EFFECTS OF BILATERAL CUTANEOUS ELECTRICAL STIMULATION IN IMPROVING LOWER LIMB MOTOR FUNCTIONS AND LEVEL OF COMMUNITY INTEGRATION IN PEOPLE WITH STROKE

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PhD

The Hong Kong Polytechnic University

2018

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Effects of Bilateral Cutaneous Electrical Stimulation in Improving Lower Limb Motor Functions and Level of Community Integration in People with Stroke

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

December 2017

CERTIFICATE OF ORIGINALITY

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ABSTRACT

Stroke is one of the leading causes of long-term disability globally. The residual physical impairments after stroke reduce both the quality and the quantity of the survivor’s social participation. Transcutaneous electrical nerve stimulation (TENS) has been used to enhance the paretic lower limb motor functions in people with stroke. Besides, clinical studies demonstrated that the bilateral motor training was superior to unilateral training in improving the motor recovery in people with stroke. Current evidence showed that bilateral intervention recruits the spare neural substrates which can be utilized to enhance motor recovery.

It was hypothesized that bilateral TENS (Bi-TENS) applied over both paretic and non-paretic legs induce greater and earlier improving in lower limb motor functions when compared to unilateral TENS (Uni-TENS). The aim of the work presented in this thesis was to compare the efficacy of Bi-TENS + task-oriented training (TOT) and Uni-TENS + TOT in enhancing motor recovery and augment the level of community integration in people with chronic stroke.

This thesis starts with a systematic review and meta-analyses that summarised the effects of TENS on lower-limbs motor recovery in people with stroke. Results of the meta-analysis indicates that TENS is effective at enhancing walking capacity and reducing spasticity.

The subsequence cross-sectional study 2 and 3 investigate the influence of assessment procedures of Berg Balance Scale and Five-Times-Sit-to-Stand Test. Results of these studies showed that selection of weight-bearing leg affects the Berg Balance Scale total score, and the arm positions or foot placements affects the Five-Times-Sit-to-Stand Test completion time. Thus, standardising the assessment procedure is necessary for using these outcomes in the randomised control trial.

Study 4 describes the translation and validation processes of the Subjective Index of Physical and Social Outcome. Results show that the translated questionnaire is reliable and valid to measure the level of community integration in people with stroke in Hong Kong.

Study 5 evaluates the relationship between physical functions and level of community integration in community-dwelling people with stroke. Results show that paretic ankle dorsiflexion strength, walking endurance and balance performance were predictors of the level of community integration. Therefore, this study forms the rationale of measuring the level of community integration in the randomised control trial

Study 6 is the main study which compares the efficacy of the Bi-TENS + TOT versus Uni-TENS + TOT in improving paretic ankle muscle strength, balance performance, walking capacity and level of community integration in people with chronic stroke. Eighty subjects were randomly assigned to Bi-TENS + TOT or Uni-TENS +TOT group and received 20-session of training. Results showed that Bi-TENS

with TOT was superior to Uni-TENS with TOT in improving the paretic ankle dorsiflexion strength after 10-session of training and Timed Up and Go test completion time after 20-session of training.

Since the neurophysiological machanism that mediate the effects of Uni-TENS and Bi-TENS remains unclear, study 7 aims to evaluate the effects of Bi-TENS and Uni-TENS on cortical perfusion and motor performance in healthy older adults. The results showed that Bi-TENS applied over the peroneal nerve reduced the maximal change of Oxyhaemogobin concentration during isometric ankle dorsiflexion when compared to placebo stimulation and Uni-TENS. However, there was no significant difference existed in motor performance.

RESEARCH OUTPUT ARISING FROM THIS THESIS

PUBLICATIONS

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Kwong PW, Ng GY, Chung RC, Ng SS. Transcutaneous electrical nerve stimulation improves walking capacity and reduces spasticity in stroke survivors: a systematic review and meta-analysis. Clin Rehabil. 2017 Dec 1:269215517745349. doi: 10.1177/0269215517745349. [Epub ahead of print]

Kwong PW, Ng GY, Chung RC, Ng SS. Bilateral transcutaneous electrical nerve stimulation (TENS) improves lower-limb motor function in subjects with chronic stroke: a randomised controlled trial. Journal of the American Heart Association. 7(4), e007341.

CONFERENCE PRESENTATIONS

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ACKNOWLEDGEMENT

I would like to express my deepest gratitude to my chief supervisor Dr. Shamay Ng, for her invaluable support, guidance and encouragements to me. Dr. Ng has always been a listening ear when I faced difficulties and tirelessly pointed me in the correct direction when I felt lost. Dr. Ng was always there to guide me while I was formulating my research plan, conducting the research and writing this thesis with her immense knowledge and experiences. I could not have had a better supervisor for my PhD study. I would also like to express my sincerest gratitude to my co-supervisor; Professor Gabriel Ng. Professor Ng is an experienced supervisor who would provide valuable comments and guidance on my research work without fail.

In addition, I would like to thank Dr. Raymond Chung for his many advices on statistical analysis. Ms. Carman Poon, Mr. TW Liu and Ms. Weeraya Ho for their kind assistance and support during my data collection. I am also extremely grateful to Mr. SS Cheung and Mr. Man Cheung for offering technical supports in the course of my study.

I would also like to offer my special thanks to all the participants who voluntarily participated in my studies. My doctoral research can never be accomplished without their active participation.

Last but not least, I would like to acknowledge the Research Grant Council of Hong Kong Special Administrative Regions for offering the financial support to this project (General Research Grant: reference number 562413).

TABLE OF CONTENTS

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Relationship between motor functions and community integration in people with stroke

Chapter 6

Bilateral transcutaneous electrical nerve stimulation (TENS) improves lower-limb motor impairments in people with chronic stroke: a randomised controlled trial

Chapter 7

Chapter 8

Chapter 9

LIST OF ABBREVIATIONS

10mWT	10-Metre walk test
6MWT	6-Minute Walk Test
ABC	Activities-specific Balance Confidence Scale
AMT	Abbreviated Mental Test
ANOVA	analysis of variance
AP	antero-posterior
AROM	active range of motion
AUC	area under curve
BBS	Berg Balance Scale
Bi-TENS	bilateral transcutaneous electrical nerve stimulation
BMI	Body Mass Index
CFI	comparative fit index
CI	confidence interval
CoG	centre of gravity
CSS	Composite Spasticity Scale
CV	coefficient of variation
DF	dorsiflexor
DGI	Dynamic Gait Index
DPF	differential pathlength factors
EEG	electroencephalogram
EMG	electromyography
EXT	extensor
FES	functional electrical stimulation
FMA	Fugl-Meyer Assessment
FMA-LE	Fugl-Meyer Assessment lower extremity subscale
fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
FTSTS	Five Times Sit to Stand Test
GABA	γ-aminobutyric acid
GDS	Geriatric Depression Scale
Hb	deoxyhemoglobin
HbO_2	oxyhaemoglobin
H_{max}	maximum H-reflex
ICC	intraclass correlation coefficient
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health

LEMOCOT	Lower Extremity Motor Coordination Test
LMM	linear mixed model
LOS	Limit of stability
M1	primary motor cortex
MAS	Modified Ashworth Scale
ML	medial-lateral
MRMI	Modified Rivermead Mobility Index
MVC	maximum voluntary contraction
nrmsEMG	normalised root-mean-square EMG
OT	occupational therapy
PEDro	Physiotherapy Evidence Database
PT	physiotherapy
RCT	randomised controlled trial
RMS	root-mean-square
ROC	Receiver operating characteristics
RR	risk ratio
RST	reticulospinal tract
S1	primary sensory cortex
SD	standard deviations
SEM	structural equation modeling
SF36	36-Item Short Form Health Survey
SIPSO	Subjective Index of Physical and Social Outcome
SIPSO-C	Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome
SLS	Single leg stance
SPSS	Statistical Package for the Social Sciences
SRMR	standardised root mean square residual
ST	Step Test
TA	tibialis anterior muscle
TENS	transcutaneous electrical nerve stimulation
TMS	transcranial magnetic stimulation
TOT	task-oriented training
TUG	Timed-up and Go test
VST	vestibulospinal tract

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

Chapter 1

General introduction

1.1 Overview

This chapter reviews the epidemiology of stroke and its impact on body functions, functional limitations and the level of community integration of stroke survivors. The mechanisms of motor recovery after stroke, and the clinical efficacy of transcutaneous electrical nerve stimulation (TENS) and task-oriented training (TOT) in stroke rehabilitation are also examined. Neural substrates that could be exploited to enhance motor recovery after a stroke are proposed. How bilateral transcutaneous electrical nerve stimulation (Bi-TENS) can promote motor recovery after a stroke is also presented. The chapter concludes with an outline of the rest of this thesis.

1.2 Epidemiology

Stroke has been defined as "*a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral haemorrhage [or] subarachnoid haemorrhages*" (Sacco et al., 2013). Stroke is a major cause of death and long-term disability globally (Mozaffarian et al., 2016). The American Heart Association estimates that 87% of stroke victims suffer cerebral infarction, 10% intra-cerebral haemorrhage, and 3% experience a sub-arachnoid haemorrhage (Mozaffarian et al., 2016). They estimate the total number of stroke victims to have been 33 million persons worldwide in 2010 (Mozaffarian et al., 2016). Hong Kong's Census and Statistic Department has reported that 2.2% of all those who suffered from chronic diseases in Hong Kong in 2014 suffered from a stroke (Census and Statistics Department of Hong Kong, 2015). The prevalence of stroke in the 35–54 years age group was only 0.2%, but it increased dramatically to 1.2% by 60–64 years and to 3.2% among those over 64 years (Census and Statistics Department of Hong Kong, 2015).

Worldwide, 16.9million new strokes were diagnosed in 2010 - 11.6million ischemic and 5.3million hemorrhagic (Mozaffarian et al., 2016). In Hong Kong, 21,492 people were admitted to local hospitals due to a stroke during 2013. The population of Hong Kong at that time was 7.19 million (Census and Statistics Department HKSAR, 2015), giving an incidence of 298 per 100,000. Among them, 6597 of the strokes were diagnosed as intracranial haemorrhage and 11,047 as cerebral infarction. The other 3848 were not specified.

The incidence of stroke is expected to continue rising due to the ageing population and changes in lifestyle. By 2036 the number of stroke survivors over 64 in Hong Kong is projected to be more than 160,000 (Yu et al., 2012). Moreover, stroke's mortality rate continues to decrease due to advances in medical support. The age-standardized mortality rate for stroke worldwide has dropped by 22.5% from 1990 to 2013 (Naghavi et al., 2015). Thus, the total number of stroke survivors can be expected to rise in the coming decades (Feigin et al., 2015; Yu et al., 2012).

1.3 Risk factors for stroke

Advanced age has been identified as one of the major risk factors for stroke (Liu et al., 2007; Wolf et al., 1992). After 55, the incidence of stroke doubles each decade (Wolf et al., 1992). In China, the incidence of stroke is thirty-fold higher among people older than 75 years compared with those aged between 35 and 44 years (Liu et al., 2007). Other independent predictors of and risk factors for stroke include severe hypertension (relative risk (RR) = 1.67) (Allen & Bayraktutan, 2008; Simons et al., 1998), atrial fibrillation (RR = 1.58) (Simons et al., 1998), diabetes mellitus (RR = 1.5 to 3) (Kuller et al., 1995), smoking (RR = 1.5) (Shinton & Beevers, 1989) and male gender (RR = 1.19) (Allen & Bayraktutan, 2008).

1.4 Stroke's Impact on Society

Stroke places a huge socioeconomic burden on society (Bergmann et al., 1991; Black-Schaffer & Osberg, 1990; Demaerschalk et al., 2010; Hsieh & Lee, 1997; Mozaffarian et al., 2016; Treger et al., 2007; van Exel et al., 2003; Yu et al., 2012). Stroke's direct costs, including emergency care, hospitalization, outpatient services, medication and home care services, are estimated to have been US$ 33 billion in the United States in 2013 (Mozaffarian et al., 2016). The indirect costs, primarily loss of productivity and subsequent informal care amounted to US$ 23.6 billion in 2008 according to one American estimate (Demaerschalk et al., 2010). In Hong Kong, the direct medical expenditures for people with stroke aged 65 or above are estimated to have been HK$ 1.33 billion in 2006 (Yu et al., 2012). The direct medical expenses are projected to be HK$ 3.98 billion in 2036 (Yu et al., 2012).

In advanced economies, those who recover poorly after a stroke usually receive residential care after being discharged from the hospital. In 2006, about 16,000 stroke survivors aged over 64 years stayed in residential care institutions in Hong Kong (Yu et al., 2012). The total cost of the government-subsidized residential care services was about HK$ 720 million and that of private residential care services was about HK$ 780 million (Yu et al., 2012).

The indirect cost in the loss of productivity is even higher. In 2010, the total opportunity cost of the time Hong Kong caregivers devoted to caring for stroke survivors aged 65 years and above was estimated to be HK$ 5.04 billion (Yu et al., 2012). A 2006 review of 16 studies revealed that the rate of returning to work among stroke survivors ranged from 19% to 73% (Treger et al., 2007). Among them, 47% to 68% reduced their working hours (Black-Schaffer & Osberg, 1990; Hsieh & Lee, 1997) or changed the nature of their work (Bergmann et al., 1991). A previous study has suggested that disability level as measured with the Barthel Index at discharge is a significant predictor of the cost of post-stroke care (van Exel et al., 2003). Thus, an effective stroke rehabilitation program could alleviate the socio-economic burden imposed by the disease.

1.5 Sensorimotor impairments after a stroke

1.5.1 Spasticity

Spasticity is defined as “velocity-dependent increase in tonic stretch reflex with exaggerated tendon jerks, resulting from the hyperexcitability of the stretch reflex” (Lance, 1980). Abnormal or hyper-excited α motor neurons are believed to contribute to spasticity caused by central nervous system lesions (Li & Francisco, 2015). In an intact central nervous system, the excitability of the spinal reflex pathways is regulated by supra-spinal input from the medial reticulospinal tract (RST), the dorsal RST and the vestibulospinal tract (VST) (Gracies, 2005). The inputs from the medial RST and the VST to α motor neurons are facilitatory, whereas input from the dorsal RST is inhibitory. The dorsal RST receives facilitatory input from the motor cortex through cortico-reticular connections (Mukherjee & Chakravarty, 2010). Lesions in the motor cortex or the internal capsule may reduce that facilitatory input to dorsal RST, reducing the descending inhibitory input to α motor neurons (Mukherjee & Chakravarty, 2010). The excitability of the spinal reflex arch is therefore enhanced due to the decrease in opposed descending input.

Apart from the imbalance in descending neural control, muscle shortening and reduced muscle compliance due to a lack of active movement will increase the sensitivity of muscle spindles (Gracies, 2005). Muscle spindles are sensory receptors in the muscle belly which activate α motor neurons when the muscle is stretched. Muscle spindle hypersensitivity can interfere with normal movement even when the muscle is lengthening in the normal range of motion. Sustained spontaneous motor unit discharges are observed in people with post-stroke spasticity (Chang et al., 2013; Mottram et al., 2010). Using the intramuscular electromyography (EMG), Chang and colleagues investigated the frequency of spontaneous motor unit discharge in people with chronic stroke who demonstrated elbow flexor spasticity. Seventy percent of their subjects demonstrated sustained spontaneous motor unit discharges while at rest (Chang et al., 2013).

Watkins and colleagues (Watkins et al., 2002) have reported that the prevalence of spasticity was 38% at 12 months post-stroke among 106 stroke survivors. Similarly, Urban and his colleagues reported a 42.6% prevalence of spasticity 6 months post-stroke among 211 subjects. Among them, 63% demonstrated spasticity in both their upper and lower limbs, 20% in the upper limbs, and 17% only in the lower limbs (Urban et al., 2010).

Although spasticity is common after a stroke, the extent to which spasticity interferes with motor function is still under debate (Bujanda et al., 2003; Canning et al., 2004; Nadeau, 1998). Several studies have reported that spasticity does not necessarily impair muscle strength (Nakamura et al., 1985), walking ability (Ada et al., 1998; Bohannon & Andrews, 1990) or upper limb function (Ada et al., 2006b; Canning et al., 2004) after a stroke. But the risk of developing muscle contracture is certainly one adverse consequence of muscle spasticity (Ada et al., 2006b; O'Dwyer et al., 1996). Contracture is muscle shortening due to a decrease in the number of sarcomeres in series (Ada et al., 2006b), shortening of the muscle fascicles (Gao et al., 2009), a reduction in the muscle fascicles' pennation angle (Gao et al., 2009), and thickening of the perimysium and endomysium (Jozsa et al., 1990).

1.5.2 Muscle weakness

Muscle weakness is one of the major motor impairments observed after a stroke (Andrews & Bohannon, 2000; Bohannon, 2007; Dorsch et al., 2015). Andrews and Bohannon have reported that at discharge, the residual lower limb muscle strength of 31 stroke survivors was only 37.2% to 44.5% of the normal value in the paretic leg and 65.4% to 83.0% of the normal value in the non-paretic leg (Andrews & Bohannon, 2000). Distal muscles are particularly susceptible to weakening. Adam and colleagues report (Adams et al., 1990) that the residual muscle strength in the paretic ankles of 16 stroke survivors was 37% to 45% of the normal value, 51% to 53% in the paretic knee and 64% to 68% in the paretic hip. Dorsch and colleagues tested 60 stroke survivors and reported that the ankle dorsiflexors are often the most severely affected among all the major lower limb muscle groups (Dorsch et al., 2015). The average isometric strength (adjusted for age, sex and body weight) of their subjects' ankle dorsiflexors measured by hand-held dynamometer in supine lying was only 35% of the average strength of healthy controls (Dorsch et al., 2015). And Ada et.al studied 22 stroke survivors and had reported that the muscle weakness appears to be more severe in the inner range (the shortened position) than in the outer range (lengthened). They measured isometric elbow extension torque at full elbow flexion as around 75% of the maximum torque, but it was only about 40% of the maximum when measured in full extension (Ada et al., 2003).

A decrease in the number of functioning motor units (Arasaki et al., 2006; Hara et al., 2000), changes in muscles' mechanical properties (Gao et al., 2009; Gray et al., 2012; Li et al., 2007) and altered metabolism (Hafer-Macko et al., 2008; Severinsen et al., 2015) are mechanisms known to cause muscle weakness after a stroke. The number of functioning motor units can be estimated using the surface motor unit action potentials deduced from the F-waves elicited by sub-maximal electrical stimulation (Doherty & Brown, 1993; Hara et al., 2000). Using this method, Hara and colleagues (Hara et al., 2000) studied 15 stroke survivors and estimated that the number of functioning motor units in the abductor pollicis brevis of a paretic hand is approximately 40% less than in a non-paretic hand. Arasaki and colleagues further demonstrated an approximately 20% decrease in the number of functioning motor units as early as 4 to 30 hours post-stroke (Arasaki et al., 2006).

Gao et.al. have reported shortening of fibres in the gastrocnemius and brachialis muscles after a stroke (Gao et al., 2009). They used ultrasonography to evaluate muscle fibre length in 10 people with ankle muscle contracture after a stroke. They found that the fibres of the paretic medial gastrocnemius muscle were significantly shorter than those of healthy controls (Gao et al., 2009). Muscle shortening altered the force-length relationship in the fascicle. In other words, the force generated tended to decrease, since the muscle could no longer function at its optimum length (Gao & Zhang, 2008; Zuurbier et al., 1994).

Severinsen and colleagues (Severinsen et al., 2015) have reported that citrate synthase activity, which represents the oxidative capacity of a muscle, was significantly lower in paretic rectus femoris muscles than in non-paretic controls. They used a respiratory gas exchange analyzer and showed that the citrate synthase activity of a paretic rectus femoris muscle correlated with the subject's peak aerobic capacity measured using a cycle ergometer ($r = 0.47$). These results suggest that reduced oxidative capacity might reduce muscle endurance and limit the number of repeated muscle contractions possible after a stroke.

Muscle weakness can, of course, impair the functioning of both the upper (Canning et al., 2004; Harris & Eng, 2010; Ng et al., 2011b) and lower limbs (Bohannon, 1989; Flansbjer et al., 2006; Kim & Eng, 2003; Lomaglio & Eng, 2005; Nadeau et al., 1999b; Ng & Hui-Chan, 2005; Suzuki et al., 1990). Several studies have reported a strong correlation between lower limb muscle strength and walking performance as measured by walking speed (Flansbjer et al., 2006; Kim & Eng, 2003; Suzuki et al., 1990), walking endurance (Bohannon, 1989; Ng & Hui-Chan, 2012), performance in the Timed Up and Go test (Ng & Hui-Chan, 2005), and ability in other functional movements such as stair walking (Flansbjer et al., 2006; Kim & Eng, 2003) and rising from sitting (Lomaglio & Eng, 2005). Concentric extension torque in a paretic knee significantly predicts the time taken in self-paced rising from sitting ($r = -0.72$)

(Lomaglio & Eng, 2005), comfortable walking speed (*r* = 0.61), maximum walking speed (*r* = 0.65 to 0.85) (Flansbjer et al., 2006; Suzuki et al., 1990) and speed when climbing stairs (*r* = 0.58) (Flansbjer et al., 2006; Lomaglio & Eng, 2005). Isokinetic flexion torque in a paretic knee after a stroke also correlates with maximum walking speed (*r* = 0.61) (Flansbjer et al., 2006) and speed in ascending stairs (*r* = 0.48 - 0.61) (Flansbjer et al., 2006). Isometric dorsiflexor strength in a paretic ankle correlates significantly with comfortable walking speed (*r* = 0.85) and the maximum distance a person can walk before being constrained by fatigue (*r* = 0.80) (Bohannon, 1989). Isometric strength in a paretic plantar flexor has been shown to predict Timed Up and Go test completion time (ρ = -0.86) (Ng & Hui-Chan, 2005), and the isokinetic torque similarly predicts comfortable walking speed (*r* = 0.845) (Kim & Eng, 2003) and stair climbing speed (*r* = 0.709) (Kim & Eng, 2003).

1.5.3 Sensory deficits

Sensory deficits are a common impairment following stroke. Their incidence ranges from 45% to 85% (Kim & Choi-Kwon, 1996; Sommerfeld & von Arbin, 2004; Tyson et al., 2013a). The large range probably arises from using different definitions and assessment methods. Kim and Choi-Kwon (Kim & Choi-Kwon, 1996) have evaluated the discriminative sensation of 67 people after stroke, assessing texture discrimination, two-point discrimination, stereognosis, point localization and position sense in both hands. Sixty of their subjects demonstrated a deficit in at least one of the tests, and 20 of them demonstrated some bilateral sensory deficit (Kim & Choi-Kwon, 1996).

Sommerfeld and von Arbin (Sommerfeld & von Arbin, 2004) tested 115 stroke survivors using pinpricks and light touching. About 50% of those giving reliable responses were classified as having impaired sensation in the paretic hand in at least one of the tests. Tyson and colleagues pooled the data from five studies which involved 439 stroke survivors and reported (Tyson et al., 2013a) that approximately 31% had an impaired ability to locate a light touch on the dorsum of the foot, 29% had an impaired ability to detect such a light touch at all, 23% had an impaired ability to detect the direction of movement at the ankle, and 18% had an impaired ability to detect movement of the ankle at all. Their results further demonstrate that the level impairment of sensation in a paretic lower limb significantly predicts ability in the activities of daily living after a stroke (β = -0.15).

1.5.4 Impaired balance

After a stroke, people demonstrate greater postural sway (Dickstein & Abulaffio, 2000; Ikai et al., 2003; Marigold et al., 2004; Marigold & Eng, 2006) and less symmetrical weight bearing when standing (Goldie et al., 1996; Ikai et al., 2003; Sackley, 1991). With their feet fixed, they can also manage only smaller excursions of their centre of gravity towards all directions (Liston & Brouwer, 1996). Using two force plates, Marigold and Eng (Marigold & Eng, 2006) have reported that the displacement of the centre of pressure in people with stroke was 45% greater in the anteroposterior direction and 47% greater in mediolateral direction when compared to healthy controls. Similarly, Dault et al. reports (Dault et al., 2003) that the lateral displacement amplitude of the centre of pressure during static standing for 10 people with subacute stroke was almost twice that of age-matched healthy adults. Marigold and colleagues (Marigold & Eng, 2006) have also demonstrated that stroke survivors demonstrate more postural sway than healthy controls when dealing with inaccurate sensory input such as a swaying surround and/or a swaying surface. Tyson and his colleagues have shown that sensation deficits, muscle weakness and unilateral neglect are all significant predictors of balance deficits measured with the Brunei Balance Assessment (Tyson et al., 2006).

Cheng and his colleagues report using a standing bio-feedback trainer to improve the body weight distribution of 54 stroke survivors and that such training reduced falls more effectively than conventional treatment (Cheng et al., 2001). Belgen and colleagues have demonstrated (Belgen et al., 2006) that a score of 52 on the Berg Balance Scale effectively discriminate fallers from non-fallers among stroke survivors.

Balance correlates strongly with walking speed (Patterson et al., 2007), walking endurance (Liston & Brouwer, 1996; Patterson et al., 2007), sit-to-stand performance (Ng, 2010) and other functional activities (Michael et al., 2005). Liston and his colleagues have reported balance ability assessed with the Balance Master system showing that sway (r = -0.67) and movement time (r = -0.72) in shifting the centre of gravity toward the limits of stability are significantly correlated with walking speed after a stroke (Liston & Brouwer, 1996). Patterson et al. also reports that Berg Balance Scale scores correlate moderately with comfortable walking speed (r = 0.64) and 6-minute walking distance (r = 0.69) after studying 85 stroke survivors (Patterson et al., 2007).

