the profile of co-ordinated muscle activation varied with the level of residual motor-function in chronic stroke.

There is abundant evidence in the literature that motor ability is stable in the post-stroke chronic period (Krakauer, 2006; Mirbagheri & Rymer, 2008; Stinear, 2010), even in the presence of some therapy protocols (Mehrholz *et al.*, 2015). It is also clear that targeted therapy can improve motor ability in contrast to control groups (Wolf *et al.*, 2006; Page *et al.*, 2008), (see (Teasell et al., 2014)). The control groups receiving usual care in these studies provide further evidence of the stability of motor performance in chronic stroke for patients not receiving therapy or receiving usual care. In our setting, stable motor performance was established using pre-baseline to baseline testing in a randomised controlled study comparing Wii-based Movement Therapy and modified Constraint-induced Movement Therapy (McNulty *et al.*, 2015b).

The statistical outcomes in this study underestimate the level of information provided by this complex series of analyses and reflect the absence of a consistent pattern of

change for between-patient EMG as identified in Chapter 2 (Hesam-Shariati *et al.*, 2017a). The number of synergies used during Wii-baseball increased (although not significantly) with therapy for patients with low and moderate motor-function. At early-therapy there was a trend between the number of synergies and the level of motor-function that suggests different patterns of co-ordinated muscle activation between motor-function groups. The VAF of muscle synergies increased with a higher number of synergies, since the muscle activation can be defined more accurately with more synergies (i.e. smaller error) (Clark et al., 2010). VAF changed significantly with the level of motor-function but not over time within a level. Clustering the synergies from all patients showed that the incidence of three clusters has an association with the level of motor-function. Cluster analyses provides a means of demonstrating changes in the muscle weighting of some synergies between control and stroke groups (Roh et al., 2015). This suggests the distribution of muscle weightings within synergies in the present study changed as a consequence of therapy, as most synergy clusters changed from early- to late-therapy.

The similarity of muscle synergies has been investigated differently across studies. For example, the similarity of muscle weightings was used to demonstrate patients with different levels of motor ability used the same muscles during an isometric force generation task (Roh et al., 2015); whereas the timing profile was used to reveal different numbers of muscle synergies according to the level of motor ability during gait cycle (Clark et al., 2010). Our results reflect those of Clark and colleagues (2010), in that the similarity of synergy timing profiles was used to distinguish the difference in the number of muscle synergies between groups: three distinct synergies defined the movement for patients with low motor-function, while four synergies were required for patients with moderate and high motor-function.

The co-ordination necessary to define a complex movement was associated with the level of residual voluntary motor-function but not the duration of the swing, with differences across time-points not as evident as those shown in EMG analysis (Hesam-Shariati *et al.*, 2017a). This was confirmed by video recordings showing

less complexity and more muscle co-activation for patients with low motor-function. Yet despite significant improvements in clinical assessments and Wii-baseball game performance, there was no difference in the number of muscle synergies over time. However, the change in the structure of muscle weightings from the cluster analysis at early- and late-therapy indicates that muscle recruitment changed between time-points; and that there was more diversity in muscle synergies after therapy.

Typically, muscle synergies for stroke patients are derived from stereotypical (Cheung et al., 2009; Clark et al., 2010) or experimentally constrained (Roh *et al.*, 2015; Li *et al.*, 2016) tasks. However in this study, the movement was largely unconstrained. Although this may have reduced the sensitivity of the analysis, it is a better reflection of task-related real-world use of the upper-limb after stroke. This approach also provides a more direct assessment of the neurophysiological changes induced by therapy (Trinh et al., 2016b). Stroke patients with different levels of motor-function use different strategies to resolve the same problem (task) (Cirstea & Levin, 2000). As highlighted in Chapter 2 (Hesam-Shariati *et al.*, 2017a), the muscle characteristics for each patient differ depending on various neuromuscular limitations including weakness, hyper-tonicity and spasticity. Such differences alter the goals of therapy (McNulty *et al.*, 2015b) and result in more deliberate movement patterns than are seen in healthy control subjects (Mouawad et al., 2011).

The movement analysed in this study was performed as part of a structured therapy program (McNulty, 2012) with no attempt at standardisation as would occur under experimental conditions (Coscia et al., 2014; Roh et al., 2015). Due to the range of motor impairment of the patients involved in this study, there were no standardised requirements for specific joint involvement or movement. The aim of this movement during therapy was to increase movement excursion (range-of-motion), velocity, strength and control based on the generalised movement parameters of a baseball swing by a healthy subject. Although little attention was paid to the rules of the game, those for Wii-baseball provided some consistency in the patient striking response, in that the ball must be pitched (by the device) within a relatively small

area (Deutsch et al., 2011). Thus, the onset of movement was determined through the delivery of the ball by the device. When the patient mistimed the movement and did not hit the ball but completed a swing, this movement was included in the analysis. While the start-point of the movement was in an unrestricted task-dependant spatiotemporal framework, the end-point, duration, speed and direction were unconstrained a priori (McNulty *et al.*, 2015b; Trinh *et al.*, 2016a).

The muscles contributing to a synergy varied from patient to patient and between patients within each level of motor-function. Synergy analysis provides a means of examining changes in motor co-ordination after stroke independent of the movement strategy of each patient (McMorland et al., 2015). Chapter 2 (Hesam-Shariati *et al.*, 2017a) focused on the dominant muscle activated during each activity. Here synergy analyses provide a means of understanding how the brain co-ordinates neuromuscular control of movement (Ting & McKay, 2007) that can be used to build a dynamic model of the post-stroke rehabilitation process.

Clearly, more than 6 muscles are necessary to produce the movement studied, even post-stroke. We were limited in the number of channels available by the recording system and have previously reported EMG of tibialis anterior (Trinh et al., 2016b). The upper body muscles in this study were selected for two main reasons. First, they included a distribution along the neuromuscular axis of the more-affected side. Second, this recording montage limits the potential for EMG cross-talk (Hug, 2011) while still reflecting the major muscle groups involved in the movement across the patient cohort (Deutsch et al., 2011). We incorporated EMG from the trapezius muscle in this analysis as a surrogate marker for trunk rotation where biceps and deltoid activation were insufficient to generate sufficient swing movements in Wii-baseball. EMG data from FDI were included to reflect the use of the hand during therapy because this muscle is readily accessible during therapy and was taken as a surrogate marker of intrinsic hand muscle activity. FDI activation was task-dependant during Wii-baseball. EMG from triceps brachii was not recorded due to technical limitations including its very low level of activation compared to biceps brachii (Bowden *et al.*, 2014b) and problems with loose skin in older patients which

when combined with gravity acted to pull the sensor away from the muscle, rendering such recordings unreliable.

Synergy analysis addresses co-ordinated muscle activation (between muscles) rather than activation within each muscle. It is impossible after stroke to assume any similarity of underlying physiology and anatomy or to individually record the activity of each motor unit contributing to compound muscle activity. Any recording of EMG or method of EMG analysis will provide a biased estimate of activity (De Luca *et al.*, 2010; Tibold & Fuglevand, 2015). The number of simultaneous recordings will not reduce the bias; in our experience it increases the potential for cross-talk and phase cancellation. Given the variability of impairment and ability after stroke both in the neuromusculature and factors impinging on the neuromusculature (e.g. somatosensation), in addition to the trial to trial variability for any given patient, it would be extremely difficult to estimate the ideal number of channels necessary for error-free synergy analyses.

Clinical implications

This study addresses the paucity of neurophysiological studies after stroke and as a consequence of therapy. This longitudinal investigation of changes in muscle synergies with therapy in chronic stroke across patients with different levels of motor-function provides initial insights into some of the neurophysiological mechanisms underpinning a therapy that is the equivalent of current best practice post-stroke, namely Constraint-induced Movement Therapy (McNulty *et al.*, 2015b). Although there were few changes in the number of synergies, the altered structure of muscle synergies suggest that the co-ordination of muscle activation did improve and that this change was reflected in improved clinical assessment data (Tropea et al., 2013). In particular the significant improvements in MALQOM scores reflect greater independence in activities of everyday living (McNulty *et al.*, 2015b).

This study demonstrates that the number of synergies, synergy timing profiles, distribution of muscle weightings, and VAF for muscle synergies differ according to the level of motor-function; particularly for patients with low motor-function at early-

therapy. These differences provide more detailed information about the neurophysiological functioning after stroke and how this changes with therapy. We hypothesise that altered muscle synergy structure reflects changes in brain connectivity but this requires specific investigations of brain imaging or brain stimulation (Bajaj et al., 2015; Rathee et al., 2016). Nevertheless, the structure of muscle synergies can be used as an approach to classify stroke patients and to inform rehabilitation methods. However muscle synergy analyses are insufficient on their own to fully understand neurophysiological changes with therapy after stroke and these analyses further emphasise the absence of any one tool to adequately quantify and explain the changes after stroke or with rehabilitation.

Study limitations

The primary focus of Wii-based Movement Therapy is on the quality of movement, and increasing independent use of the more-affected upper-limb in everyday tasks (Mouawad *et al.*, 2011; McNulty *et al.*, 2015b). For this reason therapy instructions are not those that would be used with healthy control subjects. For example, the different phases of the movement are emphasised differently depending on the level of motor impairment, and may be practiced individually before being combined during the game performance using the principles of shaping (Taub *et al.*, 1994), much like a sporting drill. Although the absence of healthy control subjects is a limitation of this study, the different movement patterns observed during game play (Mouawad *et al.*, 2011) may limit the usefulness of such comparisons.

The sample size in this study is small within each level of motor-function. However, the total number of patients compares well with previous stroke studies investigating muscle synergies (Cheung *et al.*, 2012; Coscia *et al.*, 2015; Roh *et al.*, 2015; Li *et al.*, 2016). According to clinical assessment scores this cohort included a wide range of residual voluntary motor capacity, particularly those with low motor-function who are rarely recruited in post-stroke therapy and neurophysiology studies. This approach reduces the potential for statistically significant outcomes when data are pooled (Trinh et al., 2016b) but provides data that can be more readily generalised

to the stroke population, although this study in chronic stroke cannot be generalised to the acute and sub-acute phase.

Conclusion

Motor control differs for patients with different levels of residual voluntary motor-function when performing the same movement. Despite this, muscle synergies can be identified and monitored during therapy to understand changes in motor control of a largely unconstrained complex movement. A higher number of muscle synergies reflects greater movement complexity and task-related phasic muscle activation. This result is evidence for less complexity and more co-activation in the patterns of muscle activation for patients with low motor-function. The increased number of synergies by late-therapy suggests improved motor control with more distinct phases of movement for patients with low motor-function. The change in the muscle synergy clusters by late-therapy and different patterns of recovery indicate that the recruitment and activation of muscles change during therapy.

Better motor control in a longitudinal study of complex therapy movement in chronic stroke

Chapter **4**

Abstract

Impaired motor control post-stroke is traditionally measured using clinical assessments that mostly use categorical and subjective scoring. We investigated kinematic parameters of a complex movement to obtain quantitative measures of longitudinal changes in motor performance as a consequence of Wii-based Movement Therapy in chronic stroke.

Tri-axial accelerometry was recorded from 6 sensors placed on the more-affected arm and upper body of 24 patients at early- (day 2-3) and late- (between days 12-14) therapy, and for a subset of 13 patients at 6-month follow-up. Patient motor-function was classified as low, moderate or high according to performance on two tests of manual dexterity. Acceleration magnitude, normalised velocity and jerk, and peak acceleration and deceleration were measured during Wii-baseball swings. Clinical assessments were the Wolf Motor Function Test, upper-limb motor Fugl-Meyer Assessment and the Motor Activity Log Quality of Movement scale. The effect of time and level of motor-function was examined for kinematic and clinical changes.

Acceleration magnitude increased over time but this was significant only at proximal sensors ($p<0.05$) with an effect of motor-function on the acceleration at distal sensors ($p<0.05$). Normalised velocity decreased ($p<0.05$) at all sensors over time. Peak acceleration and deceleration increased and decreased over time, respectively, predominately at proximal sensors. All clinical measures improved over time (all $p<0.01$) with an effect of level of motor-function ($p<0.001$). Only two significant correlations were found between clinical assessments and kinematic parameters, one each with peak acceleration and deceleration but at different sensors and on different axes.

This study demonstrates that kinematic parameters provide an objective and quantitative measure of change in motor-function that is not possible with clinical assessments. The changes in kinematics were largely unrelated to changes in clinical assessments. The complex patterns of change were not consistent between and within levels of motor-function but reflected improved motor control, and were sustained over time. These data emphasise the potential for ongoing improvements in motor capacity in chronic stroke with additional rehabilitation.

Introduction

Impaired voluntary control of movement after stroke is mainly attributed to weakness of the contralesional limbs, which is a consequence of many factors including reduced corticospinal drive, spasticity, and disuse muscle atrophy. Post-stroke impairment of the upper limbs is more common than of the lower limbs (Song et al., 2008). Motor recovery of the upper-limb is crucial for ADL although this may be more complicated than recovery of lower-limb (Levin et al., 2009). This complexity stems from upper-limb movement being less stereotypical and rhythmic than lower-limb movement, and requiring more degrees of freedom across multiple joints.

Traditional post-stroke motor assessments predominantly focus on task completion, often using subjective (de los Reyes-Guzmán et al., 2014) and categorical scoring (Alt Murphy & Häger, 2015; Thompson-Butel *et al.*, 2015). Few clinical measures quantify how well the task is performed (Buma et al., 2013) but can provide a measure of task improvement on test items either over time or as a consequence of therapy. Analysis of muscle activation either by the study of individual muscle electromyography (EMG) or the co-ordinated activation of a group of muscles (known as muscles synergies), provide more objective measures. EMG analysis permits the direct quantification of the output of the neuromuscular system (Hu et al., 2009) including EMG area under the curve (Hesam-Shariati *et al.*, 2017a), muscle activation duration, and muscle synergies (Cheung *et al.*, 2012; Hesam-Shariati *et al.*, 2017b). Changes in these measures reflect altered muscle activation, duration, and muscle co-ordination. However, none of these measures is individually able to define the quality of movements or a change in the quality of movement with therapy or time (Hesam-Shariati *et al.*, 2017a, b). Quantitative and objective measures of movement quality are essential for assessing therapy-induced changes and neurorehabilitation outcomes after stroke (de los Reyes-Guzmán et al., 2014); this has been strongly referred to in the recent Stroke Recovery and Rehabilitation Roundtable (Kwakkel et al., 2017). Aspects of 3-dimensional kinematics including acceleration, velocity, and displacement can quantify and define movement in space and time without reference to the forces involved (Hamill & Knutzen, 2006; Winter,

2009). Post-stroke upper-limb kinematics has been used to characterise important aspects of movement including smoothness, duration, displacement, speed and acceleration. In this way movement performance has been evaluated in tracking or pointing tasks (Knaut *et al.*, 2009; Kitago *et al.*, 2012), reach-and-grasp tasks (Lin et al., 2007; Lum et al., 2009), and ADL movements (Thies *et al.*, 2009; Alt Murphy *et al.*, 2011; Aprile *et al.*, 2014; Kim *et al.*, 2014; Bailey *et al.*, 2015).

An increase in the smoothness of movement is a characteristic of post-stroke motor recovery (Bosecker et al., 2010; Dipietro et al., 2012), motor learning (Franklin et al., 2008), and spatiotemporal co-ordination (Balasubramanian et al., 2015). Different measures have been proposed to quantify smoothness, including normalised jerk (Rohrer *et al.*, 2002; van Kordelaar *et al.*, 2014; Buma *et al.*, 2016), velocity peak count (Rohrer *et al.*, 2002; Cirstea *et al.*, 2003; Dipietro *et al.*, 2012), submovement count (Cirstea *et al.*, 2003; Kitago *et al.*, 2012; Aprile *et al.*, 2014), and spectral arc length (Balasubramanian et al., 2015). Jerk is the first derivative of acceleration and jerk-based measures appear most frequently in the literature. Dimensionless jerk is a valid and practical measure of movement smoothness (for review see (Balasubramanian et al., 2015)).

Kinematic data have been used to investigate changes in movement characteristics as a consequence of therapy, or reported in longitudinal studies for patients with chronic stroke (Wu *et al.*, 2007b; Lemmens *et al.*, 2014; Kitago *et al.*, 2015). However, movements that have been studied have predominantly been experimentally constrained, or simplified and isolated goal-oriented tasks rather than complex real-world movements, (for review see (Alt Murphy & Häger, 2015)). In this study, kinematic analyses were combined with clinical measures, to assess therapy-induced longitudinal changes in patients with chronic stroke. The kinematic parameters were derived from tri-axial accelerometer data to examine the mechanisms underlying the improvements that have previously been identified using clinical assessment tools following a 14-day program of Wii-based Movement Therapy (WMT) for patients with a broad spectrum of residual voluntary post-stroke motor capacity (Mouawad *et al.*, 2011; McNulty *et al.*, 2015b). We hypothesised that

there would be a correlation between the improvement in clinical assessment scores and changes in kinematic parameters. Our secondary hypothesis was that these changes would be associated with the level of residual motor capacity.

Methods

Participants

Accelerometry and clinical assessment data were collected from the 30 patients with chronic stroke who had completed WMT with tri-axial accelerometry recordings (see below). Patients were recruited from St Vincent's and the Prince of Wales Hospitals, Sydney, Australia. Their motor-function at baseline was classified into three groups with low, moderate or high levels of motor-function based on the ability to perform a test of gross (Box and Block Test) and fine manual dexterity (grooved pegboard test), according to the scheme of Thompson-Butel and colleagues (2014). Thirteen patients were classified with low, 9 with moderate, and 8 with high motor-function. To obtain balanced groups, data from all 8 patients with high motor-function were included, and 8 patients were randomly selected from each of the low and moderate motor-function groups using a computer-generated algorithm. All patients were enrolled in the 14-day program of WMT but only 13 patients (3 low, 5 moderate and 5 high motor-function) were available for 6-month follow-up. Ten patients were unavailable; 1 returned to work, 4 moved inter-state/overseas, 2 had unrelated health issues, and 3 had insufficient time for neurophysiological measures. The data for one patient were lost due to technical issues. Patient demographics are presented in Table 4-1. Inclusion criteria included: voluntary movement in at least one digit of the more-affected hand >10˚; cognitively competent as measured using the Mini-Mental State Examination with a score ≥24; time post-stroke ≥3 months (i.e. in the chronic post-stroke phase); and the ability to communicate in English. Exclusion criteria were: unstable blood pressure; comorbidities significantly affecting upper-limb sensorimotor function; engagement in any other upper-limb therapy program; and skin unsuitable for adhesive sensors. EMG data from the same 24 patients have been reported previously (Hesam-Shariati *et al.*, 2017a, b). The pre- and post-therapy clinical measures were reported previously; n=9 in a randomised controlled trial comparing WMT and modified Constraint-induced Movement

Therapy (McNulty *et al.*, 2015b), n=20 in other WMT trials investigating patients with low and very low motor ability, clinical motor assessments, and cardiovascular fitness (McNulty *et al.*, 2013a; Thompson-Butel *et al.*, 2015; Trinh *et al.*, 2016a), and n=20 in a post-stroke genotype study (Shiner *et al.*, 2016). The accelerometry data have not been previously reported. Clinical assessments, therapy implementation, and kinematic data recording and analyses were performed by independent assessors. All patients gave signed informed consent to the study which was approved by St Vincent's Hospital Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Table 4-1. Baseline demographics of patients with low, moderate and high level of motor-function. More-affected dominant indicates when the more-affected side of patient was their dominant side pre-stroke. isch: ischaemic, haem: haemorrhage.

	low	**moderate**	**high**	**all**	range
N	8	8	8	24	
Age	59.1±13.9	55.1±11.3	59.4±12.2	57.9±12.1	37-80
Time post-stroke (months)	33.3±9.4	27.3±8.0	19.6±4.5	26.7±4.3	3-88
Sex (f/m)	4/4	2/6	2/6	8/16	
More-affected dominant (yes/no)	1/7	3/5	3/5	7/17	
Stroke type (isch/haem)	3/5	7/1	6/2	16/8	

Therapy

Wii-based Movement Therapy (WMT) is a 14-day structured protocol that targets movement quality and independent use of the more-affected upper-limb (Mouawad *et al.*, 2011; McNulty *et al.*, 2013a; McNulty *et al.*, 2015b). It uses the Nintendo Wii and Wii-Sports games (Nintendo, Japan) of Wii-golf, -baseball, -bowling, -tennis, and -boxing, as a rehabilitation tool. The therapy consists of a one hour formal session administered by an Accredited Exercise Physiologist on ten consecutive weekdays, and is augmented by home practice which starts on day 2, the duration of which increases over the 14-day program (see Chapter 1, Fig. 1-3). The Wii-controller is held only with the more-affected hand during therapy and the difficulty of each game's activities could be varied based on the patients' level of motor-function, needs and progress during therapy. If patients were unable to use only the more-affected arm, assistance was provided by the less-affected hand or the therapist,

and this was progressively reduced or removed over the 14-day program. Analysis of accelerometry data was only applied to the Wii-baseball swing for several reasons: all 24 patients were able to complete this game, and individual swings during the game could be clearly identified in the kinematic signals, since the onset of each swing was determined by the game via pitching the ball.

Clinical assessments and game performance

Upper-limb motor-function was assessed immediately pre- and post-therapy, and for a subset of patients, at 6-month follow-up using the Wolf Motor Function Test timed-tasks (WMFT-tt) (Wolf *et al.*, 1989), and upper-limb motor Fugl-Meyer Assessment (FMA) (Fugl-Meyer *et al.*, 1974). In addition, the Motor Activity Log Quality of Movement scale (MALQOM) was used to evaluate independence in ADL (Uswatte *et al.*, 2005). These measures were unrelated to the content of therapy. The number of baseball hits was recorded during each therapy session. A hit was counted when contact was made with the ball, regardless of the rules of baseball.

Accelerometry recording

The tri-axial accelerometry data were recorded from six wireless sensors (Trigno, Delsys, USA) placed on the more-affected side of the upper body: one on the middle portion of trapezius; two on the upper arm (deltoid medius (DM) and biceps brachii (BB)); two on the forearm (extensor and flexor carpi radialis (ECR and FCR)); and one on the hand (first dorsal interosseous (FDI)). The data collection was performed at two time points during formal WMT sessions: at early- (day 2-3) and late- (between days 12-14) therapy, and for a subset of patients at 6-month follow-up. The signals were amplified 80 times, filtered at 50 Hz, and sampled at 148.15 Hz based on the intrinsic properties of the sensors using EMGworks (Delsys, USA). A concurrent high-definition video recording was made during these sessions to enable a qualitative movement overview and to confirm data alignment in sensor recordings.

While playing Wii-baseball, patients were instructed to stand side on to the television screen to enable the more-affected arm to perform the swing. The initial and final

positions of the arm during Wii-baseball swing are illustrated in Figure 4-1A together with the placement of each sensor. The x-axis of each sensor was aligned to the orientation of the targeted muscle fibres. The directions of the three axes of each sensor are shown in Figure 4-1B.

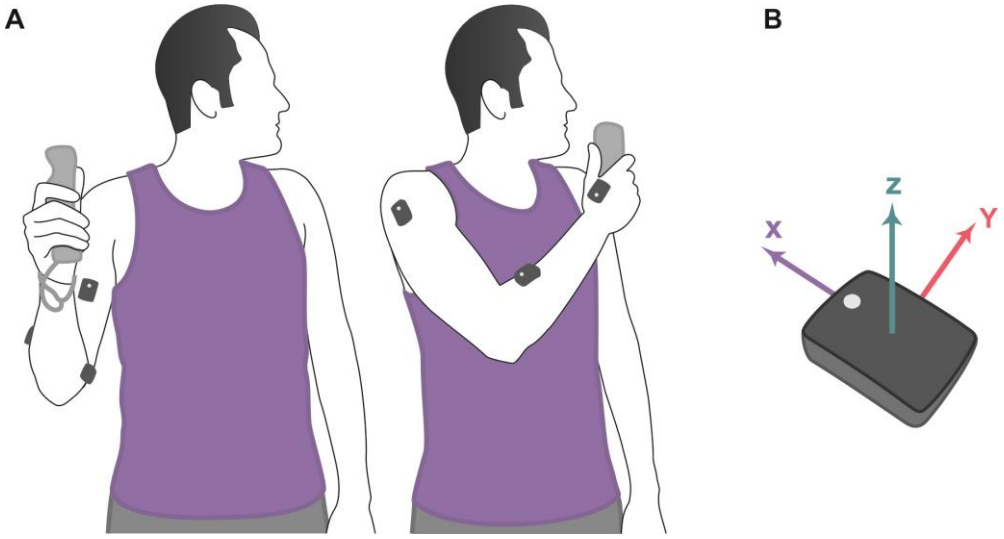

Figure 4-1. The tri-axial accelerometry recordings. (A) A typical start- and end-position of the arm during Wii-baseball swing when the controller is held only with the more-affected hand. **(B)** The direction of the x-, y-, and z-axes of the sensors used in this study.

Data analysis

The accelerometer signals from the three axes were smoothed using a sliding 50 ms window (i.e. averaged over 7 samples) in Spike2 software (CED, UK). Then, calibrated tri-axial accelerometer signals (see below) were high-pass filtered in MATLAB (MathWorks, USA). Peak acceleration and deceleration (along each axis), mean acceleration magnitude, normalised velocity magnitude, and normalised jerk magnitude were calculated and compared between patients with different levels of motor-function, and over time (see *Kinematic outcome measures* for details).

Sensor calibration procedure

To ensure the accuracy of signals, the sensors were calibrated using a procedure addressing the main sources of measurement error: sensor bias, non-orthogonality

between sensor axes, and sensor sensitivity (Skog & Händel, 2006; Jurman *et al.*, 2007). To do so, the vector model was defined as:

$$\vec{y} = STu\vec{} + \vec{b}$$

where $\vec{y}$ is the sensor output, S the sensitivity matrix, T the orthogonalisation matrix, $\vec{u}$ the desired output, and $\vec{b}$ the sensor bias. A 3x3 diagonal matrix was assigned to S, one element for the sensitivity of each axis. The matrix T was created based on the Gram-Schmidt method (Pursell & Trimble, 1991) to find the three angles between the orthogonal sensor basis and the non-orthogonal sensor frame. A 3-by-1 vector could define the sensor bias.

$$\vec{y} = \begin{bmatrix} y_x \\ y_y \\ y_z \end{bmatrix} \quad S = \begin{bmatrix} S_x & 0 & 0 \\ 0 & S_y & 0 \\ 0 & 0 & S_z \end{bmatrix} \quad T \approx \begin{bmatrix} 1 & 0 & 0 \\ \cos\alpha & 1 & 0 \\ \cos\beta & \cos\gamma & 1 \end{bmatrix} \quad \vec{u} = \begin{bmatrix} u_x \\ u_y \\ u_z \end{bmatrix} \quad \vec{b} = \begin{bmatrix} b_x \\ b_y \\ b_z \end{bmatrix}$$

Once the parameters of S, T, and $\vec{b}$ were known for each sensor, an estimation of the calibrated data could be found:

$$\vec{u} \approx T^{-1}S^{-1}(\vec{y} - \vec{b})$$

To find the nine parameters of S, T, and $\vec{b}$, at least 9 different accelerometer estimates are needed to be approximately equispaced on the surface of a sphere with the centre of the origin in the sensor frame. Thus, to ensure a more accurate result, the sensors were held still in 15-20 different positions, and the tri-axial accelerometer signals were recorded for at least 10 s in each position. The positions themselves were not important as long as they were different from each other. Newton's optimisation method (Avriel, 2003) was used to minimise the mean square error between the reference and the corresponding value of accelerometry. The Earth's gravitational acceleration in Sydney (9.7967 m/s2) (Gibbings et al., 1971) was used as the reference value. The parameter search was initialised close to the expected true parameter values:

$$\begin{bmatrix} S_x \\ S_y \\ S_z \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix} \qquad \begin{bmatrix} \alpha \\ \beta \\ \gamma \end{bmatrix} = \begin{bmatrix} \pi/2 \\ \pi/2 \\ \pi/2 \end{bmatrix} \qquad \begin{bmatrix} b_x \\ b_y \\ b_z \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

The search space is constrained based on the range that these parameters can take on, according to experimental measurement, as:

$$0.8 < S_x, S_y, S_z < 1.3 \qquad 1 \text{ rad} < \alpha, \beta, \gamma < 1.8 \text{ rad} \qquad -5\,\frac{m}{s^2} < b_x, b_y, b_z < 5\,\frac{m}{s^2}$$

Kinematic outcome measures

After determining the calibration parameters for each sensor and applying them to the tri-axial accelerometer signals, the calibrated signals were derived from the raw measurements and high-pass filtered to extract the acceleration of movement across three axes; high-pass filtering removes any low-frequency sensor noise (either electronic noise, or sensor movement where attached to the body) and approximately removes the gravitational acceleration from each measurement axis. We used a fourth-order high-pass Butterworth filter with a normalised cut-off frequency of $f_c/(f_s/2)$, while f_c was the cut-off frequency of 0.5 Hz and f_s the sensor sampling frequency of 148.15 Hz.