The Berg Balance Scale reliably predicts the walking speed of people with poor mobility (walking speed < $0.48 \mathrm{ms}^{-1}$), explaining 42% of the observed variance (Patterson et al., 2007). The Berg Balance Scale score is also a strong independent predictor of performance in the Five Times Sit to Stand test, explaining 15.7% of the variance in completion times. Beyond that, Michael and his colleagues have reported (Michael et al., 2005) that Berg Balance Scale scores can explain 30% of the variance in the total daily stride counts of people who have suffered a stroke.

1.6 Mobility after a stroke

Walking unaided in the community has been reported to be the most important goal among people who have suffered a stroke (Bohannon et al., 1988; Eng & Tang, 2007). Only 48% of those discharged with residual lower limb paresis completely regain the ability to walk at will unaided (Jorgensen et al., 1995). Reduced walking speed (Dean et al., 2001; Witte & Carlsson, 1997), reduced walking endurance (Dean et al., 2001; Mayo et al., 1999; Ng et al., 2011a; Pohl et al., 2002; Pradon et al., 2013), impaired manoeuvrability (Bowen et al., 2001; Flansbjer et al., 2005b; Fujita et al., 2017; Goh et al., 2017; Ng & Hui-Chan, 2005; Tan et al., 2017; Wong et al., 2013) and an abnormal walking pattern (Olney & Richards, 1996; Patterson et al., 2008; Patterson et al., 2010) are typical.

Many previous studies have shown that the comfortable walking speed is reduced after a stroke (Bijleveld-Uitman et al., 2013; Dean et al., 2001; Dorsch et al., 2012; Gizzi et al., 2011; Kelly et al., 2003; Kwong et al., 2015; Prajapati et al., 2011; Prajapati et al., 2013; Tang et al., 2006; Witte & Carlsson, 1997). Bohannon and Andrews (Bohannon & Williams Andrews, 2011) have estimated the normal comfortable walking speed for a healthy adult by pooling data from 41 studies which involved 23,111 participants. Their result for healthy older adults aged between 50 and 79 years was 1.13 to 1.43ms^{-1}. Studies of stroke survivors have reported that the comfortable walking speed ranges from 0.53 to 0.84ms^{-1} (Gizzi et al., 2011; Kelly et al., 2003; Prajapati et al., 2011; Prajapati et al., 2013; Tang et al., 2006) among people with subacute stroke and from 0.59 to 1.00ms^{-1} (Bijleveld-Uitman et al., 2013; Dean et al., 2001; Dorsch et al., 2012; Kwong et al., 2015; Witte & Carlsson, 1997) for those with chronic stroke. Both subacute and chronic stroke survivors walk much more slowly (Bohannon & Williams Andrews, 2011). Dorsch and his colleagues have reported (Dorsch et al., 2012) that the strength of the paretic ankle dorsiflexors explains 31% of the variance in comfortable walking speed among hemiplegic stroke survivors. Hsu and his colleagues studied ankle plantarflexor spasticity and reported that scores using the Modified Ashworth Scale significantly correlate with comfortable walking speed (r = -0.47) (Hsu et al., 2003). Suzuki and colleagues instead focused on isokinetic peak torque in a paretic knee and showed (Suzuki et al., 1990) that it is a strong independent predictor of maximum walking speed after a stroke. The knee extension peak torque explained 71.9% of the variance in maximum walking speed, and sway amplitude explained an additional 9.3%.

After a stroke, people have difficulty increasing their walking speed (Jonkers et al., 2009; Suzuki et al., 1990). A Jonkers and colleagues (Jonkers et al., 2009) compared the gait kinematics of 6 high-functioning and 6 low-functioning stroke survivors. They concluded that an inability to generate sufficient power with the paretic ankle plantarflexors and hip flexors might impair the ability to increase walking speed. Bohannon measured the walking speed of 230 healthy adults and reported that the normal, comfortable walking speed of those aged between 50 years and 79 years was 1.75 to 2.06 ms^{-1} (Bohannon, 1997). Other studies (Goh et al., 2017; Jonkers et al., 2009; Ng et al., 2012; Suzuki et al., 1990) have reported maximum walking speeds ranging from 0.62 to 1.25ms^{-1} for people with chronic stroke.

Endurance is also important for mobility, and reduced endurance is common after a stroke. Previous studies using the 6-minute Walk test (6MWT) to assess the walking endurance of people after a stroke have shown that the average distance covered in the test ranged from 100 to 300 metres (Mayo et al., 1999; Ng et al., 2011a; Pohl et al., 2002; Pradon et al., 2013), which is far shorter than the 500 to 600 metres achieved by age-matched healthy adults (Enright & Sherrill, 1998; Steffen et al., 2002). Mayo has reported (Mayo et al., 1999) that 22 of the 46 stroke survivors he tested were unable to complete the 6MWT at all. For the 24 people who completed it, the distance covered was only 40% of the normal value (Mayo et al., 1999). The walking endurance of stroke survivors might be limited by impaired lower limb muscle strength (Ng & Hui-Chan, 2012; Patterson et al., 2007), poor balance (Patterson et al., 2007) and cardiovascular unfitness (Patterson et al., 2007). Ng and Hui-Chan have reported (Ng & Hui-Chan, 2012) that the strength of paretic ankle dorsiflexors (*r* = 0.793) and paretic ankle plantarflexors (*r* =0.349) correlate with the 6MWT distances of stroke survivors with ankle plantarflexor spasticity. Patterson and his colleagues reported that isokinetic extension peak torque in a paretic knee, Berg Balance Scale scores and maximum oxygen uptake in a treadmill exercise stress test explained 60% of the variance in the distance covered in 6MWT (Patterson et al., 2007).

Stroke survivors also have difficulty performing more advanced locomotion maneuvres such as negotiating stairs (Bohannon & Walsh, 1991; Fujita et al., 2017; Hamilton & Granger, 1994), changing direction (Tan et al., 2017; Wong et al., 2013), moving between functional positions (Ng & Hui-Chan, 2005) and even walking while talking (Bowen et al., 2001; Goh et al., 2017).

Negotiating stairs is one of their greatest challenges, but very important for community ambulation. Sufficient lower limb muscle strength and adequate balance are required to manage simultaneous horizontal and vertical movement of the body (Bohannon & Walsh, 1991; Fujita et al., 2017). Hamilton and Granger (Hamilton & Granger, 1994) used the stair walking sub-score in the Functional Independence Measure to quantify the stair walking ability of 5,190 stroke survivors. Their mean score was 3.7 points approximately 5 months post-stroke. A mean score of 3.7 indicates that the majority of those tested still required at least minimal assistance in negotiating stairs.

It has been reported that people often have difficulty performing multiple tasks simultaneously, such as walking while talking, after a stroke (Bowen et al., 2001; Goh et al., 2017). When a cognitive task and a motor task must be performed concurrently, interference may impair the performance of both (Bowen et al., 2001; Goh et al., 2017). For instance, Goh and colleagues (Goh et al., 2017) have reported that serial subtraction or counting aloud reduced the comfortable walking speed of stroke survivors by 9% and their maximum walking speed by 16%. Similarly, Bowen and colleagues (Bowen et al., 2001) have reported an 8% reduction in comfortable walking speed when stroke survivors are asked to differentiate colours while walking.

Wong and colleagues (Wong et al., 2013) assessed the ability of 64 stroke survivors to walk in a figure of eight pathways and found that their completion times were almost double those of age-matched healthy controls. Tan and colleagues (Tan et al., 2017) used the Groningen Meander Walking Test. They found that stroke survivors took three times longer than age-matched healthy controls to complete the test.

The Timed Up and Go test was designed to assess functional mobility. It involves rising from sitting, turning and walking (Ng & Hui-Chan, 2005; Podsiadlo & Richardson, 1991). Ng and Hui-Chan (Ng & Hui-Chan, 2005) have reported that stroke survivors take twice as much time as age-matched healthy controls to complete the test.

Gait asymmetry is common after stroke. Kinematic analysis of 161 stroke survivors has shown that the step length on the non-paretic side averages 13% longer than that on the paretic side. And the swing phase on the paretic side is 24% longer on average (Patterson et al., 2010). Insufficient muscle strength combined with impaired proprioception on the paretic side may be to attribute (Olney & Richards, 1996). Additionally, hip hiking or hip circumduction of the paretic lower limb during the swing phase is also evident among those with poor control of ankle dorsiflexion. Such gait modifications might help compensate for motor impairment and enhance functional mobility, but they also increase the total mechanical work done by the muscles (Detrembleur et al., 2003).

1.7 Community integration after a stroke

The physical impairment and functional limitations stroke often affect survivors' level of community integration. Wolfenberger has suggested (Wolfenberger, 1972) that successful community integration comprises the ability to live in a natural environment, competency in interacting with others, and ability to participate in one's usual activities. Dijker emphasizes "discharging the roles and responsibilities that are considered normal for someone of a specific age, gender, and culture" (Dijkers, 1998) (p.1).

Pang and colleagues (Pang et al., 2007) assessed the level of community integration of 63 stroke survivors using the Reintegration to Normal Living Index. They found that only 11% of them were completely satisfied with their level of community integration. Teale and colleagues evaluated the level of community integration of 176 subjects at 6 months post-stroke using the Subjective Index of Physical and Social Outcome (SIPSO) and reported that 56% showed poor physical integration and 71% showed only poor social integration (Pang et al., 2007).

Divergent interpretations of community integration have led to the development of several instruments designed to measure it. The Community Integration Questionnaire was developed for people with traumatic brain injury (Wilier et al., 1994). It focuses on the frequency of engaging in various physical and social activities and the level of dependency displayed. McColl and colleagues (McColl et al., 2001) developed Community Integration Measures based on a model of community integration derived from groups of people with brain injuries which was focused in assessing the subjective feelings of being accommodated in the community. Wood-Dauphinee and colleagues (Wood-Dauphinee et al., 1988) have developed the Reintegration to Normal Living Index based on the "Activity and Participation" component of the International Classification of Functioning Disability and Health model for people with various clinical diagnoses to assess their ability to resume well-adjusted living after illness or trauma.

Although all these instruments have been validated in different populations with various neurological deficits, several important aspects related to the community integration of stroke survivors have not been addressed. For example, the Community Integration Questionnaire neglects subjective experience. The Community Integration Measure fails to evaluate the level of engagement in the activities of daily living and social activities. The Reintegration to Normal Living Index takes more factors into consideration, but there is a poor agreement between the scores stroke survivors give themselves and the scores estimated by persons knowledgeable about their condition (Tooth et al., 2003). The index may, therefore, be of limited use in assessing people with cognitive impairment and/or communication difficulties. A better comprehensive measure of community integration after a stroke which evaluates rehabilitation outcomes from the perspective of those reintegrating is still clearly needed.

The SIPSO questionnaire was developed by Trigg and Wood (Trigg et al., 1999; Trigg & Wood, 2000) based on a normalization approach suggested by Wolfenberger (Wolfenberger, 1972). The normalization approach advocates that people with disabilities should be able to enjoy patterns and conditions of life as close as possible to those that prevail in the wider community. Trigg defines community integration as the situation in which “the individual is free to make the same choices and enjoy a lifestyle similar to that they enjoyed prior to stroke” (Trigg et al., 1999). In the first phase of the index’s development in-depth interviews with 30 community-dwelling stroke survivors were conducted (Trigg et al., 1999). The questionnaire’s items were then developed based on results of those in-depth interviews. Final item selection was based on the comments and responses of another 100 community-dwelling stroke survivors (Trigg & Wood, 2000). These procedures ensured that all or the items are relevant to the concerns of this population. Although the questionnaire has proven reliable and valid for assessing the level of community integration after a stroke, the questionnaire has yet to be translated into Chinese and culturally adapted for use in Chinese society.

Identifying predictors of integration would help develop more effective measures for promoting community integration after a stroke. A study by Trigg and colleagues (Trigg & Wood, 2003) revealed that people living in elderly homes following a stroke tend to be significantly less well-integrated (as measured in terms of the SIPSO) than their community-dwelling counterparts who have not had a stroke. Liu reports that fear and avoidance measured with the Survey of Activities and Fear of Falling in the Elderly are good independent predictors of a person's level of community integration as measured with the Community Integration Measure ($R^2 = 11.6\%$) (Liu et al., 2015). Obembe reports that age and scores on the Geriatric Depression Scale and the Motor Assessment Scale are significant predictors of community integration after a stroke as measured with the Return to Normal Living Index ($R^2 = 41.0\%$) (Obembe et al., 2013). However, only a few studies have clearly described any relationships between lower limb motor function and the level of community integration in this population. Mayo reports that distance covered in the 6-minute Walk test significantly predicts community integration as measured with the Return to Normal Living Index, but he fails to report the strength of the association and the 6-minute Walk test's predictive power (Mayo et al., 1999).

Stroke rehabilitation programs always aim at improving lower limb motor function, especially muscle strength and walking performance. But little is known about the contribution of those factors to community integration after a stroke. A study evaluating any relationship between lower limb motor function and the level of community integration is warranted.

1.8 Recovery of motor function following stroke

It is well-recognized that neurogenesis is limited in the mature central nervous system in humans (Gallo & Deneen, 2014). After a stroke, spontaneous recovery takes place from several hours up to about 2 months through reperfusion of the ischemic penumbra (Teasell et al., 2005) and resorption of intra-cellular and extra-cellular oedema (Teasell et al., 2005). Later motor recovery is most likely attributable to the neuroplasticity (Angels Font et al., 2010). The possible physiological mechanisms may include unmasking of latent synapses (Chen et al., 2002), enhanced synaptic strength (Farkas & Toldi, 2001; McDonnell et al., 2007; Ridding & Ziemann, 2010), axon and dendrite growth (Brown et al., 2009; Dancause et al., 2005), reorganization of cortical representation in the lesioned hemisphere (Traversa et al., 1997; Ward et al., 2006), recruitment of the contralesional hemisphere (Butefisch et al., 2005; Calautti et al., 2007; Marshall et al., 2000; Rehme et al., 2012; Schaechter & Perdue, 2008), recruitment of ipsilateral descending pathways (Misawa et al., 2008) and motor compensation (Levin et al., 2008; Olney & Richards, 1996).

1.8.1 Spontaneous recovery

After a stroke, blood perfusion of the ischemic penumbra is impaired and it cannot support its normal functions. Its reperfusion results in regaining some the area’s normal functions. Reperfusion can begin several hours post-stroke and continue for several weeks (Teasell et al., 2005).

Shortly after any brain injury, swelling reduces inter-cellular space and impairs oxygen and glucose supply. That can lead to excitotoxic cell death (Choi, 1992; Rosenberg, 1999). Calcium influx resulting from the release of glutamates into the cytoplasm causes an imbalance in osmotic pressure which induces cellular swelling (Choi, 1992). Oedema around the site of a lesion jeopardizes the exchange of ions, metabolites and neurotransmitters, and thus disrupts normal axonal conduction (Sykova, 1997). Oedema gradually dissipates from a week or so up to approximately 2 months post-stroke (Teasell et al., 2005).

1.8.2 Unmasking latent synapses and enhanced synaptic strength

The unmasking of latent synapse refers to the activation of previously inactive synaptic connections (Chen et al., 2002). Enhanced synaptic strength refers to an increase in transmission frequency between two previously-connected neurons (Foster et al., 1996). Both can begin within a short period after an injury. The inflammatory responses following stroke may trigger the release of glial cytokines (Murphy & Corbett, 2009) such as tumour necrosis factor-α (Beattie et al., 2002) which can enhance synaptic efficacy in the area around the injury. Paired associative stimulation has been reported (Stefan et al., 2000) to induce an increase in corticospinal excitability as manifested by an increase of the amplitudes of motor evoked potentials within 30 minutes, at least among healthy adults. It involves brief peripheral sensory stimulation followed by a single pulse of transcranial magnetic stimulation (TMS) applied over the contralateral M1 area with an inter-stimulus interval of 25ms (Classen et al., 2004). Such paired associative stimulation has been used to induce neuroplasticity in the human motor cortex. The observed rapid changes in corticospinal excitability may indicate that synaptogenesis and the sprouting of axons not underlying the plasticity. A pharmacological study (McDonnell et al., 2007) has revealed a single dose of baclofen—a specific γ-aminobutyric acid (GABA) receptor agonist—can suppress the effects of paired associative stimulation in healthy adults. So the cortical GABA-ergic system might regulate rapid changes in neuroplasticity such as the unmasking of pre-existing but normally silent synapses or altered synaptic strength.

1.8.3 Axon and dendrite growth

The current understanding of anatomical changes after brain injury is mainly derived from animal studies (Brown et al., 2009; Dancause et al., 2005). Brown and colleagues induced ischaemic lesion in rats and observed that the rate of turnover of dendritic spines surged afterwards (Brown et al., 2009). The turnover rate in the lesioned zone peaked approximately 1 to 2 weeks after the brain surgery, indicating that the lesion induced a rapid reorganization of the postsynaptic targets of cortical connections.

Dancause observed active axon sprouting several months after an ischemic lesion of the primary motor cortex (M1) in squirrel monkeys (Dancause et al., 2005). The new axonal connections around the lesioned area and between the premotor cortex and the primary somatosensory cortex were accompanied by functional recovery.

1.8.4 Reorganization of cortical representation on the lesioned hemisphere

Neurophysiological and neuroimaging studies have shown that the activated area corresponding to a specific movement can shift to an adjacent or even to a distant area after a motor-related area is lesioned, as in stroke. Using TMS, Traversa et.al. mapped the representation area of the abductor digiti minimi muscle in the lesioned hemispheres of 15 stroke survivors. They found the motor representation area was on average 50% smaller than that of age-matched healthy volunteers. After 8 to 10 weeks of rehabilitation training the representation area was significantly enlarged, and the increases showed a positive correlation with improvements in hand function as measured with the hand motor domain of the Canadian Neurological Scale (Traversa et al., 1997). Using functional magnetic resonance imaging (fMRI), Ward and colleagues (Ward et al., 2006) demonstrated that a moderate M1 lesion caused the cortical areas activated in gripping with a paretic hand to shift to the secondary motor areas, including the premotor area, the supplementary motor area and the cingulate motor area. These results suggest that the secondary motor areas could partially compensate for functional losses in M1.

1.8.5 Recruitment of the contralesional hemisphere

The reorganization of motor representation areas could also involve the contralesional hemisphere after a stroke (Butefisch et al., 2005; Calautti et al., 2007; Marshall et al., 2000; Rehme et al., 2012; Schaechter & Perdue, 2008). There is no consensus about whether this kind of reorganization is maladaptive or compensatory (Stewart et al., 2015). Some studies have suggested that this phenomenon is common after a stroke among those with more severe motor impairments (Calautti et al., 2007). Using fMRI, Clalautti and his colleagues (Calautti et al., 2007) demonstrated that the amplitude of M1 activation in the contralesional hemisphere correlates negatively with motor performance after a stroke as measured by the number of paretic thumb opposition performed. Marshall et.al. have reported (Marshall et al., 2000) activation of the contralesional sensorimotor cortex during paretic thumb opposition early after stroke. The ratio of contralesional to ipsilesional sensorimotor cortex activity decreases 3 to 6 months post-stroke along with motor recovery (Marshall et al., 2000).

On the contrary, Schaechter and Perdue have reported (Schaechter & Perdue, 2008) that activation of the contralesional hemisphere might contribute to the restoration of dexterous movement of a paretic hand. In their study, 10 stroke survivors performed a complex and a simple manual task with their paretic hand in a fMRI scanner. The complex manual task involved flexing the fingers while extending the thumb and extending the fingers while flexing the thumb. The simple task was to make a fist and open it. Their scans showed that the simple manual task led to significantly greater activation of the primary sensorimotor cortex in the contralesional hemisphere only. The complex task led to significant activation of multiple contralesional areas of the cortex, including the ventral premotor cortex, the supplementary motor area, and the occipitoparietal cortex in addition to the primary sensorimotor cortex. Since all of the participants in the study performed the complex manual task satisfactorily, Schaechter and Perdue suggest that recruitment of contralesional cortical networks might contribute to the recovery of hand function after a stroke (Schaechter & Perdue, 2008).

Bütefisch and his colleagues studied 5 people who had recovered satisfactorily after a stroke. They observed bilateral activation of M1 and the premotor cortex during sequential movement of paretic fingers. In contrast, healthy controls showed strictly unilateral activation of M1 and the premotor cortex in the same task (Butefisch et al., 2005). Recruitment of contralesional motor-related areas apparently contributes to motor control of a paretic hand after a stroke.

1.8.6 Recruitment of ipsilateral descending pathways from the contralesional hemisphere

Brösamle and Schwab used anterograde tracing to explore the morphology of corticospinal tract fibres in the spinal cords of rats. Ipsilateral projections of the fibres were found in the ventromedial funiculus, the dorsomedial funiculus and the lateral funiculus at all of the levels investigated (C4, T8, and L4). Uncrossed ipsilateral fibres accounted for approximately 5% of the total number of corticospinal tract fibres in the rats (Brosamle & Schwab, 1997).

Previous neuroanatomical studies with animal models have shown that the uncrossed corticospinal and reticulospinal tracts in mammals can be selectively activated by intra-spinal or intra-medullary stimulation (Baczyk et al., 2014; Jankowska & Stecina, 2007; Stecina & Jankowska, 2007). Stecina and Jankowska (Stecina & Jankowska, 2007) have monitored the activities of the α-motor neurons in cats' lumbar regions to look for postsynaptic potentials resulting from stimulation of the ipsilateral descending pyramidal tract. The results of that study (Stecina & Jankowska, 2007) and a related one (Jankowska & Stecina, 2007) showed that stimulating the ipsilateral descending pyramidal tract evoked postsynaptic potentials in 34 of 47 α-motor neurons tested in the lumbar region. That result supports the idea that the ipsilateral descending pyramidal tract is able to regulate the excitability of spinal α-motor neurons on the same side of the body via postsynaptic potentials.

Some studies have suggested that the ipsilateral descending pyramidal tract could contribute to the motor control of a paretic limb after a unilateral brain lesion (de Bode et al., 2007; Misawa et al., 2008; Muller et al., 1991). Studies of people after a hemispherectomy may support the theory that ipsilateral descending pathways contribute to sensorimotor functioning on the paretic side of the body (de Bode et al., 2007; Muller et al., 1991). Using fMRI, de Bode and colleagues (de Bode et al., 2007) investigated the effects of 30 hours of locomotor training on the motor representation area of the remaining hemisphere in 12 children with cerebral hemispherectomy. They found that the training had increased the volume and intensity of blood oxygen level-dependent signals from the remaining sensorimotor cortex, the supplementary motor area, the motor cingulate cortex and the secondary somatosensory cortex during movement of the paretic ankle. Müller and colleagues (Muller et al., 1991) have reported that a person who received a right hemispherectomy at the age of 18 regained partial motor control of the left upper limb and was able to walk with an almost normal gait. That case study suggests that the contralesional hemisphere can contribute to the motor control of a paretic limb even for adults.

Using TMS, Misawa et.al (Misawa et al., 2008) investigated the relationship between excitability of the ipsilateral corticospinal projections and motor function of the proximal and distal upper limb muscles in 40 stroke survivors. They found that the presence of ipsilateral motor evoked potentials was associated with less severe paresis as measured by the Medical Research Council Scale in the trapezius and deltoid muscles. These results indicate that the ipsilateral corticospinal projections could contribute to the motor control of proximal and trunk muscles as early as 2 weeks after a stroke (Misawa et al., 2008).

1.8.7 Motor compensation

Motor compensation refers to “the appearance of new motor patterns resulting from the adaptation of remaining motor elements.” (Levin et al., 2008) (p. 315). Motor compensation is common after a stroke, especially for those with poor motor recovery (Levin et al., 2008). Physical impairments including spasticity and muscle weakness, sensory deficits and balance deficits hinder functional and purposeful movements after a stroke (Cirstea & Levin, 2000). Using residual motor abilities to compensate for lost functionality is a natural reaction. In motor compensation voluntary movement can be achieved by combining various individual joint movements still under control (Cirstea & Levin, 2000). The acquisition of new motor skills is a process of combining such individual joint movements into a coordinated and controllable movement pattern. Continuous refinement of the movement pattern by reducing unnecessary joint movements eventually comes up with the most efficient pattern, referred to as “optimal synergy” (Berkinblit et al., 1986). The approach can be applied by people with or without a brain lesion, though it is usually less efficient for people with a brain lesion due to the residual motor impairment. Cirstea and Levin (Cirstea & Levin, 2000) examined the pattern used in a forward pointing task, comparing 9 stroke survivors with a healthy control group. The healthy controls all adopted similar movement patterns (initially elbow and shoulder flexion, followed by shoulder horizontal adduction and elbow extension) to accomplish the pointing task. The stroke victims were also able to accomplish the pointing task, but they worked out varied movement patterns, such as trunk lateral flexion or shoulder abduction to compensate for insufficient shoulder flexion.

In some situations, motor compensation can reduce functional limitations imposed by poor motor recovery. This is exemplified by hip hiking and a circumduction gait, where people use excessive side flexion of the trunk and elevation of the hip or excessive abduction of the hip to compensate for insufficient ankle dorsiflexion during the swing phase of gait (Olney & Richards, 1996). Asymmetrical weight bearing is another example of motor compensation. It can increase the postural stability of some people after a stroke (Kamphuis et al., 2012; van Asseldonk et al., 2006). van Asseldonk and his colleagues report that 5 out of 8 people with stroke who scored 50/56 on the Berg Balance Scale relied primarily on the non-paretic leg to maintain dynamic postural control (van Asseldonk et al., 2006). On the other hand, Roerdink reports (Roerdink et al., 2009) that bearing more weight on the non-paretic leg allows people with a severe motor impairment to control their centre of mass more efficiently by using movements of the non-paretic ankle. Although motor compensation reduces functional limitations, prolonged use of compensation can lead to learned non-use and hinder motor recovery (Levin et al., 2008).

1.9 Electrical stimulation and neurological rehabilitation

1.9.1 Functional electrical stimulation in stroke rehabilitation

Both functional electrical stimulation (FES) and transcutaneous electrical stimulation (TENS) are commonly used in stroke rehabilitation. Functional electrical stimulation involves relatively high stimulation intensity and sequential electrical pulses which elicit contractions in targeted muscles. The electrodes are usually positioned on the motor points of the muscle bellies. The intensity is above the motor threshold to produce muscle contraction (Ada & Foongchomcheay, 2002; Lynch & Popovic, 2008). The major uses of FES in stroke rehabilitation are to strengthen weakened muscles and facilitate coordinated, function-oriented muscle contractions (Ada & Foongchomcheay, 2002; Lynch & Popovic, 2008). FES can be applied with single channel using two electrodes that stimulate a single muscle group. For example, Newsam and Baker applied single-channel FES over the paretic quadriceps concurrent with exercise training in 20 stroke survivors, 5 days a week for 3 weeks. Their maximum voluntary isometric knee extension torque on the paretic side improved by 77% on average, while an exercise training only control group showed only a 31% increase (Newsam & Baker, 2004). Motor unit recruitment as measured with the interpolated twitch test improved by 18% in the FES group, but there was no change in the control group.

FES with multiple channels can stimulate multiple muscles in a specific temporal sequence to assist the accomplishment of a functional movement. For example, Kesar and his colleagues stimulated their subjects’ paretic ankle dorsiflexors during the swing phase of walking to prevent drop foot, and then the paretic ankle plantarflexors at the end of the stance phase to facilitate push off. It immediately improved the gait of 13 stroke survivors (Kesar et al., 2009).

1.9.2 Transcutaneous electrical nerve stimulation in stroke rehabilitation

1.9.2.1 An introduction to TENS

Transcutaneous electrical nerve stimulation has been used in pain control for more than 40 years (Melzack & Wall, 1967; Sluka & Walsh, 2003). Animal studies have shown that TENS selectively stimulates the peripheral, large-diameter, non-noxious afferent A beta (Aβ) sensory fibres which can inhibit transmission in nociceptive fibres in the dorsal horn of the spinal cord (Garrison & Foreman, 1994, 1997). TENS can also activate A delta (Aδ) fibres and induce the release of endogenous opioids (Kalra et al., 2001; Sluka et al., 1999).

Three different forms of TENS are commonly used clinically. Conventional TENS combines high-frequency (60 to 100Hz) with low intensity (2 to 3 times of the sensory threshold). It usually induces a general tingling sensation over the stimulated area without inducing muscle contractions (Johnson, 2014). High-frequency stimulation can activate Aβ sensory fibres, which reduces the transmission of nociceptive signals through the spinal cord to higher centres (Garrison & Foreman, 1994, 1997).

An alternative is acupuncture-like TENS. This technique combines low frequency (2 to 4Hz) and high intensity (3 times the sensory threshold or more). Acupuncture-like TENS usually generates pulsating sensations and muscle twitching (Johnson, 2014). It mainly stimulates the Aδ fibres (Robb et al., 2008) and relieves pain by activating the release of endogenous opioids in the spinal cord which reduces the excitability of the noxious sensory pathways.

Burst TENS is designed to stimulate both the Aβ and Aδ fibres at the same time. High-frequency output (> 100Hz) is delivered in bursts, 2 to 4 bursts per second (Sherry et al., 2001). Therefore, the high frequency output (100Hz) can activate the Aβ fibres. At the same time, the high frequency output is interrupted at the rate of about 2 - 4 bursts per second, which could mimic a low-frequency stimulation and activate the Aδ fibres.

1.9.2.2 TENS and motor recovery after a stroke

TENS has been used as an adjunct therapy in stroke rehabilitation since the 1990s (Celnik et al., 2007; Chen et al., 2005b; Cho et al., 2013; Conforto et al., 2002; Conforto et al., 2007; Deshmukh et al., 2013; Hussain & Mohammad, 2013; Jung et al., 2017; Kim et al., 2013; Klaiput & Kitisomprayoonkul, 2009; Koesler et al., 2009; Laddha et al., 2016; Levin & Hui-Chan, 1992; Ng & Hui-Chan, 2007, 2009; Ng et al., 2016b; Park et al., 2014; Sonde et al., 2000; Tyson et al., 2013b; Yan & Hui-Chan, 2009; Yavuzer et al., 2007). Applying it to a paretic lower limb has various beneficial effects. It enhances muscle strength (Jung et al., 2017; Levin & Hui-Chan, 1992; Tyson et al., 2013b; Yan & Hui-Chan, 2009), balance (Cho et al., 2013; Jung et al., 2017; Ng et al., 2016b; Tyson et al., 2013b), walking speed (Hussain & Mohammad, 2013; Ng & Hui-Chan, 2007, 2009; Tyson et al., 2013b) and general functional mobility (Deshmukh et al., 2013; Ng & Hui-Chan, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009). When applied to the upper limbs it also improves motor recovery (Kim et al., 2013), including finger tapping frequency (Koesler et al., 2009), pinch grip strength (Conforto et al., 2002; Klaiput & Kitisomprayoonkul, 2009) and general hand functioning (Celnik et al., 2007; Conforto et al., 2007; Kim et al., 2013). This has been demonstrated in cases of acute (Yan & Hui-Chan, 2009), subacute (Chaitali Madhusudan Kulkarni, 2014; Deshmukh et al., 2013; Hussain & Mohammad, 2013; Klaiput & Kitisomprayoonkul, 2009; Ng et al., 2016b) and chronic (Celnik et al., 2007; Cho et al., 2013; Conforto et al., 2002; Conforto et al., 2007; Jung et al., 2017; Kim et al., 2013; Koesler et al., 2009; Ng & Hui-Chan, 2007, 2009; Park et al., 2014; Tyson et al., 2013b) stroke.

Most of the studies investigating the effects of TENS on lower limb motor recovery have stimulation frequencies of about 100Hz. The high-frequency TENS has been applied alone (Cho et al., 2013; Levin & Hui-Chan, 1992; Ng & Hui-Chan, 2007, 2009; Tyson et al., 2013b) or in combination with exercise (Chaitali Madhusudan Kulkarni, 2014; Deshmukh et al., 2013; Hussain & Mohammad, 2013; Jung et al., 2017; Ng & Hui-Chan, 2007, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009). These high-frequency lower limb studies are summarized in Table 1.1.

Table 1.1: Summary of studies investigating high-frequency TENS in lower limb motor recovery after a stroke.

Study	Study design	Sample size (TENS/ control group)	Post-stroke duration	TENS protocol			Exercise protocol		Outcome measures	Results
				Frequency (Hz)	Stimulation duration	Electrode placement	Type	Duration		
Levin and Hui-Chan 1992 (Levin & Hui-Chan, 1992)	2 groups pretest-posttest	11/6	27.5 months	99	60 min/ session; 5 days/wk for 3 wk	Posterior to the head of fibula	N/A	N/A	1. H reflex	↑ TENS; → control
									2. CSS	↑ TENS; → control
									3. DF and PF strength (maximum voluntary contraction)	PF: No change DF: ↑ TENS; → control
Ng and Hui-Chan 2007 (Ng & Hui-Chan, 2007)	RCT	21/20	5.3 years	100	60 min/ session; 5 days/wk for 4 wk	Acupuncture points on lower limb	Task-related training	60 min/ session; 5 days/wk for 4 wk	1. CSS;	TENS > control at week 2
									2. DF and PF isometric strength	PF: TENS = control DF: TENS > control at week 2
									3. Gait speed	TENS > control
Ng and Hui-Chan 2007b (Ng & Hui-Chan, 2007)	RCT	22/22	5.3 years	100	60 min/ session; 5 days/wk for 4 wk	Acupuncture points on lower limb	N/A	N/A	1. CSS	TENS > control
									2. DF and PF isometric strength	PF: TENS = control DF: TENS > control
									3. Gait speed	TENS = control
Ng and Hui-Chan 2009 (Ng & Hui-Chan, 2009)	RCT	27/25	4.7 years	100	60 min/ session; 5 days/wk for 4 wk	Acupuncture points on lower limb	Task-related training	60 min/ session; 5 days/wk for 4 wk	1. Gait speed;	TENS > control
									2. 6MWT	TENS = control
									3. TUG	TENS > control

Yan and Hui-Chan 2009 (Yan & Hui-Chan, 2009)	RCT	19/19	10 days	100	60 min/ session; 5 days/wk for 3 wk	Acupuncture points on lower limb	PT and OT	2 hr/day; 5 days/wk for 3 wk	1. EMG co-contraction ratio	TENS > control at follow-up (8 weeks)
									2. CSS	TENS = control
									3. DF strength (maximum voluntary contraction)	TENS > control at follow-up (8 weeks)
									4. TUG	TENS = control
Hussain and colleagues 2013 (Hussain & Mohammad, 2013)	RCT	15/15	4.7 months	100	30 min/ session; 5 days/wk; 4 wk	Acupuncture points on lower limb	Bobath inhibitory techniques only	15 min/ session; 5 days/wk for 4 wk	1. MAS	TENS > control
									2. AROM of DF	TENS > control
									3. Brunnstrom stage score	TENS > control
									4. DF strength (manual muscle testing)	TENS > control
									5. Gait speed	TENS > control
Deshmukh and colleagues 2013 (Deshmukh et al., 2013)	RCT	15/15	Sub-acute	100	60 min/ session; 5 days/wk for 5 wk	Acupuncture points on lower limb	Task-related training and conventional PT	60 min/ session; 5 days/wk for 5 wk	1. MAS	TENS > control
									2. TUG	TENS > control
									3. DGI	TENS > control
Cho and colleagues 2013 (Cho et al., 2013)	RCT	25/25	14 months	100	60 min; single section	Belly of gastrocnemius	PT based on Bobath concept	30 min; single section	1. MAS	TENS > control
									2. Postural sway distance	TENS > control
Tyson and colleagues 2013 (Tyson et al., 2013b)	Cross-over	29	Chronic	100	60 min; single section	Whole foot and ankle	N/A	N/A	1. Proprioception detection threshold	PF: ↑ TENS DF: → TENS
									2. DF and PF strength (maximum voluntary contraction)	PF: ↑ TENS DF: → TENS

									3. Forward Reach Test	↑ TENS
									4. Gait speed	↑ TENS
Park and colleagues 2014 (Park et al., 2014)	RCT	15/14	18.6 months	100	30 min/ session; 5 days/wk for 6 wk	Lateral and medial quadriceps and gastrocnemius muscle	Conventional PT	30 min/ session; 5 days/wk for 6 wk	1. MAS	TENS > control
									2. Balance (AP, ML velocity and velocity moment)	TENS > control
									3. Gait speed	TENS = control
									4. TUG	TENS > control
Kumar and Kulkarni 2014 (Chaitali Madhusudan Kulkarni, 2014)	RCT	10/10	> 3 months	100	60 min/ session; 5 days/wk for 4 wk	Acupuncture points on lower limb	Conventional PT	60 min/ session; 5 days/wk for 4 wk	1. MAS	TENS = control
									2. TUG	TENS = control
									3. DGI	TENS > control
Ng and colleagues 2016 (Ng et al., 2016b)	RCT	37/39	6.2 wk	100	60 min/ session; 2 days/wk for 8 wk	Route of common peroneal and sural nerves	Task-related balance training; PT and OT	60 min/ session; 2 days/wk for 8 wk	1. BBS	TENS > control
									2. MRMI	TENS > control at week 4
									3. 6mWT	TENS = control
									4. TUG	TENS > control at week 8
									5. SF36	Physical function subscale: TENS > control at week 8 and follow (3 months) Other subscales: TENS = control
Jung and colleagues 2017 (Jung et al., 2017)	RCT	20/20	6.5 months	100	30 min/ section, five days/wk for 6 wk	Peroneal nerves	Sit to stand training and conventional therapy	15 min of sit to stand training and 1 hour of conventional therapy/session,	1. CSS	TENS > control
									2. Hip ext, knee ext and PF strength	Hip ext: TENS > control

five days/wk for 6 wk	(maximum voluntary contraction)	knee ext: TENS = control PF: TENS = control
	3. Postural sway distance	TENS > control

Notes:

In the results column, outcomes of between-group comparisons are reported. > indicates greater improvement disregarding the direction of the scale. For example, “TENS > control in TUG” indicated that the TENS group demonstrated a greater reduction in average TUG test completion time than the control group.

The Ng and Hui-Chan (2007) and (2009) studies compared 4 groups, so the results of those 2 studies have been split into 2 comparisons. For instance, the TENS + exercise group was compared to the placebo-TENS + exercise group (denoted as Ng and Hui-Chan 2007a and 2009a), the TENS only group was compared to the no treatment control group (denoted as Ng and Hui-Chan 2007b and 2009b).

Another two studies, Levin and Hui-Chan (1992) and Tyson et al. (2013) did not report their between-group comparison results, so only the within-group comparison is reported in the table.

↑ indicates a significant improvement; → indicates no significant change.

10mWT: 10-metre Walk test; 6mWT: 6-minute Walk test; AP: antero-posterior; AROM: active range of motion; BBS: Berg Balance Scale; CSS: Composite Spasticity Scale; DF: dorsiflexor; DGI: Dynamic Gait Index; Ext: extensor; MAS: Modified Ashworth Score; min: minutes; ML: medial-lateral; MRMI: Modified Rivermead Mobility Index; N/A: not applicable; OT: occupational therapy; PF: plantarflexor; PT: physiotherapy; SF36: 36-Item Short Form Health Survey; TENS: transcutaneous electrical nerve stimulation; TUG: Timed Up and Go test; wk: weeks

1.9.2.3 TENS Mechanisms

The mechanism underlying the improved motor function in paretic limbs after TENS treatment is multi-factorial. It involves alleviation of the hyperexcitability of alpha motor neurons (Chen et al., 2005b; Levin & Hui-Chan, 1992), a reduction in intracortical inhibition (Celnik et al., 2007) and enhancement of cortico-muscular connectivity (Lai et al., 2016). In healthy adults, TENS has been shown to facilitate motor cortex reorganisation and to enhance corticospinal excitability (Golaszewski et al., 2004; Khaslavskaia & Sinkjaer, 2005; Knash et al., 2003; Ladda et al., 2014; Wu et al., 2005; Yamaguchi et al., 2012).

1.9.2.3.1 α-motor neuron excitability

High-frequency (Levin & Hui-Chan, 1992) and medium frequency (Chen et al., 2005b) repetitive TENS has been shown to reduce hyperexcitability of the α-motor neurons of paretic ankle plantarflexors (Chen et al., 2005b; Levin & Hui-Chan, 1992). Some of the pioneering work was reported by Levin and Hui-Chan (Levin & Hui-Chan, 1992) who found that the amplitude of the stretch reflex in the ankle plantarflexors elicited by a sudden stretch of spastic calf muscles decreased significantly after 3 weeks of repetitive high-frequency TENS (99Hz) but not after placebo-TENS (Levin & Hui-Chan, 1992). Chen reports (Chen et al., 2005b) that the latency of the H-reflex in paretic ankle plantarflexors was significantly longer after 4 weeks of repetitive medium frequency TENS (20Hz) but not in controls who received no treatment. Those authors suggest that the hyperexcitability of α-motor neurons was reduced as a result of greater pre-synaptic inhibition. Since the electrodes were placed differently in the two studies, the neural pathways that regulated the pre-synaptic inhibition were likely to have been different.

In the study of Levin and Hui-Chan, TENS was applied over the areas innervated by the common peroneal nerve. The pre-synaptic inhibition could have been augmented by activating the Ia inhibitory interneurons, as Perez has suggested (Perez et al., 2003). The Ia inhibitory interneurons receive a signal from the Ia afferents and synapse with the α-motor neurons of the antagonist muscle (Fetz et al., 1979; Pierrot-Deseilligny & Burke, 2005; Tanaka, 1976). Activation of the Ia inhibitory interneurons subsequently inhibits any hyperexcited α-motor neurons of the antagonist muscle by means of an inhibitory postsynaptic potential (Fetz et al., 1979; Pierrot-Deseilligny & Burke, 2005). In Chen and colleagues study, TENS was applied over the muscle–tendon junction of the Achilles tendon. There, pre-synaptic inhibition could be augmented by activating the Ib inhibitory pathway (Chen et al., 2005b; Pierrot-Deseilligny & Burke, 2005). The Ib afferents originate from the Golgi tendon organs situated at the tendon-muscle junction, and project to the Ib inhibitory interneurons. Activating the Golgi tendon organs by mean of TENS could excite the Ib afferents and subsequently activate the Ib inhibitory interneurons. The α-motor neurons of the ankle plantarflexors would then be inhibited by the inhibitory postsynaptic potential elicited by the Ib inhibitory interneurons (Pierrot-Deseilligny & Burke, 2005).

1.9.2.3.2 Intra-cortical inhibition

Cutaneous electrical stimulation of the upper limb has been shown to reduce intra-cortical inhibition in the ipsilesional motor cortex after a stroke (Celnik et al., 2007). The inhibition was assessed in that study using paired-pulse TMS. A sub-threshold conditioning stimulus was applied to the motor cortex followed by an above-threshold test stimulus with an inter-stimulus interval of 1 to 6ms (Celnik et al., 2007).

Intra-cortical inhibition is a normal physiological phenomenon in healthy adults and in stroke survivors as well (Celnik et al., 2007; Hummel et al., 2009). Hummel et.al. (Hummel et al., 2009) found that inhibition of the ipsilesional motor cortex at rest was comparable between 14 well-recovered stroke survivors and healthy controls. The inhibition diminished when the healthy adults were asked to perform a contralateral finger abduction task, but it remained unchanged among the stroke victims (Hummel et al., 2009).

Reduced intracortical inhibition may indicate a release of inhibitory mechanisms. It has been suggested that neuroplasticity is probably suppressed by such mechanisms under normal conditions, and their release might facilitate the reorganisation of motor representation areas (Jacobs & Donoghue, 1991) and motor learning (Smyth et al., 2010). This theory is supported by the fact that rats' representation areas can be reorganised rapidly when inhibition is blocked pharmacologically (Jacobs & Donoghue, 1991). In that study, inhibition was blocked by a GABA antagonist (bicuculline methobromide) in an area of the motor cortex representing a forelimb. That area could be activated by stimulating the adjacent area after the administration of bicuculline methobromide, but not before.

In addition, study with TMS showed that the intracortical inhibition reduced after motor skill training of contralateral hand in 20 healthy adults (Smyth et al., 2010). In that study, the participants practised a motor task in which they needed to control a cursor to keep it within a moving box for approximately 15 minutes. Cortical inhibition was found to be reduced immediately after the training. The observed reductions in cortical inhibition were correlated with the within-session improvements in motor performance.

A Celnik et.al (Celnik et al., 2007) have specifically investigated the effects of cutaneous electrical stimulation on the level of corticospinal excitability in stroke survivors. In their crossover design, stroke survivors received 2 hours of sub-threshold cutaneous electrical stimulation of both the ulnar and radial nerves or received placebo stimulation over the paretic hand, one hour prior to hand function training. The stimulation produced no change in the resting motor threshold recorded from the first dorsal interosseus muscle, but it reduced short interval intracortical inhibition as measured by TMS (in 9 subjects). Completion times in the Jebsen-Taylor Hand Function test were reduced by 10% after the stimulation. This suggests that cutaneous electrical stimulation induces disinhibition in the cortex, thus perhaps facilitating the re-organisation of motor representation areas and enhancing the effectiveness of motor training. This study has provided important evidence that cutaneous electrical stimulation modulates neural plasticity after a stroke, and that is probably related to the immediate improvement in motor performance. However, the conclusions drawn from this study may not be robust due to the small sample size and the crossover design of that study.

1.9.2.3.3 TENS and brain-muscle communication

A recent study conducted by Lai and his colleagues has reported that TENS applied to a paretic hand enhanced the coherence of electroencephalogram and electromyogram patterns (Lai et al., 2016). EEG-EMG coherence refers to the synchronization between the EEG and the EMG signals, which indicates the level of synchronization between cortical and muscular activity during movement (von Carlowitz-Ghori et al., 2014). Fang and colleagues (Fang et al., 2009) have reported that such coherence is weakened after a stroke. In the study, EEG-EMG coherence was measured during a forward reaching task which involved shoulder flexion and elbow extension. The EMG signals were measured from the anterior deltoid and biceps brachii muscles, and the results showed that the coherence between the EEG signals from the lesioned hemisphere and the EMG signals from the two upper limb muscles was significantly less in the 20 to 40Hz frequency band, but comparable at other frequencies. In view of the fact that after a stroke people often demonstrate significantly worse reaching performance (greater lateral deviation and less accuracy), Fang's results suggest that the low EEG-EMG coherence at higher frequencies band (> 30Hz) might indeed reflect poor communication between the brain and the muscles.

Lai and colleagues (Lai et al., 2016) have investigated the effects of TENS on EEG-EMG coherence in 6 people with chronic stroke. In that study, a single session of TENS (100Hz) was delivered to the median nerve with an on/off cycle of 20 seconds/20 seconds for 40 minutes. EEG-EMG coherence was measured during a 20-second steady thumb flexion task. The targeted force output of the contraction was set as 50% of the maximum voluntary contraction, as guided by real-time EMG visual feedback. The results showed that the EEG-EMG coherence in the gamma band (> 30Hz) increased significantly after the TENS, and the subjects' motor performance was significantly improved as indicated by less deviation in maintaining the force output. TENS applied over a peripheral nerve apparently enhanced communication between M1 and the muscles innervated by the stimulated nerve.

1.9.2.3.4 Cortical perfusion and corticospinal excitability

Studies using fMRI and TMS have demonstrated that cutaneous electrical stimulation can enhance cortical perfusion (Golaszewski et al., 2004; Ladda et al., 2014; Wu et al., 2005) and corticospinal excitability (Khaslavskaia & Sinkjaer, 2005; Knash et al., 2003; Yamaguchi et al., 2012) in healthy adults. Using fMRI, Golaszewski and his colleagues investigated the effects of whole-hand, sub-motor threshold cutaneous electrical stimulation (50Hz, pulse width 0.25ms) on cortical perfusion in 10 healthy adults. The blood oxygenation signals from the bilateral M1 area, the primary sensory cortex (S1), the medial frontal gyrus and the ipsilateral supplementary motor area increased during a finger tapping task after 30 minutes of stimulation (Golaszewski et al., 2004). Similarly, Wu has reported that two hours of sub-motor threshold cutaneous electrical stimulation over the median nerve at the wrist (1Hz, pulse width 1ms) increased oxygenation of the contralateral M1 area, S1, and the premotor cortex during a thumb flexion and extension task.

Knash et.al. (Knash et al., 2003) used TMS to examine the effects of 50Hz stimulation on corticospinal excitability in five healthy adults. The stimulation was applied over the common peroneal nerve at the anterior aspect of the ankle for 30 minutes. The maximum motor evoked potentials recorded from the tibialis anterior muscle increased significantly after 30 minutes of such stimulation. Khaslavskaia and Sinkjaer studied the effects of combining cutaneous electrical stimulation with voluntary exercise in terms of corticospinal excitability with a group of 12 healthy adults. Their results showed that stimulating the common peroneal nerve during active ankle dorsiflexion for 30 minutes increased the motor evoked potentials recorded from the tibialis anterior by 66%. Stimulation alone or exercise alone increased the motor evoked potentials only about half as much (Khaslavskaia & Sinkjaer, 2005).

Yamaguchi and colleagues (Yamaguchi et al., 2012) stimulated the right median nerve at the elbow in 15 healthy adults and recorded motor evoked potentials from the flexor carpi radialis and extensor carpi radialis muscles at rest, and during isometric finger flexion to 5% or 20% of the maximum voluntary flexion. They found that combining median nerve stimulation with voluntary fingers and wrist flexion increased the motor evoked potentials recorded from the flexor carpi radialis muscle but decreased the potentials recorded from the extensor carpi radialis muscle.

Taken together, these results suggest that TENS applied to an upper or lower limb can alter the cortical perfusion and corticospinal excitability in healthy adults. More work should be done to investigate if these effects can be demonstrated in people after a stroke.

1.9.3 Transcutaneous electrical nerve stimulation for other neurological conditions

In a cross-over study, Cuypers and colleagues (Cuypers et al., 2013) have reported that daily application of TENS (100Hz) to the thenar eminence for 3 weeks reduced the representation area of the abductor pollicis brevis in the cortex (as mapped by TMS) among 6 people with multiple sclerosis. Sham stimulation produced no such change (Cuypers et al., 2013). However, the motor performance of the hand was not assessed in that study, so it remains unclear whether the reduction in the representation area and volume is associated with a change in motor performance. Shaygannejad et.al. compared the effect TENS (at 100Hz) with that of baclofen in reducing lower limb spasticity among 52 people with multiple sclerosis. They found that 4 weeks of TENS was superior to baclofen in reducing the level of spasticity as measured using the Ashworth Scale (Shaygannejad et al., 2013).

Chung and Cheng reported that a single 60-minute session of TENS (at 100Hz) applied over the common peroneal nerve reduced the Composite Spasticity Score of 18 people with lower limb spasticity as a result of spinal cord injury (Chung & Cheng, 2010).

Verbeek and colleagues have summarized the results on the effectiveness of TENS in rehabilitating walking capacity after a stroke. They found a positive effect (Hedges' $g = 0.56$) for TENS after pooling the data from five randomized and controlled trials that involved 195 subjects (Veerbeek et al., 2014). Another recent systematic review has concluded that TENS is effective in alleviating spasticity resulting from central nervous system lesions, including from stroke, spinal cord injury, multiple sclerosis, cerebral palsy and Strümpell-Lorrain disease (Mills & Dossa, 2016). The data on the effect of TENS on balance have not, however, been systematically reviewed, and according to Verbeek the effect of TENS on spasticity and muscle strength has not been well established (Veerbeek et al., 2014). Moreover, the influence of stimulation frequency and duration have not been evaluated in a rigorous meta-analysis (Veerbeek et al., 2014).