To enable comparisons between kinematic parameters within and across patients and time-points, all Wii-baseball swing movements were assigned a notional duration. Thus the duration of the data extracted for each swing was 3 s to account for the longest swing recorded.

Acceleration. Peak acceleration and deceleration of each direction were respectively calculated as the 99% of maximum and minimum values of the acceleration vectors at each sensor. They were compared along three axes at all sensors. In addition, the magnitude of mean acceleration (a_{mag}) was measured at each sensor using the equation below, combining acceleration along three axes (a_x, a_y and a_z).

$$a_{\mathrm{mag}} = \sqrt{{a_{\mathrm{x}}}^2 + {a_{\mathrm{y}}}^2 + {a_{\mathrm{z}}}^2}$$

Velocity. Velocity was integrated from the acceleration data along three axes of each sensor, its magnitude was determined as for acceleration magnitude (above). Normalised velocity was calculated as the velocity magnitude ($\mathrm{v_{mag}}$) divided by the greatest value of velocity magnitude as peak velocity ($\mathrm{v_{peak}}$).

$$\text{normalised velocity} = \frac{\mathrm{v_{mag}}}{\mathrm{v_{peak}}}$$

Movement smoothness. The natural logarithm function of dimensionless jerk was used to quantify movement smoothness in this study. Jerk is the first derivative of acceleration and velocity is the integration of acceleration. In the following formula, $\mathrm{j_{mag}}$ is the jerk magnitude (combined from three axes) and $\mathrm{v_{peak}}$ is the peak of velocity magnitude.

$$\text{normalised jerk} = \ln\left(\frac{(\mathrm{t_2} - \mathrm{t_1})^3}{\mathrm{v_{peak}^2}} \int_{\mathrm{t_1}}^{\mathrm{t_2}} \mathrm{j_{mag}^2 dt}\right)$$

Statistical analysis

All kinematic parameters were averaged for 10 consecutive Wii-baseball swings of each patient at early- and late-therapy, and for a subset of patients at 6-month follow-up. Data were compared from pre- to post-therapy (clinical measures), or early- to late-therapy (kinematics measures), using paired t-tests (mean±SE) for normally-distributed data, and otherwise using Wilcoxon signed-rank tests (median, IQR). To test for normality, the Shapiro-Wilk test was used as the best approach for sample sizes <30. Longitudinal data were analysed using linear mixed model of repeated measures with factors of motor-function (low, moderate, high), time (pre-/early-therapy, post-/late-therapy, 6-month follow-up), and an interaction between motor-function and time. A linear mixed model is flexible and can provide unbiased estimates in the absence of some data, in this case at 6-month follow-up (Ashbeck & Bell, 2016), since it emphasises the pattern of changes and not the absolute

differences (Krueger & Tian, 2004). Pearson and Spearman's correlation were used as parametric and non-parametric tests, respectively, with Bonferroni corrections to examine the relationship between the therapy-induced changes in clinical measures (WMFT-tt, FMA, and MALQOM) and changes in kinematic parameters. Statistical analyses were conducted in SPSS 24 (IBM, USA) and differences were considered significant when $p<0.05$.

Results

All 24 patients completed clinical assessments and WMT including the Wii-baseball games during formal sessions and prescribed home practice. No adverse event was reported, either minor or major.

Therapy-induced changes in kinematics (early- to late-therapy)

Acceleration magnitude increased at all sensors (induced by therapy). This increase was significant only for proximal sensors on DM ($p=0.024$) and trapezius ($p=0.032$), with a non-significant trend for the sensor on BB ($p=0.071$). Normalised velocity decreased at all sensors during Wii-baseball from early- to late-therapy (FDI, $p=0.001$; ECR, $p=0.002$; FCR, $p=0.002$; BB, $p=0.013$; DM, $p=0.014$; trapezius, $p=0.012$), while normalised jerk appeared to also decrease but these changes were not significant. Therapy-induced changes in peak acceleration and deceleration along the x-, y-, and z-axes at all sensors are presented in Table 4-2.

Table 4-2. Peak acceleration and peak deceleration over time; at early-therapy, late-therapy and 6-month follow-up. Therapy-induced *p* values reflect the change as a consequence of therapy (i.e. early- to late-therapy), whereas those for effect of time and effect of motor-function indicate the longitudinal effect of these parameters from early-therapy to 6-month follow-up. Significant changes are highlighted in bold and non-significant trends in italics. Acc: acceleration, Dec: deceleration; FDI: first dorsal interosseous, ECR: extensor carpi radialis, FCR: flexor carpi radialis, BB: biceps brachii, DM: deltoid medius.

Wii-baseball swing	**early-therapy**	**late-therapy**	***p* value** therapy-induced	**follow-up**	***p* value** effect of time	***p* value** effect of motor-function
	n=24	**n=24**		**n=13**		
FDI						
Peak Acc (x)	8.5±0.8	10.2±0.9	**0.032**	9.7±1.0	0.138	**0.009**
Peak Acc (y)	13.1±0.6	14.1±0.6	0.200	14.0±0. 9	0.449	0.632
Peak Acc (z)	16.9±1.1	18.0±1.1	0.303	20.1±1. 3	0.116	0.357
Peak Dec (x)	-12.1±0.7	-14.4±0.7	**0.022**	-13.8±0.7	*0.059*	0.201
Peak Dec (y)	-12.3±0.8	-13.0±0.8	0.391	-13.8±0.8	0.434	0.475
Peak Dec (z)	-11.6±0.7	-11.9±0.5	0.731	-12.7±0.8	0.514	0.614
ECR						
Peak Acc (x)	10.4±0.8	13.1±1.0	**0.022**	14.1±1.4	**0.012**	**0.030**
Peak Acc (y)	8.7±0.9	8.2±0.8	0.535	9.7±1.3	0.693	*0.053*
Peak Acc (z)	7.3±0.8	9.8±0.8	**0.018**	11.8±1.7	**0.022**	**0.007**
Peak Dec (x)	-12.6±0.8	-14.1±0.5	**0.012**	-14.9±1.0	*0.050*	0.379
Peak Dec (y)	-8.6±1.0	-8.8±0.9	0.932	-8.4±1.2	0.560	*0.058*
Peak Dec (z)	-5.2±0.4	-6.7±0.5	**0.012**	-8.2±1.1	**0.006**	**0.008**
FCR						
Peak Acc (x)	9.0±0.8	11.3±1.0	**0.016**	11.4±1.5	**0.031**	*0.055*
Peak Acc (y)	5.3±0.6	5.8±0.6	0.391	6.5±0.9	0.463	**0.048**
Peak Acc (z)	8.1±0.9	9.0±0.8	0.0278	11.3±1.3	0.191	0.221
Peak Dec (x)	-11.8±0.9	-14.0±0.6	**0.049**	-14.8±1.3	**0.049**	*0.059*
Peak Dec (y)	-6.1±0.6	-7.2±0.5	*0.061*	-7.7±0.8	*0.058*	0.205
Peak Dec (z)	-10.0±0.9	-11.1±0.7	0.171	-12.9±1.4	0.183	*0.086*
BB						
Peak Acc (x)	3.3±0.4	3.9±0.4	**0.036**	4.2±0.6	**0.032**	0.670
Peak Acc (y)	6.4±0.7	7.0±0.6	0.341	8.6±1.2	0.172	0.288
Peak Acc (z)	7.6±0.8	9.5±0.7	**0.030**	11.1±1.4	**0.018**	*0.098*
Peak Dec (x)	-5.7±0.5	-6.3±0.5	0.106	-6.3±0.7	0.204	0.130
Peak Dec (y)	-5.7±0.7	-6.5±0.7	0.170	-9.0±1.1	**0.016**	**0.006**
Peak Dec (z)	-4.8±0.4	-7.3±0.7	**<0.001**	-7.8±1.1	**<0.001**	*0.097*
DM						
Peak Acc (x)	3.0±0.3	3.82±0.29	**0.016**	4.1±0.3	**0.014**	0.433
Peak Acc (y)	4.8±0.5	6.70±0.44	**<0.001**	6.8±0.8	**<0.001**	0.873
Peak Acc (z)	4.8±0.7	5.43±0.72	0.230	6.5±1.1	0.387	0.250
Peak Dec (x)	-4.7±0.5	-5.43±0.48	*0.074*	-5.9±0.7	0.144	0.152
Peak Dec (y)	-4.9±0.4	-6.97±0.52	**0.003**	-6.5±0.7	**0.003**	0.400
Peak Dec (z)	-2.2±0. 2	-2.40±0.18	0.266	-2.7±0.3	0.361	0.160
trapezius						
Peak Acc (x)	1.8±0.2	2.7±0.3	**0.013**	3.4±0.5	**0.008**	0.896
Peak Acc (y)	3.0±0.4	4.2±0.5	**0.009**	5.1±0.6	**0.001**	0.346
Peak Acc (z)	2.7±0.3	3.7±0.4	**0.008**	4.5±0.5	**0.001**	0.836
Peak Dec (x)	-2.0±0.2	-2.7±0.3	*0.057*	-3.7±0.7	**0.009**	0.905
Peak Dec (y)	-3.2±0.3	-4.2±0.4	**0.027**	-4.7±0.5	**0.014**	0.904
Peak Dec (z)	-2.2±0.2	-2.9±0.2	**0.005**	-2.8±0.3	**0.039**	0.517

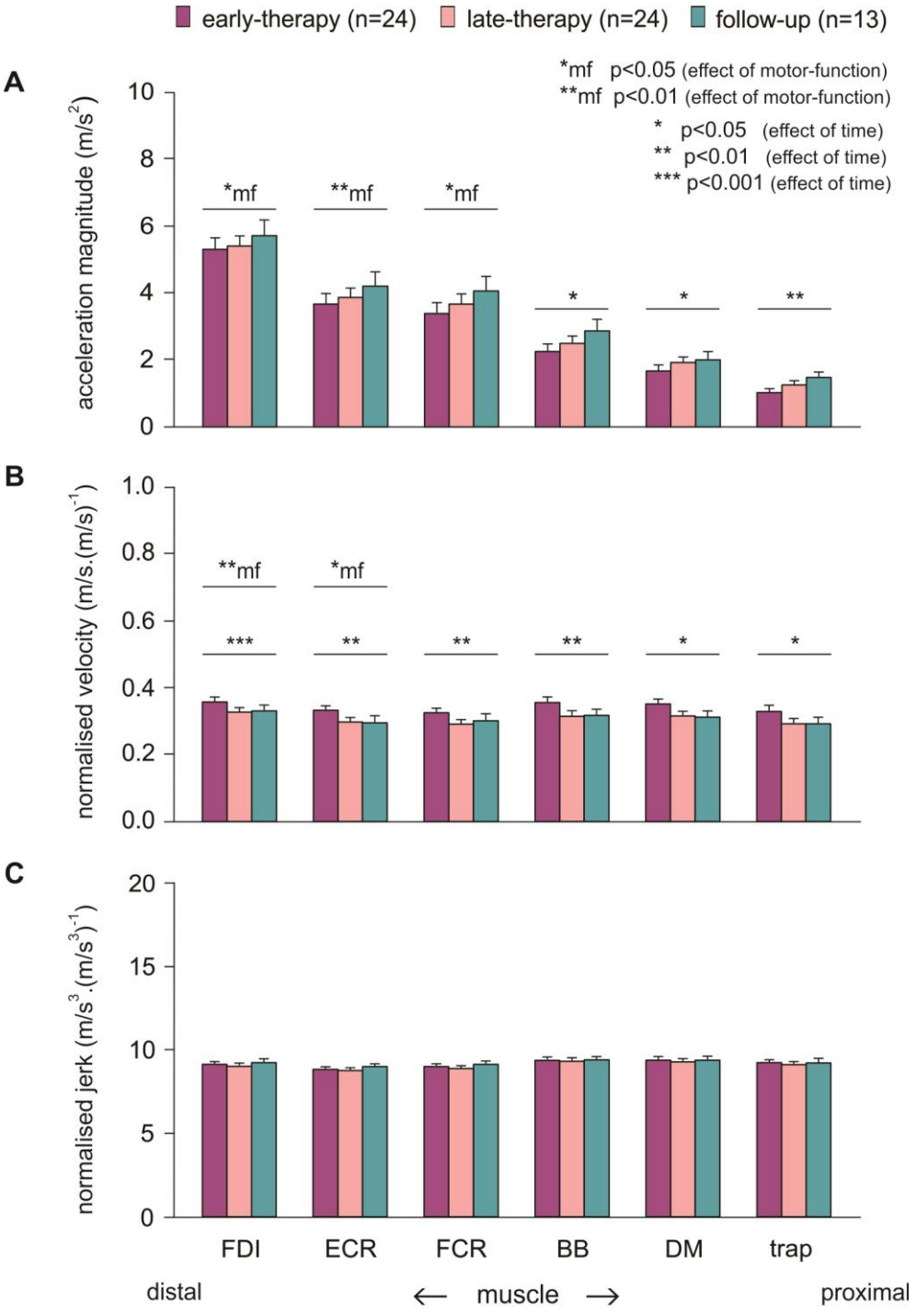

Figure 4-2. Pooled data showing changes in kinematic parameters over time. Longitudinal changes of **(A)** mean acceleration magnitude, **(B)** normalised velocity, and **(C)** normalised jerk are presented over time according to the level of residual voluntary motor-function. All data are presented as mean±SE. FDI: first dorsal interosseous, ECR: extensor carpi radialis, FCR: flexor carpi radialis, BB: biceps brachii, DM: deltoid medius; mf: the effect of motor-function.

Longitudinal changes in kinematics over time

(early-therapy, late-therapy, and follow-up)

Linear mixed models demonstrated that acceleration magnitude increased over time ($p<0.05$) at proximal sensors (BB, DM and trapezius), although there was no effect of motor-function level. At distal sensors (FDI, ECR and FCR), acceleration magnitude did not change significantly over time but there was a significant effect of the level of motor-function ($p<0.05$) at these sensors (Fig. 4-2A). Even though acceleration magnitude increased for the pooled data, Figure 4-3 shows that the pattern of change for individual patients was different and complex. Normalised velocity decreased over time at all sensors (FDI, $p<0.001$; ECR, $p=0.001$; FCR, $p=0.004$; BB, $p=0.006$; DM, $p=0.014$; trapezius, $p=0.031$), however, there was only a significant effect of motor-function at FDI ($p=0.003$) and ECR ($p=0.013$) (Fig. 4-2B). There was no change in normalised jerk at sensors over time (Fig. 4-2C). The effects of time and level of motor-function on the longitudinal changes of peak acceleration and deceleration are reported in Table 4-2.

Therapy-induced changes in clinical measures (pre- to post-therapy)

Clinical assessment scores for the pooled dataset improved significantly from pre- to post-therapy (Table 4-3). WMFT-tt completion times decreased from 38.1±7.8 s to 33.6±7.2 s ($p=0.004$); FMA scores increased from 46.6±3.6 to 48.9±3.6 ($p=0.001$); and MALQOM scores increased from 60.1±8.7 to 91.3±8.1 ($p<0.001$).

Longitudinal changes in clinical measures over time

(pre- and post-therapy, and follow-up)

Linear mixed models showed that WMFT-tt, FMA and MALQOM improved over time (all $p<0.01$) and that there was an effect of level of motor-function ($p<0.001$) on these measures (see details in Table 4-3). There was no effect of the interaction between time and level of motor-function.

Table 4-3. Clinical assessment measures over time; at pre-therapy, post-therapy and 6-month follow-up. Therapy-induced *p* values reflect the change as a consequence of therapy (i.e. pre- to post-therapy), whereas those for effect of time and effect of motor-function indicate the longitudinal effect of these parameters from pre-therapy to 6-month follow-up. WMFT-tt: Wolf Motor Function Test-timed tasks, FMA: upper-limb motor Fugl-Meyer Assessment, MALQOM: Motor Activity Log Quality of Movement.

	pre-therapy	**post-therapy**	***p* value** therapy-induced	**follow-up**	***p* value** effect of time	***p* value** effect of motor-function
N	24	24		13		
WMFT-tt (/120 s)	38.1±7.8	33.6±7.2	**0.004**	30.3±11.1	**0.008**	**<0.001**
FMA (/66)	46.6±3.6	48.9±3.6	**0.001**	52.2±5.0	**0.001**	**<0.001**
MALQOM (/150)	60.1±8.7	91.3±8.1	**<0.001**	90.9±12.6	**<0.001**	**<0.001**

Wii-baseball game performance

The number of Wii-baseball hits increased from early- (4.64±0.42) to late- (7.03±0.34) therapy ($p<0.001$) (as previously reported (Hesam-Shariati *et al.*, 2017a)). The increase over the three time-points was also significant ($p<0.001$) with mean scores of 6.03±0.67 at follow-up. There was no effect of motor-function level on the game scores.

Relationship between changes in kinematics and clinical measures

No correlations were found between therapy-induced changes in clinical measures and changes in mean acceleration magnitude ($|r|<0.42$, $p>0.12$), or normalised velocity magnitude ($|r|<0.32$, $p>0.39$). The only significant correlations found were between changes in clinical measures and those in peak acceleration in the x direction at FDI sensor ($r=-0.49$, $p=0.042$) and with peak deceleration in the z direction at DM ($r=-0.52$, $p=0.027$).

Discussion

This longitudinal study examined changes in upper-limb kinematic parameters of a largely unconstrained movement as part of a rehabilitation program in chronic stroke in a heterogeneous cohort with a broad spectrum of residual voluntary motor capacity. We studied one element of WMT, the complex Wii-baseball swing

movement at early- and late-therapy, and in a subset of patients at 6-month follow-up. As far as we can ascertain, this is the first longitudinal study of recordings made during therapy. All clinical assessments improved over time for the pooled data, whereas the changes in kinematic parameters were not consistent at each sensor (Fig. 4-2) and the pattern of changes for individual patients was complex (Fig. 4-3). Despite this complexity, acceleration magnitude for the pooled data increased over time at each sensor but this was significant only at the sensors on proximal muscles. At distal sensors there were large differences between patients across motor-function groups. There was a significant reduction in normalised velocity at all sensors over time which we interpreted as characteristic of more controlled movement. The combination of higher acceleration magnitude and lower normalised velocity over time demonstrates better motor control induced by therapy, and this was sustained at 6-month follow-up.

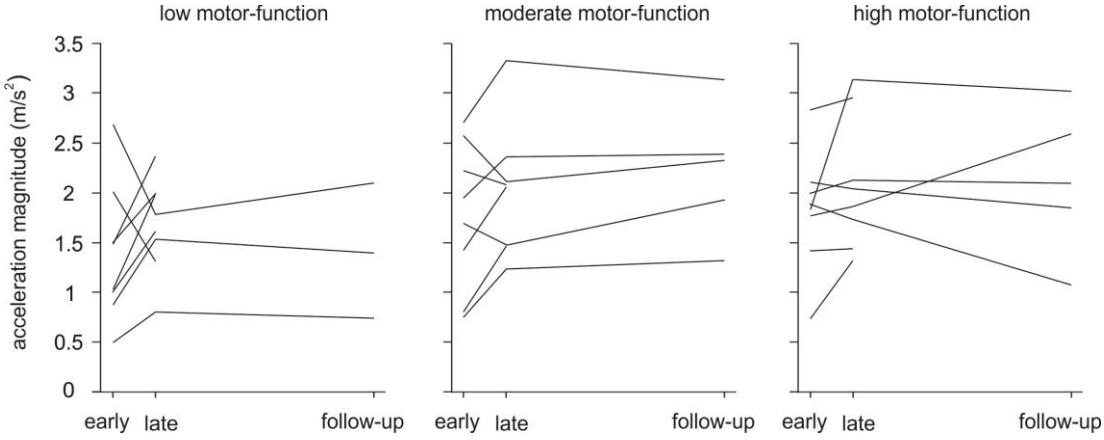

Figure 4-3. Changes in acceleration magnitude over time, individual patient data. The mean acceleration magnitude during Wii-baseball swings is shown for each patient with low (n=8), moderate (n=8) and high (n=8) motor-function at early- and late-therapy and for a subset of patients (3 low, 5 moderate, 5 high) at 6-month follow-up.

Post-stroke kinematic analyses are usually applied to simple or experimentally-restricted tasks with pre-defined start- and end-points (Caimmi *et al.*, 2008; Knaut *et al.*, 2009; Kitago *et al.*, 2012; Buma *et al.*, 2016). The Wii-baseball movement in this study was largely unconstrained in time and space; patients could choose their own start-position within the task framework and the relative end-position reflected their range-of-motion, confirmed on the video recordings. When necessary, the upper-

limb was supported either by the therapist or the patient's less-affected hand although the movement speed, duration and power were determined by the patient alone. We noted improved shoulder excursion as a consequence of therapy which was reflected in the video recordings and a previous preliminary study (McNulty *et al.*, 2015c).

We investigated movement smoothness of this largely unconstrained movement using normalised jerk analysis. However, smoothness measures have most often been used to quantify point-to-point movements (Rohrer et al., 2002; van Kordelaar et al., 2014), or rhythmic movements such as walking (Brach et al., 2010). Movement smoothness is typically task-dependant, and there is no measure sensitive enough to show changes in an unconstrained and exploratory movement (for review see (Balasubramanian et al., 2015)). The complexity of the movement analysed might have reduced the sensitivity of the smoothness analysis compared to previous studies (van Kordelaar *et al.*, 2014; Buma *et al.*, 2016), however we hypothesise that this therapy movement provides a better reflection of upper-limb use in everyday life.

The primary objectives of WMT are to improve the quality of movement and independent use of the more-affected upper-limb. Thus tri-axial accelerometry recordings and game performance were not the focus of each session. Therapy activities were not altered to accommodate or facilitate the recordings or simplify the analyses. The onset of each Wii-baseball swing was externally determined by the game but required the development of response timing (Deutsch et al., 2011). This movement was previously used to analyse muscle activation, movement duration and muscle co-ordination (Hesam-Shariati *et al.*, 2017a, b); movement acceleration, speed, and smoothness were analysed in this study. The increase in Wii-baseball game scores demonstrates that performance in the game improved over time, although game scores do not necessarily reflect quality of movement. During therapy, game difficulty is increased according to the progress of each patient (Thompson-Butel et al., 2013; Trinh et al., 2016b), and this increased difficulty temporarily reduces game scores, resulting in a fluctuating pattern with an overall

trend of improvement. These factors contribute to the heterogeneity of individual responses (Fig. 4-3) and may have reduced the magnitude of kinematic changes in this study.

We found substantial differences in the kinematic responses at proximal and distal sensors. This presumably reflects the biomechanical and neurophysiological demands of the movement studied (Deutsch et al., 2011) in combination with the specific deficits of each patient. In Wii-baseball movement, patients need to stabilise the wrist and elbow in a neutral and flexed position, respectively, while the swing is performed by the shoulder and trunk movement. The addition of gyroscopes and magnetometers (Lemmens et al., 2015) would enable the reconstruction of movement trajectory for each patient to understand the proportional contribution of each of the three axes of movement both to changes in kinematics and to the success rate of intended movements. These differences highlight the necessity for a wide repertoire of movements in therapy to target proximal and distal limb segments and the range of movements required for activities of daily living (Gates et al., 2016).

Study limitations

In this study, the sample size within each level of motor-function is small, but the pooled dataset is comparable to other therapeutic studies investigating post-stroke kinematics (Lin *et al.*, 2007; Lemmens *et al.*, 2014; Kitago *et al.*, 2015; Buma *et al.*, 2016). More importantly, the cohort in this study included a broad cross section of residual voluntary motor capacity in chronic stroke. Patients with low motor-function are rarely recruited into such studies due to the potential for limited range-of-motion, pain, and rapid fatigue. The inclusion of patients with low motor-function provides results that can be generalised to the wider population in chronic stroke.

The absence of healthy control subjects is a limitation of this study. However, our previous work (Mouawad *et al.*, 2011) demonstrated substantial differences in the movement approach of healthy people playing Wii Sports activities, including Wii-baseball. Therapy movements are initially introduced based on shaping principles (Taub *et al.*, 1994) before the component movements are combined into a single

movement to mimic the real-world correlate, albeit using a single hand to hold the controller. Healthy participants used a modified movement based on the real-word movement but adapted to the virtual environment (Mouawad *et al.*, 2011). The instructions given to stroke patients to improve movement quality during the Wii-activities are different to those that were given to healthy subjects. Thus both the intention and style of movement are different between stroke patients and healthy subjects. These differences negate the utility of comparisons with healthy subjects.

We acknowledge the absence of a control group of stroke patients undergoing a non-WMT intervention to help define our understanding of the longitudinal changes as a result of different therapy protocols. A control therapy should involve similar rehabilitation components to enable meaningful comparisons. However, the movements in previous kinematic studies are mostly stereotypical rhythmic movements of locomotion (Brach et al., 2010), reach-and-grasp (Lin et al., 2007; van Kordelaar et al., 2014) or point-to-point movements (Rohrer et al., 2002; Kitago et al., 2012) that are performed under highly constrained experimental conditions.

Clinical implications

There have been few reports of changes in acceleration with therapy post-stroke (Caimmi *et al.*, 2008; Lemmens *et al.*, 2014) and as far as we are aware, none of changes in deceleration. Several clinical assessments include a time component, most noticeably WMFT-tt, but such measures reflect the total time taken to complete a task and do not consider changes in velocity, acceleration or deceleration. In this study, increased acceleration magnitude and decreased normalised velocity during a complex movement imply faster initiation of movements and better motor control throughout the movement. These therapy-induced changes in acceleration and velocity were sustained or further improved at 6-month follow-up suggesting a translation into real-world activities that were unrelated to the content of therapy (McNulty *et al.*, 2015b). They further demonstrate the potential for ongoing improvements in motor-function in chronic stroke if additional rehabilitation is provided (Teasell *et al.*, 2014).

A reduction in peak deceleration over time indicates that patients became better able to slow down or brake at the end of each movement. This is important to prevent patients hitting themselves with the controller or hitting their hand on external objects. Increased peak acceleration and acceleration magnitude, and decreased peak deceleration occurred more at proximal sensors than distal sensors. This suggests that patients were better able to target and activate the muscles necessary for this large and fast movement and that a broad repertoire of therapy movements is necessary to cover a range of movement speed, trajectory, power and dexterity. The change in trunk and upper-arm movement over time is an indication of a more naturalistic movement performed by patients.

This study suggests that complex therapy movements performed in a standing position may provide multifaceted benefits post-stroke despite specifically targeting the more-affected upper-limb (Trinh et al., 2016a; Trinh et al., 2016b). The standing posture enables larger movements than are possible while seated (Gordon et al., 2004) and that this can provide a framework with which to address movement acceleration. Acceleration and deceleration per se were not targeted in any way during therapy; patients were encouraged to increase their range-of-motion while performing a controlled movement. We hypothesise that an increase in acceleration will enable subsequent elements of a movement sequence to be linked more smoothly with reduced effort (Chang *et al.*, 2005; Caimmi *et al.*, 2008).