1.10 Task-oriented training and neurological rehabilitation

Task-oriented training (TOT) normally involves repeatedly performing task-specific and goal-driven activities (Rensink et al., 2009). Specificity of training principles requires that the force generated by the muscles in TOT is directly related to functional movements (Ng & Hui-Chan, 2007). The structure and content of TOT are of course quite diverse. Programs based on circuit training (Wevers et al., 2009), treadmill training with or without body-weight support (Duncan et al., 2011a; Hesse et al., 1995), seated reaching training and constraint-induced movement therapy (Park et al., 2015; Wolf et al., 2006) have all been carefully investigated.

1.10.1 Task-oriented training after a stroke

Task-oriented circuit training involves several functional exercises organised into a circuit. The number of repetitions and the difficulty of the exercises are progressed according to the participant's capacity. A meta-analysis of the data from 6 randomized and controlled trials involving 307 subjects reported significant effects on walking distance (standardized effect size 0.43), walking speed (standardized effect size 0.35) and Timed Up and Go test completion time (standardized effect size 0.26) compared with placebo treatment or usual care (Wevers et al., 2009).

Treadmill training during which the body's weight is supported enables people with stroke to repeatedly perform complete gait cycles. Such training has been reported to improve the walking speed even of people with severe hemiplegia (Hesse et al., 1995). However, a recent large-scale randomized control trial with 408 subjects revealed such training is not superior to a home exercise program for improving walking capacity, balance, functional status or quality of life (Duncan et al., 2011a).

Treadmill training without body weight support is also commonly used in stroke rehabilitation for people who are basically ambulatory. It too provides intensive stepping practice (Polese et al., 2013). A meta-analysis of the data from 9 studies which involved 977 stroke survivors showed that treadmill training significantly improving walking speed (by 0.14ms^{-1} on average) and walking distance (mean difference 40m) compared with no treatment or non-walking intervention (Polese et al., 2013).

In terms of TOT for the upper limbs, there too circuit training is often used. However, the effects of upper limb circuit exercise are somewhat inconsistent. Higgins and colleagues report that 18 sessions of task-oriented upper limb circuit exercise training did not, in general, improve scores on the box and block test, the Nine-hole Peg Test or the grip strength of 91 stroke survivors any better than walking exercise (Higgins et al., 2006). Blennerhassett and Dite, however, have reported that 20 sessions of task-oriented upper limb circuit training improved the scores of 30 stroke survivors on the Jebsen Taylor Hand Function test and on the arm function items of the Motor Assessment Scale more than just the usual care (Blennerhassett & Dite, 2004).

Clinical studies have reported that seated reaching training can improve sitting balance and upper limb functions after a stroke. Dean and Shepherd have reported that 20 sessions of seated reaching training led to greater improvement in reaching distance and faster completion of reaching tasks than similar training which was not task–oriented (Dean & Shepherd, 1997). Using the same training protocol, they further demonstrated that seated reaching training improved reaching distance and completion times in a reaching test more effectively than practising manual manipulation tasks (Dean et al., 2007).

For the upper limbs, constraint-induced movement therapy involves physically restraining the non-paretic limb during intense TOT of the paretic limb (Hakkennes & Keating, 2005; Wolf et al., 2006). The efficacy of such therapy has been proven in a multi-centre study which involved 222 people (Wolf et al., 2006). A 2-week program of constraint-induced movement training led to significantly greater improvement than that resulting from the usual care in terms of Wolf Motor Function test results and the frequency of using the paretic hand.

1.10.2 Task-oriented training mechanisms

Animal studies have demonstrated that task-specific training can modify the neural architecture of a damaged brain by inducing synaptogenesis (Jones et al., 1999), dendritic branching (Greenough et al., 1985) and neuron sprouting (Stroemer et al., 1995). Using fMRI, Luft et.al. have reported that six months of treadmill exercise induced greater activation than passive stretching in the posterior cerebellar lobe and the midbrain among 32 stroke survivors (Luft et al., 2008). Greater walking speed was also positively correlated with increased activation in the contralesional posterior cerebellum in their treadmill exercise group but not in the control group. These results indicate that treadmill exercise can activate a subcortical network that contributes to regaining walking capacity.

Two weeks of upper-limb TOT has also been shown to lead to reorganization of the motor representation areas in people with an M1 lesion. After the training, blood oxygenation in the perilesional areas is lower during a finger tapping task (Dong et al., 2007). That result may be a result of TOT strengthening synaptic efficacy among the spared neurons in the injured region.

1.11 Potential neural substrates in enhancing motor recovery in people with stroke

1.11.1 Intracortical S1-M1 connections

Neuroanatomical and neurophysiological studies have provided evidence that applying TENS to the extremities leads to neuroplastic changes in the central nervous system (Golaszewski et al., 2004; Kaelin-Lang et al., 2002; Kaneko et al., 1994a, 1994b; Wu et al., 2005). Intracortical connections between the S1 and the M1 areas provide an anatomical substrate through which TENS can affect neuronal activity in the motor cortex (Kaneko et al., 1994a, 1994b). Tracer studies with cats have revealed that Brodmann area 3a (which receives input from muscle spindles) of S1 has dense connections between M1 and the supplementary motor area (Kaneko et al., 1994a, 1994b). And continuous microstimulation of the cortex with biocytin staining in the S1 area also shows that continuous stimulation of S1 produces long-term potentiation changes in M1 (Kaneko et al., 1994a, 1994b).

Cutaneous electrical stimulation modulates excitability (Hamdy et al., 1998; Kaelin-Lang et al., 2002; Ridding et al., 2000) and perfusion in multiple brain regions (Golaszewski et al., 2004; Wu et al., 2005). Using TMS, Kaelin-Lang et.al. showed that two hours of TENS (at 1Hz) applied to the ulnar nerve at the level of the wrist increased the amplitude of motor evoked potentials recorded from the abductor digiti minimi muscle (Kaelin-Lang et al., 2002). Ridding has similarly reported (Ridding et al., 2000) that 2 hours of ulnar nerve stimulation increased the amplitude of motor evoked potentials recorded from the abductor digiti minimi and also the first dorsal interosseous muscle. Hamdy investigated the effects of 10 minutes of cutaneous electrical stimulation of the pharynx with 8 healthy adults and found that the stimulation significantly increased the amplitude of motor evoked potentials recorded from the pharynx. The effect lasted for 30 minutes. Similar findings published by Golaszewski and colleagues (Golaszewski et al., 2004) and by Wu and colleagues (Wu et al., 2005) have already been discussed (section *1.9.2.3.4).*

These results suggested that sensory stimulation applied on the paretic leg could enhance the activation and excitability of the lesioned motor cortex and thus augment the efficacy of rehabilitation training.

1.11.2 Transcallosal connections between motor-related areas

There are more than 200 million axonal connections in the human corpus callosum (Wahl et al., 2007). fMRI and diffusion tensor imaging confirm that the motor areas of the two hemispheres are mainly connected via the posterior body of the corpus callosum (Wahl et al., 2007). Intact and mature corpus callosum is critical for effective inter-hemisphere interaction. People fail to perform synchronized movement bilaterally after a callosotomy (Kennerley et al., 2002). Kennerley and colleagues assessed the ability of three people to draw a circle with each hand and the ability to flex and extend both index fingers after a callosotomy. They found that the people were unable to perform synchronized bimanual tasks and that their hands oscillated at non-identical frequencies. Their findings demonstrate that interhemisphere information exchange across the corpus callosum plays a critical role in coordinating bilateral synchronized movement (Kennerley et al., 2002).

Knyazeva and his colleagues assessed the intra-hemisphere and inter-hemisphere coherence of the EEGs of 5 children with corpus callosum defects (at least 75% of the corpus callosum was absent) and compared them with the coherence in 30 normal children (aged 10–14 years) (Knyazeva et al., 1997). EEG coherence indicates the synchronous activation of neurons in different parts of the brain. Brain regions with highly synchronous activity demonstrate similar patterns of oscillation, resulting in high EEG coherence between those regions. The Knyazeva study demonstrated that children with a defective corpus callosum had less EEG coherence between the two hemispheres than normal children during both unilateral and bilateral tapping tasks. Moreover, the children with a defective corpus callosum demonstrated less stable performance in the tapping tasks, manifested by a greater standard deviation of the inter-tap durations (Knyazeva et al., 1997).

Interhemisphere inhibition can be assessed using paired-pulse TMS. A conditioned stimulus is delivered to one M1 area followed 10ms later by a test stimulus delivered to the contralateral M1. The conditioned stimulus has been shown to inhibit the size of the motor evoked potentials produced by the test stimulus. A greater suppression in motor evoked potentials induced by the conditioned stimulus indicates stronger interhemisphere inhibition (Daskalakis et al., 2002). In healthy adults, unilateral movement increases the interhemisphere inhibition imposed on the resting M1 from the activated M1 (Vercauteren et al., 2008). Vercauteren has reported that during weak isometric wrist flexor contractions, there is significantly greater interhemisphere inhibition imposed on the resting M1 from the active M1 than in a resting condition In healthy adults, the increased inhibition suppresses unwanted mirror movement during intentional unilateral movements (Vercauteren et al., 2008). Inhibition imposed on the active M1 from the resting M1 diminishes before the onset of unilateral movement (Murase et al., 2004), which suggests that the release of interhemisphere inhibition augments the accuracy of motor control of the moving hand in healthy adults.

After a stroke, disinhibition of the contralesional M1 area has been reported along with augmented interhemisphere inhibition imposed on the ipsilesional M1 (Murase et al., 2004). Shimizu found that interhemisphere inhibition imposed on the contralesional M1 from the ipsilesional M1 was significantly less than normal in 12 stroke survivors at rest (Shimizu et al., 2002). The decreased inhibition resulted in greater cortical excitability in the contralesional M1 (Shimizu et al., 2002). Murase and colleagues (Murase et al., 2004) have shown that the effect persists in people who have experienced a subcortical stroke. In contrast, the interhemisphere inhibition turns into facilitation at the onset of movement in healthy controls (Murase et al., 2004).

Some studies have shown that in healthy adults making bilateral movements, the non-dominant or ipsilesional hemisphere was actually aided by the dominant or contralesional hemisphere via the interhemispheric networks (Grefkes et al., 2008; Walsh et al., 2008), and that has also been observed after a stroke (Grefkes et al., 2010; Renner et al., 2005). Using fMRI and structural equation modelling, Walsh and colleagues (Walsh et al., 2008) showed that the activation pattern over multiple brain regions and estimated the network of activation during bilateral hand movement in 15 healthy, right-handed adults. The participants received an fMRI scan while performing a finger opposition task. The structural equation modelling showed a strong, direct and positive effect imposed on the right (non-dominant) supplementary motor area from the left (dominant) supplementary motor area during bilateral movement. The observed activation of the motor-related regions in the non-dominant hemisphere might be partially driven by the dominant hemisphere via the transcallosal connections between supplementary motor areas of the two hemispheres.

Using fMRI and dynamic causal modelling, Grefkes etal. investigated the neural coupling of motor-related areas, including M1, the premotor cortex and the supplementary motor area during bilateral movement. Dynamic causal modelling is a technique for estimating the connectivity between two brain regions. It estimates the direction and amplitude of influence between them in response to stimulation (Friston et al., 2003). In Grefkes et.al. study (Grefkes et al., 2008) participants performed synchronized and visually-paced opening and closing of their fists in the scanner. The results showed that bilateral hand movement activates the bilateral M1 areas, the premotor cortexes, and the supplementary motor areas. The dynamic causal modelling revealed that bilateral movement enhanced facilitatory neural coupling between the M1 and supplementary motor areas in both hemispheres (Grefkes et al., 2008). In other words, during bilateral hand movements, activation of the M1 and supplementary motor areas can facilitate the recruitment of homologous areas on the opposite hemisphere. The same group later demonstrated using similar methods that bilateral hand movement results in facilitatory neural coupling between the M1 and supplementary motor areas of the two hemispheres (Grefkes et al., 2010). That study involved 11 persons with subacute, subcortical stroke. Based on that evidence, they hypothesized that bilateral movement training would enhance motor recovery after a stroke.

Renner and his colleagues used TMS to show that maximum voluntary contraction of a non-paretic hand combined with less forceful contraction of a paretic hand increases the excitability of the ipsilesional motor representation area of the hand on the cortex more effectively than contracting the paretic hand alone after a subcortical stroke.

Overall, the results of clinical studies consistently demonstrate that bilateral motor training is superior to unilateral training in improving the motor recovery after a stroke. This applies to motor control (Lin et al., 2010; Pandian et al., 2015), muscle strength (Pandian et al., 2015), the kinematics of upper limb movement (Lin et al., 2010; McCombe Waller et al., 2008; Summers et al., 2007), hand dexterity (Pandian et al., 2015), and upper-limb function generally (Luft et al., 2004a; Sethy et al., 2016; Summers et al., 2007). For example, Luft has reported (Luft et al., 2004a) that after a stroke, activation of the contralesional cerebrum and the ipsilesional cerebellum increased after 6 weeks of bilateral arm training but not after dose-matched training based on neuro-development principles. After excluding those without changes in cortical activation from the analyses, bilateral arm training demonstrated greater improvement in hand function than the control treatment. More recently, Sasaki has reported (Sasaki et al., 2017) that high-frequency transcranial magnetic stimulation of the cortical motor areas representing the legs led to significantly greater improvement in Brunnstrom recovery stage scores than sham stimulation after a stroke.

These results suggested that bilateral intervention reduce the inter-hemispheric inhibition impose on the lesioned motor cortex and motor-related areas and enhance the activation of these areas. Thus, facilitate the motor recovery after a stroke. This effect can be achieved by bilateral movement and probably by bilateral TMS. While if this effect can be achieved by bilateral sensory stimulation, in term of TENS, is remained unknown.

1.11.3 Contralesional neural pathways

As has been discussed, mammals' ipsilateral descending pathways can modulate the activity of α-motor neurons. Anatomical studies with primates have shown that the ipsilateral reticulospinal pathway (Zaaimi et al., 2012) and the ipsilateral corticospinal tract (Morecraft et al., 2016) might contribute to the motor control of a paretic extremity after a brain lesion. Zaaimi reports (Zaaimi et al., 2012) that macaque monkeys partially recovered upper extremity function after an extensive, unilateral medullary corticospinal tract lesion. Intra-cellular recordings 6 months after the operation showed that stimulation of the ipsilateral medial longitudinal fasciculus elicited robust excitatory postsynaptic potentials recorded from α-motor neurons. Moreover, the total output from the ipsilateral longitudinal fasciculus to α-motor neurons was 2.5-fold greater than in the control animals. These results indicated that the ipsilateral reticulospinal tract, which descends via the medial longitudinal fasciculus, has strengthened its projections to the α-motor neurons to compensate for some of the damage after a corticospinal tract lesion. Morecraft and colleagues (Morecraft et al., 2016) examined the plasticity of monkeys' cortical spinal tract projections in response to a lesioning of motor areas on the frontal lobe. They report that the recovery of hand (paw) motor function was accompanied by an increased number of ipsilateral corticospinal projections at levels C5 to T1.

In people with an extensive lesion on the ipsilesional hemisphere, recovery of motor functions might partly rely on the contralesional hemisphere (Mohapatra et al., 2016; Sankarasubramanian et al., 2017; Yeo & Jang, 2012). Yeo and Jang (Yeo & Jang, 2012) used fMRI and diffusion tensor imaging to study the patterns of cortical activation and the integrity of the descending corticospinal tract in a person severe left side paralysis following a stroke. They found that moving either the paretic or the non-paretic hand activated the contralesional but not the ipsilesional primary sensorimotor cortex. Diffusion tensor imaging showed that the corticospinal tract originating from the contralesional hemisphere remained intact and descended along the known pathway. In contrast, the corticospinal tract originating from the lesioned hemisphere was disrupted, showing Wallerian degeneration. Based on these observations, Yeo and Jang hypothesized that motor control of the hemiplegic hand relied on a contralesional motor pathway (Yeo & Jang, 2012).

Using TMS, Mohapatra and his colleagues evaluated the functional relevance of contralesional motor areas for paretic hand control among 12 people with severe upper limb paralysis. In that study the subjects performed a reaching task with their paretic upper limb paced by a visual cue. Pulsed focal TMS above the threshold was delivered to either the contralesional M1 or the premotor cortex to disrupt neural firing just after the appearance of the visual cue. The TMS pulses led to significantly longer movement times, lower peak velocity and less-smooth reaching (Mohapatra et al., 2016). These results again suggest that contralesional motor-related areas contribute to controlling the movement of a paretic hand movement in people with severe upper limb paralysis. On the other hand, Sankarasubramanian and his colleagues have reported that 10 minutes of high-frequency TMS applied over the contralesional premotor cortex shortens the duration of a reaching task for people with severe motor impairment (a Fugl-Meyer upper extremity subscale score < 26) but not for those with mild impairment (Sankarasubramanian et al., 2017). This suggests that increase excitability of the contralesional motor areas such as the premotor cortex could improve motor control of a paretic upper limb for people with severe motor impairment.

Apart from noninvasive brain stimulation, Pandian and colleagues (Pandian et al., 2015) evaluated the effect on motor recovery of simply training the non-paretic limb. Their 35 stroke survivors were given training involving their less-affected side or dosage matched conventional training that targeted on the paretic side only. Subjects in the experimental group received progressive resistance training and bilateral training with symmetrical and asymmetric movements of both the upper and lower limbs. After 24 sessions of training, those in the experimental group demonstrated greater average improvement in their Brunnstrom recovery stage scores and Fugl-Meyer Assessment scores than the controls (Pandian et al., 2015). In another study, Dragert and Zehr administered six weeks of high-intensity ankle dorsiflexion resistance training of the non-paretic ankles in 19 people with chronic stroke. It generated a 34% increase in that non-paretic ankle's dorsiflexion strength, but also a 31% increase in the dorsiflexor strength of the paretic ankle (Dragert & Zehr, 2013). Those two studies both involved stroke survivors (Dragert & Zehr, 2013; Pandian et al., 2015), but similar findings have been reported with healthy adults (Ladda et al., 2014) Cutaneous electrical stimulation applied over the non-dominant hand combined with motor training has been shown to improve bilateral hand motor function (Ladda et al., 2014). In that study, the participants received 20 minutes of stimulation of their left hands prior to 1 hour of hand exercises for 2 weeks. The training led to a 34% improvement in Arm Ability Training completion times for the left hand, but the right hand also improved by 24% (Ladda et al., 2014).

Taken together, these studies support the idea that contralesional neural pathways can be recruited to help control ipsilesional limbs. Furthermore, those pathways can be activated by non-invasive stimulation and by exercising the non-paretic limb. A previous study showed that cutaneous electrical stimulation applied over left hand combined with motor training augment the function of the right hand in healthy adults (Ladda et al., 2014). It is possible that cutaneous electrical stimulation applied over the non-paretic limbs could also facilitate the motor recovery of paretic limbs in stroke survivors.

Chapter 2

Overview of Dissertation

2.1 The research gaps and agenda

The review of the literature presented in chapter 1 has identified several gaps in our knowledge for further research. First, the existing body of knowledge on the effects of TENS on lower limb motor recovery after a stroke could be improved by conducting a systematic review that includes the most recent studies, and that explores the influence of the stimulation variables. Second, a growing body of clinical research has used the SIPSO questionnaire as an outcome measure for community integration in people with stroke (Baseman et al., 2010; Fogg-Rogers et al., 2016; Harrington et al., 2010; Kersten et al., 2002; Kilbride et al., 2013; Lord et al., 2008; McKenna et al., 2015; Okoye et al., 2016; Plummer et al., 2014; Teale et al., 2013), but that questionnaire has yet to be translated into Chinese, and neither has its validity been evaluated in a Chinese community. Third, only a few studies have explored the association between motor function after a stroke and the level of community integration. Identifying predictors for community integration should help researchers and clinicians develop more effective interventions.

Clearly, existing treatments for improving lower limb function and walking ability after a stroke could be improved. This literature review highlights S1-M1 connections in the cortex (Golaszewski et al., 2004; Wu et al., 2005), transcallosal networks (Grefkes et al., 2010; Murase et al., 2004; Walsh et al., 2008), and contralesional neural pathways (Ladda et al., 2014; Pandian et al., 2015) as neural substrates which might potentially be harnessed to enhance the motor recovery of those who have suffered a stroke.

Bilateral synchronized movement induces disinhibition of the ipsilesional M1 (Grefkes et al., 2008; Renner et al., 2005; Walsh et al., 2008), and bilateral training improves motor functions in a paretic limb after a stroke (Lin et al., 2010; Luft et al., 2004a; McCombe Waller et al., 2008; Pandian et al., 2015; Sethy et al., 2016; Summers et al., 2007). We hypothesised that TENS, when applied bilaterally, could mimic the effect of bilateral movement in reducing interhemisphere inhibition imposed on the ipsilesional motor-related areas from the motor areas of the contralesional hemisphere. Moreover, unilateral cutaneous electrical stimulation combined with motor training has been shown to improve the functioning of both hands, at least in healthy adults (Ladda et al., 2014). Exercise training of the non-paretic ankle similarly improved the strength of the paretic ankle after a stroke (Pandian et al., 2015). TENS applied to a non-paretic limb might activate the contralesional motor-related areas and activate the ipsilateral descending pyramidal tract to enhance motor output.

No published study has yet investigated the effectiveness of bilateral TENS for promoting motor recovery after a stroke. A recent animal study showed that applying electrical sensory stimulation to both the paretic and non-paretic limbs of rats led to better recovery from cortical lesions (Bandla et al., 2016). After occlusion of the middle cerebral artery, nine rats were divided into 3 groups and received either unilateral, bilateral or no stimulation (frequency: 3Hz; pulse width: 0.2ms) on the forepaws for 2 hours. A substantial reduction in infarct volume and an increase in somatosensory evoked potentials were observed in the bilateral stimulation group. Those results suggest that Bi-TENS might facilitate recovery following an ischemic stroke (Bandla et al., 2016).

The hypothesis tested in this study was that Bi-TENS might have a stronger effect than unilateral TENS (Uni-TENS) in terms of modulating plastic changes in a lesioned brain. It might thus augment the response of the neuromuscular system to conventional training after a stroke. Clinical studies comparing the effectiveness of Bi-TENS and Uni-TENS as adjunct therapy are therefore warranted. And the influence of Bi-TENS and Uni-TENS on the central nervous system should also be further explored.

2.2 An outline of this dissertation

This dissertation presented studies that investigated the efficacy of Bi-TENS for reducing lower limb impairment, augmenting mobility, as well as enhancing the level of community integration of stroke survivors. It will be described in chapter 2 to chapter 7 of this thesis.

2.2.1 Chapter 3: Transcutaneous electrical nerve stimulation improves walking capacity and reduces spasticity after a stroke: A systematic review and meta-analysis of prior research

Eleven randomized and controlled trials which investigated the effectiveness of TENS in reducing lower-limb spasticity and improving lower-limb motor function after a stroke were systematically reviewed and their data were combined in a meta-analysis.

2.2.2 Chapter 4: General methodology

This chapter introduces the general methodology of the experiments carried out in our own laboratory, including the participant selection criteria and the outcome measures. Three preliminary studies which aimed to validate the Berg Balance Scale and the Five Times Sit to Stand test as assessment tools are also described. Translation and cultural adaption of the Subjective Index of Physical and Social Outcome into Chinese is also described.

2.2.3 Chapter 5: Lower limb motor function and community integration

This chapter explores the association between lower limb motor function and level of community integration on stroke survivors in Hong Kong using the validated Chinese version of the Subjective Index of Physical and Social Outcome.

2.2.4 Chapter 6: Bilateral transcutaneous electrical nerve stimulation improves lower limb impairment after a stroke

This chapter describes a randomized and controlled trial conducted to compare the effects of Bi-TENS +TOT with that of Uni-TENS + TOT. The study design, the intervention protocols and the statistical methods used are described in detail. This chapter focus on investigating the effects of the two protocols on motor impairments. The effects Bi-TENS +TOT and Uni-TENS + TOT on paretic lower limb muscle strength, lower limb coordination and balance performance are reported and discussed.

2.2.5 Chapter 7: Bilateral transcutaneous electrical nerve stimulation improves lower limb motor function and community integration after a stroke

This chapter focus on evaluating the effects of the two protocols on motor functions and level of community integration. This chapter compares the effects of Bi-TENS +TOT with those of Uni-TENS + TOT in terms of dynamic standing balance, sit-to-stand performance, walking ability and community integration after a stroke with the same sample of chapter 6. Predictors which can identify those will or those will not respond to Bi-TENS + TOT are also proposed.

2.2.6 Chapter 8: Transcutaneous nerve stimulation and cortical activation

This chapter evaluates a pilot trial on the effects of Bi-TENS and Uni-TENS on cortical perfusion, EMG amplitudes, muscle strength, and the ability to maintain a steady force output based on tests of healthy older adults using functional near-infrared spectroscopy.

2.2.7 Chapter 9: Summary and Conclusions

This chapter summarises the findings of this thesis and presents the conclusions of each chapter as well as the suggestions for future study.

Chapter 3

Transcutaneous electrical nerve stimulation (TENS) reduces spasticity and improves walking capacity in people with stroke – a systematic review and meta-analysis

This chapter has been published by the author of this thesis.

Kwong PW, Ng GY, Chung RC, Ng SS. Transcutaneous electrical nerve stimulation improves walking capacity and reduces spasticity in stroke survivors: a systematic review and meta-analysis. Clinical Rehabilitation. 2017 Dec 1:269215517745349. doi: 10.1177/0269215517745349. [Epub ahead of print] (Appendix 3.1)

3.1 Abstract

Previous systematic review and meta-analyses have reported a positive effect in favour of TENS after for treating limb spasticity in people with central nervous system lesions and improving walking capacity in people with stroke. However, the effect of TENS on muscle strength and balance performance were not clearly described in the previous meta-analysies involving people with stroke. Moreover, the influence of stimulation parameters, including frequency and duration, was not evaluated in the previous meta-analysies.

To evaluate (1) the effectiveness of TENS at improving lower extremity motor recovery in people with stroke, and (2) the optimal stimulation parameters for TENS through systematic review and meta-analysis of RCT.

A systematic search was conducted for studies published up to March 2017 using eight electronic databases (CINAHL, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, PEDro, PubMed and Web of Science). RCT that evaluated the effectiveness of the application of TENS in improving lower extremity motor recovery in people with stroke were assessed for inclusion. Outcomes of interest included plantarflexor spasticity, muscle strength, walking capacity, and balance.

Eleven studies met the inclusion criteria. The meta-analysis showed that TENS improved walking capacity, as measured by either gait speed or the Timed Up and Go (TUG) test, (Hedges'g = 0.392; 95%CI = 0.178 to 0.606) compared to the placebo or no-treatment control groups. TENS also reduced paretic plantarflexor spasticity, as measured using the Modified Ashworth Scale and Composite Spasticity Scale (Hedges'g = -0.884; 95%CI = -1.140 to -0.625). The effect of TENS on walking capacity in studies involving 60 min per sessions was significant (Hedges'g = 0.468; 95%CI = 0.201 to 0.734) but not in study with shorter sessions (20 or 30 min) (Hedges'g= 0.254; 95%CI = -0.106 to 0.614).

The results support the use of repetitive TENS as an adjunct therapy for improving walking capacity and reducing spasticity in people with stroke.

3.2 Introduction

Previous studies have demonstrated that the application of TENS or somatosensory electrical stimulation to the paretic lower extremities of people with stroke can reduce plantarflexor spasticity (Chen et al., 2005b; Cho et al., 2013; Karakoyun et al., 2015; Levin & Hui-Chan, 1992; Martins et al., 2012; Sonde et al., 2000; Yan & Hui-Chan, 2009), increase muscle strength (Hussain & Mohammad, 2013; Levin & Hui-Chan, 1992; Tyson et al., 2013b; Yan & Hui-Chan, 2009) and improve motor function (Cho et al., 2013; Karakoyun et al., 2015; Ng & Hui-Chan, 2007, 2009; Sonde et al., 2000; Tyson et al., 2013b). The mechanisms behind motor recovery following the use of TENS include enhanced presynaptic inhibition of the hyperactive stretch reflexes in spastic muscles (Chen et al., 2005b; Hiraoka, 2002; Levin & Hui-Chan, 1992) and decreased co-contraction of the spastic antagonist muscles(Yan & Hui-Chan, 2009).

A previous meta-analysis conducted by Veerbeek and colleagues (Veerbeek et al., 2014) found a positive effect (Hedges' g=0.56, 95%CI=0.27–0.84) in favour of TENS after pooling five randomised controlled trials that involved 195 people with stroke (Veerbeek et al., 2014). However, it should be noted that 3 of the included studies reported results from the same research projects. The effect size estimates could have been overestimated. A recent systematic review (Mills & Dossa, 2016) concluded that TENS is effective for treating limb spasticity in people with central nervous system lesions, including stroke, spinal cord lesions, multiple sclerosis, cerebral palsy and Strümpell-Lorrain disease.

Nevertheless, the effects of TENS on muscle strength were not clearly described in the previous meta-analysis and the effect of TENS on balance has not been systematically reviewed (Mills & Dossa, 2016; Veerbeek et al., 2014). Moreover, the influence of stimulation parameters, including frequency and duration, was not evaluated. Several randomised controlled trials on the effect of TENS on motor recovery including lower limb spasticity, muscle strength, balance and walking capacity in people with stroke have been published in the last few years (Jung et al., 2017; Kumar & Kulkarni, 2014; Ng et al., 2016b; Park et al., 2014). The existing body of knowledge on the effects of TENS on lower-extremity motor recovery in people with stroke could be improved by conducting a systematic review that includes the most recent studies and that explores the influence of the stimulation parameters.

Therefore, the objective of this review was to evaluate the effects of TENS and its parameters on lower-extremity motor recovery in people with stroke, including its effects on spasticity, muscle strength, balance and walking capacity by systematically reviewing the available randomised controlled trials.

3.3 Methods

3.3.1 Identification and selection of studies

The study protocol was prospectively registered with the PROSPERO database of systematic reviews (registration number: CRD42016039754). A systematic search was conducted in seven electronic databases, including CINAHL, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, the Physiotherapy Evidence Database (PEDro), and Web of Science. Articles written in English were selected for further assessment. The general search strategy combined the disease group search string (e.g. stroke), Intervention search string (eg.TENS), and Outcome variables search string (eg.muscle strength). The detailed searching strategy was presented in Appendix 3.1. Studies were included in the review if they: 1) used an RCT design, 2) involved people with stroke, 3) used repetitive TENS/ electrical somatosensory stimulation, 4) applied the stimulation to lower extremity and 5) included at least one outcome measure on lower extremity motor function. Studies were excluded if they: 1) did not include a placebo or no-treatment control group, 2) investigated the effect of electro-acupuncture, 3) did not report the central tendency and/or variability of the outcome of interest, and 4) reported that the stimulation intensity was above the motor threshold.

There were no restrictions regarding the earliest publication date, and the latest publication date was set at October 2017. The reference lists of the included studies were also reviewed (backward tracking), and literature which citing the included studies were tracked (forward tracking) to look for additional studies. Two investigators (PWK and

TL) independently screened the retrieved records and reviewed the full-text articles of the relevant studies. Disagreements regarding eligibility were resolved by discussion with a third-party reviewer (SSN).

3.3.2 Assessment of study quality

The PEDro scale (Moseley et al., 2002) was used to evaluate the methodological quality of the included studies. Where possible, the PEDro score of each study was identified from the PEDro database, in cases where there was no PEDro score in the database, two reviewers (PWK and TL) independently rated the study using the scale. Disagreements regarding the PEDro scores were resolved by discussion with a third-party reviewer (SSN).

3.3.3 Data extraction

A standardized data extraction form was used to extract the data from the included studies. The extracted information included the study design, sample size, dropout rate, characteristics of participants (age, gender and post-stroke duration), TENS protocol (frequency, duration of each session and placement of electrodes), intervention protocol (type of rehabilitation exercise, length and frequency of intervention and follow-up period), outcomes (type of outcome measures and means and standard deviations (SD) of the outcomes) and occurrences of adverse events.

3.3.4 Data synthesis and analysis

The primary outcome measures were measures of the participants' walking capacity. The meta-analysis of walking capacity involved pooling the gait speed and Timed Up & Go test (TUG) results. Where a study reported both measures, the TUG results were used because this test provides a more comprehensive measure of the walking capacity of people with stroke than gait speed (Ng & Hui-Chan, 2005). For one study (Chen et al., 2005b), the standard deviations (SDs) of gait speed was estimated from the mean 10-meter walk test completion time and its SDs using the delta method (Feiveson, 2005). The secondary outcome measures included the spasticity, muscle strength and balance.

The statistical analyses were carried out using the Comprehensive Meta-Analysis Software (Version 2, Biostat, Englewood NJ). Meta-analyses were conducted whenever three or more studies used the same outcome measure. The effect size estimate was calculated using the means and SDs of the pre- and post-intervention measurements. Hedges' g was selected to estimate the overall effect of TENS on spasticity and walking capacity as it is less biased than other measures when sample sizes are small (Hedges & Olkin, 2014). To provide clinically relevant value, separate meta-analyses of walking capacity (gait speed, TUG completion times) and spasticity (Modified Ashworth Scale (MAS) score and Composite Spasticity Scale (CSS) score) were conducted with the mean differences as effect size estimate.

3.3.5 Measuring heterogeneity and publication bias

I^2 statistic was used to quantify the statistical heterogeneity. We intended to use a random effects model for each meta-analysis if the result of I^2 statistic was significant ($p < 0.05$) or if the I^2 value greater than 50%, which represented a substantial heterogeneity (Cochrane Collaboration, 2008). A fixed effects model would be used if I^2 statistic was non-significant.

A funnel plot and Egger's regression test were used to assess the degree of publication bias. In the funnel plot, the estimated Hedges' g of each study was plotted against its standard error (Egger et al., 1997). Egger's regression test evaluates whether the intercept of the regression line of the precision (inverse of the standard error) of each study against the weighted effect size deviates significantly from 0. A statistically significant Egger's regression test indicates that the funnel plot is skewed (Egger et al., 1997).

3.3.6 Sensitivity analysis

The influence of the methodological quality of the studies on the effect size estimate associated with walking capacity was evaluated using a sensitivity analysis, which entailed repeating the meta-analysis without the studies that were rated as having fair or poor PEDro scores (< 6) (Foley et al., 2003). A significant discrepancy between the effect size estimates from the two meta-analyses would reflect a strong influence of studies with fair to poor PEDro scores.

3.3.7 Subgroup analyses and meta-regression

Subgroup analyses were conducted to evaluate whether the effectiveness of TENS depends on the chronicity of stroke (i.e., chronic versus acute/subacute) or the duration of stimulation per session (i.e., 60 min versus < 60 min). In addition, a fixed effects meta-regression analysis (in which the studies were weighted by the inverse of the within-study variance (Thompson & Higgins, 2002)) was conducted to evaluate the influence of the cumulative duration of stimulation on the overall heterogeneity. The cumulative duration of stimulation was calculated by multiplying the duration of stimulation per session by the total number of sessions.

All of the statistical tests were two-tailed, and $p < 0.05$ was considered to represent statistical significance, except in Egger's regression test, for which a statistical significance threshold of $P< 0.1$ was used (Egger et al., 1997).

3.4 Results

3.4.1 Identification and selection of studies

The search identified 1053 records after duplicates were removed. The abstracts of these records were reviewed. Twenty-five studies were considered to be relevant, and so the full-text of those articles were reviewed (Figure 3.1). The list of excluded studies and the reasons for exclusion were provided in Appendix 3.2.

Finally, eleven RCTs (Chen et al., 2005b; Deshmukh et al., 2013; Hussain & Mohammad, 2013; Jung et al., 2017; Kumar & Kulkarni, 2014; Ng & Hui-Chan, 2007, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009; Yavuzer et al., 2007) were eligible for inclusion according to the inclusion and exclusion criteria. These studies were published between 2005 and 2017. Two studies (Ng & Hui-Chan, 2009) allocated the participants to four groups (TENS + exercise, placebo TENS + exercise, TENS only and no-treatment control) and one study (Ng & Hui-Chan, 2007; Yan & Hui-Chan, 2009) allocated the participants to three groups (TENS + exercise, placebo TENS + exercise and exercise only). In these three studies, only the data on the TENS + exercise and placebo TENS + exercise groups were extracted.

The eleven studies randomized 439 people with stroke into TENS and control groups, and 29 participants dropped out. Of the remaining 410 participants, 206 were allocated to the TENS groups, and 204 were in the control groups. The extracted numerical data of outcome measures which had been meta-analyses was provided in Appendix 3.3.

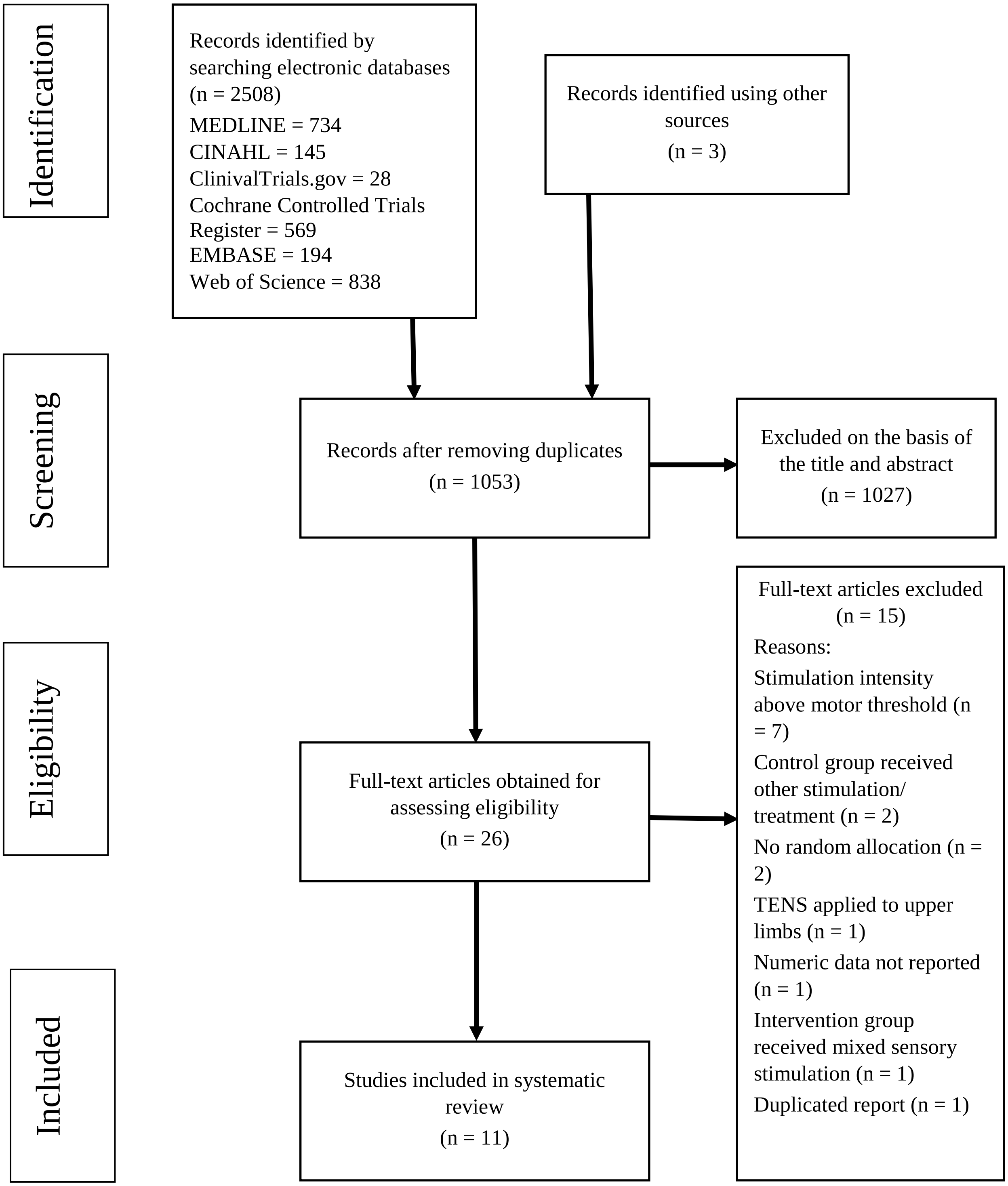


Figure 3.1. Flow diagram showing the selection of studies.

3.4.2 Quality of studies

The PEDro score of seven studies (Chen et al., 2005b; Ng & Hui-Chan, 2007, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009; Yavuzer et al., 2007) were rated by the PEDro database. However, the item of participant blinding was rated as fulfilled for two of the studies (Chen et al., 2005b; Park et al., 2014). For this item, participants were considered blinded if they were unable to distinguish between the intervention applied to experimental and control groups. Since the stimulation intensity was above sensory threshold in both studies (Chen et al., 2005b; Park et al., 2014), participants in the experimental group should be able to distinguish the differences between the interventions in the two groups. Thus, this item should be rated as not fulfilled for the two studies (Chen et al., 2005b; Park et al., 2014). The methodological quality of seven studies (Chen et al., 2005b; Deshmukh et al., 2013; Jung et al., 2017; Ng & Hui-Chan, 2007, 2009; Ng et al., 2016b; Yavuzer et al., 2007) was considered to be good (PEDro score of 6 to 8), and that of the other four studies (Hussain & Mohammad, 2013; Kumar & Kulkarni, 2014; Park et al., 2014; Yan & Hui-Chan, 2009) was considered to be fair (PEDro score of 4 to 5) (Table 3.1).

3.4.3 Characteristics of included studies

The characteristics of the included studies are summarized in Table 3.2. Five studies recruited people with chronic stroke (> 6 months post-stroke) (Chen et al., 2005b; Jung et al., 2017; Ng & Hui-Chan, 2007, 2009; Park et al., 2014), five recruited people with subacute stroke (Deshmukh et al., 2013; Hussain & Mohammad, 2013; Kumar & Kulkarni, 2014; Ng et al., 2016b; Yavuzer et al., 2007) (1 to 6 months post-stroke) and one recruited people with acute stroke (Yan & Hui-Chan, 2009) (< 1 month post-stroke).

Regarding the TENS protocols, nine studies (Deshmukh et al., 2013; Hussain & Mohammad, 2013; Jung et al., 2017; Kumar & Kulkarni, 2014; Ng & Hui-Chan, 2007, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009) used high-frequency stimulation of 100 Hz. Chen and colleagues (Chen et al., 2005b) used a 20 Hz stimulation, and Yavuzer and colleagues (Yavuzer et al., 2007) used a 35 Hz stimulation. Six studies (Deshmukh et al., 2013; Hussain & Mohammad, 2013; Kumar & Kulkarni, 2014; Ng & Hui-Chan, 2007, 2009; Yan & Hui-Chan, 2009) applied TENS to four acupuncture points (ST36, LV3, GB34, and UB60) on the participants' paretic lower limbs. In the four remaining studies, the electrodes were placed at the distal end of the Achilles tendon (Chen et al., 2005b), the belly of tibialis anterior muscle (Yavuzer et al., 2007), the quadriceps and gastrocnemius muscle (Park et al., 2014), along the peroneal nerve (Jung et al., 2017) or along the course of the common peroneal and sural nerves (Ng et al., 2016b).

The duration of simulation per session varied among studies. Six applied TENS for 60 min per session (Deshmukh et al., 2013; Ng & Hui-Chan, 2007, 2009; Ng et al., 2016b; Yan & Hui-Chan, 2009), four used a 30 min duration (Hussain & Mohammad, 2013; Jung et al., 2017; Kumar & Kulkarni, 2014; Park et al., 2014; Yavuzer et al., 2007) and one used a 20 min duration (Chen et al., 2005b).

All of the studies combined TENS with rehabilitation exercises except one (Chen et al., 2005b). Two used home-based task-related training (Ng & Hui-Chan, 2007, 2009), which involved functional training such as sit-to-stand tasks and moving past obstacles. One used task-related balance training (Ng et al., 2016b), which included standing on a balance board, kicking with alternate legs and heel raising.

Deshmukh (Deshmukh et al., 2013) combined task-related training with conventional physiotherapy training, which was focused on promoting posture control. In Kumar and Kulkarni' study(Kumar & Kulkarni, 2014), the participants received passive stretching, resistive training, reaching exercises and gait re-education. Park and colleagues' study (Park et al., 2014) involved the supervised range of motion exercises, mat exercises and gait re-education. Hussain and colleagues (Hussain & Mohammad, 2013) used the Bobath inhibitory technique, which aims to inhibit abnormal reflex patterns. Jung and colleagues (Jung et al., 2017) offered sit to stand training in conjunction with conventional therapy. The participants of the two remaining studies (Yan & Hui-Chan, 2009; Yavuzer et al., 2007) received physiotherapy and occupational therapy, but the type and focus of the training were not reported. Four studies arranged follow-up assessments to evaluate the long-term effect of TENS. The follow-up periods were 4 (Ng & Hui-Chan, 2009), 5 (Ng & Hui-Chan, 2007; Yan & Hui-Chan, 2009) and

12 weeks (Ng et al., 2016b) post-intervention. None of the studies reported any adverse events.

Table 3.1 PEDro scores of included studies

Study	PEDro score	1.eligibility criteria specified	2.Random allocation	3.Concealed allocation	4. Group similar at baseline	5.Participants blinding	6. Therapists blinding	7.Assessors blinding	8. < 15% dropouts	9.Intention-to treat analysis	10. Between-group difference reported	11. Point estimate and variability reported
Chen and colleagues 2005	6	N	Y	N	Y	N++	N	Y	Y	N	Y	Y
Ng and Hui-Chan 2007	6	Y	Y	N	Y	N	N	Y	Y	N	Y	Y
Yavuzer and colleagues 2007	7	Y	Y	Y	Y	N	N	Y	Y	N	N	Y
Ng and Hui-Chan 2009	8	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Yan and Hui-Chan 2009	5	N	Y	N	Y	N	N	Y	N	N	Y	Y
Hussain and colleagues 2013+	5	Y	Y	N	N	N	N	Y	Y	N	Y	Y
Deshmukh and colleagues 2013 +	6	Y	Y	Y	N	N	N	N	Y	Y	Y	Y
Park and colleagues 2014	5	Y	Y	N	Y	N++	N	N	Y	N	Y	Y
Kumar and Kulkarni 2014 +	5	Y	Y	N	Y	N	N	N	Y	Y	Y	Y
Ng and colleagues 2016	7	N	Y	N	Y	N	N	Y	Y	Y	Y	Y
Jung and colleagues 2017 +	7	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y

The results associated with criterion 1 (specification of eligibility criteria) were not counted in the PEDro scores.

+: PEDro scores rated by the study authors rather than being identified from the PEDro database.

++: Rating of the item was adjusted.

Table 3.2 Characteristics of the included studies

Study	Sample size (TENS/ control group)	Post-stroke duration	TENS protocol			Exercise protocol		Outcome measures	Follow-up assessment	Number of dropouts
			Frequency (Hz)	Stimulation duration	Electrode placement	Type	Duration			
Chen and colleagues 2005[2]	12/12	12–35 months	20	20 min/ session; 6 days/wk for 4 wk	Junction of gastrocnemius muscle and Achilles tendon	N/A	N/A	1. Gait speed (10 mW); 2. H-reflex (latency and H_{max}/M_{max} ratio)	No	0
Ng and Hui-Chan 2007[11]	21/20	5.3 years	100	60 min/ session; 5 days/wk for 4 wk	Acupuncture points	Task-related training	60 min/ session; 5 days/wk for 4 wk	1. Gait speed (Gaitrite); 2. CSS; 3. Peak DF and PF strength	4 wk	3
Yavuzer and colleagues 2007[28]	15/15	3.5 months	35	30 min/ session; 5 days/wk for 4 wk	Belly of tibialis anterior muscle	PT and OT	2–5 hr/ day; 5 days/wk for 4 wk	1. Gait speed and gait kinematics (VICON system); 2. Brunnstrom stages score	No	0
Ng and Hui-Chan 2009[10]	27/25	4.7 years	100	60 min/ session; 5 days/wk for 4 wk	Acupuncture points	Task-related training	60 min/ session; 5 days/wk for 4 wk	1. TUG; 2. Gait speed (Gaitrite); 3. 6mWT	4 wk	3
Yan and Hui-Chan 2009[7]	19/19	10 days	100	60 min/ session; 5 days/wk for 3 wk	Acupuncture points	PT and OT	2 hr/day; 5 days/wk for 3 wk	1. TUG; 2. CSS; 3. DF strength (maximum voluntary contraction); 4. EMG cocontraction ratio	5 wk	4

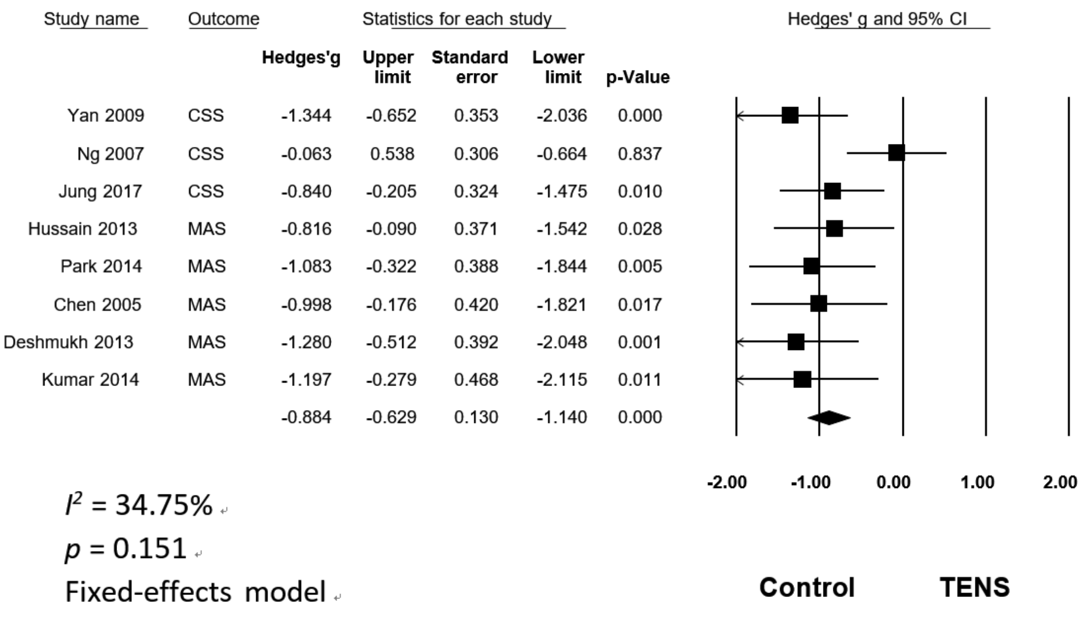
Hussain and colleagues 2013[9]+	15/15	4.7 months	100	30 min/ session; 5 days/wk; 4 wk	Acupuncture points	Bobath inhibitory techniques only	15 min/ session; 5 days/wk for 4 wk	1. Gait speed (10mWT); 2. MAS; 3. DF strength (manual muscle testing); 4. AROM of DF; 5. Brunnstrom stage score	No	5
Deshmukh and colleagues 2013[29] +	15/15	Sub-acute	100	60 min/ session; 5 days/wk for 5 wk	Acupuncture points	Task-related training and conventional PT	60 min/ session; 5 days/wk for 5 wk	1. TUG; 2. MAS; 3. DGI	No	0
Park and colleagues 2014[17]	15/14	18.6 months	100	30 min/ session; 5 days/wk for 6 wk	Lateral and medial quadriceps and gastrocnemius muscle	Conventional PT	30 min/ session; 5 days/wk for 6 wk	1. TUG; 2. MAS; 3. Balance (AP, ML velocity and velocity moment)	No	4
Kumar and Kulkarni 2014[18] +	10/10	> 3 months	100	60 min/ session; 5 days/wk for 4 wk	Acupuncture points	Conventional PT	60 min/ session; 5 days/wk for 4 wk	1. TUG; 2. DGI; 3. MAS	No	2
Ng and colleagues 2016[30]	37/39	6.2 wk	100	60 min/ session; 2 days/wk for 8 wk	Route of common peroneal and sural nerves	Task-related balance training; PT and OT	60 min/ session; 2 days/wk for 8 wk	1. TUG; 2. 6mWT; 3. MRMI; 4. BBS; 5. SF36	12 wk	7

Jung and colleagues 2017[16]	20/20	6.5 months	100	30 min/ section, five days/wk for 6 wk	Peroneal nerves	Sit to stand training and conventional therapy	15 min of sit to stand training and 1 hour of conventional therapy/session, five days/wk for 6 wk	1. CSS; 2. hip Ext, knee Ext and PF strength (handheld dynamometer); 3; Postural sway distance (eyes open and closed	No	1

Remarks:
10mWT: 10-m walk test; 6mWT: 6-minute walk test; AP: antero-posterior; AROM: active range of motion; BBS: Berg Balance Scale; CSS: Composite Spasticity Scale; DF: dorsiflexor; DGI: Dynamic Gait Index; Ext: extensor; MAS: Modified Ashworth Score; min: minute; ML: medial-lateral; MRMI: Modified Rivermead Mobility Index; N/A: not applicable; OT: occupational therapy; PF: plantarflexor; PT: physiotherapy; SF36: 36-Item Short Form Health Survey; TENS: transcutaneous electrical nerve stimulation; TUG: Timed Up and Go test; wk: week

3.4.4 Spasticity

Eight studies (Chen et al., 2005b; Deshmukh et al., 2013; Hussain & Mohammad, 2013; Jung et al., 2017; Kumar & Kulkarni, 2014; Ng & Hui-Chan, 2007; Park et al., 2014; Yan & Hui-Chan, 2009) used clinical scales to rate the plantarflexor spasticity of the participants' paretic ankles, three of them used Composite Spasticity Scale (Jung et al., 2017; Ng & Hui-Chan, 2007; Yan & Hui-Chan, 2009) and five of them used the Modified Ashworth Scale (Chen et al., 2005b; Deshmukh et al., 2013; Hussain & Mohammad, 2013; Kumar & Kulkarni, 2014; Park et al., 2014) . These studies (involving 252 participants) were pooled in a meta-analysis. The effect of TENS on plantarflexor spasticity was significant (Hedges' g = -0.884, 95%CI = -1.140 to -0.629, $p< 0.001$) and homogeneous ($I^2 = 34.75\%$, $p = 0.151$) (Figure 3.2). However, separated meta-analysis pooing data from the three studies (Jung et al., 2017; Ng & Hui-Chan, 2007; Yan & Hui-Chan, 2009) (involving 119 participants) showed that there is no evidence that TENS had an effect on CSS score (difference in means = -1.26, 95%CI = -2.73 to 0.21, $p = 0.093$; $I^2 = 74.71$ %, $p = 0.019$) (Figure 3.3A). Five studies (Chen et al., 2005b; Deshmukh et al., 2013; Hussain & Mohammad, 2013; Kumar & Kulkarni, 2014; Park et al., 2014) (involving 133 participants) were pooled in a meta-analysis of MAS score. The effect of TENS on MAS score was significant (difference in means = -0.59, 95%CI = -0.77 to -0.41, $p < 0.001$) and homogeneous ($I^2 = 0.00\%$, $p = 0.624$; Figure 3.3B).