The absence of a systematic relationship between changes in kinematic parameters and clinical assessments suggests that clinical tools are not sufficiently sensitive to measure changes in movement parameters (Hesam-Shariati *et al.*, 2017a, b)and that no one tool is suitable across the spectrum of post-stroke movement capacity (Thompson-Butel et al., 2015). Although there were substantial changes in clinical assessments, there was no consistent pattern of change in kinematic measures either within or between groups with different levels of motor-function. These data highlight the importance of the pattern of change for individual patients and provides further emphasis that there is no one pattern or mechanism of improved movement capacity (Hesam-Shariati *et al.*, 2017a).

Many studies demonstrate the stability of motor function in chronic stroke (Krakauer, 2006; Mirbagheri & Rymer, 2008; Stinear, 2010). In a randomised controlled trial of WMT and Constraint-Induced Movement Therapy (McNulty *et al.*, 2015b), stable motor ability was established by pre-baseline to baseline comparison, including 9 patients from this study. It is also evident that targeted therapy in the chronic phase can improve motor function compared to control groups receiving usual care or no therapy (Wolf *et al.*, 2006; Page *et al.*, 2008). Thus it is extremely unlikely that the improvements in kinematics and clinical assessments seen in this study are due to time alone.

Conclusion

This study demonstrates that kinematic analyses provide objective and quantitative measures of changes in post-stroke motor-function. Higher acceleration magnitude and lower normalised velocity over time suggest it is possible to promote better motor control in chronic stroke and that clinical tools do not provide information about the change in movement quality. The differences at proximal and distal sensors suggest a complex repertoire of therapy movements is necessary to target the requirements of activities of daily living. Although there were no consistent patterns of change in kinematic parameters these data emphasise that ongoing improvement is possible in the chronic period post-stroke.

A multimodal approach to investigate the variability in post-stroke responses to therapy

Chapter 5

Abstract

There is a high variability in post-stroke outcomes and response to therapy. This study was designed to investigate the correlates and identify predictors of improvement induced by therapy, both immediately post-therapy and longitudinally. Patient characteristics, clinical assessments, EMG and kinematic measures in chronic stroke were used as candidate predictor variables.

Twenty-four patients ≥3 months post-stroke completed the 14-day Wii-based Movement Therapy program. Clinical motor-function was assessed pre- and post-therapy, and EMG and kinematics at early- and late-therapy. All were repeated at 6-month follow-up for a subset of 13 patients. Principal component analysis (PCA) was used to coalesce baseline measures, and therapy-induced and longitudinal changes for both motor-function and movement acceleration. Significant bivariate correlations between PCA scores and independent candidate predictors were identified and entered into a multivariate regression to identify variables that could predict baseline status, therapy-induced and longitudinal improvements in motor-function and movement acceleration.

Therapy-induced improvement in motor-function could be predicted in two models: 31% by baseline depression scores (r^2=0.310, p=0.006), and 51% by a combination of depression scores and sex (r^2=0.514, p=0.001). Longitudinal improvement in motor-function was predicted about 54% by baseline depression scores (r^2=0.544, p=0.006), and 68% by a combination of baseline depression and EMG area under the curve of Wii-tennis backhand (r^2=0.681, p=0.006). Baseline muscle synergy counts extracted from EMG during Wii-baseball could predict 33% of therapy-induced (r^2=0.330, p=0.003) and 38% of longitudinal (r^2=0.387, p=0.023) improvements in Wii-baseball movement acceleration. In addition, a combination of baseline muscle synergy counts and movement acceleration could predict 41% of the therapy-induced increase in acceleration magnitude (r^2=0.418, p=0.003).

Despite the evident inter-patient variability in post-stroke motor outcomes and responses to therapy, this study demonstrated baseline depression could predict some of the therapy-induced and longitudinal improvement in motor-function alone, and in combination. These findings emphasise that patients in the chronic phase retain the capacity for improved motor function and that the magnitude of improvement can be partially predicted.

Introduction

The multifaceted and heterogeneous outcomes after stroke result in substantial variability in recovery patterns and response to therapy. This inconsistency when combined with non-standardised therapy approaches (Hatem *et al.*, 2016) complicates the classification of patients (Cramer, 2010), predictions of recovery, and as a consequence, the development of assessment and rehabilitation methods (Stinear, 2010; Burke & Cramer, 2013).

The initial severity of impairment is thought to be an indicator of motor recovery (Stinear, 2010; Zarahn *et al.*, 2011); yet, the heterogeneity of outcomes makes accurate prediction difficult (Kwakkel & Kollen, 2007) during the period of acute and subacute stroke when the rate and nature of recovery is most rapid (Langhorne *et al.*, 2011; Bernhardt *et al.*, 2017). The impact of age (Bagg *et al.*, 2002), stroke subtype (Burke Quinlan *et al.*, 2015), genotype (Cramer & Procaccio, 2012), neural function (Cramer *et al.*, 2007; Burke Quinlan *et al.*, 2015), brain injury (Groisser *et al.*, 2014), cognitive status (Burke *et al.*, 2014), active range of motion (Beebe & Lang, 2009) and neurophysiology (Byblow *et al.*, 2015; Stinear *et al.*, 2017a) have been investigated but the most accurate prediction of motor recovery across the spectrum of impairment is still not known. Thus, a multimodal approach across multiple domains could help to understand the variability of motor recovery and identify the most critical measures (Stinear *et al.*, 2014; Burke Quinlan *et al.*, 2015).

Post-stroke motor outcomes in the acute and subacute phases have been used to predict motor recovery in the late subacute and chronic phase (Prabhakaran *et al.*, 2008; Beebe & Lang, 2009; Stinear *et al.*, 2014; Byblow *et al.*, 2015). Prior studies predominately included patients with mild to moderate deficits and showed that the motor recovery for patients with mild to moderate upper-limb impairment in acute stroke can be predicted by clinical measures (Feys *et al.*, 2000; Prabhakaran *et al.*, 2008; Winters *et al.*, 2015). Yet, the motor recovery of patients with severe impairment cannot be easily predicted (Prabhakaran *et al.*, 2008; Zarahn *et al.*, 2011). A recent multi-modal series of studies focused on patients 3 to 6 months

post-stroke with moderate to severe impairment (Burke *et al.*, 2014; Burke Quinlan *et al.*, 2015). Reduced corticospinal tract integrity and the absence of a motor response to transcranial magnetic stimulation, known as a motor evoked potential (MEP) were identified as the best predictors of poorer motor outcome (Burke *et al.*, 2014), while a smaller reduction in corticospinal tract integrity combined with greater functional connectivity were best predictors of therapy-induced improvements (Burke Quinlan *et al.*, 2015). More recently, a systematic review included patients with severe impairment (mostly >6 months post-stroke) to investigate brain biomarkers of recovery (Hayward *et al.*, 2017). In this review, the presence of an MEP was identified as the only predictor associated with motor outcome.

The variability of patient responses to therapy in chronic stroke (>6 months post-stroke (Bernhardt *et al.*, 2017)) is poorly understood, particularly with respect to the neurophysiological mechanisms underpinning improvements in movement capacity. Quantifying and demonstrating this variability were the main findings in Chapters 2 and 3 (Hesam-Shariati *et al.*, 2017a, b). In this study we investigated the interaction between patient characteristics and baseline motor-function and acceleration, and potential predictors of baseline motor-function, as well as therapy-induced and longitudinal improvements in motor-function and acceleration in chronic stroke. The candidate predictors were patient characteristics including age, sex, stroke type, time post-stroke, genotype, and cognitive status; and baseline measures including mood status, clinical motor-function, electromyography (EMG), and accelerometry. We hypothesised that a combination of baseline clinical motor-function measures would predict therapy-induced and longitudinal changes of motor-function in chronic stroke.

Methods

Participants

The 30 patients with EMG and accelerometry recordings during therapy (see below) were included from those consecutively recruited for studies of Wii-based Movement Therapy (WMT) from St Vincent's and Prince of Wales Hospitals, Sydney. All patients gave signed informed consent to the studies which were approved by St

Vincent's Hospital Human Research Ethics Committee, Sydney and conducted in accordance with the Declaration of Helsinki. All patients had unilateral stroke with contralesional upper-limb motor impairment; voluntary movement >10˚ in at least one digit of the more-affected hand; ≥3 months post-stroke; cognitive competency defined as a Mini Mental State Examination score ≥24; and the ability to communicate in English. Exclusion criteria were: enrolment in any other formal upper-limb movement therapy; unstable blood pressure; and co-morbidities significantly affecting upper-limb sensorimotor function. The motor-function level of each patient was classified using the scheme of Thompson-Butel and colleagues (2014) (see Chapter 1), so that 13 patients were classified with low, 9 with moderate and 8 with high motor-function. To ensure an equal distribution of patients across levels of motor-function, all 8 patients with high motor-function were included in the study and 8 patients were randomly selected from both the moderate and low motor-function groups. Thus, data from 24 patients were available at pre- and post-therapy (all clinical assessments) and early- and late-therapy (EMG and accelerometry measures) and from 13 patients at 6-month follow-up. Ten patients did not return for follow-up: 1 patient returned to work, 4 had moved away from Sydney, 2 had unrelated health issues, and 3 had not enough time for neurophysiological recordings; data for another patient was lost due to technical issues. The constituent data from this exploratory analysis have been reported previously (see below for details).

Therapy

All patients completed the 14-day program of WMT which uses the Nintendo Wii and Wii-Sports as a rehabilitation tool to target the upper-limb quality of movement and independence in daily activities (Mouawad *et al.*, 2011; McNulty *et al.*, 2015b). WMT consists of daily 1-hour therapy sessions with an Accredited Exercise Physiologist on each of 10 consecutive weekdays, with a prescribed home practice schedule every day from day 2. The duration of home practice was progressively increased according to patient progress. Patients were instructed to perform pre-defined Wii-activities including Wii-golf, -baseball, -tennis, -bowling and -boxing using only the more-affected arm. The required therapy activities and movements were individually

customised based on the residual voluntary motor capacity, range of motion, strength, needs, and progress of each patient.

Patient characteristics

Demographics

Age, sex, type of stroke (ischaemic/haemorrhagic), and time post-stroke were recorded for all patients and are presented in Table 5-1. A variable of *more-affected dominant* was defined as 1 when the more-affected side was the pre-stroke dominant side of the patient, and 0 when it was not. Patients were recruited using the previously accepted definition of chronic stroke, i.e. ≥3 months. According to the latest consensus regarding time post-stroke (Bernhardt et al., 2017), 3 patients would now be classified in the late subacute period: one patient each at 3 months (with high motor-function), 5 months (with moderate motor-function) and 6 months (with high motor-function), while the remainder were >6 months, i.e. in the chronic phase. For simplicity, and given the median time post-stroke of 21.5 months, we refer to all patients as in the chronic phase post-stroke.

Level of motor-function

The level of motor-function was considered a categorical variable defined as low, moderate or high based on the scheme of Thompson-Butel and colleagues (2014). This classification scheme is detailed in the *Introduction* (Chapter 1) and is based on gross manual dexterity, assessed using the Box and Block Test; and fine manual dexterity, assessed using the grooved pegboard test.

Genotype

Blood samples were collected from a subset of patients and genotyped to determine the presence or absence of two common genetic polymorphisms: the brain-derived neurotrophic factor (BDNF) val66met polymorphism (n=19) and the *apolipoprotein E* (APOE) ε4 allele (n=20). The genotype data for both alleles were included in a previously published study which contains all details of collection and analysis (Shiner et al., 2016).

Cognition status

The Mini Mental State Exam (MMSE) was used to screen for cognitive competency at recruitment. It is used in this analysis as a measure of cognitive status.

Clinical assessments

Mood status

The Montgomery-Åsberg Depression Rating Scale (MADRS) was used to assess depression severity at baseline, post-therapy and at 6-month follow-up, since the incidence of post-stroke depression is known to persist in chronic stroke (Aström et al., 1993; Hackett et al., 2005; Cumming et al., 2016). The MADRS is a ten-item self-report questionnaire producing a score from 0 to 60. The accepted bands for MADRS scores are: 0-6, not depressed; 7-18, mild; 19-34, moderate; and ≥35, severe depression (Müller et al., 2000; Chatterjee et al., 2010). The MADRS data have not been reported before.

Motor-function assessment

A suite of motor-function measures was assessed pre- and post-therapy and at 6-month follow-up included the Wolf Motor Function Test-timed tasks (WMFT-tt) (Wolf et al., 1989) and Fugl-Meyer Assessment (FMA) (Fugl-Meyer et al., 1974) as measures of upper-limb motor-function; and the Motor Activity Log Quality of Movement (MALQOM) scale (Uswatte et al., 2005) as an index of independence in daily life; the Box and Block Test (BBT) (Mathiowetz *et al.*, 1985b) to assess gross manual dexterity; and grip strength was assessed using a hand-held dynamometer (Jamar, USA) (Bohannon et al., 2006). Results from these assessments have been published in previous studies (McNulty *et al.*, 2015b; Thompson-Butel *et al.*, 2015; Trinh *et al.*, 2016a; Hesam-Shariati *et al.*, 2017a, b).

Electromyography and accelerometry measures

Surface EMG and tri-axial accelerometry data were recorded simultaneously using 6 telemetry wireless sensors (Delsys, USA) at early- and late-therapy, and for a subset of patients at 6-month follow-up. The sensors were placed on the trapezius (middle portion), deltoid medius (DM), biceps brachii (BB), extensor carpi radialis

(ECR), flexor carpi radialis (FCR), and first dorsal interosseus (FDI) muscles of the more-affected side.

Electromyography measure

The EMG signal recorded from one muscle per patient was analysed for Wii-golf putting, -baseball swing and -tennis forehand and backhand (see Chapter 2 (Hesam-Shariati *et al.*, 2017a) for more details). The muscle with the most distinct and clear EMG activation was selected for each patient; for most, this was DM/BB when analysing Wii-golf and -tennis, and FCR/FDI for Wii-baseball swings. The area under the curve was measured as the combination of movement duration and EMG amplitude for 10 consecutive swings, then normalised and averaged. The data were normalised to the mean EMG amplitude of a weighted condition measured over 3 s of a stable period while the patient resisted the application of 1 kg weight applied over the activated muscle of an unsupported limb.

EMG from all 6 muscles was used to extract the muscle synergies required to define the Wii-baseball swing. The muscle synergy analysis was applied only to this movement as the Wii-baseball game was completed by all patients, and the game determined the onset of each swing by pitching the ball. This facilitated analysis through clearer and more consistent EMG signals. We used non-negative matrix factorisation to determine the minimum number of muscle synergies required to define the movements of each patient (see Chapter 3 (Hesam-Shariati *et al.*, 2017b) for full details of this analysis).

Therapy-induced and longitudinal (including 6-month follow-up) changes in EMG measures have been published previously (Hesam-Shariati *et al.*, 2017a, b). The complexity and variability of EMG changes precluded them as dependent variables. Thus, only early-therapy (baseline) EMG measures were used as potential predictors of change in motor-function and acceleration magnitude.

Accelerometry measure

Similarly, Wii-baseball swings were used in the analysis of tri-axial accelerometry data. The data were calibrated for sensor bias, non-orthogonality between sensor axes, and sensor sensitivity using an established procedure (see Chapter 4 for full details). The calibrated accelerometry signals of each sensor were high-pass filtered to approximately remove gravity and provide acceleration across three axes during the Wii-baseball movement. The mean acceleration magnitude was measured and averaged for 10 consecutive swings and was presented in detail in Chapter 4.

Data analysis

Principal Component Analysis (PCA) was used to generate a single composite score for each patient (Ward et al., 2003; Burke Quinlan et al., 2015). The use of a single score helps overcome the floor or ceiling effects inherent in clinical assessments (Rossiter et al., 2014; Thompson-Butel et al., 2015). PCA was applied to 5 upper-limb motor-function measures (WMFT-tt, FMA, MALQOM, BBT, and grip strength) to derive a motor-function score. Similarly, PCA was applied to the acceleration magnitude at 6 sensors during the Wii-baseball swing movement to derive a single acceleration magnitude score. Six PCA scores were generated, three for clinical motor-function and three for acceleration magnitude. Three motor-function PCA scores were: baseline; therapy-induced changes from pre- to post-therapy; longitudinal changes from pre-therapy to 6-month follow-up. The three acceleration PCA scores were: baseline; therapy-induced changes from early-to late-therapy; longitudinal changes from early-therapy to 6-month follow-up.

Statistical analysis

PCA scores of motor-function and acceleration magnitude were used in the subsequent bivariate correlation and multivariate modelling as dependent variables. For bivariate correlation, Pearson, Spearman's rank-order, and Point-Biserial correlations were used, respectively, for normally distributed, non-normally distributed, and categorical variables. These two-tailed comparisons were considered significant when $p<0.05$. The Shapiro-Wilk test was used to define normally distributed data as it is recommended as the most robust normality test for

sample sizes <30 (Ghasemi & Zahediasl, 2012). The correlates from the bivariate correlation were entered into the multivariate modelling to predict motor recovery. A stepwise linear regression was applied to the variables with significant correlations, variables were entered into the model when $p<0.1$ and were removed from the model when $p>0.15$. Boxplots were used to identify outliers with values >1.5 times the interquartile range (IQR) beyond the upper or lower bounds of the range. All analyses were conducted in SPSS 24 (IBM, USA).

Results

All patients completed clinical assessments pre- and post-therapy with EMG recorded during early-therapy and accelerometry at early- and late-therapy. All measures were repeated at 6-month follow-up in a subset of patients. To streamline the presentation of results, pre-therapy and early-therapy measures are both reported as baseline hereafter.

Patient characteristics and baseline clinical assessments, EMG and accelerometry measures are presented in Table 5-1, in addition to the post-therapy clinical motor-function results, late-therapy accelerometry, and 6-month follow-up measures. The range of time post-stroke was wide, being 3-88 months with one outlier at 88 months (for a patient with low motor-function). The BDNF and APOE genotype data were available for 19 and 20 patients, respectively. Ten of 19 were BDNF Met carriers, and 5 of 20 were APOE-ε4 carriers (see Table 5-1). At baseline one patient with high motor-function had moderate depression, i.e. a MADRS score between 19-34; while 8 had mild depression (2 low, 3 moderate, 3 high motor-function) with scores between 7-18. MADRS scores improved from pre- to post-therapy ($p=0.004$) and over time (pre-therapy, post-therapy and follow-up) ($p=0.027$). EMG of Wii-golf putting could not be analysed for one patient with moderate motor-function due to tonic muscle activity that obscured the task-related muscle activation. One patient with low motor-function was unable to engage in Wii-tennis due to limited shoulder movement.

Table 5-1. Outcome measures at 3 time-points. Age is reported as mean±SD, time post-stroke as median (interquartile range), and remaining data as mean±SE. MMSE: Mini-Mental State Exam, MADRS: Montgomery-Åsberg Depression Rating Scale, WMFT-tt: Wolf Motor Function Test-timed tasks, FMA: upper-limb motor Fugl-Meyer Assessment, MALQOM: Motor Activity Log Quality of Movement scale, BBT: Box and Block Test. Where appropriate the maximum score is indicated for clinical assessments.

	baseline	**post- or late-therapy**	**6-month follow-up**
Patient characteristics			
Age (year)	57.88±12.11		
Sex (f/m)	8/16		
Stroke type (isch/haem)	16/8		
Time post-stroke (month)	21.50 (11.50-37.00)		
More-affected dominant (y/n)	7/17		
BDNF val66met (met carrier/non-carrier)	10/9		
APOE-ε4 (ε4 carrier/non-carrier)	5/15		
MMSE (/30)	28.50±0.35		
Clinical assessments			
MADRS (/60)	7.21±1.10	5.48±1.06	4.00±1.19
WMFT-tt (/120 s)	38.14±7.78	33.55±7.16	30.34±11.13
FMA (/66)	46.58±3.60	48.88±3.58	52.15±5.01
MALQOM (/150)	60.13±8.67	91.25±8.13	90.85±12.60
BBT (count per 60 s)	19.50±3.85	22.08±4.45	28.85±6.26
Grip strength (kg)	14.91±2.59	16.19±2.82	21.83±4.66
EMG and accelerometry measures			
EMG area, Wii-golf putting (mV.s/mV)	2.99±0.43		
EMG area, Wii-baseball swing (mV.s/mV)	3.88±1.12		
EMG area, Wii-tennis forehand (mV.s/mV)	2.87±0.30		
EMG area, Wii-tennis backhand (mV.s/mV)	3.47±0.46		
Muscle synergy counts	3.71±0.13		
Acceleration magnitude, FDI (m/s^2)	5.28±0.31	5.39±0.25	5.69±0.42
Acceleration magnitude, ECR (m/s^2)	3.66±0.27	3.86±0.23	4.20±0.37
Acceleration magnitude, FCR (m/s^2)	3.38±0.28	3.66±0.26	4.04±0.39
Acceleration magnitude, BB (m/s^2)	2.24±0.19	2.49±0.17	2.86±0.30
Acceleration magnitude, DM (m/s^2)	1.66±0.14	1.92±0.12	2.00±0.20
Acceleration magnitude, trapezius (m/s^2)	1.02±0.08	1.25±0.09	1.47±0.12

Principal component analysis

At baseline the motor-function PCA converged to one component that accounted for 84.7% of the variance for the 5 variables entered. Lower scores at baseline corresponded to poorer motor-function. For therapy-induced and longitudinal change scores, the first component of the PCA explained 48.4% and 45.4% of the variance, respectively. To explain >50% of the variance and a stronger PCA component, the analysis was repeated using the 3 targeted multi-domain clinical measures (WMFT-tt, FMA and MALQOM). In this analysis the first component of PCA explained 54.9% and 56.4% of the variance for therapy-induced and longitudinal changes, respectively.

For baseline acceleration magnitude, the PCA provided one measure that explained 85.5% of the variance. For both therapy-induced and longitudinal changes in acceleration magnitude, the PCA converged to one component that accounted for 79.6% and 79.3% of the variance, respectively.

Correlations of baseline motor-function and acceleration magnitude

The relationship between patient characteristics and baseline motor-function (PCA of 5 clinical measures) were investigated using bivariate correlation (Table 5-2). Time post-stroke was negatively correlated with baseline motor-function ($r=-0.407$, $p=0.048$). However, when the time post-stroke outlier at 88 months was removed from the analysis, the relationship was not significant ($r=-0.360$, $p=0.092$). For baseline acceleration magnitude (PCA of acceleration from 6 sensors), bivariate screening determined a non-significant trend with time post-stroke ($r=-0.383$, $p=0.064$). However, when the time post-stroke outlier was removed, the relationship was not significant ($r=-0.315$, $p=0.143$).

Table 5-2. Correlations of patient characteristics with baseline motor-function (PCA of 5 clinical motor-function measures) **and baseline acceleration** (PCA of measures at 6 sensors). When the outlier of time post-stroke (at 88 months) was removed, * the correlation became non-significant (p=0.092) and #p=0.143 for acceleration. Significant relationships are highlighted in bold and non-significant trends in italics.

	baseline motor-function		**baseline acceleration**	
	r	***p***	***r***	***p***
Patient characteristics				
Age	-0.097	0.652	-0.183	0.391
Sex	0.306	0.145	0.180	0.400
Stroke type	-0.204	0.338	-0.126	0.557
Time post-stroke	-0.407	**0.048***	-0.383	*0.064*[#]
More-affected dominant	0.060	0.782	0.116	0.590
BDNF val66met	0.000	1.000	-0.044	0.860
APOE-ε4	0.130	0.584	0.025	0.918
MMSE	0.192	0.369	0.294	0.163

Correlates of therapy-induced and longitudinal improvements

Independent variables including patient characteristics and baseline measures of clinical assessments, EMG area under the curve for Wii-golf putting, -baseball swing, -tennis forehand, -tennis backhand, muscle synergy counts, and acceleration magnitude were used as candidate predictors for therapy-induced and longitudinal changes in both motor-function and acceleration magnitude.

Therapy-induced change of motor-function. Four of the independent variables were identified as significant in bivariate correlations with therapy-induced changes in motor-function (Table 5-3a). Female patients had greater improvements in motor-function during therapy (r=0.508, p=0.011); and for all patients therapy-induced improvement in motor-function was correlated with a longer time post-stroke (r=0.480, p=0.018), higher MADRS scores (r=0.516, p=0.010), and a smaller EMG area under the curve of Wii-tennis forehand (r=-0.542, p=0.007). Multivariate modelling indicated that baseline MADRS scores (r^2=0.310, p=0.006) and a combination of sex and baseline MADRS scores (r^2=0.514, p=0.001) predict therapy-induced improvement in motor-function (Fig. 5-1A, Table 5-3b). Time post-

stroke, baseline MADRS scores, and baseline EMG area under the curve of Wii-tennis forehand all included an outlier (not the same patient); when the outliers were removed from the analysis, the correlations remained significant between therapy-induced improvements in motor-function and time post-stroke (r=0.505, p=0.014), MADRS scores (r=0.449, p=0.032) and EMG area under the curve of Wii-tennis forehand (r=-0.502, p=0.017). The result of multivariate modelling after removing the outliers determined a combination of sex and MADRS scale (r^2=0.448, p=0.005) as the only predictor of therapy-induced change in motor-function.

Longitudinal change of motor-function. Longitudinal changes of motor-function from pre-therapy to 6-month follow-up were positively correlated with higher baseline MADRS scores (r=0.657, p=0.015), and less EMG area under the curve of both Wii-tennis forehand (r=-0.776, p=0.003) and backhand (r=-0.769, p=0.003) (see Table 5-3a). Entering these variables in the multivariate model, baseline MADRS scores (r^2=0.544, p=0.006) and a combination of baseline MADRS and EMG area under the curve of Wii-tennis backhand (r^2=0.681, p=0.006) predicted longitudinal improvements in motor-function (Fig. 5-1B, Table 5-3b). Since baseline MADRS, early-therapy EMG area under the curve of Wii-tennis forehand and backhand included an outlier (not the same patient); the analysis was repeated without the outliers. Due to the smaller sample size for longitudinal changes, the correlation with baseline MADRS became a non-significant trend (r=0.562, p=0.057), but significant correlations remained with baseline EMG area under the curve of Wii-tennis forehand (r=-0.709, p=0.015) and backhand (r=-0.700, p=0.016). The linear regression applied to the two latter variables identified early-therapy EMG area under the curve of Wii-tennis forehand as a predictor (r^2=0.379, p=0.044).

Table 5-3a. Bivariate correlations of the candidate variables with therapy-induced and longitudinal improvements in motor-function (PCA of change scores in 3 motor-function measures). MMSE: Mini-Mental State Exam, MADRS: Montgomery-Åsberg Depression Rating Scale, EMG area: EMG area under the curve. Significant relationships are highlighted in bold and non-significant trends in italics.

	improvement in motor-function			
	therapy-induced		**longitudinal**	
	r	***p***	***r***	***p***
Patient characteristics				
Age	0.002	0.991	-0.022	0.943
Sex	-0.508	**0.011**	-0.211	0.488
Stroke type	-0.121	0.574	-0.423	0.150
Time post-stroke	0.480	**0.018**	0.484	*0.094*
More-affected dominant	-0.136	0.527	-0.312	0.300
Level of motor-function	-0.170	0.428	-0.070	0.819
BDNF val66met	-0.025	0.920	-0.115	0.735
APOE-ε4	-0.069	0.774	-0.478	0.137
MMSE	-0.186	0.384	-0.298	0.322
Clinical assessments				
MADRS	0.516	**0.010**	0.657	**0.015**
Upper-limb motor-function (PCA)	-0.295	0.162	-0.319	0.289
EMG and accelerometry measures				
EMG area, Wii-golf putting	0.014	0.950	-0.371	0.236
EMG area, Wii-baseball swing	-0.343	0.100	-0.209	0.494
EMG area, Wii-tennis forehand	-0.542	**0.007**	-0.776	**0.003**
EMG area, Wii-tennis backhand	-0.397	*0.061*	-0.769	**0.003**
Muscle synergy counts	-0.086	0.691	-0.104	0.735
Acceleration magnitude (PCA)	-0.315	0.133	0.214	0.482

Table 5-3b. Predictors of therapy-induced and longitudinal improvements in motor-function using multivariate modelling. Outliers are included in the analysis.