Study name	Outcome	Hedges's g	Upper limit	Standard error	Lower limit	p-Value
Yan 2009	CSS	-1.344	-0.652	0.353	-2.036	0.000
Ng 2007	CSS	-0.063	0.538	0.306	-0.664	0.837
Jung 2017	CSS	-0.840	-0.205	0.324	-1.475	0.010
Hussain 2013	MAS	-0.816	-0.090	0.371	-1.542	0.028
Park 2014	MAS	-1.083	-0.322	0.388	-1.844	0.005
Chen 2005	MAS	-0.998	-0.176	0.420	-1.821	0.017
Deshmukh 2013	MAS	-1.280	-0.512	0.392	-2.048	0.001
Kumar 2014	MAS	-1.197	-0.279	0.468	-2.115	0.011
		-0.884	-0.629	0.130	-1.140	0.000

$I^2 = 34.75\%$

$p = 0.151$

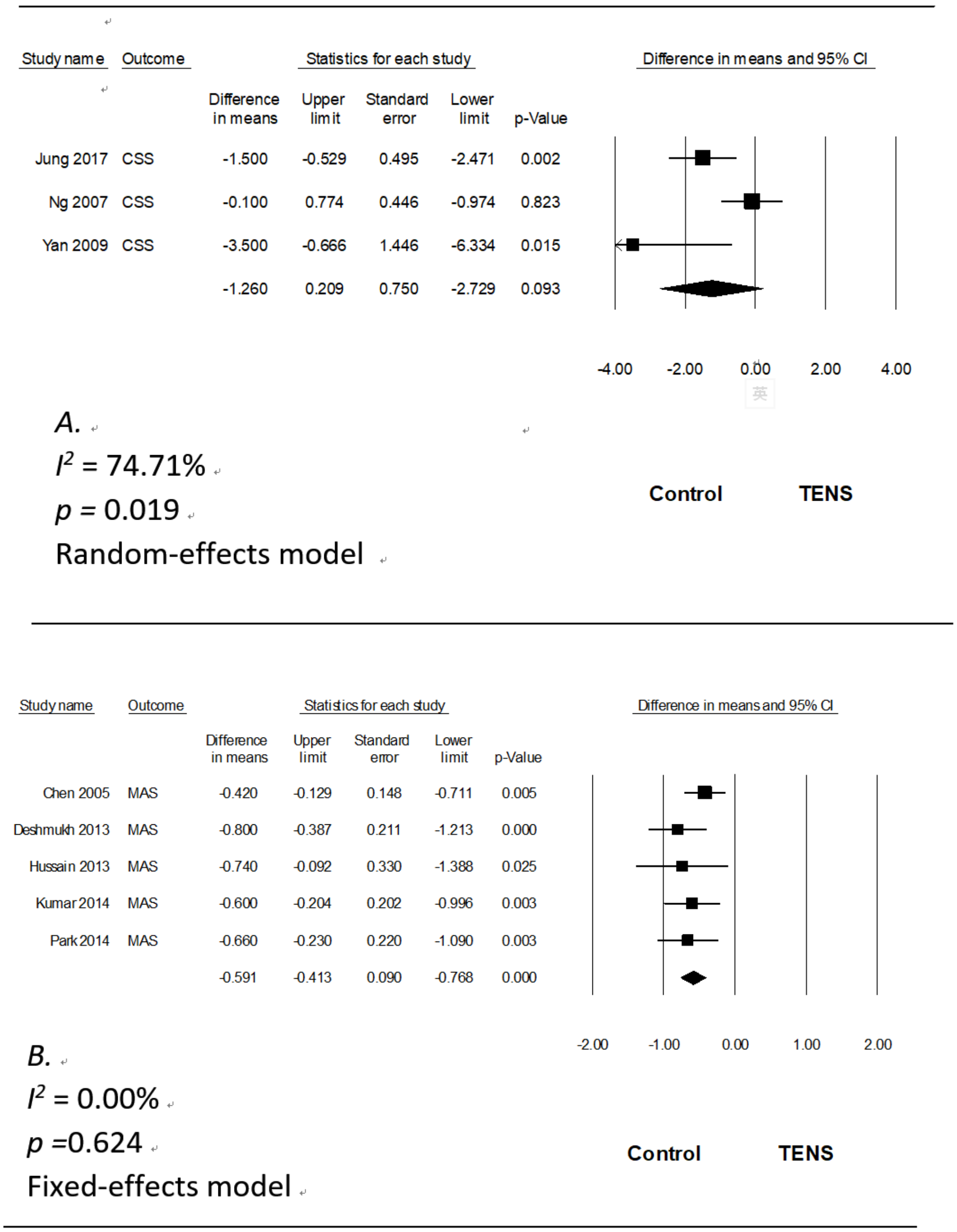
Fixed-effects model

Figure 3.2. Hedges'g (95% CI) of the effect of TENS compared to placebo or no treatment on measures of spasticity by pooling data from 8 studies (n = 252).

Remarks:

CI = confidence interval; CSS = Composite Spasticity Scale; MAS = Modified Ashworth Scale; TENS = transcutaneous electrical nerve stimulation.

The sizes of the squares indicate the relative weight of each study.



Study name	Outcome	Difference in means	Upper limit	Standard error	Lower limit	p-Value
Jung 2017	CSS	-1.500	-0.529	0.495	-2.471	0.002
Ng 2007	CSS	-0.100	0.774	0.446	-0.974	0.823
Yan 2009	CSS	-3.500	-0.666	1.446	-6.334	0.015
		-1.260	0.209	0.750	-2.729	0.093

A.

$I^2 = 74.71\%$

$p = 0.019$

Random-effects model

Study name	Outcome	Difference in means	Upper limit	Standard error	Lower limit	p-Value
Chen 2005	MAS	-0.420	-0.129	0.148	-0.711	0.005
Deshmukh 2013	MAS	-0.800	-0.387	0.211	-1.213	0.000
Hussain 2013	MAS	-0.740	-0.092	0.330	-1.388	0.025
Kumar 2014	MAS	-0.600	-0.204	0.202	-0.996	0.003
Park 2014	MAS	-0.660	-0.230	0.220	-1.090	0.003
		-0.591	-0.413	0.090	-0.768	0.000

B.

$I^2 = 0.00\%$

$p = 0.624$

Fixed-effects model

Figure 3.3. Difference in means (95% CI) of the effect of TENS compared to placebo or no treatment on measures of (A) CSS score by pooling data from 3 studies (n = 119), and (B) MAS score by pooling data from 5 studies (n = 133).
Remarks:
CI = confidence interval; CSS = Composite Spasticity Scale; MAS = Modified Ashworth Scale; TENS = Transcutaneous electrical nerve stimulation.
The sizes of the squares indicate the relative weight of each study.

Chen and colleagues (Chen et al., 2005b) quantified the degree of paretic ankle plantarflexor spasticity using electrophysiological measurements, i.e., the tibial F_{max}/M_{max} ratio, H-reflex latency and H-reflex recovery curve. There was a reduction in the F_{max}/M_{max} ratio, an increase in the H-reflex latency and a downward shift of the H-reflex recovery curve in the TENS group but not in the control group. These results indicated that TENS reduced the degree of plantarflexor spasticity.

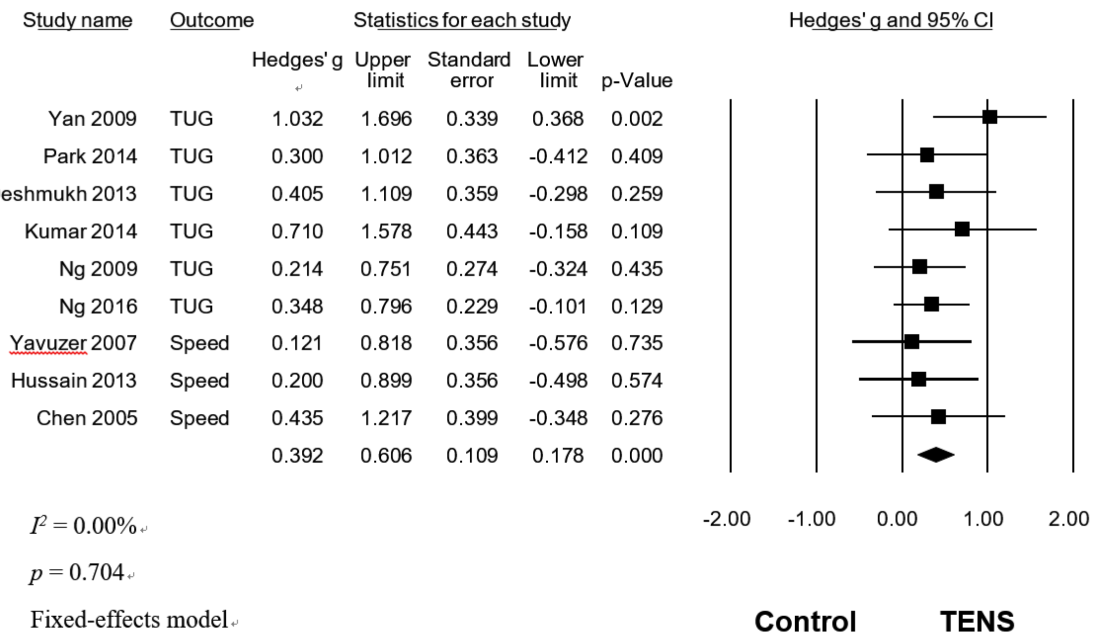
3.4.5 Muscle strength

Three studies (Hussain & Mohammad, 2013; Ng & Hui-Chan, 2007; Yan & Hui-Chan, 2009) measured the peak dorsiflexor strength of the participants' paretic ankles. Two of these studies (Ng & Hui-Chan, 2007; Yan & Hui-Chan, 2009) measured the maximum voluntary contraction (MVC) of the paretic ankle dorsiflexor, and the other study (Hussain & Mohammad, 2013) used manual muscle testing to assess the paretic ankle dorsiflexor strength. Due to the heterogeneity of the assessment methods, the three studies were not pooled. Two of the studies (Hussain & Mohammad, 2013; Yan & Hui-Chan, 2009) reported a significant between-group difference in favour of TENS. One of the three studies (Ng & Hui-Chan, 2007) also assessed the MVC of the paretic ankle plantarflexion, but no between-group improvement in plantarflexor strength was found. Jung and colleagues (Jung et al., 2017) assessed the peak isometric paretic hip extensor, knee extensor, and ankle plantarflexor strength with a handheld dynamometer.

Significant between-group differences in favour of TENS was demonstrated in hip extensor strength only.

3.4.6 Walking capacity

Ten studies measured walking capacity using gait speed (Chen et al., 2005b; Hussain & Mohammad, 2013; Ng & Hui-Chan, 2007, 2009; Park et al., 2014; Yavuzer et al., 2007) and/or TUG completion times (Deshmukh et al., 2013; Kumar & Kulkarni, 2014; Ng & Hui-Chan, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009). One of the studies that measured gait speed (Ng & Hui-Chan, 2007) was not included in the meta-analysis of walking capacity because a considerable number of participants of that study also participated in another study (Ng & Hui-Chan, 2009). Therefore, nine studies (involving 324 participants) measuring either gait speed (Chen et al., 2005b; Hussain & Mohammad, 2013; Yavuzer et al., 2007) or TUG (Deshmukh et al., 2013; Kumar & Kulkarni, 2014; Ng & Hui-Chan, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009) were pooled in a meta-analysis of walking capacity. The effect of TENS on walking capacity was significant (Hedges' g = 0.392; 95%CI = 0.178 to 0.606; $p < 0.001$) and homogeneous ($I^2 = 0.00\%$; $p = 0.704$) (Figure 3.4).



Study name	Outcome	Hedges' g	Upper limit	Standard error	Lower limit	p-Value
Yan 2009	TUG	1.032	1.696	0.339	0.368	0.002
Park 2014	TUG	0.300	1.012	0.363	-0.412	0.409
eshmukh 2013	TUG	0.405	1.109	0.359	-0.298	0.259
Kumar 2014	TUG	0.710	1.578	0.443	-0.158	0.109
Ng 2009	TUG	0.214	0.751	0.274	-0.324	0.435
Ng 2016	TUG	0.348	0.796	0.229	-0.101	0.129
Yavuzer 2007	Speed	0.121	0.818	0.356	-0.576	0.735
Hussain 2013	Speed	0.200	0.899	0.356	-0.498	0.574
Chen 2005	Speed	0.435	1.217	0.399	-0.348	0.276
		0.392	0.606	0.109	0.178	0.000

$I^2 = 0.00\%$

$p = 0.704$

Fixed-effects model

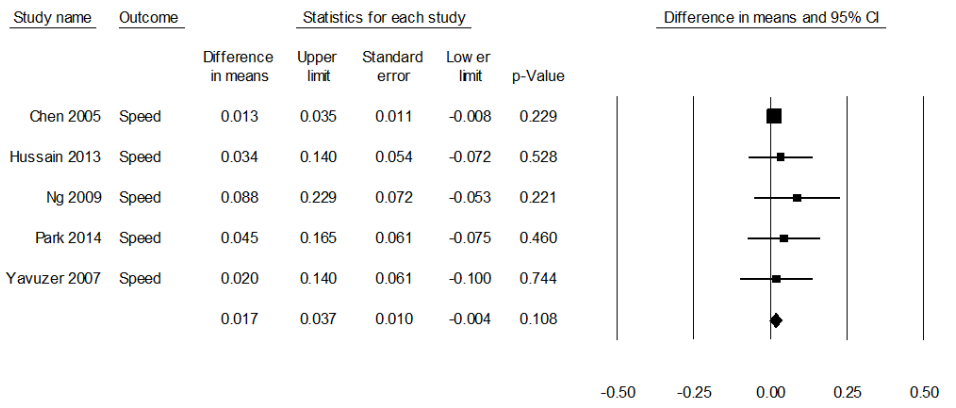
Figure 3.4. Hedges'g (95% CI) of the effect of TENS compared to placebo or no treatment on measures of walking capacity by pooling data from 9 studies (n = 329).

Remarks:

CI = confidence interval; TENS = Transcutaneous electrical nerve stimulation; TUG = Timed Up and Go test.

The sizes of the squares indicate the relative weight of each study.

Five studies (Chen et al., 2005b; Hussain & Mohammad, 2013; Ng & Hui-Chan, 2009; Park et al., 2014; Yavuzer et al., 2007) (involving 165 participants) were pooled in a meta-analysis of gait speed. There is no evidence that TENS had an effect on walking speed (difference in means = 0.017, 95%CI = -0.004 to 0.037, p = 0.108; I^2 = 0.00%, p = 0.842) (Figure 3.5A). Six studies (Deshmukh et al., 2013; Kumar & Kulkarni, 2014; Ng & Hui-Chan, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009) (involving 245 participants) were pooled in a meta-analysis of TUG completion times. The effect of TENS on TUG completion times was significant (difference in means = 4.37, 95%CI = 0.72 to 8.03), $p <$ 0.001) and heterogeneous (I^2 = 64.70%; p = 0.015). On average, people with stroke in the TENS group improved 4.37s more in TUG completion time than those in control group (Figure 3.5B). Two studies (Ng & Hui-Chan, 2009; Ng et al., 2016b) assessed walking endurance using a 6-minute walk test. Neither of the studies reported a significant effect in the TENS group compared to the placebo-control group.



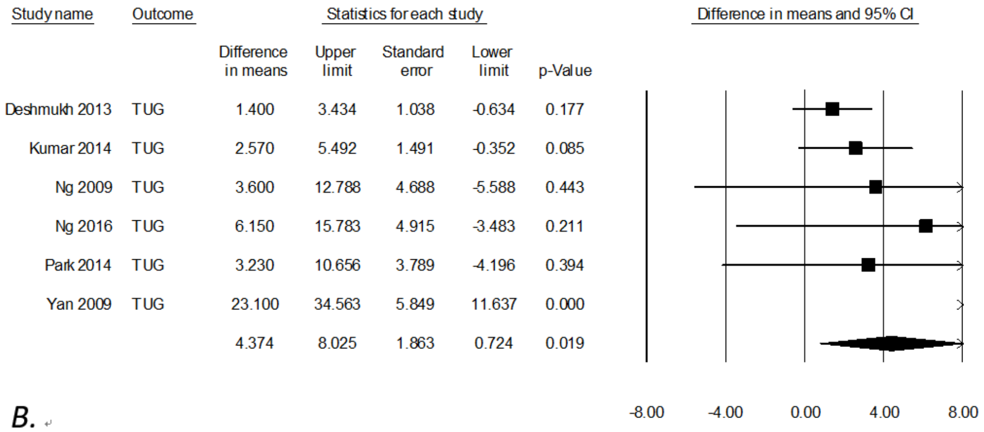
Study name	Outcome	Difference in means	Upper limit	Standard error	Lower limit	p-Value
Chen 2005	Speed	0.013	0.035	0.011	-0.008	0.229
Hussain 2013	Speed	0.034	0.140	0.054	-0.072	0.528
Ng 2009	Speed	0.088	0.229	0.072	-0.053	0.221
Park 2014	Speed	0.045	0.165	0.061	-0.075	0.460
Yavuzer 2007	Speed	0.020	0.140	0.061	-0.100	0.744
		0.017	0.037	0.010	-0.004	0.108

A.

I^2 = 0.00%

p = 0.842

Fixed-effect model



Study name	Outcome	Difference in means	Upper limit	Standard error	Lower limit	p-Value
Deshmukh 2013	TUG	1.400	3.434	1.038	-0.634	0.177
Kumar 2014	TUG	2.570	5.492	1.491	-0.352	0.085
Ng 2009	TUG	3.600	12.788	4.688	-5.588	0.443
Ng 2016	TUG	6.150	15.783	4.915	-3.483	0.211
Park 2014	TUG	3.230	10.656	3.789	-4.196	0.394
Yan 2009	TUG	23.100	34.563	5.849	11.637	0.000
		4.374	8.025	1.863	0.724	0.019

B.

I^2 = 64.70%

p = 0.015

Random-effects model

Figure 3.5. Difference in means (95% CI) of the effect of TENS compared to placebo or no treatment on measures of (A) gait speed by pooling data from 5 studies (n = 165), and (B) TUG by pooling data from 6 studies (n = 245).

Remarks:

CI = confidence interval; TENS = transcutaneous electrical nerve stimulation; TUG: Timed Up and Go Test.

The sizes of the squares indicate the relative weight of each study.

3.4.7 Balance performance

Three studies (Jung et al., 2017; Ng et al., 2016b; Park et al., 2014) assessed balance performance, but they had used different methods. Ng and colleagues (Ng et al., 2016b) used the Berg Balance Scale (BBS) to assess balance performance. The BBS score was significantly greater in the TENS group compared to the placebo-control group at 4 weeks during the intervention period, at the end of the 8 weeks intervention period and 12 weeks after the intervention had completed.

Park and colleagues (Park et al., 2014) used computerized posturography (i.e., the Good Balance system) to measure postural stability in eyes-open and eyes-closed conditions during static standing. There were greater reductions in the anterior-posterior and medial-lateral postural sway speeds as well as the speed moment in the TENS group than the placebo-control group. Jung and colleagues (Jung et al., 2017) used the Wii balance board to assess the postural sway distance during static standing with eyes open and eyes closed conditions. Results of the study showed that people with stroke in the TENS group demonstrated a significantly greater reduction in the sway distances than those in the control group.

3.4.8 Publication bias

The funnel plot appeared symmetrical for the meta-analysis of walking capacity (Figure 3.6). Egger's regression test revealed that the intercept of the regression line did not significantly deviate from 0 (intercept = 0.83; *p*= 0.291), indicating that there was no evidence of publication bias.

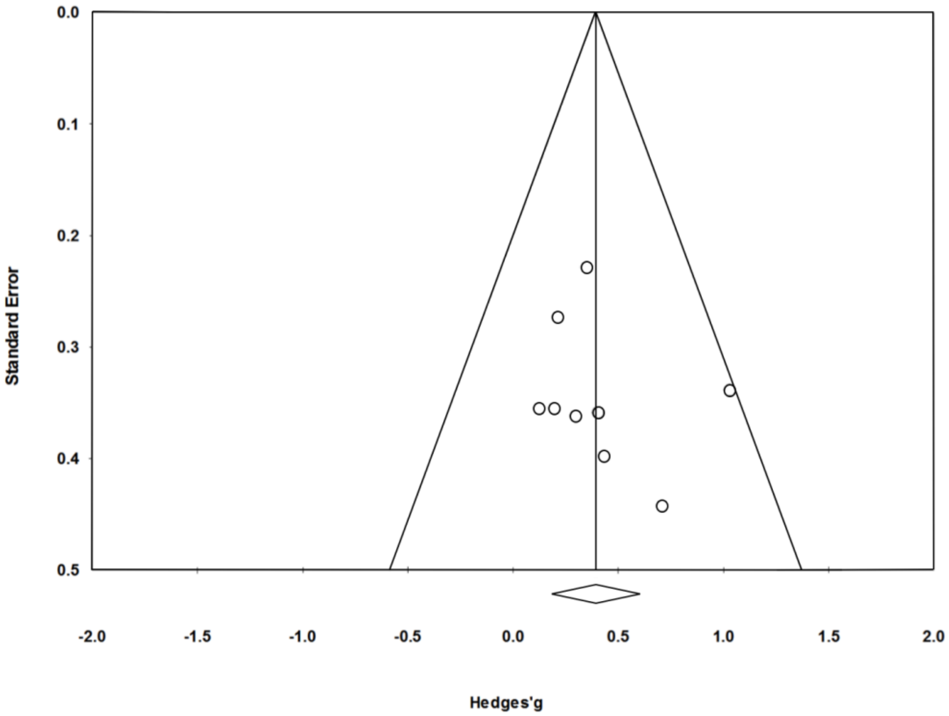


Figure 3.6. Funnel plot of the standard errors of each study against the standardized mean difference, using walking capacity (gait speed or TUG) as the outcome variables

3.4.9 Sensitivity analysis

A second meta-analysis of walking capacity was carried out without the four studies that had PEDro scores of less than 6 (Deshmukh et al., 2013; Kumar & Kulkarni, 2014; Park et al., 2014; Yan & Hui-Chan, 2009). The effect size estimate decreased but remained statistically significant (Hedges' g = 0.271, 95% CI = 0.005 to 0.536, p = 0.046) and homogeneous (I^2 = 0.00%, p = 0.969).