Baseline predictor variables	**improvement in motor-function**					
	therapy-induced			**longitudinal**		
	R	**R^2**	***p***	**R**	**R^2**	***p***
MADRS	0.557	0.310	**0.006**	0.738	0.544	**0.006**
MADRS and sex	0.717	0.514	**0.001**			
MADRS and EMG area, Wii-tennis backhand				0.825	0.681	**0.006**

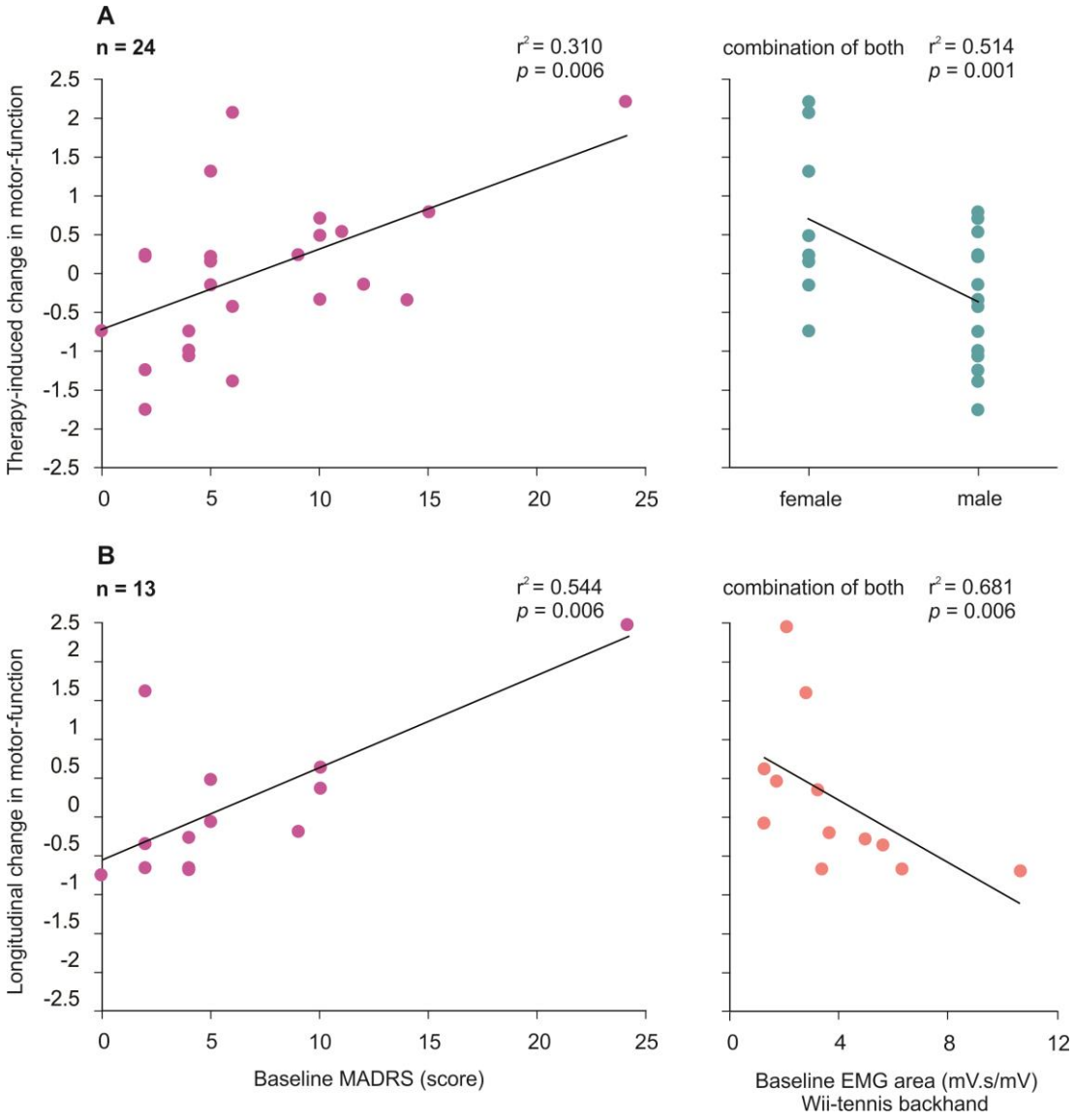

Figure 5-1. The relationships between potential predictors and therapy-induced and longitudinal changes in motor-function (PCA of 3 motor-function measures). **(A)** The therapy-induced change in motor-function could be predicted 31% by baseline MADRS scores; and 51% by the combination of baseline MADRS scores and sex. **(B)** The longitudinal change in motor-function could be predicted 54% by baseline MADRS scores; and 68% by the combination of baseline MADRS scores and baseline EMG area under the curve of Wii-tennis backhand.

Table 5-4a. Bivariate correlations of candidate variables with therapy-induced and longitudinal improvements in acceleration magnitude (PCA of measures at 6 sensors). MMSE: Mini-Mental State Exam, MADRS: Montgomery-Åsberg Depression Rating Scale, EMG area: EMG area under the curve.

	improvement in movement acceleration			
	therapy-induced		**longitudinal**	
	r	***p***	***r***	***p***
Patient characteristics				
Age	0.244	0.251	0.176	0.565
Sex	-0.105	0.624	0.114	0.712
Stroke type	-0.170	0.427	-0.132	0.667
Time post-stroke	0.037	0.865	0.324	0.280
More-affected dominant	-0.297	0.159	-0.542	*0.056*
Level of motor-function	-0.103	0.631	-0.100	0.746
BDNF val66met	-0.005	0.982	0.031	0.929
APOE-ε4	-0.149	0.529	-0.111	0.746
MMSE	-0.230	0.280	0.012	0.970
Clinical assessments				
MADRS	-0.076	0.723	-0.036	0.906
Upper-limb motor-function (PCA)	-0.124	0.563	-0.170	0.578
EMG and accelerometry measures				
EMG area, Wii-golf putting	-0.134	0.541	-0.203	0.527
EMG area, Wii-baseball swing	-0.143	0.504	-0.077	0.803
EMG area, Wii-tennis forehand	0.026	0.907	0.014	0.966
EMG area, Wii-tennis backhand	-0.239	0.272	-0.336	0.286
Muscle synergy counts	-0.589	**0.002**	-0.694	**0.009**
Acceleration magnitude (PCA)	-0.550	**0.005**	-0.459	0.115

Table 5-4b. Predictors of therapy-induced and longitudinal improvements in movement acceleration using multivariate modelling.

Baseline predictor variables	**improvement in movement acceleration**					
	therapy-induced			**longitudinal**		
	R	**R^2**	***p***	**R**	**R^2**	***p***
Muscle synergy counts	0.574	0.330	**0.003**	0.622	0.387	**0.023**
Muscle synergy counts and acceleration magnitude	0.646	0.418	**0.003**			

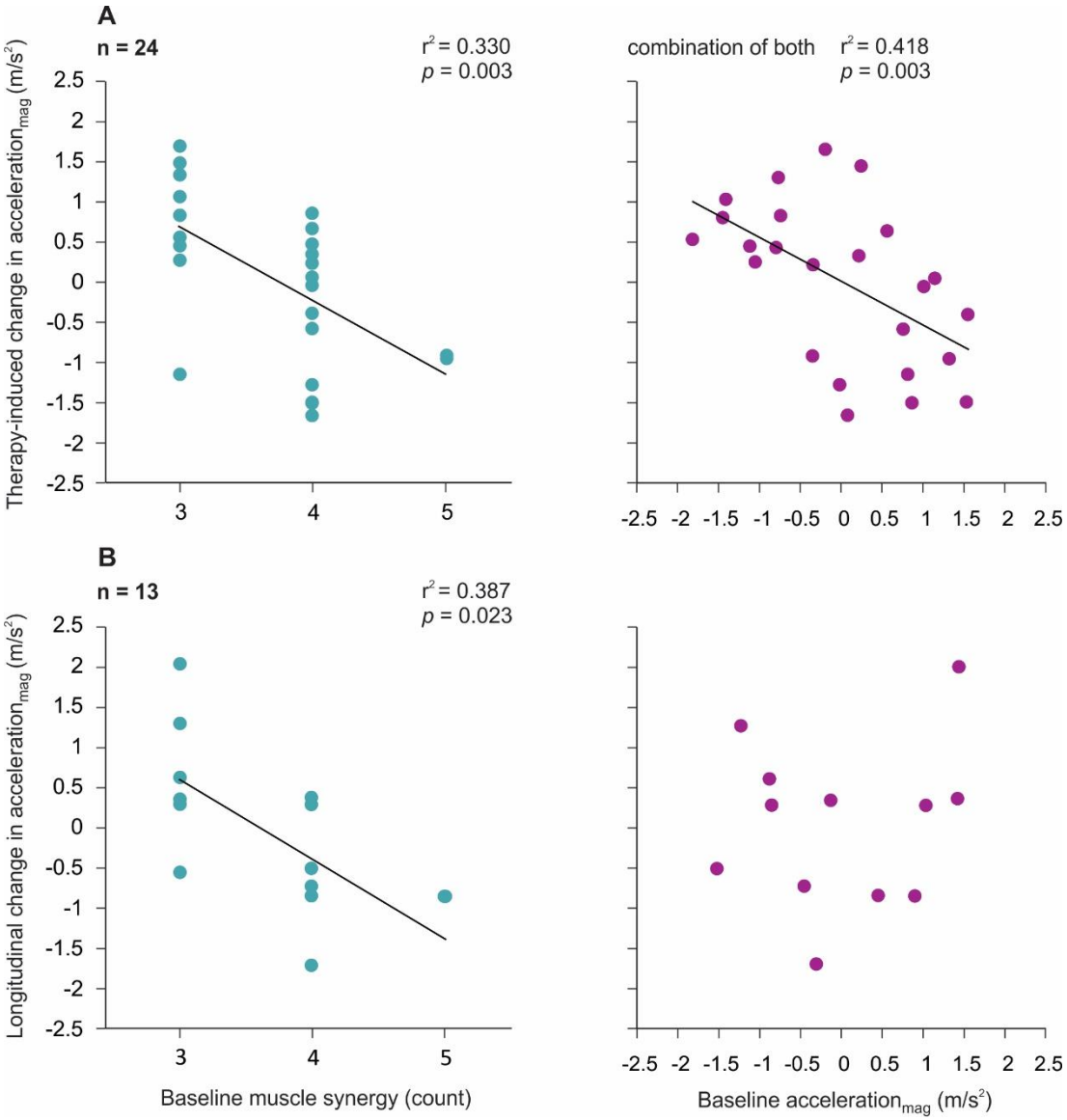

Figure 5-2. The relationships between potential predictors and therapy-induced and longitudinal changes in acceleration (PCA of measures at 6 sensors). (A) The therapy-induced change in acceleration magnitude could be predicted for 33% by baseline muscle synergy counts; and 41% by the combination of baseline muscle synergy counts and baseline acceleration magnitude. (B) The longitudinal change in acceleration magnitude could be predicted for 38% only by baseline muscle synergy counts.

Therapy-induced change of acceleration magnitude. Table 5-4a shows that number of muscle synergies extracted from baseline EMG recordings (r=-0.589, p=0.002) and baseline acceleration magnitude (r=-0.550, p=0.005) during Wii-baseball swings were negatively correlated with therapy-induced change of acceleration magnitude. Linear regression demonstrated two models for predicting

increased acceleration from early-therapy to late-therapy (Fig. 5-2A, Table 5-4b), one using baseline muscle synergy counts (r^2=0.330, p=0.003), the other requiring a combination of baseline muscle synergy counts and acceleration magnitude (r^2=0.418, p=0.003). Baseline muscle synergy counts showed a non-significant trend with the level of motor-function (r=0.398, p=0.054), while baseline acceleration was correlated with the level of motor-function (r=0.435, p=0.034).

Longitudinal change of acceleration magnitude. The longitudinal increase in acceleration magnitude was negatively correlated with baseline muscle synergy counts (r=-0.694, p=0.009). This baseline measure was the only predictor of increased acceleration magnitude from early-therapy to 6-month follow-up (r^2=0.387, p=0.023) (Fig. 5-2B, Table 5-4b).

Discussion

Chronic stroke patients typically have heterogeneous motor recovery and responses to therapy. The aim of this study was to investigate correlates and potential predictors of therapy-induced and longitudinal changes in motor-function and movement acceleration using a multivariate approach. A complex dataset of patient characteristics, clinical assessments, EMG, and accelerometry measures was included as candidate predictors in these analyses. The novel approach of this study was that acceleration and EMG parameters including area under the curve and muscle synergy counts were recorded during largely unconstrained therapy movements (Hesam-Shariati *et al.*, 2017a, b). More importantly, patients from a broad spectrum of residual voluntary motor capacity in chronic stroke were included in this study, those rarely involved in post-stroke neurophysiological and therapy studies. We demonstrated that 31% of the magnitude of therapy-induced improved motor-function could be predicted by baseline depression scores alone and 51% by the combination of depression and sex. Longitudinally, baseline depression could predict 54% of motor improvement or 68% when combined with EMG area under the curve during Wii-tennis backhand. In contrast, 33% of therapy-induced improvements in movement acceleration magnitude could be predicted by the number of muscle synergies in a complex movement, and 38% longitudinally. When

combined with baseline acceleration, 41% of therapy-induced improvements in movement acceleration could be predicted. These data emphasise that not only do patients in the chronic phase post-stroke have the capacity for improved motor-function, but that the magnitude of this improvement can be predicted to some extent, but not by time post-stroke.

Contrary to our hypothesis, baseline clinical motor-function could not predict the magnitude of changes in motor-function. The variables that had some power to predict improvements in motor-function were depression, sex and EMG area under the curve. Of these, only depression scores showed significant improvements both with therapy and over time. The incidence of mild or moderate depression in our cohort (37%) is similar to the prevalence of post-stroke depression reported in a recent large meta-analysis (Mitchell *et al.*, 2017). Patients with higher depression scores in this study had greater improvements in motor-function than those with no depression (i.e. MADRS scores <7) and that these improvements were sustained over time. Depression in chronic stroke has been negatively associated with motor recovery (Belagaje, 2017; Karaahmet *et al.*, 2017); used as predictor of reduced mobility (van Wijk *et al.*, 2006); and was a limiting factor for participation in rehabilitation programs (Andrenelli *et al.*, 2015). Conversely, motor programs that targeted upper- or lower-limb motor-function have a demonstrated benefit for psychological status including depression (Calabrò *et al.*, 2015; Shin *et al.*, 2015). In our study, both upper-limb motor-function and depression improved with therapy and over time. More importantly, baseline depression scores had some power to predict the magnitude of motor-function improvements, both therapy-induced and longitudinal.

A recent survey of community-dwelling stroke survivors in Australia identified 82% of respondents with unmet needs associated with movement ability and 79% with psychological wellbeing (Andrew *et al.*, 2014). Given that the patients in this study were drawn from a similar environment, it is reasonable to assume similar levels of unmet needs in our cohort. Thus, the opportunity to receive additional therapy as part of a clinical trial could explain both the improved depression scores and the

improvement in motor-function scores, i.e. those with more depression had a greater capacity for improvement as the provision of rehabilitation may have alleviated their depression. However this hypothesis requires further specific testing.

When combined with baseline depression, sex could predict 51% of the therapy-induced improvement in motor-function, with females improving more than males. As far as we can ascertain, there is no difference in the therapy responsivity of females and males in chronic stroke, and this fits with our clinical observations. Compared to males, females in a large (n=1370) study of chronic ischaemic stroke had lower quality of life with reference to mobility, pain, and depression at 3 and 12 months post-stroke (Bushnell *et al.*, 2014). Half the females in our cohort (4 of 8) had low motor-function, and hence a greater capacity for improvement compared to the males with mostly moderate and high motor-function (12 of 16). However, this result may reflect the unequal sex distribution in this study, as commonly occurs in the literature.

When combined with baseline depression scores, EMG area under the curve of Wii-tennis backhand could predict 68% of the longitudinal changes in motor-function. This result was unexpected given the absence of any systematic pattern of change in EMG with therapy (see Chapter 2 (Hesam-Shariati *et al.*, 2017a)). However, it presumably reflects the coalescence of patients with lower motor-function, for whom there was a significant improvement in EMG area, who were more depressed and had more capacity for improvement seen as a smaller EMG area at baseline (for Wii-tennis backhand) compared to those with moderate and high motor-function (Hesam-Shariati *et al.*, 2017a). Alternatively, it may reflect better motor control with therapy that enabled patients to change to the backhand side more easily during Wii-tennis.

Fewer muscle synergies at baseline had some power to predict the increase in acceleration magnitude induced both by therapy and longitudinally. This measure was associated with patients with low motor-function (Hesam-Shariati *et al.*, 2017b). A combination of fewer muscle synergies and smaller acceleration during Wii-

baseball at baseline was a stronger predictor of therapy-induced improvements in acceleration magnitude. Although there was no direct association between level of motor-function and increase in acceleration magnitude, fewer muscle synergies and lower baseline acceleration were related to a lower level of motor-function. Differences in the number of muscle synergies according to the level of post-stroke impairment has been identified previously during rhythmic movements such as walking (Clark *et al.*, 2010). An association between the level of impairment and lower-limb kinematic variables was also evident during walking (Bujanda *et al.*, 2003). Our results suggest that the combination of poor acceleration and fewer muscle synergies contribute to low motor-function but that these patients retain the capacity to improve kinematic variables even in chronic stroke.

There is no one measure that can adequately quantify motor-function in stroke (Thompson-Butel *et al.*, 2015; Kwakkel *et al.*, 2017). In this study, we used PCA to provide an integrated score based on the results of up to 5 clinical motor-function assessments that summarises individual variability of post-stroke motor outcomes encompassing movement speed, co-ordination, independent more-affected upper-limb use, manual dexterity and strength. Regardless of the heterogeneous post-stroke outcomes, PCA provides a more holistic measure overcoming the bias of the floor and ceiling effects that vary across levels of residual voluntary motor-function (Ward *et al.*, 2003; Burke Quinlan *et al.*, 2015). In this way PCA scores may provide a compromise between clinical assessments that are quick to perform but suffer from categorical and subjective scoring, and more detailed neurophysiological or kinematic measurements that are costly in time and resources. Similarly, PCA provides a combined score for the acceleration variable at 6 sensors moving concurrently that accounts for differences in acceleration along the proximal to distal axis of the more-affected upper-limb during a complex movement.

The stability of motor-function has been robustly demonstrated in chronic stroke (Krakauer, 2006; Stinear, 2010). However, many studies have shown that improvement is possible with targeted therapies (for example see (Wolf *et al.*, 2006; Page *et al.*, 2008); for comment see (Teasell *et al.*, 2014)). A recent study from our

group demonstrated a continued pattern of improvement for every upper-limb assessment when additional therapy was provided in the chronic period (McNulty *et al.*, 2015a). Thus, the ability to predict the magnitude of motor improvement has the potential to provide a means of targeting the optimal type, intensity and duration of therapy in chronic stroke, and identifying the most appropriate methods of assessment. Motor recovery has been predicted at the acute and sub-acute phases (Prabhakaran *et al.*, 2008; Byblow *et al.*, 2015), but in order to address the unmet needs of community-dwelling stroke survivors (Andrew *et al.*, 2014), there is a need to be able to predict further improvements in chronic stroke (Hubbard *et al.*, 2015). The inter-patient variability, particularly in EMG parameters (see (Hesam-Shariati *et al.*, 2017a)), complicates the prediction of therapy responsivity. The results of this study suggest that multivariate analyses could help to understand the heterogeneity of chronic stroke and provide justification for ongoing funding of stroke rehabilitation (NSF, 2015).

Study considerations and limitations

The sample size of this study is relatively small but comparable with multivariate predictive studies (Beebe & Lang, 2009; Burke Quinlan *et al.*, 2015). However, we recognise that the results of this study need confirmation with a larger cohort, given the number and diversity of the variables entered into the model. Thus, the results from this preliminary study should be interpreted with caution.

We recognise that this study does not include direct measures of neural function and connectivity such as brain imaging or MEPs (Burke *et al.*, 2014; Stinear & Byblow, 2014; Burke Quinlan *et al.*, 2015; Puig *et al.*, 2017). Such techniques give rise to two important variables: the asymmetry index of corticospinal tract projections, and the presence or absence of MEPs, both of which are common indices used to predict recovery or improvements in motor-function (Boyd *et al.*, 2017; Kim & Winstein, 2017). The variables we implemented covered a wide range of methods and domains from relatively quick and simple clinical assessments to detailed quantitative neurophysiological (EMG) and kinematic analyses. As far as

we can ascertain, this is the first study to include EMG and kinematic variables in a predictor model.

The effect of mood and cognition status could not be fully investigated in this study as the cohort did not include any severely depressed or cognitively impaired patients (the MMSE was used as a screening tool to exclude cognitively impaired patients). The results suggest that a full neuropsychological screening should be included in a larger study to quantify other mood and cognitive disorders such as anxiety, and reduced motivation and memory.

Clinical implications

This study was designed to test the outcome measures presented in previous chapters in one model to identify a suite of assessments that could be used to define post-stroke impairment status and changes with therapy. Since there is no one tool to adequately assess patients across the spectrum of post-stroke impairment (Alt Murphy *et al.*, 2015; Kwakkel *et al.*, 2017), there has long been a search to identify the minimal quantitative dataset with strong predictive ability (Boyd *et al.*, 2017). Our findings clearly demonstrate that stroke survivors retain the capacity for motor improvement in the chronic phase (Teasell *et al.*, 2014) and therefore argue strongly for increasing the availability of rehabilitation in chronic stroke (Andrew *et al.*, 2014) particularly for patients with low levels of motor-function. This study also emphasises the importance of addressing depression in chronic stroke and the potential role of ongoing motor rehabilitation to help alleviate mood disorders.

The rapidly advancing fields of electronic miniaturisation, machine learning and telemetric sensors will improve the feasibility of automated EMG and accelerometry analyses (Roy *et al.*, 2013) and enable the replacement of subjective and categorical clinical assessments with more objective and detailed neurophysiological and kinematic analyses. This is best illustrated by the predictive power of muscle synergy counts in this study. Muscle synergies reflect the neural co-ordinated recruitment of muscles to perform a motor task (Hesam-Shariati *et al.*, 2017b).

Changes in kinematics reflect better motor control which is a multivariate construct encompassing velocity, acceleration and deceleration that is crucial for more efficient performance of activities of daily living.

Conclusion

Despite the heterogeneity of outcomes and responses to therapy post-stroke, this study identified novel variables that could predict some of the magnitude of improvement in motor-function and movement acceleration after therapy, and longitudinally. Depression, rather than baseline motor-function or time post-stroke, was the strongest predictor of improved motor-function, whereas the number of muscle synergies during a complex movement was the strongest predictor of increased movement acceleration. Our findings emphasise the multivariate nature of improved motor-function post-stroke and that patients in the chronic phase have the capacity for continued improvement that is unrelated to time post-stroke.

General discussion

Chapter **6**

The aims of this thesis were to investigate the neurophysiological and kinematic changes underpinning the improvements in motor-function with WMT and to examine whether the observed changes were sustained at 6-month follow-up. The secondary aim was to study these improvements and the relationship between therapy-induced changes in motor-function measured using clinical assessment tools compared to changes in neurophysiological and kinematic parameters measured using detailed quantitative methods. Finally, the correlates and potential predictors of therapy-induced and longitudinal changes were investigated in a multivariate model to explore the rich dataset arising from this thesis.

The novel aspects of this thesis were:

- the recording of neurophysiological and kinematic data during formal therapy sessions;
- the investigation of neurophysiological and kinematic data during largely unconstrained movements to better reflect real-world use of the more-affected upper-limb;
- the combination of clinical, neurophysiological and kinematic parameters in the same cohort of patients;
- longitudinal studies combining clinical, neurophysiological and kinematic parameters;
- the inclusion of a broad spectrum of stroke patients with different levels of residual voluntary motor capacity, including those with minimal voluntary movement.

It has often been stated that stroke patients in the chronic phase do not have the capacity for further improvements in motor-function (Stinear & Byblow, 2014; van Kordelaar *et al.*, 2014; Krakauer & Marshall, 2015). This belief may reflect the inadequacy of many clinical assessment tools (Kwakkel *et al.*, 2017); the pooling of data across too wide a spectrum of motor-function, i.e. without classification (Thompson-Butel *et al.*, 2014; Trinh *et al.*, 2016b); the targeted selection of patients with high levels of motor-function who are more likely to recover quickly and do not have the potential for large improvements (e.g. (van Kordelaar *et al.*, 2014)); or the

efficacy of the applied therapy (Laver *et al.*, 2015; Mehrholz *et al.*, 2015). However, data from our group show a continuous trajectory of motor improvement in chronic stroke on all upper-limb assessments following the provision of additional therapy (McNulty *et al.*, 2015a). The studies in this thesis were also designed to investigate an hypothesis that there is no one pattern of improvement across the general stroke population, and that neurophysiological and kinematic data would reveal more subtle changes than can be detected using clinical assessment tools alone.

The cohort of stroke patients studied in this thesis included a broad spectrum of residual voluntary motor-function, as assessed using clinical motor-function tools. In the literature, patients with severe impairment and low motor-function are rarely recruited in therapy, neurophysiological or kinematic studies, particularly when a more heterogeneous cohort is recruited. Such patients present many challenges in methodology, and rarely meet selection and exclusion criteria. However, there is a growing body of evidence that specifically targets this population as a more homogenous group (Brauer *et al.*, 2013; Hayward *et al.*, 2017). Patients with low and very low motor-function require careful assistance during assessment and therapy sessions due to multiple impairments, pain, fatigue and limited mobility (NSF, 2010). Previous work in our group has shown that patients with low and minimal voluntary movement retain the capacity to improve (McNulty *et al.*, 2013a; Shiner *et al.*, 2016). This thesis specifically included a balanced cohort of patients from those with minimal impairment to those with severe impairment.

Wii-based Movement Therapy was used in this thesis as a rehabilitation tool to help understand the effect of a standardised therapy protocol on a diverse cohort of patients with chronic stroke. The focus and primary objectives of WMT are the quality of movement and increasing the use of the more-affected arm in activities of daily living (McNulty *et al.*, 2015b), not the rules of the games being played, the game performance, or the neurophysiological and kinematic recordings. Therapy activities were not modified in any way to refine the recordings; target the game scores; or standardise the number of repetitions, speed, power and displacement of each movement. The game scores were used during therapy but only as a

motivation factor for patients, while the recordings (EMG, accelerometry) made during therapy were utilised to understand the mechanisms of previously observed improvements in clinical motor-function assessments with WMT (Thompson-Butel *et al.*, 2013; McNulty *et al.*, 2015b; Trinh *et al.*, 2016b). The progressively increasing home-practice component of WMT was designed so that the patients help themselves by reducing their reliance on the therapist (McNulty *et al.*, 2013a). This factor may help explain why the benefits of therapy were sustained at 6-month follow-up. The content of clinical assessments previously used with WMT is unrelated to the activities performed during this therapy which suggests that the improvements evoked by WMT generalise to unrelated movements and ADL (McNulty *et al.*, 2015b). Conversely, the studies of this thesis permitted a more specific investigation of the mechanisms by which WMT produced changes in neurophysiological and kinematic parameters that would enable the tasks of clinical assessment tools to improve, i.e. by the parameters associated with fine motor control. Neurorehabilitation studies most often measure the outcomes before and after implementation of the therapy protocol. In this thesis, the EMG and accelerometry data were recorded *during* therapy while performing complex movements required by WMT. We are unaware of any other studies to do so.