3.4.10 Meta-regression and subgroup analyses

Regarding the duration of stimulation per session, the effect of TENS on walking capacity in studies involving 60 min sessions (Deshmukh et al., 2013; Ng & Hui-Chan, 2009; Ng et al., 2016b; Yan & Hui-Chan, 2009) was significant (Hedges' g = 0.468, 95%CI = 0.201 to 0.734, p = 0.001) and homogeneous (I^2 = 6.92%, p = 0.367). In contrast, the effect of TENS on walking capacity in studies involving shorter sessions (20 or 30 min) (Chen et al., 2005b; Hussain & Mohammad, 2013; Park et al., 2014; Yavuzer et al., 2007) was non-significant (Hedges' g = 0.254, 95%CI = -106 to 0.614, p= 0.166) and homogeneous (I^2 = 0.00%, p = 0.943).

The meta-regression analysis indicated that there was no significant correlation between the cumulative duration of stimulation and the effect size estimate associated with walking capacity (slope = 0.00015, $p = 0.699$).

Among the 10 studies that assessed walking capacity, 6 of those (Deshmukh et al., 2013; Hussain & Mohammad, 2013; Kumar & Kulkarni, 2014; Ng et al., 2016b; Yan & Hui-Chan, 2009; Yavuzer et al., 2007) recruited people with acute or subacute stroke and 4 of those (Chen et al., 2005b; Ng & Hui-Chan, 2007, 2009; Park et al., 2014) recruited people with chronic stroke. The effect of TENS on walking capacity in people with acute or subacute stroke was significant (Hedges' g = 0.441, 95% CI = 0.181 to 0.702, $p = 0.001$) and homogeneous ($I^2 = 0.00\%$, $p = 0.432$). In contrast, the effect of TENS on walking capacity in people with chronic stroke (after one study (Ng & Hui-Chan, 2007) was removed from the meta-analysis because many of the participants in this study also participated in another study that was included in the meta-analysis (Ng & Hui-Chan, 2009)) was nonsignificant (Hedges' g = 0.289, 95% CI = -0.087 to 0.665, $p = 0.132$) and homogeneous ($I^2 = 0.00\%$, $p = 0.896$).

3.5 Discussion

This systematic review provides evidence that the repeated application of TENS is effective at improving walking capacity and reducing paretic ankle plantarflexor spasticity in people with stroke.

3.5.1 Effect of TENS on motor recovery

The meta-analysis showed that people with stroke who underwent TENS had greatly reduced paretic plantarflexor spasticity (0.59 MAS points in average), compared to those in the control groups. However, this finding should be interpreted with caution as the MAS was treated as an interval scale in the meta-analysis, (i.e., the distances between each level of the scale were treated as equal), which may not be appropriate.

Moreover, the validity of using the MAS to assess spasticity of paretic extremities has been questioned since MAS assessment of spasticity is confounded by contracture, despite the fact that this assessment has commonly been used in clinical and research settings (Bakheit et al., 2003; Patrick & Ada, 2006). A previous study (Bakheit et al., 2003) compared the H-reflex latency, and the ratio of the maximum H-reflex (H_{max}) to the maximum motor evoked potential (M_{max}) of the paretic soleus of 24 people with stroke with MAS scores of 1 or 2. The study found that the H-reflex latency and the H_{max}: M_{max} ratio were comparable between people with stroke with different MAS scores.

People with stroke in the TENS groups had a significantly greater improvement in walking capacity than those in the control groups. In addition, TENS significantly reduced the TUG completion time by 4.37 seconds but did not increase the gait speed. The exact mechanisms by which TENS improve the walking capacity are unknown. A study that carried out a regression analysis using data from 73 people with chronic stroke revealed that the MVC of paretic ankle dorsiflexor was a significant predictor of TUG completion times ($\beta = -6.13$, $p < 0.001$) (Ng & Hui-Chan, 2013). An additional study of 22 people with chronic stroke found that peak isometric paretic ankle dorsiflexor strength was significantly correlated with self-paced sit-to-stand durations ($r = -0.450$, $p < 0.05$) (Lomaglio & Eng, 2005). The improvements in peak paretic ankle dorsiflexor strength may directly influence the TUG completion times and indirectly influence the TUG completion times via its effects on the TUG subtasks, such as the sit-to-stand and turning tasks.

Only three studies included measures of balance (BBS (Ng et al., 2016b) and sway distance (Jung et al., 2017; Park et al., 2014)) and both have reported the application of TENS to paretic lower extremities would lead to improvements in balance. However, the lack of studies using balance-specific outcome measures makes it difficult to draw firm conclusions about the effect of TENS on the balance of people with stroke as a meta-analysis could not be conducted.

3.5.2 Effect of quality of studies

In the first meta-analysis of walking capacity, the studies rated as being of fair methodological quality (Hussain & Mohammad, 2013; Kumar & Kulkarni, 2014; Park et al., 2014; Yan & Hui-Chan, 2009) (i.e., PEDro scores of 4 to 5) were included. As the risk of bias is relatively high in these studies, overestimation of the effect size was possible in this meta-analysis. However, an additional meta-analysis showed that the effect of TENS on walking capacity remained statistically significant when studies rated as being of fair methodological quality were excluded. This result indicates that the major finding of this systemic review is robust to the inclusion of studies rated as being of fair methodological quality.

3.5.3 Effect of stimulation parameters

The optimal TENS frequency for motor recovery in stroke rehabilitation is unknown. Most of the studies used a high stimulation frequency of 100 Hz (Deshmukh et al., 2013; Hussain & Mohammad, 2013; Jung et al., 2017; Kumar & Kulkarni, 2014; Ng & Hui-Chan, 2007, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009) and favourable effects on walking capacity were consistently demonstrated. Whether high stimulation frequency is superior to low frequency could not be determined because of the small number of studies that used low frequency (Chen et al., 2005b; Yavuzer et al., 2007). In addition, the effect of stimulation frequencies over 100 Hz remains unknown.

The subgroup analysis revealed a duration of 60 min per session is more effective than a short session (20 or 30 min) at improving walking capacity in people with stroke. However, it should be noted that all of the studies (Deshmukh et al., 2013;

Ng & Hui-Chan, 2009; Ng et al., 2016b; Yan & Hui-Chan, 2009) that involved 60 min sessions had used TUG completion times as the measure of walking capacity. In contrast, three (Chen et al., 2005b; Hussain & Mohammad, 2013; Yavuzer et al., 2007) out of the four studies (Chen et al., 2005b; Hussain & Mohammad, 2013; Kumar & Kulkarni, 2014; Yavuzer et al., 2007) that involved short stimulation durations assessed walking capacity using gait speed. As our results showed that the effect of TENS on gait speed is small and nonsignificant (Figure 3.4), it is possible that the difference in effect size estimates between the two subgroups resulted from the use of different outcome measures.

The results of the meta-regression show that the cumulative duration of stimulation did not significantly influence the effect of TENS on walking capacity. This phenomenon may be explained by the potential existence of a non-linear improvement rate, where there is a greater improvement at the beginning of intervention programmes than at the end. This may occur because the stimulation may induce more neural plastic changes in the first few weeks and then gradually have less effect over time due to adaptation.

3.5.4 Effect of duration since stroke

The subgroup analysis on the effect of the post-stroke duration revealed that TENS led to a significant improvement in walking capacity in the people with acute or subacute stroke but not in the people with chronic stroke. This result is inconsistent with the previous systematic review conducted by Veerbeek and colleagues (Veerbeek et al., 2014), which found that post-stroke phases were not associated with the effect of TENS. Veerbeek and colleagues' review presented a meta-analysis of three studies (Hui-Chan et al., 2009; Ng & Hui-Chan, 2007, 2009) that recruited people with chronic stroke. However, these studies were conducted by the same research team, and their authors reported that some of the data were used in all of the three studies. Pooling the results from the three studies, therefore may lead to an overestimation of the effect size.

A previous study showed that motor recovery after stroke (as measured using the Fugl-Meyer assessment) is rapid during the first month and gradually plateaus at 3 months post-stroke (Duncan et al., 1994). Therefore, it was not surprising that TENS was found to have a greater effect in people with acute or subacute stroke than in people with chronic stroke.

Nevertheless, the non-significant effect of TENS on walking capacity in people with chronic stroke should be interpreted with caution as only three studies were included in the meta-analysis. Of these three studies (Chen et al., 2005b; Ng & Hui-Chan, 2009; Park et al., 2014), two reported significantly greater improvements of TUG completion times in the TENS group compared to the placebo-control group (Ng & Hui-Chan, 2009; Park et al., 2014). However, the small numbers of studies and participants included in this subgroup analysis led to a low statistical power to detect effects.

3.5.5 Limitations

This review has several limitations. First, only eleven RCTs were included, and most of these RCTs had small sample sizes. Second, due to the heterogeneity of assessment methods and the small sample sizes, it was not possible to carry out meta-analyses of the effects of TENS on muscle strength and balance. Third, many of the included studies used the MAS to measure the level of spasticity of the paretic ankle plantarflexor despite the fact that the validity of using the MAS to measure spasticity has been questioned. moreover, the MAS was treated as interval scale in the current study, the result of that analysis may not be robust. Although the review shows that TENS significantly decreases MAS scores, the effect of TENS on paretic ankle plantarflexor spasticity need further investigation. Fourth, the long-term effect of TENS could not be determined as only four studies carried out follow-up assessments, with the longest follow-up period being 12 weeks.

Most of the studies included in the current meta-analysis adopted the stimulation frequency of 100Hz. It is plausible that the 100Hz stimulation frequency could be chosen in clinical practice. However, an RCT is warranted to compare the effects of different stimulation frequency. Besides, the optimal length of the intervention program could not be deduced from the current review. Future work should aim at identifying the optimal length of the training program to enhance its cost-effectiveness. Muscle strength, balance performance and neurophysiological measures of spasticity have not been meta-analysed. Further studies of TENS that use balance-specific outcome measures and electrophysiological assessments to evaluate the effects of TENS on spasticity in people with stroke are warranted.

3.6 Conclusion

This review demonstrated that TENS is effective at enhancing walking capacity (especially regarding TUG completion times) and it can reduce spasticity (as measured using MAS scores) in people with stroke. The use of TENS as an adjunct therapy in both clinical and home-based settings is recommended as TENS is non-invasive and safe. The stimulation duration of 60 min per session appeared more effective than a short session (20 or 30 min) at improving walking in people with stroke. Most of the studies included in the current meta-analysis adopted the stimulation frequency of 100Hz. It is plausible that the 100Hz stimulation frequency could be chosen in clinical practice. However, a randomised controlled trial is warranted to compare the effects of different stimulation frequency. Besides, the optimal length of the intervention program could not be deduced from the current review. Future work should aim at identifying the optimal length of the training program to enhance its cost-effectiveness. Muscle strength, balance performance and neurophysiological measures of spasticity have not been meta-analysed. Further studies of TENS that use balance-specific outcome measures and electrophysiological assessments to evaluate the effects of TENS on spasticity in people with stroke are warranted.

This review summarised the therapeutic effects of the use of TENS in stroke rehabilitation and provided insight in establishing the TENS protocol for the subsequence randomised controlled trial. Next chapter will evaluate the validity and reliability of outcome measures that will be used in the randomised controlled trial.

Chapter 4

General methodology

Three studies presented in this chapter have been published by the author of this thesis.

1: Kwong PW, Ng SS, Liu TW, Chung RC, Ng GY. Effect of Leg Selection on the Berg Balance Scale Scores of Hemiparetic Stroke Survivors: A Cross-Sectional Study. Arch Phys Med Rehabil. 2016;97(4):545-51. (Appendix 4.1)

2: Kwong PW, Ng SS, Chung RC, Ng GY. Foot placement and arm position affect the five times sit-to-stand test time of individuals with chronic stroke. BioMed research international. 2014;636530. (Appendix 4.2)

3: Kwong PW, Ng SS, Ng GY. An investigation of the psychometric properties of the Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome (SIPSO). Clin Rehabil. 2017;31(11):1538-1547. (Appendix 4.3)

4.1 Abstract

This chapter presented the general methodology which would be adopted in chapter 5, 6 and 7. The contents included selection criteria of participants, the rationale of selecting the outcome measures, psychometric properties of the selected outcomes, assessment procedures of these outcome measures and ethical consideration. In the section of outcome measures, 3 cross-sectional studies were included. These studies were:

1. Effect of leg selection on the Berg Balance Scale (BBS) scores of people with stroke: a cross-sectional study.

Biomechanical studies showed that the selection of weight-bearing leg would affect the balance performance of functional tasks in people with stroke. However, no clear guideline on the selection of weight-bearing leg in using BBS to measure balance performance in people with stroke. This cross-sectional study investigated the influence of selection of weight bearing leg on performance of the BBS in people with stroke. Results of this study showed that selecting the paretic leg as primary weight bearing leg reduced the total score of BBS and thus dampened the ceiling effects of the scale.

2. Foot and arm positions affect the Five Times Sit to Stand Test (FTSTS) completion time of people with chronic stroke.

Previous studies showed that initial foot placement and arm position would affect the sit to stand performance in people with stroke. However, there are no existing guideline on selecting the initial foot placement and arm position on conducting the FTSTS in people with stroke. This cross-sectional study evaluated the influence of 3 arm positions and 2 foot placements on the completion time of FTSTS. Results of this study showed that both arm positions and foots placements significantly affects the completion time of FTSTS in people with stroke. The augmented arm position combined with posterior foot placement led to the shortest completion time. Results of this study indicated that standardizing the arm position and foot placement in the test procedure is essential in clinical and research setting.

3. An investigation of the psychometric properties of the Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome (SIPSO).

The SIPSO was commonly used to assess the level of community integration in people with stroke in Europe and North America. However, it is yet to be translated into Chinese, and neither has its reliability and validity been evaluated in a Chinese community. This cross-sectional study started with the description of the translation process of the SIPSO questionnaire. The psychometric properties including test re-test reliability, factor structure and discriminative validity of the Chinese version of SIPSO were also assessed in the study. Results of the study showed that the Chinese version of SIPSO is a reliable and valid instrument to assess the level of community integration in community-dwelling people with stroke who is living in Hong Kong.

This chapter describes the general methodology that will be adopted in the following chapters. All selected outcome measures demonstrate satisfactory reliability and validity. Moreover, results of cross-sectional studies presented in this chapter provide insight in how to standardize the assessment procedure of BBS and FTSTS test and support the use of SIPSO-C in assessing the level of community integration of people with stroke in Hong Kong.

4.2 Introduction

This chapter describes the general methodology adopted in different studies presented in this chapter and studies presented in chapter 5, 6 and 7. Its scope includes selection criteria of participants, outcome measures, and ethical considerations.

4.3. Participants

People with stroke were recruited from local self-help groups via poster advertising. People with stroke were eligible to participate if they (1) were between 50 and 85 years of age. Subjects aged above 85 years were excluded since old age frailty is commonly seen in this age group (Fried et al., 2001) and the presence of old age frailty could impair the motor recovery following stroke (Smithard, 2017); (2) had received a diagnosis of ischaemic or haemorrhagic stroke by magnetic resonance imaging or computed tomographic scan more than 1 year earlier; (3) were able to walk 3 m independently; (5) were able to score at least 6 of 10 on the Abbreviated Mental Test (Chu et al., 1995). An Abbreviated Mental Test score of 6 or above indicated that the subject is very likely having a normal cognitive function with a sensitivity of 96% and specificity of 94%; (6) were able to follow instructions and give informed consent. An additional inclusion criterion of (7) had no skin allergy that would prevent the application of the TENS equipment was applied to the subjects recruited in the randomised control trials presented in chapter 5 and 6.

People with stroke were excluded if they had (1) any existing medical, cardiovascular or orthopaedic condition that hindered training or assessment; or (2) participated in other drug studies or clinical trials. Two additional exclusion criteria of having (3) cardiac pacemaker; or (4) significant lower-limb peripheral neuropathy (e.g., diabetic polyneuropathy) were applied to the subjects recruited in the randomised control trials presented in chapter 5 and 6.

4.4 Outcome measures

4.4.1 Measurement Battery

Demographic characteristics of participants were collected via interview, and past medical history was retrieved from discharge summary issued by hospitals.

Outcome measures in this thesis included the measurements of:

1. The level of lower limb motor recovery in term of the lower extremity motor subscale of the Fugl-Meyer Assessment(FMA-LE);
2. Muscle function in term of peak isokinetic torque of knee extensor and flexor and maximum isometric voluntary contraction strength of ankle dorsiflexor and plantarflexor;
3. Coordination of lower-limb in term of Lower Extremity Motor Coordination Test (LEMOCOT) score;
4. Balance performance in term of the limit of stability (LOS) score, Step Test (ST) score and Berg Balance Scale (BBS) score;

5. Sit to stand performance in term of Five Times Sit to Stand Test (FTSTS) completion time;
6. Walking capacity in term of 10 meter Walk Test (10mWT) walking speed, 6 minute Walk test (6MWT) distance and Timed Up and Go test (TUG) completion time;
7. Level of community integration in term of Subjective Index of Physical and Social Outcome (SIPSO) score;
8. Psychological well-bearing in term of Geriatric Depression Scale (GDS) score and Activities-specific Balance Confidence Scale (ABC) score.

These outcome measurements were selected based on the World Health Organization International Classification of Functioning, Disability and Health (ICF) conceptual model (World Health Organization, 2001). Measurements 1 to 4 derived from the body functions domain of ICF, 5,6 derived from the activities domain of ICF and 7-8 derived from the participation domain of ICF.

4.4.2 Lower limb motor recovery

The lower extremity motor subscale of the Fugl-Meyer assessment (FMA-LE) was used to measure the level of lower extremity motor recovery after stroke. Quality of reflexes, coordination and voluntary movements of the paretic leg were assessed using a 34-point scale (Gladstone et al., 2002). Higher FMA-LE score indicated a better level of motor recovery. Excellent inter-rater and intra-rater reliability (Duncan et al., 1983)

(ICC = 0.959 to 0.963) and test-retest repeatability (Hiengkaew et al., 2012) (ICC = 0.94) have previously been reported for the FMA-LE.

4.4.3 Lower Limbs muscles strength

4.4.3.1 Rationale of measurement

As mentioned in section 1.3.2, muscle weakness is a common motor impairment following stroke (Andrews & Bohannon, 2000; Bohannon, 2007; Dorsch et al., 2015) and loss of muscle strength directly contributed to physical disability in people with stroke (Canning et al., 2004; Chae et al., 2002; Gerrits et al., 2009; Nadeau et al., 1999a; Ng et al., 2011b). Both isokinetic peak torque and maximum isometric torque have been used to assess the muscle weakness in people with stroke.

In this study, the knee muscle strength was measured with an isokinetic dynamometer. Isokinetic knee muscle torque was commonly assessed in clinical study involving stroke population (Engardt et al., 1995; Flansbjer et al., 2005a; Flansbjer et al., 2006; Lomaglio & Eng, 2005; Nakamura et al., 1988; Patterson et al., 2007) since it was strongly correlated with walking velocity (Flansbjer et al., 2006; Nakamura et al., 1988; Patterson et al., 2007), walking duration (Flansbjer et al., 2006; Patterson et al., 2007), sit to stand duration (Lomaglio & Eng, 2005), stair-climbing duration (Flansbjer et al., 2006) and Timed Up and Go completion time (Flansbjer et al., 2006). However, some of the participants in this study demonstrated severe ankle plantarflexor spasticity, which made it difficult to measure the isokinetic strength of the leg muscles due to the limited range of motion in the ankle. Thus the maximum isometric ankle muscle strength was measured instead.

4.4.3.2 Isokinetic peak torque of knee

The strength of both paretic and non-paretic knee flexor and extensor were measured by the Cybex 6000 Dynamometer (Cybex, Ronkonkoma, NY). Peak concentric isokinetic peak torques of knee flexion and extension at 90^{o}/sec were measured in sitting position. Watkins and colleagues (Watkins et al., 1984) have reported that people with stroke who demonstrated moderate spasticity had difficulty in performing the isokinetic knee flexion and extension at high angular velocity (180 ^{o}/sec) but not at low angular velocity (30 ^{o}/sec). Besides, we observed that variation of the peak torque was high at low angular velocity test for some of the participants. It could be due to muscle fatigue induced by the test trials. Therefore, a relatively low angular velocity (90^{o}/sec) was selected to measure the isokinetic peak torque. Excellent test-retest reliability (ICC = 0.94) of using Cybex 6000 Dynamometer in measuring peak isokinetic torques in people with chronic stroke have been reported in a previous study (Hsu et al., 2002). Three practice trials were offered, and the averaged of five test trials were used for analysis.

4.4.3.3 Maximum isometric voluntary contraction of ankle

The maximum isometric voluntary contraction of the paretic ankle dorsiflexor and plantarflexor were measured with a Nicholas handheld dynamometer (model 01,160, Lafayette Instrument Company, Lafayette, IN). The ankle strength was assessed with participant lying supine with the ankle in neutral position. The dynamometer was placed proximal to metatarsophalangeal joints on the dorsal and plantar surface of the foot to assess the dorsiflexion and plantarflexion strength, respectively (Bohannon, 1986). Good to excellent reliability (ICC = 0.84 to 0.99) has been reported for the use of a handheld dynamometer to assess ankle muscle strength in subjects with chronic stroke (Bohannon & Andrews, 1987). One practice trial was offered, and the averaged of three test trials were used for analysis.

4.4.4 Lower Limb coordination

4.4.4.1 Rationale of measurement

Motor coordination referred to the ability to perform a purposeful movement in a smooth and accurate manner (Bourbonnais et al., 1991). Coordinated movement depended on the precise order of muscle activation (Canning et al., 2000), adequate sensory input (Buschges, 2005; Dannenbaum & Dykes, 1988; Gao et al., 2010) and correct body schema (Galati et al., 2001). The ability to perform controlled, accurate and rapid movement was impaired in people with stroke (Bourbonnais et al., 1991; Dannenbaum & Dykes, 1988). Some studies have suggested that additional sensory stimulation could restore sensation in people with stroke (Chen et al., 2005a) and increase the limb awareness in children with unilateral cerebral palsy (Dong & Fong, 2016). It is plausible that TENS can also restore sensation and increase limb awareness in people with stroke, thus, improve the motor coordination.

4.4.4.2 Lower Extremity Motor Coordination Test (LEMOCOT)

The LEMOCOT was developed to measure the intra-limb coordination of the paretic leg in people with stroke (Desrosiers et al., 2005). Good test-retest reliability of the LEMOCOT (ICC = 0.83 to 0.88) has been reported for the assessment of people with stroke (Desrosiers et al., 2005). Two flat, circular targets were secured on the floor 30 cm apart in an anteroposterior direction. The participants were seated with their hips and knees in 90 degrees of flexion. The participants then touched the two targets alternately with their big toe for 20 s. The number of touches was counted. One practice trial was offered, and the averaged of three test trials were used for analysis.

4.4.5 Balance performance

4.4.5.1 Rationale of measurement

Balance deficiency is common in people with stroke (Goldie et al., 1996; Ikai et al., 2003; Liston & Brouwer, 1996; Sackley, 1991; Tyson et al., 2006) and is considered as one of the determinants of the risk of falling (Mackintosh et al., 2006; Maeda et al., 2009; Teasell et al., 2002). In view of the adverse consequences of fall, including restrictions on activities (Forster & Young, 1995; Schmid & Rittman, 2009) and fracture (Poole et al., 2002; Teasell et al., 2002), training programs that can enhance the balance performance of people with stroke should be implemented in clinical settings. Although increasing number of clinical trials have reported an overall favourable effect of using TENS as an adjunct modality in stroke rehabilitation, only a few of them (Jung et al., 2017; Ng et al., 2016b; Park et al., 2014) have adopted balance-specific measures. In order to evaluate the effect of TENS on balance performance, several balance-specific measures have been included in this study.

4.4.5.2 Limit of Stability (LOS)

LOS evaluated participants' ability to shift their body centre of gravity towards different direction on a fixed base of support without losing balance. The test was conducted with the Equitest® machine (Neurocom, Inc, Clackamas, OR, US). Excellent test-retest reliability (ICC = 0.84) of LOS has been reported for the assessment of people with chronic stroke (Liston & Brouwer, 1996). During the test, participants were instructed to stand on a forced platform with barefoot. The foot alignment was adjusted according to the instruction provided by the system. A human shape cursor which represents the centre of gravity of the participants would be displayed on a monitor, which is approximately 1 m in front of them. The participants were instructed to shift their centre of gravity toward highlighted targets indicated on the monitor without making a step or bending the trunk. In each trial, the participant shifted their centre of gravity toward eight directions (anterior, posterior, left, right and the 4 corners) in a randomized order. To prevent accidental fall, all participants worn a harness during the assessment. Maximum excursion score, which was defined as the maximum percentage of displacement of COG toward a target with reference to age-matched normal value was selected to represent overall weight shifting ability. One practice trial was given, and the averaged of three test trials were used for analysis.

4.4.5.3 Step Test (ST)

The step test (ST) was developed by Hill and colleagues (Hill et al., 1996) to evaluate the dynamic standing balance in people with stroke. It measures the number of times the participants placed one foot on a 7.5 cm step and back to the ground within 15 s. The manoeuvre challenged the participant’s ability to stabilize the body over the stance leg while the other leg is stepping up and down. The ST scores showed excellent intra-rater and inter-rater reliability in subjects with chronic stroke (ICC = 0.98 to 0.99) (Hong et al., 2012). The number of repetitions with the paretic leg and non-paretic leg were denoted as the paretic ST score and the non-paretic ST score, respectively. Both paretic and non-paretic ST score showed significant correlation with isometric knee flexor strength (r = 0.80 to 0.81), isometric ankle dorsiflexor strength (r = 0.70 to 0.73) and the Lower Extremity Motor Coordination Test score (r = 0.83 to 0.90) (Hong et al., 2012). Furthermore, the paretic ST score was significantly correlated with the comfortable walking speed (r = 0.70) and the non-paretic ST score was significantly correlated with the BBS score (*r* = 0.73) (Hong et al., 2012). One practice trial was offered, and the averaged of three test trials were used for analysis.