The complex therapy movements of this thesis were largely unconstrained, i.e. there was no precise spatiotemporal start- or end-point. Moreover, patients were free to move the targeted more-affected upper-limb in three-dimensional space, with the only restraint being that the controller was only held with the more-affected hand. In contrast, EMG and kinematic data are typically recorded in simple point-to-point movements or stereotypical activities such as reaching and tracking tasks (Dipietro *et al.*, 2012; Lemmens *et al.*, 2014). Kinematic data have been measured in more complex movements of activities of daily living (Kim *et al.*, 2014; Bailey *et al.*, 2015) but either the movements were experimentally restricted or the studies do not involve any therapy programs with multiple measures.

Post-stroke outcome measures

Clinical motor-function tools are typically quick and simple to perform but lack sensitivity and cannot quantify the detailed differences between patients, between different mechanisms of improvement (e.g. increased task-related phasic EMG compared to reduced tonic EMG) and the quality of movements. For example, the clinical assessments used in this thesis assessed gross and fine manual dexterity (BBT and grooved pegboard tests, respectively); the amount of time taken to perform a task (WMFT-tt); and how well a task is performed using either categorical scoring by an assessor (FMA) or categorical scoring by the patients themselves (MALQOM). More importantly, the WMFT has a floor effect for patients with low motor-function and FMA has a ceiling effect for patients with high motor-function (Lin *et al.*, 2009; Thompson-Butel *et al.*, 2015). Unlike such assessments, EMG area under the curve provides a quantitative continuous measure of how much the muscle is activated during a movement and for how long. Compound EMG measures neuromuscular activity by the recruitment of multiple single motor units (Basmajian & De Luca, 1985). Thus, EMG provides a direct measure of the motoneurons activated by the central nervous system, in addition to the intrinsic properties of the muscles (De Luca, 1997; Burden, 2007; Farina *et al.*, 2014). Although the analysis of an individual muscle can provide some measure of cerebral and corticomotor changes and an index of changes over time, the co-ordination of multiple muscles needs to be investigated by the analysis of muscle synergies. The count, timing profiles and structure of muscle synergies provides some information about the neuromuscular co-ordination used to produce a complex movement (Bizzi & Cheung, 2013). However, neither clinical assessments nor EMG analysis measures are able to quantify the quality of any given movement. For this purpose, kinematic measures are necessary to assess the outcome of co-ordinated muscle activations and the quality of motor performance (Roy *et al.*, 2009). Furthermore, movement parameters cannot be reconstructed simply by increasing the number of muscles from which recordings are made, as a larger EMG montage will result in more cross-talk between signals (De Luca *et al.*, 2012) and a high probability of phase cancellation within any one signal (Staudenmann *et al.*, 2010).

Ideally outcome measures should capture multiple aspects of changes in motor-function post-stroke (Sivan *et al.*, 2011). Muscle activation parameters including muscle synergies can be distinguished using EMG recordings while accelerometry data is necessary to quantify how patients overcome inertia at the onset of a movement and momentum at the end of the movement (i.e. deceleration). Thus, it is necessary to use EMG and kinematic recordings in addition to clinical assessments to provide more objective and quantitative measures (Lum *et al.*, 2009), investigate the mechanisms of motor outcomes (Colombo *et al.*, 2010), and motor learning and compensation (Levin *et al.*, 2009).

Until the recent Stroke Recovery and Rehabilitation Roundtable (Kwakkel *et al.*, 2017), there has been no standardised approach to measure post-stroke motor outcomes and recovery. This group of eminent stroke researchers has now identified and recommended a core set of clinical assessments with additional kinematic measures, but with no neurophysiological measures. Furthermore, different suites of tools have been recommended at specific times post-stroke (for example see (Geyh *et al.*, 2004; Sivan *et al.*, 2011)). The multimodal assessment in this thesis investigated the variability of outcomes post-stroke and in the response to therapy and provides some insights into optimal measurement tools.

Longitudinal changes in outcome measures

The clinical motor-function measures used throughout this thesis including WMFT-tt, FMA, and MALQOM, improved from pre- to post-therapy and the changes were sustained to the 6-month follow-up. In contrast, the changes in EMG were complex with no single pattern of change either between or within each level of motor-function. The absence of a consistent pattern of change was also observed in the muscle synergy analysis and for the changes in kinematic parameters at each sensor. This highlights the importance of examining individual responses, in addition to pooled data after therapy, as was previously identified in another study from our group, in an EMG study of lower-limb muscles (Trinh *et al.*, 2016b). In contrast, many EMG and kinematic studies are based on relatively homogenous cohorts of patients (Alt Murphy *et al.*, 2013; Song & Tong, 2013; van Kordelaar *et al.*, 2014;

Bailey *et al.*, 2015; Ramos-Murguialday *et al.*, 2015). The heterogeneity of responses both within and between classifications of motor-function in this thesis emphasises that in order to generalise research studies to the broader stroke population a more heterogeneous sample is essential.

EMG analysis of the dominant muscle of each patient for each activity including movement duration, EMG peak amplitude, and EMG area under the curve highlighted differences between patients and how each movement was performed. This reflects the variability of problem solving by each patient according to their specific pattern of impairment and ability. The studies in this thesis were based on compound muscle EMG which does not address issues such as disuse muscle atrophy (Triandafilou & Kamper, 2012), change in muscle fibre phenotype (Scherbakov *et al.*, 2013), or changes in single motor unit firing rates (McNulty et al., 2014). The nature of the recordings in this study did not permit the investigation of the relationship between EMG parameters and the net power produced during each movement. Although it has been suggested that the EMG-force relationship is impaired post-stroke (Tang & Rymer, 1981; Zhou *et al.*, 2013), the relation between force and EMG amplitude is complex and dependent on multiple muscular and neural factors (Bhadane *et al.*, 2016). It is conceivable that differences in EMG-torque relationships between agonist and antagonist muscles and between proximal and distal muscles could determine the dominant muscle each patient uses for a given movement, or to alter the balance of co-ordinated muscle activation within a muscle synergy. However, it is important to note that many studies of EMG-torque relationship (Chang *et al.*, 2013; Bhadane *et al.*, 2016), co-contraction (Wagner *et al.*, 2007; Sin *et al.*, 2014), and single motor unit properties (Chou *et al.*, 2013; Hu *et al.*, 2015) are investigated during isometric contractions and not largely unconstrained therapy movements. In addition to more direct consequences of stroke, such as reduced corticospinal drive, clinical observation suggested that each patient had different patterns of spasticity (O'dwyer *et al.*, 1996; Li & Francisco, 2015), contracture (Ada *et al.*, 2006), and co-contraction (Silva *et al.*, 2014) that potentially influenced the quality of movement and how each movement was performed.

The kinematic parameters in post-stroke therapeutic studies are measured predominantly during joint flexion-extension (Kim *et al.*, 2013; Buma *et al.*, 2016), abduction-adduction (Bartolo *et al.*, 2014), and reaching (Wu *et al.*, 2011; Kitago *et al.*, 2015) or reach-to-grasp (Lin *et al.*, 2007) movements. In these studies, patients were seated during both the therapy protocol and kinematic measurements with no freely performed movements that might have engaged other limbs. Although WMT focuses on the more-affected upper-limb, patients need to be aware of the rest of their body according to the nature of the movements. It has been shown previously that the standing posture used whenever possible during WMT provides diverse ancillary benefits. These include improved lower-limb EMG patterns and stepping (Trinh *et al.*, 2016b), balance (Meldrum *et al.*, 2012), walking distance (Shiner *et al.*, 2014), cardiovascular fitness (Trinh *et al.*, 2016a), and lifestyle outcomes (McNulty *et al.*, 2015b). Wii-activities help with motor learning in patients and are more generalisable to real-world movements (Dipietro *et al.*, 2012). Even patients with low motor-function find a solution within their capacity to perform the activities i.e. compensation (McNulty *et al.*, 2013a).

The aim for Wii-baseball swings, and -tennis forehand and backhand during therapy is a larger range-of-motion whereas for Wii-golf putting, smaller movements are targeted. Preliminary data from our group demonstrated that WMT promotes smaller shoulder excursion during Wii-golf putting, yet showed higher acceleration suggesting better movement initiation (Thompson-Butel *et al.*, 2013; McNulty *et al.*, 2015c). In this telemetric electrogoniometer study, peak deceleration decreased for all Wii-activities examined (Wii-golf putting, -bowling, and -boxing); suggesting patients were better able to brake movements at the end of range-of-motion (Thompson-Butel *et al.*, 2013). This is important to avoid patients either hitting themselves with the controller, or hitting their hand on objects in the environment. Often patients used the same movement for all Wii-Sports tasks at early-therapy, particularly those with low motor-function but by late-therapy they could choose to select small, large, slow or fast movements as required by the task (McNulty *et al.*, 2013a; McNulty *et al.*, 2013b).

The acceleration magnitude increased over time but only significantly at proximal sensors. Wii-baseball swing involves shoulder abduction, internal rotation and elbow flexion in which the patient needs to stabilise the lower arm and hand (distal) while the drive of swing occurs from the shoulder and trunk movement (proximal) (Deutsch *et al.*, 2011). This movement pattern may explain greater changes in acceleration magnitude at proximal sensors. Distally, there were substantial differences between the levels of motor-function. Patients with low motor-function had less control at early-therapy and some required assistance to maintain the start-point positioning (i.e. elbow flexion) by the less-affected hand or the therapist. It will be in important in future studies to contrast movements such as Wii-baseball swings with movements that demand greater use of the hand (Wii-golf and bowling via button pushing), wrist (Wii-tennis) and elbow (Wii-boxing).

The general pattern of kinematic changes can be summarised as an increase in acceleration magnitude and peak acceleration, and a reduction in peak deceleration and normalised velocity over time. The combined effect of such changes is seen as more-controlled movements, hence better motor control (Kitago *et al.*, 2012; van Kordelaar *et al.*, 2013) induced by therapy and maintained at 6-month follow-up. An increase in acceleration and decrease in normalised velocity is hypothesised to enable subsequent elements of a movement sequence to be linked more smoothly with reduced effort (Chang *et al.*, 2005; Caimmi *et al.*, 2008). Acceleration and deceleration *per se* were not specifically targeted during the therapy activities analysed in these studies; patients were encouraged to increase their range-of-motion while performing a controlled movement. The greatest changes in peak acceleration and deceleration were in x- and z-directions of proximal sensors in which there were considerably larger movement excursion, and this presumably provides greater potential for improvement. Surprisingly, the normalised jerk measure did not change over time, although clinical observation would suggest patients performed smoother movements. Measures of movement smoothness are typically analysed during simple movements (Rohrer *et al.*, 2002; van Kordelaar *et al.*, 2014). It is possible that these techniques are not sufficiently sensitive for

complex movements (Balasubramanian *et al.*, 2015), like the largely unconstrained Wii-baseball swings used in Chapter 4.

The common use of the Wii-baseball swing in chapters 2-5 allows the specific comparison of differences in EMG and kinematic measures between levels of motor-function. Few studies have compared EMG and kinematic parameters across such a broad spectrum of post-stroke impairment. In this thesis, EMG signals from distal muscle were analysed for most patients at Wii-baseball swings. While EMG area under the curve for patients with low motor-function was smaller at early-therapy compared to those with moderate and high motor-function, there was an effect of level of motor-function on acceleration magnitude at distal sensors. In addition, there was a significant difference between patients with low and high motor-function in the number of muscle synergies at early-therapy. Acceleration magnitude at distal muscles did not change with therapy and the only therapy-induced change in EMG under the curve for Wii-baseball swings was for patients with moderate motor-function. Thus, multiple measures were able to distinguish different aspects of changes both post-stroke and with therapy, and the dissimilarities between patients with different levels of motor-function.

Regardless of the pattern of changes in EMG, muscle synergies, and kinematics, the improvement in MALQOM scores reflects greater independence in activities of daily living, both immediately after therapy and over time. There were no systematic relationship between changes in clinical motor-function assessments and those in EMG and kinematic parameters. This suggests that the clinical tools used in this thesis are not sufficiently sensitive to measure changes in movement parameters (Alt Murphy & Häger, 2015; Hesam-Shariati *et al.*, 2017a, b) and that there is no one tool suitable across the spectrum of stroke patients (Kwakkel *et al.*, 2017). Single clinical tools are quick, and provide an indication of motor status, but multivariate models are necessary to truly understand the mechanisms of therapy-induced and longitudinal changes. Without understanding the mechanisms of improved motor performance, it is difficult to design and implement alternate strategies, or investigate a lack of improvement.

Multimodal approach

A multimodal approach was designed to include all the measures presented in this thesis and investigate the correlates and potential predictors of responses to therapy. Patient characteristics including demographics, genetics, and cognition status (Burke Quinlan *et al.*, 2015); and baseline clinical assessments such as mood (Burke *et al.*, 2014) and motor-function (Zarahn *et al.*, 2011; Stinear *et al.*, 2012) status have been used in previous multimodal studies. From these potential predictors, only the strength of shoulder abduction and finger extension (Stinear *et al.*, 2017a) and baseline FMA score (Zarahn *et al.*, 2011) have been identified as a predictor of motor recovery in stroke patients. The best predictors identified in multivariate studies include the presence of an MEP, the integrity of the corticospinal tract, functional connectivity, and asymmetry index between hemispheres (Burke *et al.*, 2014; Burke Quinlan *et al.*, 2015; Stinear *et al.*, 2017a; Stinear *et al.*, 2017b) which are beyond the scope of these studies.

Obviously, not all aspects of improvement in motor-function and kinematics could be predicted by the variables presented in this thesis. The multivariate modelling was performed as an exploratory analysis to investigate different modalities. The outcomes of this analysis emphasised that for the heterogeneity of stroke survivors there is no one tool that can sufficiently quantify the changes in chronic stroke and with therapy. The multimodal approach revealed that patients in the chronic phase post-stroke not only have the capacity for improvement in motor-function and motor performance, but also that the magnitude of this improvement can be partially predicted. Particularly patients with low motor-function should not be eliminated from therapeutic studies as they retain the capacity to improve.

This thesis demonstrated for the first time that WMT also can improve depression in chronic stroke (Chapter 5). Patients with higher depression scores at baseline had retained the capacity for improved motor-function and the magnitude of their improvement was larger. This result suggests that when rehabilitation is engaging and fun (McNulty *et al.*, 2013a), patient compliance is high (McNulty *et al.*, 2015b),

significant improvements in motor-function are possible (Shiner *et al.*, 2014; Thompson-Butel *et al.*, 2015; Trinh *et al.*, 2016b), the continued trajectory of improvement can be sustained with additional therapy (McNulty *et al.*, 2015a), and depression can be alleviated. This confirms previous reports showing a variety of physical activity based therapies not only improved upper-limb (Shin *et al.*, 2015) and lower-limb (Stuart *et al.*, 2009; Calabrò *et al.*, 2015) motor-function but also significantly reduced depression in chronic stroke. Thus, these data suggest there is a synergistic relationship between depression and motor-function when physical activity based therapy is provided and that it is critically important to address ongoing depression in chronic stroke (Egede, 2007).

The characteristics of Wii-activities

Wii-activities investigated in this thesis were Wii-golf putting, Wii-baseball swing and Wii-tennis forehand and backhand. Each of these activities demands different movements (Deutsch *et al.*, 2011). The self-paced Wii-golf putting requires smaller and more controlled range of movements compared to Wii-baseball and -tennis swings for which the onsets are paced by the game and require a larger range of motion. The challenge in Wii-golf putting was to release a button while performing the movement, and this was not easy for some patients, particularly those with low motor-function (McNulty *et al.*, 2013a). Co-ordinating the swing timing for the oncoming ball in Wii-baseball and -tennis was challenging. Distinguishing the need for either a forehand or backhand was also difficult for some patients but improved by the end of therapy as indicated by a significant increase in the number of balls hit (Trinh *et al.*, 2016b; Hesam-Shariati *et al.*, 2017a). Thus, Wii-activities have different aspects targeting co-ordination, movement speed, hand-eye co-ordination, and range-of-motion (Deutsch *et al.*, 2011) which better emulates upper-limb activities in daily life compared to conventional therapies (McNulty, 2012). The largely unconstrained complex movements of this thesis also reflect the neurophysiological demands of the motor system during movement, and how this changes in chronic stroke.

Methodological limitations

In this thesis, the sample size is relatively small but comparable with many post-stroke therapeutic studies investigating neurophysiological and kinematic measures (Tropea *et al.*, 2013; Burke Quinlan *et al.*, 2015; Kitago *et al.*, 2015; Buma *et al.*, 2016). However, there are no other longitudinal rehabilitation studies that report clinical, neurophysiological and kinematic data recorded during therapy. This sample size may limit the statistical power in Chapter 5 as it includes multiple and diverse measures in a multivariate model. Despite the limitation of sample size, significant results were obtained in all studies.

The variables and biomarkers known to have the most predictive power (Boyd *et al.*, 2017) were not available for inclusion in this thesis. Most multimodal approaches predict motor outcomes and recovery based on corticospinal tract integrity and the presence or absence of MEPs, in addition to clinical measures (Burke *et al.*, 2014; Stinear *et al.*, 2017a). The lack of neuroimaging measures and TMS is recognised in Chapter 5, although this is the first study to include EMG measures and acceleration as potential predictors, and the increase in acceleration magnitude as a dependant variable.

The absence of gyroscope and magnetometer recordings limited the ability to determine movement trajectories and displacement (Lemmens *et al.*, 2015). Thus, the focus of kinematic study (Chapter 4) was on acceleration magnitude and triaxial peak acceleration and deceleration which could be extracted from calibrated and filtered accelerometry signals. Dimensionless measures of velocity and jerk were also calculated from first integration and derivative of acceleration, respectively. A richer data set will enable the reconstruction of therapy movements and potentially permit the identification of the most salient factors promoting or limiting motor improvements with therapy.

The analysis of EMG, muscle synergies and kinematics are typically compared with the data from healthy subjects. However, as shown by a previous study (Mouawad *et al.*, 2011), the approach of engaging in Wii activities is different between stroke

and healthy participants. The therapy instructions given to stroke patients are based on shaping principles (Taub *et al.*, 1994) and focus on improving the quality of movement and increasing the use of more-affected side (McNulty *et al.*, 2015b). In contrast, healthy subjects used movement patterns different to the real-world equivalents (Mouawad *et al.*, 2011). For example, during a Wii-tennis serve healthy participants perform two rapid wrist movements, whereas stroke patients were encouraged to use their shoulder and elbow. This evidence limits the utility of comparisons between stroke and healthy participants in this thesis.

The absence of control therapies is a limitation to this thesis, although the primary focus was not to investigate the efficacy of WMT but to understand the longitudinal changes in muscle activation and kinematic parameters for patients with a wide range of motor-function. As described in the Introduction, the movement parameters of WMT are unlike those of any other formal, standardised upper-limb therapy for stroke. Most therapies, like CIMT (the current best practice) are predominantly sedentary and involve small movements constrained within the workspace that are either externally paced or performed as fast as possible using only the more-affected upper-limb (Maciejasz *et al.*, 2014; Kwakkel *et al.*, 2015; Trinh *et al.*, 2016a). Despite these contrasting movement profiles, a recent randomised controlled study found no differences between dose-matched WMT and mCIMT, even for measures of dexterity (McNulty *et al.*, 2015b).

The complex movements studied in this thesis were largely unconstrained in time and space, as discussed in previous chapters. Most movements are composed of multiple sub-movements that cross multiple planes of movement (Deutsch *et al.*, 2011) and that also require postural stability, both dynamic and static balance (Trinh *et al.*, 2016b), hand-eye co-ordination, appropriate reaction times, and simultaneous fine and gross motor control. In contrast to WMT, almost all post-stroke studies of muscle activation and kinematic parameters use simplified tasks with pre-defined timing and start- and end positions (Caimmi *et al.*, 2008; Song *et al.*, 2008; Song & Tong, 2013; Sin *et al.*, 2014; Alt Murphy & Häger, 2015) or rhythmic semi-automated tasks such as locomotion. Thus, comparisons between WMT and other therapies

would provide little meaningful data to help understand the mechanisms of motor recovery or improvement other than simple totals of muscle activation and movement duration.

Future directions

There is no one clinical motor-function assessment that can provide a complete insight into motor-function outcome and recovery after stroke (Lang *et al.*, 2013; Thompson-Butel *et al.*, 2015). None of the analyses of single muscle EMG, co-ordinated activation of muscles in a voluntary task, and kinematics of a complex movement are able to fully explain the post-stroke changes and in the presence of therapy. However, a combination of these measures might help to understand the underlying mechanisms and develop targeted rehabilitative interventions.

Neuroimaging techniques such as functional MRI and diffusion-weighted MRI can be used to visualise post-stroke recovery and response to therapy (for review see (Farr & Wegener, 2010)). It would be advantageous to investigate how the different patterns of change in EMG and kinematics with WMT correspond to changes in cerebral connectivity and thereby investigate if simple approaches such as increased therapy intensity can further improve connectivity (Carter *et al.*, 2012; Wu *et al.*, 2015). Non-invasive brain stimulation methods such as TMS and tDCS have enormous potential in measurement and therapy (Sharma & Cohen, 2012; Silasi & Murphy, 2014). The absence or presence of an MEP has demonstrated predictive power in acute and subacute stroke (Boyd *et al.*, 2017). Similarly, short term TMS can improve motor performance (Le *et al.*, 2014) and there is potential for its use as an adjunct therapy as a form of brain-priming with WMT (Shiner *et al.*, 2014).

The automation of EMG and accelerometry analyses (Roy *et al.*, 2013) would indicate the feasibility of replacing clinical assessments with more objective and quantitative neurophysiological and kinematic measures in the near future. For instance, the combination of muscle synergy counts, and the structure and timing profiles within muscle synergies could be standardised and used as a method for classification of stroke patients to individually tailor therapy to specific deficits.

The cohort of this thesis was limited to cognitive competent and normal/mild depressed patients, with one moderately depressed patient. To identify the effect of cognition and mood status on motor improvements in chronic stroke using such detailed quantitative methods, a wide range of patients with cognition and psychological issues needs to be investigated together with the implementation of a full neuropsychological screening.

Conclusion

This thesis demonstrates that clinical assessment tools only provide an overview of motor improvement in chronic stroke. The subtleties and mechanisms underpinning such improvements can only be identified using detailed quantitative methods. These studies provide further evidence of the capacity of patients in the chronic period to benefit from additional therapy, particularly those with low motor-function. It further highlights the importance of addressing depression in chronic stroke. Thus, intense and targeted therapeutic interventions can improve motor-function and mood status. The sensitivity of the analyses in this thesis was affected by the complexity of the movements. However, such movements are essential for reflecting the range of movement necessary for activities of daily living better than the restricted and stereotypical movements used in most studies. While recent guidelines advocate the inclusion of kinematic assessments post-stroke, this thesis emphasises the unique information that can be gained from EMG recordings, particularly when muscle synergies are considered.

References

Ada, L, O'Dwyer, N, Ada, L, O'Dwyer, N, & O'Neill, E. (2006). Relation between spasticity, weakness and contracture of the elbow flexors and upper limb activity after stroke: An observational study. *Disability & Rehabilitation, 28*(13-14), 891-897.

Ada, L, O'Dwyer, N, Green, J, Yeo, W, & Neilson, P. (1996). The nature of the loss of strength and dexterity in the upper limb following stroke. *Human movement science, 15*(5), 671-687.

AIHW. (2014). Australia's health. Australian Institute of Health and Welfare, Canberra, Australia: Australian Institute of Health and Welfare.

AIHW. (2016). Australia's health. Australian Institute of Health and Welfare, Canberra, Australia: Australian Institute of Health and Welfare.

Ajiboye, AB, & Weir, R. (2009). Muscle synergies as a predictive framework for the emg patterns of new hand postures. *Journal of neural engineering, 6*(3), 036004.

Alia, C, Spalletti, C, Lai, S, Panarese, A, Lamola, G*, et al.* (2017). Neuroplastic changes following brain ischemia and their contribution to stroke recovery: Novel approaches in neurorehabilitation. *Frontiers in Cellular Neuroscience, 11*.

Alt Murphy, M, & Häger, CK. (2015). Kinematic analysis of the upper extremity after stroke–how far have we reached and what have we grasped? *Physical therapy reviews, 20*(3), 137-155.

Alt Murphy, M, Resteghini, C, Feys, P, & Lamers, I. (2015). An overview of systematic reviews on upper extremity outcome measures after stroke. *BMC neurology, 15*(1), 29.

Alt Murphy, M, Willén, C, & Sunnerhagen, KS. (2011). Kinematic variables quantifying upper-extremity performance after stroke during reaching and drinking from a glass. *Neurorehabilitation and neural repair, 25*(1), 71-80.

Alt Murphy, M, Willén, C, & Sunnerhagen, KS. (2013). Responsiveness of upper extremity kinematic measures and clinical improvement during the first three months after stroke. *Neurorehabilitation and neural repair, 27*(9), 844-853.

Ameli, M, Grefkes, C, Kemper, F, Riegg, F, Rehme, A*, et al.* (2009). Differential effects of high-frequency rtms over ipsilesional primary motor cortex in cortical and subcortical mca stroke. *Ann. Neurol, 66*(3), 298-309.

Andrenelli, E, Ippoliti, E, Coccia, M, Millevolte, M, Cicconi, B*, et al.* (2015). Features and predictors of activity limitations and participation restriction 2 years after intensive rehabilitation following first-ever stroke. *European journal of physical and rehabilitation medicine, 51*(5), 575-585.

Andrew, NE, Kilkenny, M, Naylor, R, Purvis, T, Lalor, E*, et al.* (2014). Understanding long-term unmet needs in australian survivors of stroke. *International Journal of Stroke, 9*(A100), 106-112.

Andrews, RJ. (1991). Transhemispheric diaschisis. A review and comment. *Stroke, 22*(7), 943-949.

Aprile, I, Rabuffetti, M, Padua, L, Di Sipio, E, Simbolotti, C*, et al.* (2014). Kinematic analysis of the upper limb motor strategies in stroke patients as a tool towards advanced neurorehabilitation strategies: A preliminary study. *BioMed research international, 2014*.

Ashbeck, EL, & Bell, ML. (2016). Single time point comparisons in longitudinal randomized controlled trials: Power and bias in the presence of missing data. *BMC medical research methodology, 16*(1), 43.

Askim, T, Indredavik, B, Vangberg, T, & Håberg, A. (2009). Motor network changes associated with successful motor skill relearning after acute ischemic stroke: A longitudinal functional magnetic resonance imaging study. *Neurorehabilitation and neural repair, 23*(3), 295-304.

Aström, M, Adolfsson, R, & Asplund, K. (1993). Major depression in stroke patients. A 3-year longitudinal study. *Stroke, 24*(7), 976-982.

Attias, H. (2000). *Independent factor analysis with temporally structured sources.* Paper presented at the Advances in neural information processing systems.

Avriel, M. (2003). *Nonlinear programming: Analysis and methods*: Courier Corporation.

Bagg, S, Pombo, AP, & Hopman, W. (2002). Effect of age on functional outcomes after stroke rehabilitation. *Stroke, 33*(1), 179-185.

Bailey, RR, Klaesner, JW, & Lang, CE. (2015). Quantifying real-world upper-limb activity in nondisabled adults and adults with chronic stroke. *Neurorehabilitation and neural repair, 29*(10), 969-978.

Bajaj, S, Butler, AJ, Drake, D, & Dhamala, M. (2015). Brain effective connectivity during motor-imagery and execution following stroke and rehabilitation. *NeuroImage: Clinical, 8*, 572-582.

Bajaj, S, Housley, SN, Wu, D, Dhamala, M, James, G*, et al.* (2016). Dominance of the unaffected hemisphere motor network and its role in the behavior of chronic stroke survivors. *Frontiers in Human Neuroscience, 10*.

Balasubramanian, S, Melendez-Calderon, A, & Burdet, E. (2012). A robust and sensitive metric for quantifying movement smoothness. *IEEE transactions on biomedical engineering, 59*(8), 2126-2136.

Balasubramanian, S, Melendez-Calderon, A, Roby-Brami, A, & Burdet, E. (2015). On the analysis of movement smoothness. *Journal of neuroengineering and rehabilitation, 12*(1), 112.

Bartolo, M, De Nunzio, AM, Sebastiano, F, Spicciato, F, Tortola, P*, et al.* (2014). Arm weight support training improves functional motor outcome and movement smoothness after stroke. *Functional neurology, 29*(1), 15.

Basmajian, JV, & De Luca, CJ. (1985). *Muscles alive: Their functions revealed by electromyography*: Williams & Wilkins.

Beebe, JA, & Lang, CE. (2009). Active range of motion predicts upper extremity function 3 months after stroke. *Stroke, 40*(5), 1772-1779.

Belagaje, SR. (2017). Stroke rehabilitation. *CONTINUUM: Lifelong Learning in Neurology, 23*(1, Cerebrovascular Disease), 238-253.

Bernal-Rusiel, JL, Greve, DN, Reuter, M, Fischl, B, Sabuncu, MR*, et al.* (2013). Statistical analysis of longitudinal neuroimage data with linear mixed effects models. *Neuroimage, 66*, 249-260.

Bernhardt, J, Hayward, KS, Kwakkel, G, Ward, NS, Wolf, SL*, et al.* (2017). Agreed definitions and a shared vision for new standards in stroke recovery research: The stroke recovery and rehabilitation roundtable taskforce. *International Journal of Stroke, 12*(5), 444-450.

Bernhardt, J, Langhorne, P, Lindley, RI, Thrift, AG, Ellery, F*, et al.* (2015). Efficacy and safety of very early mobilisation within 24 h of stroke onset (avert): A randomised controlled trial. *Lancet, 386*(9988), 46-55.

Berry, MW, Browne, M, Langville, AN, Pauca, VP, & Plemmons, RJ. (2007). Algorithms and applications for approximate nonnegative matrix factorization. *Computational statistics & data analysis, 52*(1), 155-173.

Bhadane, M, Liu, J, Rymer, WZ, Zhou, P, & Li, S. (2016). Re-evaluation of emg-torque relation in chronic stroke using linear electrode array emg recordings. *Scientific reports, 6*, 28957.

Bizzi, E, Cheung, V, d'Avella, A, Saltiel, P, & Tresch, M. (2008). Combining modules for movement. *Brain research reviews, 57*(1), 125-133.

Bizzi, E, & Cheung, VC. (2013). The neural origin of muscle synergies. *Frontiers in computational neuroscience, 7*, 51.

Bodin, P, & Morris, M. (1991). *Inter-rater reliability of the modified ashworth scale for wrist flexor spasticity following stroke.* Paper presented at the Proceedings of the 11th Congress of the World Confederation for Physical Therapy.

Bohannon, RW, Peolsson, A, Massy-Westropp, N, Desrosiers, J, & Bear-Lehman, J. (2006). Reference values for adult grip strength measured with a jamar dynamometer: A descriptive meta-analysis. *Physiotherapy, 92*(1), 11-15.

Bohannon, RW, & Smith, MB. (1987). Interrater reliability of a modified ashworth scale of muscle spasticity. *Physical therapy, 67*(2), 206-207.

Borzelli, D, Berger, DJ, Pai, D, & D'avella, A. (2013). Effort minimization and synergistic muscle recruitment for three-dimensional force generation. *Frontiers in computational neuroscience, 7*, 186.

Bosecker, C, Dipietro, L, Volpe, B, & Krebs, HI. (2010). Kinematic robot-based evaluation scales and clinical counterparts to measure upper limb motor performance in patients with chronic stroke. *Neurorehabilitation and neural repair, 24*(1), 62-69.

Bourbonnais, D, & Noven, SV. (1989). Weakness in patients with hemiparesis. *American Journal of Occupational Therapy, 43*(5), 313-319.

Bowden, JL, Lin, GG, & McNulty, PA. (2014a). The prevalence and magnitude of impaired cutaneous sensation across the hand in the chronic period post-stroke. *PloS one, 9*(8), e104153.

Bowden, JL, Taylor, JL, & McNulty, PA. (2014b). Voluntary activation is reduced in both the more-and less-affected upper limbs after unilateral stroke. *Frontiers in neurology, 5*, 239.

Boyd, LA, Hayward, KS, Ward, NS, Stinear, CM, Rosso, C*, et al.* (2017). Biomarkers of stroke recovery: Consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *International Journal of Stroke, 12*(5), 480-493.

Brach, JS, McGurl, D, Wert, D, VanSwearingen, JM, Perera, S*, et al.* (2010). Validation of a measure of smoothness of walking. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 66*(1), 136-141.

Brainin, M. (2013). Poststroke spasticity treating to the disability. *Neurology, 80*(3 Supplement 2), S1-S4.

Brainin, M, Norrving, B, Sunnerhagen, KS, Goldstein, LB, Cramer, SC*, et al.* (2011). Poststroke chronic disease management: Towards improved identification and interventions for poststroke spasticity-related complications. *International Journal of Stroke, 6*(1), 42-46.

Brauer, SG, Hayward, KS, Carson, RG, Cresswell, AG, & Barker, RN. (2013). The efficacy of smart arm training early after stroke for stroke survivors withsevere upper limb disability: A protocol for a randomised controlled trial. *BMC neurology, 13*(1), 71.

Brazzelli, M, Chappell, FM, Miranda, H, Shuler, K, Dennis, M*, et al.* (2014). Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Annals of neurology, 75*(1), 67-76.

Brewer, BR, McDowell, SK, & Worthen-Chaudhari, LC. (2007). Poststroke upper extremity rehabilitation: A review of robotic systems and clinical results. *Topics in stroke rehabilitation, 14*(6), 22-44.

Bujanda, ED, Nadeau, S, Bourbonnais, D, & Dickstein, R. (2003). Associations between lower limb impairments, locomotor capacities and kinematic variables in the frontal plane during walking in adults with chronic stroke. *Journal of Rehabilitation Medicine, 35*(6), 259-264.

Buma, FE, Kordelaar, J, Raemaekers, M, Wegen, EE, Ramsey, NF*, et al.* (2016). Brain activation is related to smoothness of upper limb movements after stroke. *Experimental brain research, 234*(7), 2077-2089.

Buma, FE, Kwakkel, G, & Ramsey, NF. (2013). Understanding upper limb recovery after stroke. *Restorative neurology and neuroscience, 31*(6), 707-722.

Burden, A. (2007). Surface electromyography. *Biomechanical evaluation of movement in sport and exercise*, 77.

Burke, E, & Cramer, SC. (2013). Biomarkers and predictors of restorative therapy effects after stroke. *Current neurology and neuroscience reports, 13*(2), 329.

Burke, E, Dodakian, L, See, J, McKenzie, A, Riley, JD*, et al.* (2014). A multimodal approach to understanding motor impairment and disability after stroke. *Journal of neurology, 261*(6), 1178-1186.

Burke Quinlan, E, Dodakian, L, See, J, McKenzie, A, Le, V*, et al.* (2015). Neural function, injury, and stroke subtype predict treatment gains after stroke. *Annals of neurology, 77*(1), 132-145.

Bushnell, CD, Reeves, MJ, Zhao, X, Pan, W, Prvu-Bettger, J*, et al.* (2014). Sex differences in quality of life after ischemic stroke. *Neurology, 82*(11), 922-931.

Byblow, WD, Stinear, CM, Barber, PA, Petoe, MA, & Ackerley, SJ. (2015). Proportional recovery after stroke depends on corticomotor integrity. *Annals of neurology, 78*(6), 848-859.

Caimmi, M, Carda, S, Giovanzana, C, Maini, ES, Sabatini, AM*, et al.* (2008). Using kinematic analysis to evaluate constraint-induced movement therapy in chronic stroke patients. *Neurorehabilitation and neural repair, 22*(1), 31-39.

Calabrò, RS, De Cola, MC, Leo, A, Reitano, S, Balletta, T*, et al.* (2015). Robotic neurorehabilitation in patients with chronic stroke: Psychological well-being beyond motor improvement. *International Journal of Rehabilitation Research, 38*(3), 219-225.

Canning, CG, Ada, L, Adams, R, & O'Dwyer, NJ. (2004). Loss of strength contributes more to physical disability after stroke than loss of dexterity. *Clinical Rehabilitation, 18*(3), 300-308.

Canning, CG, Ada, L, & O'Dwyer, NJ. (2000). Abnormal muscle activation characteristics associated with loss of dexterity after stroke. *Journal of the neurological sciences, 176*(1), 45-56.

Carmichael, ST, Tatsukawa, K, Katsman, D, Tsuyuguchi, N, & Kornblum, HI. (2004). Evolution of diaschisis in a focal stroke model. *Stroke, 35*(3), 758-763.

Carrera, E, & Tononi, G. (2014). Diaschisis: Past, present, future. *Brain, 137*(9), 2408-2422.

Carter, AR, Shulman, GL, & Corbetta, M. (2012). Why use a connectivity-based approach to study stroke and recovery of function? *Neuroimage, 62*(4), 2271-2280.

Casadio, M, Tamagnone, I, Summa, S, & Sanguineti, V. (2013). Neuromotor recovery from stroke: Computational models at central, functional, and muscle synergy level. *Frontiers in computational neuroscience, 7*, 97.

Castilho, J, Ferreira, LAB, Pereira, WM, Neto, HP, da Silva Morelli, JG*, et al.* (2012). Analysis of electromyographic activity in spastic biceps brachii muscle following neural mobilization. *Journal of bodywork and movement therapies, 16*(3), 364-368.

Celinder, D, & Peoples, H. (2012). Stroke patients' experiences with wii sports® during inpatient rehabilitation. *Scandinavian Journal of Occupational Therapy, 19*(5), 457-463.

Cesqui, B, Tropea, P, Micera, S, & Krebs, HI. (2013). Emg-based pattern recognition approach in post stroke robot-aided rehabilitation: A feasibility study. *Journal of neuroengineering and rehabilitation, 10*(1), 75.

Chalela, JA, Kidwell, CS, Nentwich, LM, Luby, M, Butman, JA*, et al.* (2007). Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: A prospective comparison. *The Lancet, 369*(9558), 293-298.

Chang, J-J, Wu, T-I, Wu, W-L, & Su, F-C. (2005). Kinematical measure for spastic reaching in children with cerebral palsy. *Clinical Biomechanics, 20*(4), 381-388.

Chang, SH, Zhou, P, Rymer, WZ, & Li, S. (2013). Spasticity, weakness, force variability, and sustained spontaneous motor unit discharges of resting spastic–paretic biceps brachii muscles in chronic stroke. *Muscle & nerve, 48*(1), 85-92.

Chatterjee, K, Fall, S, & Barer, D. (2010). Mood after stroke: A case control study of biochemical, neuro-imaging and socio-economic risk factors for major depression in stroke survivors. *BMC neurology, 10*(1), 125.

Cheung, VC, d'Avella, A, Tresch, MC, & Bizzi, E. (2005). Central and sensory contributions to the activation and organization of muscle synergies during natural motor behaviors. *The Journal of neuroscience, 25*(27), 6419-6434.

Cheung, VC, Piron, L, Agostini, M, Silvoni, S, Turolla, A*, et al.* (2009). Stability of muscle synergies for voluntary actions after cortical stroke in humans. *Proceedings of the National Academy of Sciences, 106*(46), 19563-19568.

Cheung, VC, Turolla, A, Agostini, M, Silvoni, S, Bennis, C*, et al.* (2012). Muscle synergy patterns as physiological markers of motor cortical damage. *Proceedings of the National Academy of Sciences, 109*(36), 14652-14656.

Chiovetto, E, Berret, B, Delis, I, Panzeri, S, & Pozzo, T. (2013). Investigating reduction of dimensionality during single-joint elbow movements: A case study on muscle synergies. *Frontiers in computational neuroscience, 7*, 11.

Choi, JH, Han, EY, Kim, BR, Kim, SM, Im, SH*, et al.* (2014). Effectiveness of commercial gaming-based virtual reality movement therapy on functional recovery of upper extremity in subacute stroke patients. *Annals of rehabilitation medicine, 38*(4), 485-493.

Chou, L-W, Palmer, JA, Binder-Macleod, S, & Knight, CA. (2013). Motor unit rate coding is severely impaired during forceful and fast muscular contractions in individuals post stroke. *Journal of neurophysiology, 109*(12), 2947-2954.

Chvatal, SA, Macpherson, JM, Torres-Oviedo, G, & Ting, LH. (2013). Absence of postural muscle synergies for balance after spinal cord transection. *Journal of neurophysiology, 110*(6), 1301-1310.

Chvatal, SA, & Ting, LH. (2013). Common muscle synergies for balance and walking. *Frontiers in computational neuroscience, 7*.

Chvatal, SA, Torres-Oviedo, G, Safavynia, SA, & Ting, LH. (2011). Common muscle synergies for control of center of mass and force in nonstepping and stepping postural behaviors. *Journal of neurophysiology, 106*(2), 999-1015.

Cirstea, M, & Levin, MF. (2000). Compensatory strategies for reaching in stroke. *Brain, 123*(5), 940-953.
Cirstea, M, Ptito, A, & Levin, M. (2003). Arm reaching improvements with short-term practice depend on the severity of the motor deficit in stroke. *Experimental Brain Research, 152*(4), 476-488.
Clark, DJ, Ting, LH, Zajac, FE, Neptune, RR, & Kautz, SA. (2010). Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke. *Journal of neurophysiology, 103*(2), 844-857.
Cole, BT, Roy, SH, De Luca, CJ, & Nawab, SH. (2014). Dynamical learning and tracking of tremor and dyskinesia from wearable sensors. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 22*(5), 982-991.
Colebatch, J, & Gandevia, S. (1989). The distribution of muscular weakness in upper motor neuron lesions affecting the arm. *Brain, 112*(3), 749-763.
Colombo, R, Sterpi, I, Mazzone, A, Delconte, C, Minuco, G*, et al.* (2010). Measuring changes of movement dynamics during robot-aided neurorehabilitation of stroke patients. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 18*(1), 75-85.
Conroy, SS, Whitall, J, Dipietro, L, Jones-Lush, LM, Zhan, M*, et al.* (2011). Effect of gravity on robot-assisted motor training after chronic stroke: A randomized trial. *Archives of physical medicine and rehabilitation, 92*(11), 1754-1761.
Corbetta, D, Sirtori, V, Castellini, G, Moja, L, & Gatti, R. (2015). Constraint-induced movement therapy for upper extremities in people with stroke. *The Cochrane Library*.
Corbetta, D, Sirtori, V, Castellini, G, Moja, L, & Gatti, R. (2016). Constraint-induced movement therapy for upper extremities in people with stroke. *Stroke, 47*(8), e205-e206.
Coscia, M, Cheung, VC, Tropea, P, Koenig, A, Monaco, V*, et al.* (2014). The effect of arm weight support on upper limb muscle synergies during reaching movements. *Stroke, 13*(14), 32-34.
Coscia, M, Monaco, V, Martelloni, C, Rossi, B, Chisari, C*, et al.* (2015). Muscle synergies and spinal maps are sensitive to the asymmetry induced by a unilateral stroke. *Journal of neuroengineering and rehabilitation, 12*(1), 39.
Cramer, SC. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of neurology, 63*(3), 272-287.
Cramer, SC. (2010). Stratifying patients with stroke in trials that target brain repair. *Stroke, 41*(10 suppl 1), S114-S116.
Cramer, SC, & Bastings, EP. (2000). Mapping clinically relevant plasticity after stroke. *Neuropharmacology, 39*(5), 842-851.
Cramer, SC, Parrish, TB, Levy, RM, Stebbins, GT, Ruland, SD*, et al.* (2007). Predicting functional gains in a stroke trial. *Stroke, 38*(7), 2108-2114.
Cramer, SC, & Procaccio, V. (2012). Correlation between genetic polymorphisms and stroke recovery: Analysis of the gain americas and gain international studies. *European journal of neurology, 19*(5), 718-724.
Cumming, TB, Blomstrand, C, Skoog, I, & Linden, T. (2016). The high prevalence of anxiety disorders after stroke. *The American Journal of Geriatric Psychiatry, 24*(2), 154-160.
Cumming, TB, Brodtmann, A, Darby, D, & Bernhardt, J. (2014). The importance of cognition to quality of life after stroke. *Journal of psychosomatic research, 77*(5), 374-379.

Cumming, TB, Churilov, L, Lindén, T, & Bernhardt, J. (2013). Montreal cognitive assessment and mini–mental state examination are both valid cognitive tools in stroke. *Acta Neurologica Scandinavica, 128*(2), 122-129.

Cumming, TB, Tyedin, K, Churilov, L, Morris, ME, & Bernhardt, J. (2012). The effect of physical activity on cognitive function after stroke: A systematic review. *International psychogeriatrics, 24*(4), 557-567.

d'Avella, A, & Lacquaniti, F. (2013). Control of reaching movements by muscle synergy combinations. *Frontiers in computational neuroscience, 7*.

d'Avella, A, Saltiel, P, & Bizzi, E. (2003). Combinations of muscle synergies in the construction of a natural motor behavior. *Nature neuroscience, 6*(3), 300-308.

Davis, A, Gunesch, A, Wagner, S, Wegner, M, & Westerfield, C. (2013). Constraint-induced movement therapy (cimt) as a post stroke intervention.

Davis, SM, & Norrving, B. (2013). Organizational update world stroke organization. *Stroke, 44*(12), e173-e173.

de Jong, LD, Nieuwboer, A, & Aufdemkampe, G. (2006). Contracture preventive positioning of the hemiplegic arm in subacute stroke patients: A pilot randomized controlled trial. *Clinical Rehabilitation, 20*(8), 656-667.

de los Reyes-Guzmán, A, Dimbwadyo-Terrer, I, Trincado-Alonso, F, Monasterio-Huelin, F, Torricelli, D*, et al.* (2014). Quantitative assessment based on kinematic measures of functional impairments during upper extremity movements: A review. *Clinical Biomechanics, 29*(7), 719-727.

De Luca, CJ. (1997). The use of surface electromyography in biomechanics. *Journal of applied biomechanics, 13*(2), 135-163.

De Luca, CJ, Gilmore, LD, Kuznetsov, M, & Roy, SH. (2010). Filtering the surface emg signal: Movement artifact and baseline noise contamination. *Journal of biomechanics, 43*(8), 1573-1579.

De Luca, CJ, Kuznetsov, M, Gilmore, LD, & Roy, SH. (2012). Inter-electrode spacing of surface emg sensors: Reduction of crosstalk contamination during voluntary contractions. *Journal of biomechanics, 45*(3), 555-561.

de Nap Shelton, F, & Reding, MJ. (2001). Effect of lesion location on upper limb motor recovery after stroke. *Stroke, 32*(1), 107-112.

Deloitte. (2013). The economic impact of stroke in australia. Australia: Deloitte Access Economics.

Deutsch, JE, Brettler, A, Smith, C, Welsh, J, John, R*, et al.* (2011). Nintendo wii sports and wii fit game analysis, validation, and application to stroke rehabilitation. *Topics in stroke rehabilitation, 18*(6), 701-719.

Dewald, JP, Pope, PS, Given, JD, Buchanan, TS, & Rymer, WZ. (1995). Abnormal muscle coactivation patterns during isometric torque generation at the elbow and shoulder in hemiparetic subjects. *Brain, 118*(2), 495-510.

Di Lazzaro, V, Pellegrino, G, Di Pino, G, Ranieri, F, Lotti, F*, et al.* (2016). Human motor cortex functional changes in acute stroke: Gender effects. *Frontiers in neuroscience, 10*.

Ding, Q, Stevenson, IH, Wang, N, Li, W, Sun, Y*, et al.* (2013). Motion games improve balance control in stroke survivors: A preliminary study based on the principle of constraint-induced movement therapy. *Displays, 34*(2), 125-131.

Dipietro, L, Krebs, H, Fasoli, S, Volpe, B, Stein, J*, et al.* (2007). Changing motor synergies in chronic stroke. *Journal of neurophysiology, 98*(2), 757-768.

Dipietro, L, Krebs, H, Volpe, B, Stein, J, Bever, C*, et al.* (2012). Learning, not adaptation, characterizes stroke motor recovery: Evidence from kinematic changes induced by robot-assisted therapy in trained and untrained task in

the same workspace. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 20*(1), 48-57.

Dirnagl, U, Iadecola, C, & Moskowitz, MA. (1999). Pathobiology of ischaemic stroke: An integrated view. *Trends in neurosciences, 22*(9), 391-397.

Do Lee, C, Folsom, AR, & Blair, SN. (2003). Physical activity and stroke risk a meta-analysis. *Stroke, 34*(10), 2475-2481.

Donoho, D, & Stodden, V. (2004). *When does non-negative matrix factorization give a correct decomposition into parts?* Paper presented at the Advances in neural information processing systems.

Douiri, A, Rudd, AG, & Wolfe, CD. (2013). Prevalence of poststroke cognitive impairment. *Stroke, 44*(1), 138-145.

Dudek, N, & Trudel, G. (2008). Joint contractures. *Essentials of Physical Medicine and Rehabilitation. 2nd ed. Philadelphia, Pa: Saunders Elsevier*.

Easton, JD, Saver, JL, Albers, GW, Alberts, MJ, Chaturvedi, S*, et al.* (2009). Definition and evaluation of transient ischemic attack a scientific statement for healthcare professionals from the american heart association/american stroke association stroke council; council on cardiovascular surgery and anesthesia; council on cardiovascular radiology and intervention; council on cardiovascular nursing; and the interdisciplinary council on peripheral vascular disease: The american academy of neurology affirms the value of this statement as an educational tool for neurologists. *Stroke, 40*(6), 2276-2293.

Egede, LE. (2007). Major depression in individuals with chronic medical disorders: Prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *General Hospital Psychiatry, 29*(5), 409-416.

Emara, T, El Nahas, N, Elkader, HA, Ashour, S, & El Etrebi, A. (2009). Mri can predict the response to therapeutic repetitive transcranial magnetic stimulation (rtms) in stroke patients. *Journal of vascular and interventional neurology, 2*(2), 163.

Farina, D, Merletti, R, & Enoka, RM. (2014). The extraction of neural strategies from the surface emg: An update. *Journal of Applied Physiology, 117*(11), 1215-1230.

Farr, TD, & Wegener, S. (2010). Use of magnetic resonance imaging to predict outcome after stroke: A review of experimental and clinical evidence. *Journal of Cerebral Blood Flow & Metabolism, 30*(4), 703-717.

Feigin, VL, Forouzanfar, MH, Krishnamurthi, R, Mensah, GA, Connor, M*, et al.* (2014). Global and regional burden of stroke during 1990–2010: Findings from the global burden of disease study 2010. *The Lancet, 383*(9913), 245-255.

Feys, H, De Weerdt, W, Nuyens, G, Van De Winckel, A, Selz, B*, et al.* (2000). Predicting motor recovery of the upper limb after stroke rehabilitation: Value of a clinical examination. *Physiotherapy Research International, 5*(1), 1-18.

Fleet, A, Page, SJ, MacKay-Lyons, M, & Boe, SG. (2014). Modified constraint-induced movement therapy for upper extremity recovery post stroke: What is the evidence? *Topics in stroke rehabilitation, 21*(4), 319-331.

Fleuren, JF, Voerman, GE, Erren-Wolters, CV, Snoek, GJ, Rietman, JS*, et al.* (2010). Stop using the ashworth scale for the assessment of spasticity. *Journal of Neurology, Neurosurgery & Psychiatry, 81*(1), 46-52.

Flynn, R, MacWalter, R, & Doney, A. (2008). The cost of cerebral ischaemia. *Neuropharmacology, 55*(3), 250-256.

Franklin, DW, Burdet, E, Tee, KP, Osu, R, Chew, C-M*, et al.* (2008). Cns learns stable, accurate, and efficient movements using a simple algorithm. *Journal of neuroscience, 28*(44), 11165-11173.

Fregni, F, Boggio, PS, Valle, AC, Rocha, RR, Duarte, J*, et al.* (2006). A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke, 37*(8), 2115-2122.

Frère, J, & Hug, F. (2012). Between-subject variability of muscle synergies during a complex motor skill. *Frontiers in computational neuroscience, 6*, 99.

Fugl-Meyer, AR, Jääskö, L, Leyman, I, Olsson, S, & Steglind, S. (1974). The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scandinavian journal of rehabilitation medicine, 7*(1), 13-31.

Fusco, A, Assenza, F, Iosa, M, Izzo, S, Altavilla, R*, et al.* (2014). The ineffective role of cathodal tdcs in enhancing the functional motor outcomes in early phase of stroke rehabilitation: An experimental trial. *BioMed research international, 2014*.

Gates, DH, Walters, LS, Cowley, J, Wilken, JM, & Resnik, L. (2016). Range of motion requirements for upper-limb activities of daily living. *American Journal of Occupational Therapy, 70*(1), 7001350010p7001350011-7001350010p7001350010.

Geyh, S, Cieza, A, Schouten, J, Dickson, H, Frommelt, P*, et al.* (2004). Icf core sets for stroke. *Journal of Rehabilitation Medicine, 36*(0), 135-141.

Ghasemi, A, & Zahediasl, S. (2012). Normality tests for statistical analysis: A guide for non-statisticians. *International journal of endocrinology and metabolism, 10*(2), 486.

Gibbings, DL, Patterson, J, & Bell, G. (1971). The absolute determination of the gravitational acceleration at sydney, australia. *Bulletin Géodésique (1946-1975), 100*(1), 147-157.

Gizzi, L, Nielsen, JF, Felici, F, Ivanenko, YP, & Farina, D. (2011). Impulses of activation but not motor modules are preserved in the locomotion of subacute stroke patients. *Journal of neurophysiology, 106*(1), 202-210.

Gladstone, DJ, Danells, CJ, & Black, SE. (2002). The fugl-meyer assessment of motor recovery after stroke: A critical review of its measurement properties. *Neurorehabilitation and neural repair, 16*(3), 232-240.

Goldstein, LB, & Samsa, GP. (1997). Reliability of the national institutes of health stroke scale. *Stroke, 28*(2), 307-310.

Gordon, NF, Gulanick, M, Costa, F, Fletcher, G, Franklin, BA*, et al.* (2004). Physical activity and exercise recommendations for stroke survivors. *Stroke, 35*(5), 1230-1240.

Granger, CV, Dewis, LS, Peters, NC, Sherwood, C, & Barrett, J. (1979). Stroke rehabilitation: Analysis of repeated barthel index measures. *Archives of physical medicine and rehabilitation, 60*(1), 14-17.

Granger, CV, Hamilton, BB, Linacre, JM, Heinemann, AW, & Wright, BD. (1993). Performance profiles of the functional independence measure. *American Journal of Physical Medicine & Rehabilitation, 72*(2), 84-89.

Graziadio, S, Tomasevic, L, Assenza, G, Tecchio, F, & Eyre, J. (2012). The myth of the 'unaffected'side after unilateral stroke: Is reorganisation of the non-infarcted corticospinal system to re-establish balance the price for recovery? *Experimental neurology, 238*(2), 168-175.

Groisser, BN, Copen, WA, Singhal, AB, Hirai, KK, & Schaechter, JD. (2014). Corticospinal tract diffusion abnormalities early after stroke predict motor outcome. *Neurorehabilitation and neural repair, 28*(8), 751-760.

Hackett, ML, Yapa, C, Parag, V, & Anderson, CS. (2005). Frequency of depression after stroke. *Stroke, 36*(6), 1330-1340.

Hafer-Macko, CE, Ryan, AS, Ivey, FM, & Macko, RF. (2008). Skeletal muscle changes after hemiparetic stroke and potential beneficial effects of exercise intervention strategies. *Journal of rehabilitation research and development, 45*(2), 261.

Halaki, M, & Ginn, K. (2012). Normalization of emg signals: To normalize or not to normalize and what to normalize to?

Hamill, J, & Knutzen, KM. (2006). *Biomechanical basis of human movement*: Lippincott Williams & Wilkins.

Hatem, SM, Saussez, G, della Faille, M, Prist, V, Zhang, X*, et al.* (2016). Rehabilitation of motor function after stroke: A multiple systematic review focused on techniques to stimulate upper extremity recovery. *Frontiers in Human Neuroscience, 10*.

Hausen, HS, Lachmann, EA, & Nagler, W. (1997). Cerebral diaschisis following cerebellar hemorrhage. *Archives of physical medicine and rehabilitation, 78*(5), 546-549.

Hayward, KS, Schmidt, J, Lohse, KR, Peters, S, Bernhardt, J*, et al.* (2017). Are we armed with the right data? Pooled individual data review of biomarkers in people with severe upper limb impairment after stroke. *NeuroImage: Clinical, 13*, 310-319.

Henderson, A, Korner-Bitensky, N, & Levin, M. (2007). Virtual reality in stroke rehabilitation: A systematic review of its effectiveness for upper limb motor recovery. *Topics in stroke rehabilitation, 14*(2), 52-61.

Hesam-Shariati, N, Trinh, T, Thompson-Butel, AG, Shiner, CT, & McNulty, PA. (2017a). A longitudinal electromyography study of complex movements in poststroke therapy. 1: Heterogeneous changes despite consistent improvements in clinical assessments. *Frontiers in neurology, 8*.

Hesam-Shariati, N, Trinh, T, Thompson-Butel, AG, Shiner, CT, & McNulty, PA. (2017b). A longitudinal electromyography study of complex movements in poststroke therapy. 2: Changes in coordinated muscle activation. *Frontiers in neurology, 8*.

Hidler, JM, Carroll, M, & Federovich, EH. (2007). Strength and coordination in the paretic leg of individuals following acute stroke. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 15*(4), 526-534.

Howard, RM, Conway, R, & Harrison, AJ. (2016). A survey of sensor devices: Use in sports biomechanics. *Sports biomechanics, 15*(4), 450-461.

Hu, X, Suresh, AK, Rymer, WZ, & Suresh, NL. (2015). Assessing altered motor unit recruitment patterns in paretic muscles of stroke survivors using surface electromyography. *Journal of neural engineering, 12*(6), 066001.

Hu, X, Tong, K, Song, R, Zheng, X, Lui, K*, et al.* (2009). Quantitative evaluation of motor functional recovery process in chronic stroke patients during robot-assisted wrist training. *Journal of Electromyography and Kinesiology, 19*(4), 639-650.

Hubbard, IJ, Carey, LM, Budd, TW, & Parsons, MW. (2015). Reorganizing therapy: Changing the clinical approach to upper limb recovery post-stroke. *Occupational therapy international, 22*(1), 28-35.

Hug, F. (2011). Can muscle coordination be precisely studied by surface electromyography? *Journal of Electromyography and Kinesiology, 21*(1), 1-12.

Hughes, A, Freeman, C, Burridge, J, Chappell, P, Lewin, P*, et al.* (2010). Shoulder and elbow muscle activity during fully supported trajectory tracking in people

who have had a stroke. *Journal of Electromyography and Kinesiology, 20*(3), 465-476.
Hyvärinen, A, & Oja, E. (2000). Independent component analysis: Algorithms and applications. *Neural networks, 13*(4), 411-430.
Jang, S-H, Kim, Y-H, Cho, S-H, Lee, J-H, Park, J-W*, et al.* (2003). Cortical reorganization induced by task-oriented training in chronic hemiplegic stroke patients. *Neuroreport, 14*(1), 137-141.
Joo, LY, Yin, TS, Xu, D, Thia, E, Chia, PF*, et al.* (2010). A feasibility study using interactive commercial off-the-shelf computer gaming in upper limb rehabilitation in patients after stroke. *Journal of Rehabilitation Medicine, 42*(5), 437-441.
Jurman, D, Jankovec, M, Kamnik, R, & Topič, M. (2007). Calibration and data fusion solution for the miniature attitude and heading reference system. *Sensors and Actuators A: Physical, 138*(2), 411-420.
Juth, V, Holman, EA, Chan, MK, & Cramer, SC. (2016). Genetics as a molecular window into recovery, its treatment, and stress responses after stroke. *Journal of Investigative Medicine*, jim-2016-000126.
Kamper, DG, Fischer, HC, Cruz, EG, & Rymer, WZ. (2006). Weakness is the primary contributor to finger impairment in chronic stroke. *Archives of physical medicine and rehabilitation, 87*(9), 1262-1269.
Kang, H-J, Stewart, R, Kim, J-M, Jang, J-E, Kim, S-Y*, et al.* (2013). Comparative validity of depression assessment scales for screening poststroke depression. *Journal of affective disorders, 147*(1), 186-191.
Kang, N, Summers, JJ, & Cauraugh, JH. (2015). Transcranial direct current stimulation facilitates motor learning post-stroke: A systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*, jnnp-2015-311242.
Kannel, WB. (1996). Blood pressure as a cardiovascular risk factor: Prevention and treatment. *Jama, 275*(20), 1571-1576.
Karaahmet, OZ, Gurcay, E, Avluk, OC, Umay, EK, Gundogdu, I*, et al.* (2017). Poststroke depression: Risk factors and potential effects on functional recovery. *International Journal of Rehabilitation Research, 40*(1), 71-75.
Karakus, K, Kunt, R, Memis, CO, Kunt, DA, Dogan, B*, et al.* (2017). The factors related to early-onset depression after first stroke. *Psychogeriatrics*.
Kargo, WJ, & Nitz, DA. (2003). Early skill learning is expressed through selection and tuning of cortically represented muscle synergies. *Journal of Neuroscience, 23*(35), 11255-11269.
Katrak, PH, Black, D, & Peeva, V. (2009). Do stroke patients with intracerebral hemorrhage have a better functional outcome than patients with cerebral infarction? *PM&R, 1*(5), 427-433.
Kautz, S, & Brown, D. (1998). Relationships between timing of muscle excitation and impaired motor performance during cyclical lower extremity movement in post-stroke hemiplegia. *Brain, 121*(3), 515-526.
Khedr, EM, Ahmed, MA, Fathy, N, & Rothwell, JC. (2005). Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology, 65*(3), 466-468.
Kim, B, & Winstein, C. (2017). Can neurological biomarkers of brain impairment be used to predict poststroke motor recovery? A systematic review. *Neurorehabilitation and neural repair, 31*(1), 3-24.
Kim, DY, Lim, JY, Kang, EK, You, DS, Oh, MK*, et al.* (2010). Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. *American Journal of Physical Medicine & Rehabilitation, 89*(11), 879-886.

Kim, DY, Quinlan, EB, Gramer, R, & Cramer, SC. (2016). Bdnf val66met polymorphism is related to motor system function after stroke. *Physical therapy, 96*(4), 533-539.

Kim, H, Miller, LM, Fedulow, I, Simkins, M, Abrams, GM*, et al.* (2013). Kinematic data analysis for post-stroke patients following bilateral versus unilateral rehabilitation with an upper limb wearable robotic system. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 21*(2), 153-164.

Kim, K, Song, W-K, Lee, J, Lee, H-Y, Park, D-S*, et al.* (2014). Kinematic analysis of upper extremity movement during drinking in hemiplegic subjects. *Clinical Biomechanics, 29*(3), 248-256.

Kim, Y-H, You, SH, Ko, M-H, Park, J-W, Lee, KH*, et al.* (2006). Repetitive transcranial magnetic stimulation–induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke, 37*(6), 1471-1476.

Kiper, P, Agostini, M, Luque-Moreno, C, Tonin, P, & Turolla, A. (2014). Reinforced feedback in virtual environment for rehabilitation of upper extremity dysfunction after stroke: Preliminary data from a randomized controlled trial. *BioMed research international, 2014*.

Kitago, T, Goldsmith, J, Harran, M, Kane, L, Berard, J*, et al.* (2015). Robotic therapy for chronic stroke: General recovery of impairment or improved task-specific skill? *Journal of neurophysiology, 114*(3), 1885-1894.

Kitago, T, Liang, J, Huang, VS, Hayes, S, Simon, P*, et al.* (2012). Improvement after constraint-induced movement therapy recovery of normal motor control or task-specific compensation? *Neurorehabilitation and neural repair*, 1545968312452631.

Kleim, JA, & Jones, TA. (2008). Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *Journal of speech, language, and hearing research, 51*(1), S225-S239.

Kløve, H. (1963). Clinical neuropsychology. *Medical Clinics of North America, 47*(6), 1647-1658.

Knaut, LA, Subramanian, SK, McFadyen, BJ, Bourbonnais, D, & Levin, MF. (2009). Kinematics of pointing movements made in a virtual versus a physical 3-dimensional environment in healthy and stroke subjects. *Archives of physical medicine and rehabilitation, 90*(5), 793-802.

Krakauer, JW. (2006). Motor learning: Its relevance to stroke recovery and neurorehabilitation. *Current opinion in neurology, 19*(1), 84-90.

Krakauer, JW, & Marshall, RS. (2015). The proportional recovery rule for stroke revisited. *Annals of neurology, 78*(6), 845-847.

Krueger, C, & Tian, L. (2004). A comparison of the general linear mixed model and repeated measures anova using a dataset with multiple missing data points. *Biological research for nursing, 6*(2), 151-157.

Kvistad, C, Thomassen, L, Waje-Andreassen, U, Moen, G, Logallo, N*, et al.* (2013). Clinical implications of increased use of mri in tia. *Acta Neurologica Scandinavica, 128*(1), 32-38.

Kwakkel, G, & Kollen, BJ. (2007). Predicting improvement in the upper paretic limb after stroke: A longitudinal prospective study. *Restorative neurology and neuroscience, 25*(5, 6), 453-460.

Kwakkel, G, & Kollen, BJ. (2013). Predicting activities after stroke: What is clinically relevant? *International Journal of Stroke, 8*(1), 25-32.

Kwakkel, G, Kollen, BJ, & Krebs, HI. (2007). Effects of robot-assisted therapy on upper limb recovery after stroke: A systematic review. *Neurorehabilitation and neural repair*.

Kwakkel, G, Kollen, BJ, & Twisk, J. (2006). Impact of time on improvement of outcome after stroke. *Stroke, 37*(9), 2348-2353.
Kwakkel, G, Lannin, NA, Borschmann, K, English, C, Ali, M*, et al.* (2017). Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *International Journal of Stroke, 12*(5), 451-461.
Kwakkel, G, Veerbeek, JM, van Wegen, EE, & Wolf, SL. (2015). Constraint-induced movement therapy after stroke. *The Lancet Neurology, 14*(2), 224-234.
Lang, CE, Bland, MD, Bailey, RR, Schaefer, SY, & Birkenmeier, RL. (2013). Assessment of upper extremity impairment, function, and activity after stroke: Foundations for clinical decision making. *Journal of Hand Therapy, 26*(2), 104-115.
Langhorne, P, Bernhardt, J, & Kwakkel, G. (2011). Stroke rehabilitation. *The Lancet, 377*(9778), 1693-1702.
Langhorne, P, Coupar, F, & Pollock, A. (2009). Motor recovery after stroke: A systematic review. *The Lancet Neurology, 8*(8), 741-754.
Laver, KE, George, S, Thomas, S, Deutsch, JE, & Crotty, M. (2015). Virtual reality for stroke rehabilitation. *The Cochrane Library*.
Le, Q, Qu, Y, Tao, Y, & Zhu, S. (2014). Effects of repetitive transcranial magnetic stimulation on hand function recovery and excitability of the motor cortex after stroke: A meta-analysis. *American Journal of Physical Medicine & Rehabilitation, 93*(5), 422-430.
LeBlanc, S, Paquin, K, Carr, K, & Horton, S. (2013). Non-immersive virtual reality for fine motor rehabilitation of functional activities in individuals with chronic stroke: A review. *Aging Sci, 1*(105), 2.
Lee, DD, & Seung, SH. (1999). Learning the parts of objects by non-negative matrix factorization. *Nature, 401*(6755), 788-791.
Lee, JH, Kim, SB, Lee, KW, Kim, MA, Lee, SJ*, et al.* (2015). Factors associated with upper extremity motor recovery after repetitive transcranial magnetic stimulation in stroke patients. *Annals of rehabilitation medicine, 39*(2), 268-276.
Lee, KC, Carson, L, Kinnin, E, & Patterson, V. (1989). The ashworth scale: A reliable and reproducible method of measuring spasticity. *Neurorehabilitation and neural repair, 3*(4), 205-209.
Lee, SW, Wilson, KM, Lock, BA, & Kamper, DG. (2011). Subject-specific myoelectric pattern classification of functional hand movements for stroke survivors. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 19*(5), 558-566.
Lee, WA. (1984). Neuromotor synergies as a basis for coordinated intentional action. *Journal of motor behavior, 16*(2), 135-170.
Lefaucheur, J-P. (2006). Stroke recovery can be enhanced by using repetitive transcranial magnetic stimulation (rtms). *Neurophysiologie Clinique/Clinical Neurophysiology, 36*(3), 105-115.
Lemmens, RJ, Janssen-Potten, YJ, Timmermans, AA, Smeets, RJ, & Seelen, HA. (2015). Recognizing complex upper extremity activities using body worn sensors. *PloS one, 10*(3), e0118642.
Lemmens, RJ, Timmermans, AA, Janssen-Potten, YJ, Pulles, SA, Geers, RP*, et al.* (2014). Accelerometry measuring the outcome of robot-supported upper limb training in chronic stroke: A randomized controlled trial. *PloS one, 9*(5), e96414.

Levin, MF, Kleim, JA, & Wolf, SL. (2009). What do motor “recovery” and “compensation” mean in patients following stroke? *Neurorehabilitation and neural repair*.

Levy, DE. (1988). How transient are transient ischemic attacks? *Neurology, 38*(5), 674-674.

Lewis, GN, Woods, C, Rosie, JA, & Mcpherson, KM. (2011). Virtual reality games for rehabilitation of people with stroke: Perspectives from the users. *Disability and Rehabilitation: Assistive Technology, 6*(5), 453-463.

Li, S, & Francisco, GE. (2015). New insights into the pathophysiology of post-stroke spasticity. *Frontiers in Human Neuroscience, 9*.

Li, S, Zhuang, C, Zhang, X, Niu, CM, Xie, Q*, et al.* (2016). *Analysis of muscle synergy for evaluation of task-specific performance in stroke patients.* Paper presented at the Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the.

Li, X, Holobar, A, Gazzoni, M, Merletti, R, Rymer, WZ*, et al.* (2015). Examination of poststroke alteration in motor unit firing behavior using high-density surface emg decomposition. *IEEE transactions on biomedical engineering, 62*(5), 1242-1252.

Lin, J-H, Hsu, M-J, Sheu, C-F, Wu, T-S, Lin, R-T*, et al.* (2009). Psychometric comparisons of 4 measures for assessing upper-extremity function in people with stroke. *Physical therapy, 89*(8), 840-850.

Lin, K-C, Wu, C-Y, Wei, T-H, Gung, C, Lee, C-Y*, et al.* (2007). Effects of modified constraint-induced movement therapy on reach-to-grasp movements and functional performance after chronic stroke: A randomized controlled study. *Clinical Rehabilitation, 21*(12), 1075-1086.

Lindenberg, R, Renga, V, Zhu, L, Nair, D, & Schlaug, G. (2010). Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology, 75*(24), 2176-2184.

Lüdemann-Podubecká, J, Bösl, K, Theilig, S, Wiederer, R, & Nowak, DA. (2015). The effectiveness of 1hz rtms over the primary motor area of the unaffected hemisphere to improve hand function after stroke depends on hemispheric dominance. *Brain Stimulation, 8*(4), 823-830.

Lukács, M. (2005). Electrophysiological signs of changes in motor units after ischaemic stroke. *Clinical Neurophysiology, 116*(7), 1566-1570.

Lukacs, M, Vécsei, L, & Beniczky, S. (2008). Large motor units are selectively affected following a stroke. *Clinical Neurophysiology, 119*(11), 2555-2558.

Luker, JA, Bernhardt, J, Graham, ID, Middleton, S, Lynch, EA*, et al.* (2017). Interventions for the uptake of evidence-based recommendations in acute stroke settings. *The Cochrane Library*.

Lum, PS, Burgar, CG, & Shor, PC. (2004). Evidence for improved muscle activation patterns after retraining of reaching movements with the mime robotic system in subjects with post-stroke hemiparesis. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 12*(2), 186-194.

Lum, PS, Burgar, CG, Shor, PC, Majmundar, M, & Van der Loos, M. (2002). Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. *Archives of physical medicine and rehabilitation, 83*(7), 952-959.

Lum, PS, Mulroy, S, Amdur, RL, Requejo, P, Prilutsky, BI*, et al.* (2009). Gains in upper extremity function after stroke via recovery or compensation: Potential differential effects on amount of real-world limb use. *Topics in stroke rehabilitation, 16*(4), 237-253.

Maciejasz, P, Eschweiler, J, Gerlach-Hahn, K, Jansen-Troy, A, & Leonhardt, S. (2014). A survey on robotic devices for upper limb rehabilitation. *Journal of neuroengineering and rehabilitation, 11*(1), 3.

Makin, SD, Doubal, FN, Dennis, MS, & Wardlaw, JM. (2015). Clinically confirmed stroke with negative diffusion-weighted imaging magnetic resonance imaging. *Stroke, 46*(11), 3142-3148.

Man, D. (2010). Common issues of virtual reality in neuro-rehabilitation *Virtual reality*: InTech.

Marquez, J, Vliet, P, McElduff, P, Lagopoulos, J, & Parsons, M. (2015). Transcranial direct current stimulation (tdcs): Does it have merit in stroke rehabilitation? A systematic review. *International Journal of Stroke, 10*(3), 306-316.

Masiero, S, Armani, M, Ferlini, G, Rosati, G, & Rossi, A. (2014). Randomized trial of a robotic assistive device for the upper extremity during early inpatient stroke rehabilitation. *Neurorehabilitation and neural repair, 28*(4), 377-386.

Mathiowetz, V, Volland, G, Kashman, N, & Weber, K. (1985a). Adult norms for the box and block test of manual dexterity. *Am J Occup Ther, 39*(6), 386-391.

Mathiowetz, V, Volland, G, Kashman, N, & Weber, K. (1985b). Adult norms for the box and block test of manual dexterity. *American Journal of Occupational Therapy, 39*(6), 386-391.

Matsuzaki, S, Hashimoto, M, Yuki, S, Koyama, A, Hirata, Y*, et al.* (2015). The relationship between post-stroke depression and physical recovery. *Journal of affective disorders, 176*, 56-60.

McDonnell, MN, & Stinear, CM. (2017). Tms measures of motor cortex function after stroke: A meta-analysis. *Brain Stimulation*.

McHughen, SA, Rodriguez, PF, Kleim, JA, Kleim, ED, Crespo, LM*, et al.* (2009). Bdnf val66met polymorphism influences motor system function in the human brain. *Cerebral Cortex, 20*(5), 1254-1262.

McMorland, AJ, Runnalls, KD, & Byblow, WD. (2015). A neuroanatomical framework for upper limb synergies after stroke. *Frontiers in Human Neuroscience, 9*, 82.

McNulty, PA. (2012). Games for rehabilitation: Wii-based movement therapy improves poststroke movement ability. *GAMES FOR HEALTH: Research, Development, and Clinical Applications, 1*(5), 384-387.

McNulty, PA, Lin, G, & Doust, CG. (2014). Single motor unit firing rate after stroke is higher on the less-affected side during stable low-level voluntary contractions. *Frontiers in Human Neuroscience, 8*.

McNulty, PA, Thompson-Butel, AG, Shiner, CT, & Trinh, T. (2013a). Wii-based movement therapy benefits stroke patients with low and very low movement ability. *Social Care and Neurodisability, 4*(3/4), 5-5.

McNulty, PA, Thompson-Butel, AG, Shiner, CT, & Trinh, T. (2015a). Regaining or retraining motor function in chronic stroke: What is the capacity for sustained improvements with additional therapy? *International Journal of Stroke, 10*, 50.

McNulty, PA, Thompson-Butel, AG, Faux, SG, Lin, G, Katrak, PH*, et al.* (2015b). The efficacy of wii-based movement therapy for upper limb rehabilitation in the chronic poststroke period: A randomized controlled trial. *International Journal of Stroke*.

McNulty, PA, Trinh, T, Lee, P, Lin, G, Thompson-Butel, AG*, et al.* (2015c). Measuring the efficacy of therapy in chronic stroke, active and passive range-of-motion do not reflect improvements in upper-limb motor-function. *Presented at the Society for Neuroscience Annual Meeting, Chicago USA*.

McNulty, PA, Trinh, T, Lee, P, & Shiner, CT. (2013b). *Improvements in joint kinematics recorded during therapy sessions are not reflected in more traditional pre- and post-therapy functional assessments.* Paper presented at the American Society for NeuroRehabilitation, Translational Motor Control.

Mehrholz, J, Haedrich, A, Platz, T, Kugler, J, & Pohl, M. (2012). Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database Syst Rev, 6*.

Mehrholz, J, Pohl, M, Platz, T, Kugler, J, & Elsner, B. (2015). Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. *The Cochrane Library*.

Meldrum, D, Glennon, A, Herdman, S, Murray, D, & McConn-Walsh, R. (2012). Virtual reality rehabilitation of balance: Assessment of the usability of the nintendo wii® fit plus. *Disability and Rehabilitation: Assistive Technology, 7*(3), 205-210.

Meyer, S, Karttunen, AH, Thijs, V, Feys, H, & Verheyden, G. (2014). How do somatosensory deficits in the arm and hand relate to upper limb impairment, activity, and participation problems after stroke? A systematic review. *Physical therapy, 94*(9), 1220-1231.

Mirbagheri, MM, & Rymer, WZ. (2008). Time-course of changes in arm impairment after stroke: Variables predicting motor recovery over 12 months. *Archives of physical medicine and rehabilitation, 89*(8), 1507-1513.

Mitchell, AJ, Sheth, B, Gill, J, Yadegarfar, M, Stubbs, B*, et al.* (2017). Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder. *General Hospital Psychiatry, 47*, 48-60.

Morris, DM, Uswatte, G, Crago, JE, Cook, EW, & Taub, E. (2001). The reliability of the wolf motor function test for assessing upper extremity function after stroke. *Archives of physical medicine and rehabilitation, 82*(6), 750-755.

Mottram, CJ, Heckman, CJ, Powers, RK, Rymer, WZ, & Suresh, NL. (2014). Disturbances of motor unit rate modulation are prevalent in muscles of spastic-paretic stroke survivors. *Journal of neurophysiology, 111*(10), 2017-2028.

Mottram, CJ, Suresh, NL, Heckman, C, Gorassini, MA, & Rymer, WZ. (2009). Origins of abnormal excitability in biceps brachii motoneurons of spastic-paretic stroke survivors. *Journal of neurophysiology, 102*(4), 2026-2038.

Mouawad, MR, Doust, CG, Max, MD, & McNulty, PA. (2011). Wii-based movement therapy to promote improved upper extremity function post-stroke: A pilot study. *Journal of Rehabilitation Medicine, 43*(6), 527-533.

Müller, MJ, Szegedi, A, Wetzel, H, & Benkert, O. (2000). Moderate and severe depression: Gradations for the montgomery–åsberg depression rating scale. *Journal of affective disorders, 60*(2), 137-140.

Mullick, AA, Subramanian, SK, & Levin, MF. (2015). Emerging evidence of the association between cognitive deficits and arm motor recovery after stroke: A meta-analysis. *Restorative neurology and neuroscience, 33*(3), 389-403.

Murphy, TH, & Corbett, D. (2009). Plasticity during stroke recovery: From synapse to behaviour. *Nature Reviews Neuroscience, 10*(12), 861-872.

Norrving, B, & Kissela, B. (2013). The global burden of stroke and need for a continuum of care. *Neurology, 80*(3 Supplement 2), S5-S12.

NSF. (2010). Clinical guidelines for stroke management. National Stroke Foundation, Melbourne, Australia: National Stroke Foundation.

NSF. (2012). National stroke audit: Rehabilitation services report. National Stroke Foundation, Melbourne, Australia: National Stroke Foundation.
NSF. (2013). National stroke audit: Acute services organisational survey report. National Stroke Foundation, Melbourne, Australia: National Stroke Foundation.
NSF. (2015). National stroke audit: Acute services report. National Stroke Foundation, Melbourne, Australia: National Stroke Foundation.
O'Donnell, MJ, Xavier, D, Liu, L, Zhang, H, Chin, SL*, et al.* (2010). Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the interstroke study): A case-control study. *The Lancet, 376*(9735), 112-123.
O'dwyer, N, Ada, L, & Neilson, P. (1996). Spasticity and muscle contracture following stroke. *Brain, 119*(5), 1737-1749.
Overduin, SA, d'Avella, A, Roh, J, & Bizzi, E. (2008). Modulation of muscle synergy recruitment in primate grasping. *Journal of Neuroscience, 28*(4), 880-892.
Paatero, P, & Tapper, U. (1994). Positive matrix factorization: A non-negative factor model with optimal utilization of error estimates of data values. *Environmetrics, 5*(2), 111-126.
Page, SJ, Levine, P, Leonard, A, Szaflarski, JP, & Kissela, BM. (2008). Modified constraint-induced therapy in chronic stroke: Results of a single-blinded randomized controlled trial. *Physical therapy, 88*(3), 333.
Page, SJ, Levine, P, Sisto, S, Bond, Q, & Johnston, MV. (2002). Stroke patients' and therapists' opinions of constraint-induced movement therapy. *Clinical Rehabilitation, 16*(1), 55-60.
Page, SJ, Sisto, S, Levine, P, Johnston, MV, & Hughes, M. (2001). Modified constraint induced therapy: A randomized feasibility and efficacy study. *Journal of rehabilitation research and development, 38*(5), 583.
Page, SJ, Sisto, S, Levine, P, & McGrath, RE. (2004). Efficacy of modified constraint-induced movement therapy in chronic stroke: A single-blinded randomized controlled trial. *Archives of physical medicine and rehabilitation, 85*(1), 14-18.
Paquin, K, Ali, S, Carr, K, Crawley, J, McGowan, C*, et al.* (2015). Effectiveness of commercial video gaming on fine motor control in chronic stroke within community-level rehabilitation. *Disability and rehabilitation, 37*(23), 2184-2191.
Parikh, RM, Lipsey, JR, Robinson, RG, & Price, TR. (1987). Two-year longitudinal study of post-stroke mood disorders: Dynamic changes in correlates of depression at one and two years. *Stroke, 18*(3), 579-584.
Paul, SL, Srikanth, VK, & Thrift, AG. (2007). The large and growing burden of stroke. *Current drug targets, 8*(7), 786-793.
Pavlovic, AM, Barras, CD, Hand, PJ, Tress, BM, Desmond, PM*, et al.* (2010). Brain imaging in transient ischemic attack–redefining tia. *Journal of Clinical Neuroscience, 17*(9), 1105-1110.
Persson, HC, Opheim, A, Lundgren-Nilsson, Å, Alt Murphy, M, Danielsson, A*, et al.* (2016). Upper extremity recovery after ischaemic and haemorrhagic stroke: Part of the salgot study. *European Stroke Journal, 1*(4), 310-319.
Piron, L, Turolla, A, Agostini, M, Zucconi, C, Cortese, F*, et al.* (2009). Exercises for paretic upper limb after stroke: A combined virtual-reality and telemedicine approach. *Journal of Rehabilitation Medicine, 41*(12), 1016-1020.
Ploughman, M, & Corbett, D. (2004). Can forced-use therapy be clinically applied after stroke? An exploratory randomized controlled trial. *Archives of physical medicine and rehabilitation, 85*(9), 1417-1423.

Prabhakaran, S, Zarahn, E, Riley, C, Speizer, A, Chong, JY*, et al.* (2008). Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabilitation and neural repair, 22*(1), 64-71.

Prange, GB, Jannink, MJ, Groothuis-Oudshoorn, CG, Hermens, HJ, & IJzerman, MJ. (2006). Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. *Journal of rehabilitation research and development, 43*(2), 171.

Puig, J, Blasco, G, Daunis-I-Estadella, J, Thomalla, G, Castellanos, M*, et al.* (2013). Decreased corticospinal tract fractional anisotropy predicts long-term motor outcome after stroke. *Stroke, 44*(7), 2016-2018.

Puig, J, Blasco, G, Schlaug, G, Stinear, CM, Daunis-i-Estadella, P*, et al.* (2017). Diffusion tensor imaging as a prognostic biomarker for motor recovery and rehabilitation after stroke. *Neuroradiology*, 1-9.

Pursell, L, & Trimble, S. (1991). Gram-schmidt orthogonalization by gauss elimination. *The American Mathematical Monthly, 98*(6), 544-549.

Ramos-Murguialday, A, García-Cossio, E, Walter, A, Cho, W, Broetz, D*, et al.* (2015). Decoding upper limb residual muscle activity in severe chronic stroke. *Annals of clinical and translational neurology, 2*(1), 1-11.

Ramsay, JW, Barrance, PJ, Buchanan, TS, & Higginson, JS. (2011). Paretic muscle atrophy and non-contractile tissue content in individual muscles of the post-stroke lower extremity. *Journal of biomechanics, 44*(16), 2741-2746.

Rand, D, Givon, N, Weingarden, H, Nota, A, & Zeilig, G. (2014). Eliciting upper extremity purposeful movements using video games a comparison with traditional therapy for stroke rehabilitation. *Neurorehabilitation and neural repair*, 1545968314521008.

Rand, D, Kizony, R, & Weiss, PTL. (2008). The sony playstation ii eyetoy: Low-cost virtual reality for use in rehabilitation. *Journal of Neurologic Physical Therapy, 32*(4), 155-163.

Rathee, D, Cecotti, H, & Prasad, G. (2016). *Estimation of effective fronto-parietal connectivity during motor imagery using partial granger causality analysis.* Paper presented at the Neural Networks (IJCNN), 2016 International Joint Conference on.

Reynolds, K, Lewis, B, Nolen, JDL, Kinney, GL, Sathya, B*, et al.* (2003). Alcohol consumption and risk of stroke: A meta-analysis. *Jama, 289*(5), 579-588.

Roh, J, Rymer, WZ, & Beer, RF. (2012). Robustness of muscle synergies underlying three-dimensional force generation at the hand in healthy humans. *Journal of neurophysiology, 107*(8), 2123-2142.

Roh, J, Rymer, WZ, & Beer, RF. (2015). Evidence for altered upper extremity muscle synergies in chronic stroke survivors with mild and moderate impairment. *Frontiers in Human Neuroscience, 9*.

Roh, J, Rymer, WZ, Perreault, EJ, Yoo, SB, & Beer, RF. (2013). Alterations in upper limb muscle synergy structure in chronic stroke survivors. *Journal of neurophysiology, 109*(3), 768-781.

Rohrer, B, Fasoli, S, Krebs, HI, Hughes, R, Volpe, B*, et al.* (2002). Movement smoothness changes during stroke recovery. *Journal of Neuroscience, 22*(18), 8297-8304.

Rossi, C, Sallustio, F, Di Legge, S, Stanzione, P, & Koch, G. (2013). Transcranial direct current stimulation of the affected hemisphere does not accelerate recovery of acute stroke patients. *European journal of neurology, 20*(1), 202-204.

Rossiter, HE, Boudrias, M-H, & Ward, NS. (2014). Do movement-related beta oscillations change after stroke? *Journal of neurophysiology, 112*(9), 2053-2058.

Roy, SH, Cheng, MS, Chang, S-S, Moore, J, De Luca, G*, et al.* (2009). A combined semg and accelerometer system for monitoring functional activity in stroke. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 17*(6), 585-594.

Roy, SH, Cole, BT, Gilmore, LD, Luca, CJ, Thomas, CA*, et al.* (2013). High-resolution tracking of motor disorders in parkinson's disease during unconstrained activity. *Movement Disorders, 28*(8), 1080-1087.

Ryu, J-S, Lee, J-W, Lee, S-I, & Chun, M-H. (2015). Factors predictive of spasticity and their effects on motor recovery and functional outcomes in stroke patients. *Topics in stroke rehabilitation*.

Sacco, RL. (2004). Risk factors for tia and tia as a risk factor for stroke. *Neurology, 62*(8 suppl 6), S7-S11.

Sacco, RL, Kasner, SE, Broderick, JP, Caplan, LR, Culebras, A*, et al.* (2013). An updated definition of stroke for the 21st century a statement for healthcare professionals from the american heart association/american stroke association. *Stroke, 44*(7), 2064-2089.

Safavynia, SA, Torres-Oviedo, G, & Ting, LH. (2011). Muscle synergies: Implications for clinical evaluation and rehabilitation of movement. *Topics in spinal cord injury rehabilitation, 17*(1), 16-24.

Sagen, U, Vik, TG, Moum, T, Mørland, T, Finset, A*, et al.* (2009). Screening for anxiety and depression after stroke: Comparison of the hospital anxiety and depression scale and the montgomery and åsberg depression rating scale. *Journal of psychosomatic research, 67*(4), 325-332.

Sahathevan, R, Linden, T, Villemagne, VL, Churilov, L, Ly, JV*, et al.* (2016). Positron emission tomographic imaging in stroke. *Stroke, 47*(1), 113-119.

Saposnik, G, Cohen, LG, Mamdani, M, Pooyania, S, Ploughman, M*, et al.* (2016). Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (evrest): A randomised, multicentre, single-blind, controlled trial. *The Lancet Neurology, 15*(10), 1019-1027.

Saposnik, G, Mamdani, M, Bayley, M, Thorpe, K, Hall, J*, et al.* (2010). Effectiveness of virtual reality exercises in stroke rehabilitation (evrest): Rationale, design, and protocol of a pilot randomized clinical trial assessing the wii gaming system. *International Journal of Stroke, 5*(1), 47-51.

Schepers, VP, Ketelaar, M, Visser-Meily, AJ, de Groot, V, Twisk, JW*, et al.* (2008). Functional recovery differs between ischaemic and haemorrhagic stroke patients. *Journal of Rehabilitation Medicine, 40*(6), 487-489.

Scherbakov, N, Von Haehling, S, Anker, SD, Dirnagl, U, & Doehner, W. (2013). Stroke induced sarcopenia: Muscle wasting and disability after stroke. *International journal of cardiology, 170*(2), 89-94.

Schlaug, G, Renga, V, & Nair, D. (2008). Transcranial direct current stimulation in stroke recovery. *Archives of neurology, 65*(12), 1571-1576.

Secretariat, MA, & Ontario, HQ. (2011). Constraint-induced movement therapy for rehabilitation of arm dysfunction after stroke in adults: An evidence-based analysis. *Ontario Health Technology Assessment Series, 11*(6), 1.

Seitz, RJ, Azari, NP, Knorr, U, Binkofski, F, Herzog, H*, et al.* (1999). The role of diaschisis in stroke recovery. *Stroke, 30*(9), 1844-1850.

Semenov, S, Planas, R, Hopfer, M, Hamidipour, A, Vasilenko, A*, et al.* (2015). *Electromagnetic tomography for brain imaging: Initial assessment for stroke*

detection. Paper presented at the Biomedical Circuits and Systems Conference (BioCAS), 2015 IEEE.

Sharma, N, & Cohen, LG. (2012). Recovery of motor function after stroke. *Developmental psychobiology, 54*(3), 254-262.

Shin, J-H, Park, SB, & Jang, SH. (2015). Effects of game-based virtual reality on health-related quality of life in chronic stroke patients: A randomized, controlled study. *Computers in biology and medicine, 63*, 92-98.

Shiner, CT. (2015). *Characterising post-stroke heterogeneity from brain to muscle: Implications for clinical assessment and motor rehabilitation.* (PhD), University of New South Wales, Sydney, Australia.

Shiner, CT, Byblow, WD, & McNulty, PA. (2014). Bilateral priming before wii-based movement therapy enhances upper limb rehabilitation and its retention after stroke a case-controlled study. *Neurorehabilitation and neural repair, 28*(9), 828-838.

Shiner, CT, Pierce, KD, Thompson-Butel, AG, Trinh, T, Schofield, PR*, et al.* (2016). Bdnf genotype interacts with motor function to influence rehabilitation responsiveness poststroke. *Frontiers in neurology, 7*.

Shiner, CT, Tang, H, Johnson, BW, & McNulty, PA. (2015). Cortical beta oscillations and motor thresholds differ across the spectrum of post-stroke motor impairment, a preliminary meg and tms study. *Brain research, 1629*, 26-37.

Shinton, R, & Beevers, G. (1989). Meta-analysis of relation between cigarette smoking and stroke. *Bmj, 298*(6676), 789-794.

Silasi, G, & Murphy, TH. (2014). Stroke and the connectome: How connectivity guides therapeutic intervention. *Neuron, 83*(6), 1354-1368.

Silva, CC, Silva, A, Sousa, A, Pinheiro, AR, Bourlinova, C*, et al.* (2014). Co-activation of upper limb muscles during reaching in post-stroke subjects: An analysis of the contralesional and ipsilesional limbs. *Journal of Electromyography and Kinesiology, 24*(5), 731-738.

Sin, H, & Lee, G. (2013). Additional virtual reality training using xbox kinect in stroke survivors with hemiplegia. *American Journal of Physical Medicine & Rehabilitation, 92*(10), 871-880.

Sin, M, Kim, W-S, Park, D, Min, Y-S, Kim, WJ*, et al.* (2014). Electromyographic analysis of upper limb muscles during standardized isotonic and isokinetic robotic exercise of spastic elbow in patients with stroke. *Journal of Electromyography and Kinesiology, 24*(1), 11-17.

Sivan, M, O'Connor, RJ, Makower, S, Levesley, M, & Bhakta, B. (2011). Systematic review of outcome measures used in the evaluation of robot-assisted upper limb exercise in stroke. *Journal of Rehabilitation Medicine, 43*(3), 181-189.

Skog, I, & Händel, P. (2006). *Calibration of a mems inertial measurement unit.* Paper presented at the XVII IMEKO World Congress.

Smania, N, Picelli, A, Munari, D, Geroin, C, Ianes, P*, et al.* (2010). Rehabilitation procedures in the management of spasticity. *Eur j phys rehabil med, 46*(3), 423-438.

Song, R, Tong, K-y, Hu, X, & Li, L. (2008). Assistive control system using continuous myoelectric signal in robot-aided arm training for patients after stroke. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 16*(4), 371-379.

Song, R, & Tong, KY. (2013). Emg and kinematic analysis of sensorimotor control for patients after stroke using cyclic voluntary movement with visual feedback. *Journal of neuroengineering and rehabilitation, 10*(1), 18.

Srivastava, A, Taly, AB, Gupta, A, & Murali, T. (2010). Post-stroke depression: Prevalence and relationship with disability in chronic stroke survivors. *Annals of Indian Academy of Neurology, 13*(2), 123.

Staudenmann, D, Roeleveld, K, Stegeman, DF, & Van Dieën, JH. (2010). Methodological aspects of semg recordings for force estimation–a tutorial and review. *Journal of Electromyography and Kinesiology, 20*(3), 375-387.

Sterr, A, Szameitat, A, Shen, S, & Freivogel, S. (2006). Application of the cit concept in the clinical environment: Hurdles, practicalities, and clinical benefits. *Cognitive and behavioral neurology, 19*(1), 48-54.

Stewart, JC, & Cramer, SC. (2017). Genetic variation and neuroplasticity: Role in rehabilitation after stroke. *Journal of Neurologic Physical Therapy, 41*, S17-S23.

Stinear, CM. (2010). Prediction of recovery of motor function after stroke. *The Lancet Neurology, 9*(12), 1228-1232.

Stinear, CM. (2016). Stroke rehabilitation research needs to be different to make a difference. *F1000Research, 5*.

Stinear, CM, Ackerley, SJ, & Byblow, WD. (2013). Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not.

Stinear, CM, Barber, PA, Petoe, M, Anwar, S, & Byblow, WD. (2012). The prep algorithm predicts potential for upper limb recovery after stroke. *Brain, 135*(8), 2527-2535.

Stinear, CM, & Byblow, WD. (2014). Predicting and accelerating motor recovery after stroke. *Current opinion in neurology, 27*(6), 624-630.

Stinear, CM, Byblow, WD, Ackerley, SJ, Barber, PA, & Smith, M-C. (2017a). Predicting recovery potential for individual stroke patients increases rehabilitation efficiency. *Stroke*, STROKEAHA. 116.015790.

Stinear, CM, Byblow, WD, Ackerley, SJ, Smith, M-C, Borges, VM*, et al.* (2017b). Proportional motor recovery after stroke. *Stroke, 48*(3), 795-798.

Stinear, CM, Byblow, WD, & Ward, S. (2014). An update on predicting motor recovery after stroke. *Annals of physical and rehabilitation medicine, 57*(8), 489-498.

Stuart, M, Benvenuti, F, Macko, R, Taviani, A, Segenni, L*, et al.* (2009). Community-based adaptive physical activity program for chronic stroke: Feasibility, safety, and efficacy of the empoli model. *Neurorehabilitation and neural repair, 23*(7), 726-734.

Subramanian, SK, Lourenço, CB, Chilingaryan, G, Sveistrup, H, & Levin, MF. (2013). Arm motor recovery using a virtual reality intervention in chronic stroke: Randomized control trial. *Neurorehabilitation and neural repair, 27*(1), 13-23.

Sulter, G, Steen, C, & De Keyser, J. (1999). Use of the barthel index and modified rankin scale in acute stroke trials. *Stroke, 30*(8), 1538-1541.

Sun, J-H, Tan, L, & Yu, J-T. (2014). Post-stroke cognitive impairment: Epidemiology, mechanisms and management. *Annals of translational medicine, 2*(8).

Sung, W-H, Wang, C-P, Chou, C-L, Chen, Y-C, Chang, Y-C*, et al.* (2013). Efficacy of coupling inhibitory and facilitatory repetitive transcranial magnetic stimulation to enhance motor recovery in hemiplegic stroke patients. *Stroke, 44*(5), 1375-1382.

Takeuchi, N, Tada, T, Toshima, M, Chuma, T, Matsuo, Y*, et al.* (2008). Inhibition of the unaffected motor cortex by 1 hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. *Journal of Rehabilitation Medicine, 40*(4), 298-303.

Tang, A, & Rymer, W. (1981). Abnormal force--emg relations in paretic limbs of hemiparetic human subjects. *Journal of Neurology, Neurosurgery & Psychiatry, 44*(8), 690-698.

Taub, E. (1976). Movement in nonhuman primates deprived of omatosensory feedback. *Exercise and sport sciences reviews, 4*(1), 335-374.

Taub, E, Crago, JE, Burgio, LD, Groomes, TE, Cook, EW*, et al.* (1994). An operant approach to rehabilitation medicine: Overcoming learned nonuse by shaping. *Journal of the experimental analysis of behavior, 61*(2), 281-293.

Taub, E, Crago, JE, & Uswatte, G. (1998). Constraint-induced movement therapy: A new approach to treatment in physical rehabilitation. *Rehabilitation Psychology, 43*(2), 152.

Taub, E, & Morris, DM. (2001). Constraint-induced movement therapy to enhance recovery after stroke. *Current atherosclerosis reports, 3*(4), 279-286.

Taub, E, Uswatte, G, & Elbert, T. (2002). New treatments in neurorehabiliation founded on basic research. *Nature Reviews Neuroscience, 3*(3), 228-236.

Taub, E, Uswatte, G, King, DK, Morris, D, Crago, JE*, et al.* (2006a). A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. *Stroke, 37*(4), 1045-1049.

Taub, E, Uswatte, G, Mark, VW, & Morris, D. (2006b). The learned nonuse phenomenon: Implications for rehabilitation. *Eura Medicophys, 42*, 241-255.

Taylor, MJ, McCormick, D, Shawis, T, Impson, R, & Griffin, M. (2011). Activity-promoting gaming systems in exercise and rehabilitation. *Journal of rehabilitation research and development, 48*(10), 1171-1186.

Teasell, RW, Murie Fernandez, M, McIntyre, A, & Mehta, S. (2014). Rethinking the continuum of stroke rehabilitation. *Archives of physical medicine and rehabilitation, 95*(4), 595-596.

Thies, SB, Tresadern, PA, Kenney, LP, Smith, J, Howard, D*, et al.* (2009). Movement variability in stroke patients and controls performing two upper limb functional tasks: A new assessment methodology. *Journal of neuroengineering and rehabilitation, 6*(1), 2.

Thompson-Butel, AG, Lin, G, Shiner, CT, & McNulty, PA. (2015). Comparison of three tools to measure improvements in upper-limb function with poststroke therapy. *Neurorehabilitation and neural repair, 29*(4), 341-348.

Thompson-Butel, AG, Lin, GG, Shiner, CT, & McNulty, PA. (2014). Two common tests of dexterity can stratify upper limb motor function after stroke. *Neurorehabilitation and neural repair*, 1545968314523678.

Thompson-Butel, AG, Scheuer, SE, & McNulty, PA. (2013). Improving motor activation patterns after stroke with wii-based movement therapy *Stimulation and inhibition of neurons* (pp. 301-314): Springer.

Tibold, R, & Fuglevand, AJ. (2015). Prediction of muscle activity during loaded movements of the upper limb. *Journal of neuroengineering and rehabilitation, 12*(1), 6.

Ting, LH, & Macpherson, JM. (2005). A limited set of muscle synergies for force control during a postural task. *Journal of neurophysiology, 93*(1), 609-613.

Ting, LH, & McKay, JL. (2007). Neuromechanics of muscle synergies for posture and movement. *Current opinion in neurobiology, 17*(6), 622-628.

Tombaugh, TN, & McIntyre, NJ. (1992). The mini-mental state examination: A comprehensive review. *Journal of the American Geriatrics Society, 40*(9), 922-935.

Torres-Oviedo, G, Macpherson, JM, & Ting, LH. (2006). Muscle synergy organization is robust across a variety of postural perturbations. *Journal of neurophysiology, 96*(3), 1530-1546.

Torres-Oviedo, G, & Ting, LH. (2007). Muscle synergies characterizing human postural responses. *Journal of neurophysiology, 98*(4), 2144-2156.

Tresch, MC, Cheung, VC, & d'Avella, A. (2006). Matrix factorization algorithms for the identification of muscle synergies: Evaluation on simulated and experimental data sets. *Journal of neurophysiology, 95*(4), 2199-2212.

Tresch, MC, Saltiel, P, & Bizzi, E. (1999). The construction of movement by the spinal cord. *Nature neuroscience, 2*(2), 162-167.

Tresch, MC, Saltiel, P, d'Avella, A, & Bizzi, E. (2002). Coordination and localization in spinal motor systems. *Brain Research Reviews, 40*(1), 66-79.

Triandafilou, KM, & Kamper, DG. (2012). Investigation of hand muscle atrophy in stroke survivors. *Clinical Biomechanics, 27*(3), 268-272.

Trinh, T, Scheuer, SE, Thompson-Butel, AG, Shiner, CT, & McNulty, PA. (2016a). Cardiovascular fitness is improved post-stroke with upper-limb wii-based movement therapy but not dose-matched constraint therapy. *Topics in stroke rehabilitation, 23*(3), 208-216.

Trinh, T, Shiner, CT, Thompson-Butel, AG, & McNulty, PA. (2016b). Targeted upper-limb wii-based movement therapy also improves lower-limb muscle activation and functional movement in chronic stroke. *Disability and rehabilitation*, 1-11.

Tropea, P, Monaco, V, Coscia, M, Posteraro, F, & Micera, S. (2013). Effects of early and intensive neuro-rehabilitative treatment on muscle synergies in acute post-stroke patients: A pilot study. *Journal of neuroengineering and rehabilitation, 10*(1), 103.

Turolla, A, Dam, M, Ventura, L, Tonin, P, Agostini, M*, et al.* (2013). Virtual reality for the rehabilitation of the upper limb motor function after stroke: A prospective controlled trial. *Journal of neuroengineering and rehabilitation, 10*(1), 85.

Uswatte, G, Taub, E, Morris, D, Vignolo, M, & McCulloch, K. (2005). Reliability and validity of the upper-extremity motor activity log-14 for measuring real-world arm use. *Stroke, 36*(11), 2493-2496.

Van der Lee, JH, De Groot, V, Beckerman, H, Wagenaar, RC, Lankhorst, GJ*, et al.* (2001). The intra-and interrater reliability of the action research arm test: A practical test of upper extremity function in patients with stroke. *Archives of physical medicine and rehabilitation, 82*(1), 14-19.

van Dijk, MJ, de Man-van Ginkel, JM, Hafsteinsdóttir, TB, & Schuurmans, MJ. (2016). Identifying depression post-stroke in patients with aphasia: A systematic review of the reliability, validity and feasibility of available instruments. *Clinical Rehabilitation, 30*(8), 795-810.

van Kordelaar, J, van Wegen, E, & Kwakkel, G. (2014). Impact of time on quality of motor control of the paretic upper limb after stroke. *Archives of physical medicine and rehabilitation, 95*(2), 338-344.

van Kordelaar, J, van Wegen, EE, Nijland, RH, Daffertshofer, A, & Kwakkel, G. (2013). Understanding adaptive motor control of the paretic upper limb early poststroke: The explicit-stroke program. *Neurorehabilitation and neural repair, 27*(9), 854-863.

van Wijk, I, Algra, A, van de Port, IG, Bevaart, B, & Lindeman, E. (2006). Change in mobility activity in the second year after stroke in a rehabilitation population: Who is at risk for decline? *Archives of physical medicine and rehabilitation, 87*(1), 45-50.

Veerbeek, JM, Langbroek-Amersfoort, AC, van Wegen, EE, Meskers, CG, & Kwakkel, G. (2017). Effects of robot-assisted therapy for the upper limb after stroke: A systematic review and meta-analysis. *Neurorehabilitation and neural repair*, 1545968316666957.

Wagner, JM, Dromerick, AW, Sahrmann, SA, & Lang, CE. (2007). Upper extremity muscle activation during recovery of reaching in subjects with post-stroke hemiparesis. *Clinical Neurophysiology, 118*(1), 164-176.

Ward, N, Brown, M, Thompson, A, & Frackowiak, R. (2003). Neural correlates of motor recovery after stroke: A longitudinal fmri study. *Brain, 126*(11), 2476-2496.

Webster, D, & Celik, O. (2014). Systematic review of kinect applications in elderly care and stroke rehabilitation. *Journal of neuroengineering and rehabilitation, 11*(1), 108.

Werring, DJ, Toosy, AT, Clark, CA, Parker, GJ, Barker, GJ*, et al.* (2000). Diffusion tensor imaging can detect and quantify corticospinal tract degeneration after stroke. *Journal of Neurology, Neurosurgery & Psychiatry, 69*(2), 269-272.

Westover, AN, McBride, S, & Haley, RW. (2007). Stroke in young adults who abuse amphetamines or cocaine: A population-based study of hospitalized patients. *Archives of general psychiatry, 64*(4), 495-502.

Wiethoff, S, Hamada, M, & Rothwell, JC. (2014). Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimulation, 7*(3), 468-475.

Winter, DA. (2009). *Biomechanics and motor control of human movement*: John Wiley & Sons.

Winters, C, van Wegen, EE, Daffertshofer, A, & Kwakkel, G. (2015). Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. *Neurorehabilitation and neural repair, 29*(7), 614-622.

Witte, OW, Bidmon, H-J, Schiene, K, Redecker, C, & Hagemann, G. (2000). Functional differentiation of multiple perilesional zones after focal cerebral ischemia. *Journal of Cerebral Blood Flow & Metabolism, 20*(8), 1149-1165.

Wolf, PA, D'Agostino, RB, Kannel, WB, Bonita, R, & Belanger, AJ. (1988). Cigarette smoking as a risk factor for stroke: The framingham study. *Jama, 259*(7), 1025-1029.

Wolf, SL. (2007). Revisiting constraint-induced movement therapy: Are we too smitten with the mitten? Is all nonuse “learned”? And other quandaries. *Physical therapy, 87*(9), 1212-1223.

Wolf, SL, Catlin, P, Ellis, M, Archer, A, Morgan, B*, et al.* (2001). Assessing wolf motor function test as outcome measure for research in patients after stroke. *Stroke, 32*(7), 1635-1639.

Wolf, SL, Lecraw, DE, Barton, LA, & Jann, BB. (1989). Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. *Experimental neurology, 104*(2), 125-132.

Wolf, SL, Thompson, PA, Winstein, CJ, Miller, JP, Blanton, SR*, et al.* (2010). The excite stroke trial. *Stroke, 41*(10), 2309-2315.

Wolf, SL, Winstein, CJ, Miller, JP, Taub, E, Uswatte, G*, et al.* (2006). Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The excite randomized clinical trial. *Jama, 296*(17), 2095-2104.

Wolf, SL, Winstein, CJ, Miller, JP, Thompson, PA, Taub, E*, et al.* (2008). Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: The excite randomised trial. *The Lancet Neurology, 7*(1), 33-40.

Wu, C-y, Chen, C-l, Tang, SF, Lin, K-c, & Huang, Y-y. (2007a). Kinematic and clinical analyses of upper-extremity movements after constraint-induced movement therapy in patients with stroke: A randomized controlled trial. *Archives of physical medicine and rehabilitation, 88*(8), 964-970.

Wu, C-y, Chuang, L-l, Lin, K-c, Chen, H-c, & Tsay, P-k. (2011). Randomized trial of distributed constraint-induced therapy versus bilateral arm training for the rehabilitation of upper-limb motor control and function after stroke. *Neurorehabilitation and neural repair, 25*(2), 130-139.

Wu, C-y, Lin, K-c, Chen, H-c, Chen, I-h, & Hong, W-h. (2007b). Effects of modified constraint-induced movement therapy on movement kinematics and daily function in patients with stroke: A kinematic study of motor control mechanisms. *Neurorehabilitation and neural repair, 21*(5), 460-466.

Wu, J, Quinlan, EB, Dodakian, L, McKenzie, A, Kathuria, N*, et al.* (2015). Connectivity measures are robust biomarkers of cortical function and plasticity after stroke. *Brain, 138*(8), 2359-2369.

Yavuzer, G, Senel, A, Atay, M, & Stam, H. (2008). "Playstation eyetoy games"improve upper extremity-related motor functioning in subacute stroke: A randomized controlled clinical trial. *European journal of physical and rehabilitation medicine, 44*(3), 237-244.

Zarahn, E, Alon, L, Ryan, SL, Lazar, RM, Vry, M-S*, et al.* (2011). Prediction of motor recovery using initial impairment and fmri 48 h poststroke. *Cerebral Cortex, 21*(12), 2712-2721.

Zariffa, J, Steeves, J, & Pai, DK. (2012). Changes in hand muscle synergies in subjects with spinal cord injury: Characterization and functional implications. *The journal of spinal cord medicine, 35*(5), 310-318.

Zeiler, SR, & Krakauer, JW. (2013). The interaction between training and plasticity in the post-stroke brain. *Current opinion in neurology, 26*(6), 609.

Zhang, X, Yue, Z, & Wang, J. (2017). Robotics in lower-limb rehabilitation after stroke. *Behavioural Neurology, 2017*.

Zhang, X, & Zhou, P. (2012). High-density myoelectric pattern recognition toward improved stroke rehabilitation. *IEEE transactions on biomedical engineering, 59*(6), 1649-1657.

Zhou, P, Li, X, & Zev Rymer, W. (2013). Emg-force relations during isometric contractions of the first dorsal interosseous muscle after stroke. *Topics in stroke rehabilitation, 20*(6), 537-543.