4.4.5.4 Berg Balance Scale (BBS)

The Berg Balance Scale (BBS) was first introduced in 1989 to assess balance performance in older adults (Berg et al., 1989). The scale consists of 14 items, each rating a participant's ability to maintain stability in a specified functional task on a 5 point (0–4) scale (Berg et al., 1989; Berg et al., 1992). The BBS has demonstrated excellent test-retest reliability (ICC = 0.95 to 0.98) (Hiengkaew et al., 2012; Liston & Brouwer, 1996) and inter-rater reliability (ICC = 0.95) (Mao et al., 2002) for participants with stroke. It has been extensively used for measuring the functional balance performance of elderly participants (Lajoie & Gallagher, 2004; Muir et al., 2008), stroke survivors (Flansbjer et al., 2012; Mao et al., 2002) and participants with Parkinson's disease (Dibble & Lange, 2006). It has also been used to evaluate the risk of falling with participants who have suffered a stroke (Andersson et al., 2006; Mackintosh et al., 2006). While one of the shortcomings of BBS is that BBS demonstrated a large ceiling effect in stroke survivors who had a high physical function (Salbach et al., 2001).

The last two items of BBS, 'Item 13- standing unsupported one foot in front' and 'Item 14- standing on one leg', are considered the most difficult items because both items require narrowing the base of support during asymmetric weight bearing (Kornetti et al., 2004; Wang et al., 2006). In item 13 of BBS, the participant is asked to stand with one foot in front of the other. A score of 4 is given if the participant can maintain this tandem stance for at least 30 seconds, with one foot placed directly anterior to the other and the longitudinal axis of the two feet aligned (Speers et al., 1998). A biomechanical study with healthy adults has shown that body weight is loaded significantly more on the posterior leg in that tandem stance position (Jonsson et al., 2005). Single leg stance (SLS) is an even more extreme form of asymmetrical weight bearing. SLS duration on a paretic leg after stroke is significantly shorter when compared with those on a non-paretic leg (Flansbjer et al., 2012). Previous studies have demonstrated that participants with stroke tended to bear more weight on their non-paretic leg when standing in order to better control postural stability (Bohannon & Larkin, 1985; Genthon et al., 2008).

4.4.5.5 Cross-sectional study 1. Effect of leg selection on the Berg Balance Scale scores of people with stroke: a cross-sectional study

Exhaustive literature searching showed that the effect of leg selection on the performance of these 2 BBS items had not been studied. The standard instructions for items 13 and 14 in a BBS assessment do not restrict the selection of the weight-bearing leg (Berg et al., 1989), but the choice is likely to affect the scores on those items and the total score, especially in patients with asymmetric motor control.

It was hypothesized that the item scores would be significantly lower when a participant stepped forward with the non-paretic leg in item 13, and stand on the paretic leg in item 14. BBS total score with this formulation, thus, would be significantly lower than those alternative formulations. It had been reported that BBS demonstrated a large ceiling effect in stroke survivors who had a high physical function (Salbach et al., 2001). By bringing down the total score of BBS, This BBS formulation might also have less of a ceiling effect than the other formulations. Lastly, this BBS formulation might demonstrate stronger correlation with other outcome measures.

Thus, the primary purpose of this study was to investigate whether the total BBS score would differ when participants were required to use their more-involved leg in either weight bearing or non-weight bearing fashion for items 13 and 14. A secondary purpose was to examine the concurrent validity of the 4 BBS scoring strategies by considering the correlations between the BBS performances and other measures of standing balance.

4.4.5.5.1 Methods

Participants

Participants were recruited from local self-help groups by posting advertisements in local community centres. participants were eligible for this study if they: (1) were aged ≥ 50; (2) had been diagnosed as having had a stroke; (3) had suffered a single stroke at least 1 year previously; (4) were able to walk for 6 meters without assistance with or without walking aid. Participants were excluded if they were: (1) cognitively impaired (abbreviated mental test score below 6) (Chu et al., 1995); (2) medically unstable; or (3) suffering from any other neurological or musculoskeletal condition that would affect mobility and balance performance.

Sample size estimation was conducted with the aid of G*Power (version 3.1). A sample size of 62 participants would be adequate to detect a significant difference (α = 0.05; power = 0.8) between the four formulations of BBS total scores, with a small effect size (Cohen's f = 0.15) and moderate correlation among repeated measures (r = 0.5) were assumed. The Ethics Committee of the administrating institution approved the study's assessment protocol. All of the participants gave written consent before starting the experiments. The study was conducted in accordance with the Declaration of Helsinki for human experiments.

Assessment procedures

This was a cross-sectional study. The experiment was conducted in the Balance and Neural Control Laboratory of The Hong Kong Polytechnic University. All of the participants completed the BBS and other assessments in a random order determined by drawing lots. Five minutes of rest was allowed in between each assessment in order to avoid fatigue.

Outcome measures

Fall History

Participants were asked whether they had any fall in the past 6 months, no matter the fall resulted in any injury or not. A fall was defined as " an unexpected event in which the participants come to rest on the ground, floor, or lower level." (Lamb et al., 2005). It had been reported that the accuracy of recalling of fall was satisfactory in elderly even for a 1 year period of time (sensitivity: 89% specificity: 95%) (Hale et al., 1993).

Berg Balance Scale Score

Items 1 to 12 of the assessments were conducted in accordance with the standard instructions. Items 13 (tandem stance) and 14 (SLS) were performed twice so that both legs could execute the weight bearing component of the item (i.e. for Item 13: the posterior leg was weight bearing; for Item 14: the stance leg was weight bearing). The sequence of performance was randomized for these 2 items. This produced 4 total BBS scores as listed below:

BBS_1 = $BBS_{item1-12}$ + BBS_{item13} (non-paretic leg in front) + BBS_{item14} (SLS on the paretic leg)

BBS_2 = $BBS_{item1-12}$ + BBS_{item13} (paretic leg in front) + BBS_{item14} (SLS on the paretic leg)

BBS_3 = BBS $_{item1-12}$ + BBS $_{item13}$ (non-paretic leg in front) + BBS $_{item14}$ (SLS on the non-paretic leg)

BBS_4 = BBS $_{item1-12}$ + BBS $_{item13}$ (paretic leg in front) + BBS $_{item14}$ (SLS on the non-paretic leg)

Fugl- Meyer Assessment- Lower Extremity Score

Please refer to section 4.4.2.

Five Times Sit-to-stand Time

Please refer to section 4.4.6.2 for details.

10 metre Walk Time

Please refer to section 4.4.7.2 for details.

Activities-specific Balance Confidence Scale Score

Please refer to section 4.4.9.2 for details.

Statistical analysis

The frequency of scorings of the two conditions in items 13 and 14 of the BBS assessment and the percentage of participants who received the maximum score in the four BBS formations were listed to evaluate the ceiling effect of the four formations. Wilcoxon’s signed-rank test was used to compare the item scores of the two conditions in items 13 and 14. Friedman's analysis of variance (ANOVA) technique was used to compare the four BBS total scores. Post-hoc analysis was done with Wilcoxon's signed-rank test. There were 4 BBS total scores included in the Friedman's ANOVA, and thus 6 pairs of comparisons in the Wilcoxon signed-rank tests. To avoid inflation of type 1 error, the critical level of confidence for significance was adjusted to be 0.05/6= 0.0083 in the post-hoc analysis with signed-rank tests. Internal consistency of the variation of the four BBS formations was measured by Cronbach's α. Receiver operating characteristics (ROC) analysis was adopted to exanimate the ability of the four BBS total scores in discriminating fallers from non-fallers.

Correlations between BBS total scores and other outcome measures were examined using Spearmen's rho. The strength of any correlation of the four BBS total scores with the other outcome measures for that participant was assessed using Steiger's Z test (Myers & Sirois, 2006). A p value ≤ 0.05 was considered as statistically significant. For Steiger's Z test, a critical z value larger than 1.96 indicated a significant difference between the strengths of the correlations with $p \leq 0.05$ (Garbin; Myers & Sirois, 2006). The Z test was conducted with the aid of FZT software (Garbin). All the other statistical analyses were conducted with version 20.0 of the SPSS software package. Any case with missing data was omitted from analysis.

4.4.5.5.2 Results

Sixty-three people with stroke were recruited to participate in this study, demographic characteristics of these subjects were shown in Table 4.1

Table 4.1. Characteristics of the participants of cross-sectional study 1 (n = 63).

Variables	Number (%)
Gender (male/female)	43 (68.3)/20 (31.7)
Side of hemiplegia (right/left)	37 (62.2)/26 (37.8)
Type of stroke (ischemic/hemorrhagic)	41 (65.1)/22 (34.9)
Faller (at least one fall within the previous 6 months)	14(22.2)
	Mean (SD); range
Age (y)	61.9 (6.8); 50 – 79
Height (cm)	161.9 (7.0); 142.0 – 178.0
Body weight (kg)	64.9 (10.7); 41.0 – 93.2
Body mass index (kgm^{-2})	24.6 (3.0); 18.0 – 32.2
Post-stroke duration (y)	7.7 (4.5); 1.0 – 20.8

Remarks: SD: standard deviation

In item 13, 35 participants received the maximum item score when they stepped forward with the non-paretic leg, while 18 of them received the maximum item score when stepped forward with the paretic leg. In item 14, 18 participants received the maximum item score when they were SLS on the non-paretic leg. Meanwhile only 9 of them received the maximum item score when SLS with the paretic leg (Table 4.2). Only 4.8% participants received the maximum total score in BBS_1, which was less than the other BBS formations (BBS_2: 6.3%; BBS_3: 12.6% and BBS_4:14.3%). There were significant differences in the scores for the 2 items (Item 13: mean difference = 0.4, Z = -3.10, $p = 0.002$; Item 14: mean difference = 1.6, $Z = -5.49$, $p \leq 0.001$).

The BBS total scores ranged from 48.4 to 50.7. The BBS_1 total score was the lowest and BBS_4 was the highest on average. Mean FMA-LE score, FTSTS completion time, walking speed and ABC score were 23.9, 21.29 s, 0.837 ms^{-1} and 72.8 respectively (Table 4.2). The Friedman's ANOVA revealed a significant difference between four BBS total scores ($X^2 = 87.41$, $p \leq 0.001$). Post-hoc analysis showed that each model was significantly different from the others (Table 4.3). Cronbach's α value of BBS_1 was the highest (0.721) among the four formulations (BBS_2: 0.715; BBS_3:7.02; BBS_4:7.07).

Table 4.2 Scoring frequencies on items 13 & 14, mean BBS total scores and other outcome measures

	Frequency of scorings				
	0	1	2	3	4
Item 13 non-paretic leg in front	11	3	11	20	18
Item 13 paretic leg in front	6	4	6	12	35
Item 14 SLS on non-paretic leg	10	2	9	24	18
Item 14 SLS on paretic leg	20	24	5	5	9
	Mean (SD) range				
BBS$_1$	48.4 (4.4) 35 – 56				
BBS$_2$	48.9 (4.3) 37 – 56				
BBS$_3$	50.0 (4.4) 37 – 56				
BBS$_4$	50.7 (4.4) 39 – 56				
FMA-LE	23.9 (5.9) 13 – 34				
FTSTS (sec)	21.29 (11.67) 11.01 –84.19				
10mWT (m/sec)	0.837 (0.324) 0.22 – 1.89				
ABC	72.8 (17.4) 31.25 – 100				

Remarks:

ABC: Activities-specific Balance Confidence Scale , BBS: Berg Balance Scale, FMA-LE: Fugl- Meyer Assessment- Lower Extremity, FTSTS: Five Times Sit to Stand Test, SLS: Single Leg Stance, 10mWT: Ten Metre Walk Time

Table 4.3: Results of Wilcoxon's signed-rank test and mean differences of the 4 BBS total score formations.

Pair	Z	*p*	Mean difference (95%CI)
$BBS_1 - BBS_2$	3.15	0.002	0.5 (0.2, 0.7)
$BBS_1 - BBS_3$	5.63	≤ 0.001	1.6 (1.2, 2.0)
$BBS_1 - BBS_4$	5.83	≤ 0.001	2.1 (1.6, 2.6)
$BBS_2 - BBS_3$	4.56	≤ 0.001	1.1 (0.7, 1.6)
$BBS_2 - BBS_4$	5.63	≤ 0.001	1.6 (1.2, 2.0)
$BBS_3 - BBS_4$	3.15	0.002	0.5 (0.2, 0.7)

BBS: Berg Balance Scale

Result of ROC analysis showed that total score of the 4 BBS formations unable to discriminate faller from non-faller in the current study (BBS_1: area under curve (AUC) = 0.52, $p = 0.85$; BBS_2: AUC = 0.51, $p = 0.88$; BBS_3: AUC = 0.53, $p = 0.74$; BBS_3: AUC = 0.60, $p = 0.75$). The BBS total scores demonstrated significant correlation with the FMA-LE score, FTSTS completion times, walking speed and ABC scores ($p \leq 0.001$ in each case) (Table 4.4). The correlation coefficients of the BBS_1 total scores with the other outcome measures were larger than those of the other models. Steiger's Z test showed that the BBS_1 total scores had stronger correlations with the walking speeds and ABC scores than the BBS_3 or BBS_4. In addition, the BBS_1 total scores showed significantly stronger correlation with FTSTS completion times than the BBS_4 total scores. No significant difference in strength of correlation existed between the $BBS_1$and BBS_2 total scores (Table 4.5).

Table 4.4 Spearman's rho relating the four BBS total scores with the other outcome measures.

	Spearman's rho correlation coefficient			
Outcome measure	BBS_1	BBS_2	BBS_3	BBS_4
FMA-LE	***0.658****	0.621	0.633	0.570
FTSTS	***-0.604****	-0.563	-0.566	-0.491
10mWT	***0.717*** *	0.703	0.646	0.631
ABC	***0.618****	0.559	0.557	0.468

Remarks:
* indicates the highest correlation coefficients for each outcome measure
All the correlation coefficients were significantly different from 0 at the $p \leq 0.001$ level

Table 4.5 Results of Steiger's Z test comparing the strength of correlation of BBS1 total scores with the other outcome measures with those of the BBS2, BBS3 and BBS4 total scores.

	Steiger's Z		
Outcome measures	BBS_2	BBS_3	BBS_4
FMA-LE	1.11	1.01	1.88
FTSTS	-1.16	-1.44	-2.27*
10mWT	0.46	3.00*	1.98*
ABC	1.67	2.32*	3.00*

Remarks:
* indicates a difference in correlation strength significant at the $p \leq 0.05$ level of confidence
ABC: Activities-specific Balance Confidence Scale , BBS: Berg Balance Scale, FMA-LE: Fugl- Meyer Assessment- Lower Extremity, FTSTS: Five Times Sit to Stand Test, 10mWT: Ten Metre Walk Time.

4.4.5.5.3 Discussion

Results of the current study supported the hypotheses that the item scores were significantly lower when a participant stepped forward with the non-paretic leg in item 13, and stand on the paretic leg in item 14. The BBS_1 total score was significantly lower than those alternative formulations and demonstrated a smaller ceiling effect. This formulation also demonstrated marginally stronger correlations with other outcome measures.

Item 13 challenges a participant's postural control by reducing the lateral base of support (Speers et al., 1998). In this study, the participants scored significantly lower on Item 13 when required to place their paretic leg posteriorly. Jonsson and colleagues (Jonsson et al., 2005) reported that the rear leg is the primary weight-bearing leg in tandem stance. Jonsson demonstrated that with a healthy adult the body weight supported by the rear leg is double that of the forward leg (Jonsson et al., 2005). In light of that, participants with chronic stroke have poorer postural stability when placing their paretic leg posteriorly during weight-bearing activities.

As would be expected, the scores in item 14 were significantly lower when the participants stood on their paretic leg alone. Flansbjer has reported similar findings (Flansbjer et al., 2012). In another study by Goldie et al, the participants were required to transfer as much of their body weight as possible onto one leg and found that the weight transferred to the paretic leg was significantly less than that of the non-paretic leg (Goldie et al., 1996).

Our results show that the selection of the weight-bearing leg in items 13 and 14 would affect the BBS total score. The BBS_1 formulation where the participant placed the non-paretic leg in front in item 13 and stood on the paretic leg in item 14 gave the lowest total score. Fewer participants received the maximum item scores in this combination, confirming that these were the more challenging conditions of these two test items. It should also be noted that fewer participants achieved the maximum score with the BBS1 formulation, indicated that the ceiling effect was dampened. Salbach and colleagues (Salbach et al., 2001) reported that even in the acute phase of stroke, 26% of the stroke survivors received the maximum score in BBS. By bringing down the item scores with the more challenging conditions, BBS_1 might be more capable in detecting changes of balance ability over time in participates with high physical function.

In fact, when the BBS was first developed, it called for testing both legs alternately in items 13 and 14 (Berg et al., 1989). The protocol was later amended to testing the participant’s preferred leg only (Berg et al., 1989; Berg et al., 1992). A Rasch analysis by Straube et al (Straube et al., 2013) found that Items 13 and 14 of the BBS showed a high level of variance in the item scores in participants with stroke, with infit mean square values of 2.0 and 1.6 respectively. An infit mean square value larger than 1.4 indicates an unusually high level of variance (Straube et al., 2013). Straube hypothesized that the self-selection in items 13 and 14 caused item misfit in assessing participants with chronic stroke. Participants with poor balance were speculated to select their non-paretic legs, leading to higher item scores; while some with better balance might select their paretic leg, resulting in a lower item 13 and item 14 scores and greater variance, impairing the scale's precision (Straube et al., 2013). The results of the current study support Straube's hypothesis and the need to standardize the testing procedures for items 13 and 14 of the BBS. Besides, analysis of the internal consistency of the variation showed that BBS_1 demonstrated highest inter items correlation. However, the result was not conclusive since the differences between Cronbach's α value were small.

The fall rate in the current study (22%) was lower than that reported in previous studies (36 to 50%) (Harris et al., 2005; Mackintosh et al., 2006). Our ROC analysis showed that none of the 4 BBS formulations was able to discriminate between fallers and non-fallers. Similar results have been reported by Harris and colleagues (Harris et al., 2005) who examined the relationship between falls and several outcome measures in a sample of 99 subjects with chronic stroke. They found no difference in BBS score between fallers and non-fallers and that a low BBS score was not a risk factor for multiple falls (odds ratio = 1.1, 95%CI = 0.91 to 1.1).

A significant moderate correlation was found between all four BBS total scores and FMA-LE scores. Similar correlations between BBS total score and FMA-LE score have been reported previously for participants with stroke (e.g. $r = 0.661$) (Kim et al., 2012). However, Steiger's Z test did not reveal significant differences in the strength of correlations between the FMA-LE scores and any of four BBS total scores tested

(Steiger's Z > 1.96). The FMA-LE assesses the quality of reflexes, coordination and voluntary movements. That could explain why the leg selected in items 13 and 14 did not significantly affect the strength of correlation between the BBS total scores and the FMA-LE score.

Significant correlations were found among the four BBS total score formulations and FTSTS completion times. This could be explained by the fact that there are several items in the BBS which assess a participant's ability to transit between sitting and standing (items 1, 4 and 5). The correlation between BBS_1 total score and FTSTS completion time was significantly stronger than that of the BBS_4 score (Steiger's Z = -2.27). This reflects the fact that the postural stability on the paretic leg affects the ability to sit down and stand up. Chou et al documented (Chou et al., 2003) that stroke survivors who took longer to rise from sitting also demonstrated greater asymmetry in weight bearing during the manoeuvre. Also, Lomaglio and Eng (Lomaglio & Eng, 2005) have reported that weight-bearing symmetry at lift off from a chair (defined as the ratio between the peak vertical forces applied through the paretic and non-paretic legs) is negatively correlated in stroke survivors with the time needed to complete the sit-to-stand movement ($r = -0.565$, $p \leq 0.01$).

Significant moderate correlations were shown between all four BBS total scores and walking speed. Patterson and colleagues (Patterson et al., 2007) have reported that BBS total score is a significant predictor of 30-foot walking velocity for participants with stroke who demonstrated moderate to severe motor deficits (adjusted $R^2 = 0.42$, $p \leq$

0.001). The strength of correlation between BBS_1 and walking speed was significantly stronger than those of BBS_3 and BBS_4 ($BBS_{3:}$ Steiger's Z = 3.00; BBS_4 Steiger's Z = 1.98), suggesting that the weight-bearing ability of paretic leg might affect walking speed. Aruin and colleagues (Aruin et al., 2012) have previously demonstrated a 10.5% increase in walking speed after weight-bearing training in a study of 9 participants with chronic stroke. Their results revealed that improving weight-bearing ability in the paretic leg could improve walking speed after stroke.

Significant correlations were found between all four BBS total score formulations and the ABC scores. Balance performance and subjective balance confidence are well known to be correlated in participants with stroke (Botner et al., 2005). The BBS_1 formulation correlated more strongly with the ABC scores than either BBS_3 or BBS_4 ($BBS_{3:}$ Steiger's Z = 2.32; BBS_4 Steiger's Z = 3.00). To the best of our knowledge, no study has previously investigated the influence of the weight-bearing ability of a paretic leg on subjective balance confidence. These results suggested that subjective balance confidence is influenced by the weight-bearing ability of a paretic leg for stroke survivors.

Results of the within-subject comparison showed that leg selection could significantly affect the BBS total score. Although the mean differences between the four BBS formulation were small (0.5-2 points), It should be noted that the reliability of BBS is almost excellent in participants with chronic stroke. The standard error of mean of BBS for participants with chronic was ranging from 1.49 to 1.79 points (Flansbjer et al., 2012; Hiengkaew et al., 2012; Liston & Brouwer, 1996). The minimal detectable change was calculated to be 2.5 points according to Liston et.al. (Liston & Brouwer, 1996) study. The effect of leg selection could still influence the interpretation of the BBS total score. The results also showed that there were fewer participants receiving the maximum score in BBS_1 and standardizing the selection of weight bearing leg could effectively reduce the variation. Further research would be required to determine whether the improved standardization and a dampened of ceiling effect could improve the ability of BBS in categorizing patients and/or detecting change over time or not.

It should be emphasized that the participants recruited in our study had relatively good functional mobility and balance ability. The results are only applicable to stroke survivors who fulfil the study's inclusion criteria and should not be directly applied to other participants with severe mobility deficits. Note too that several functional assessments were conducted within one assessment session, so fatigue might have influenced some participants' performance. Another limitation of this study was that it did not assess item 13 and item 14 performance with the participants' preferred legs, though they are usually tested in conducting a BBS assessment. Besides, it was speculated that challenging BBS formulation (i.e. BBS_1) might lead to greater test-retest variability. The reliability of the four formulations of BBS is worth further investigation.

4.4.5.5.4 Conclusions

The BBS total score is significantly lower for stroke survivors if they place the paretic legs posteriorly in item 13, and to stand on the paretic leg in item 14. The result indicated that standardization of the BBS protocol would be necessary. A BBS total score developed in that way (BBS_1) demonstrates a dampened ceiling effect and stronger correlation with FTSTS completion time, walking speed and ABC score than alternative formulations. Further research was required to investigate if the improved standardization and a dampened of ceiling effect could make BBS a more useful tool in assessing people with stroke with high physical function.

4.4.6 Sit to stand performance

4.4.6.1 Rationale of measurement

Sit to stand was one of the fundamental movements in daily living. Dall and Kerr (Dall & Kerr, 2010) reported that an adult performed 55 cycles of sit-to-stand on each non-working day in average. The ability to perform sit to stand independently and efficiently, therefore, would be critical for participating in daily activities (Gill et al., 1995). Transferring from a sitting to standing position requires sufficient sensory integration (Lord et al., 2002), lower limb muscle strength (Lord et al., 2002; McCarthy et al., 2004) and balance control (Lord et al., 2002; Ng, 2010; Whitney et al., 2005). In a longitudinal follow up study, Janssen and colleagues (Janssen et al., 2010) have reported that around 17% of the people with stroke unable to rise from sitting independently at 1-year post-stroke. Although sit to stand is an important movement in daily activity, no previous study has investigated the effects of TENS combined with TOT on the sit to stand performance. In view of the functional relevance of the sit to stand movement, the sit to stand performance should be measured in the current study.

4.4.6.2 Five Times Sit to Stand Test (FTSTS)

The Five Times Sit to Stand Test (FTSTS) was designed by Csuka and McCarty in 1985 (Csuka & McCarty, 1985). It is used to assess the functional muscle strength of the lower limbs, especially in older adults. The participant is instructed to stand up from sitting for five times as quickly as possible without using the hands for support. The total duration is recorded in seconds. The FTSTS is an outcome measure commonly used in stroke rehabilitation (Belgen et al., 2006; Byl, 2012; Mong et al., 2010; Ng, 2010; Weiss et al., 2000; Wong et al., 2012). The test has been shown to have excellent intra-rater reliability (ICC $_{3,1}$ = 0.970 to 0.976), inter-rater reliability (ICC $_{3,2}$ = 0.999) and test-retest reliability (ICC$_{2,1}$= 0.994 to 1.000) in people with chronic stroke (Mong et al., 2010). In addition, good test-retest reliability has also been reported with healthy participants of different ages (Bohannon et al., 2010; Bohannon, 2011). Although Mong and colleagues demonstrated that the FTSTS times had good reliability under their adopted protocol (Mong et al., 2010), the testing procedures of FTSTS were not well standardized across different clinical studies.

The time for performing the FTSTS has also been found to be negatively correlated with knee flexor strength in both the affected leg (ρ = -0.753) and the unaffected leg (ρ = -0.830) in people with chronic stroke (Mong et al., 2010). In addition, the FTSTS times were found to be negatively correlated with lower limb muscle strength among older women (McCarthy et al., 2004), and a useful independent predictor of deterioration of ability in the activities of daily living over subsequent 3 years for the elderly (Zhang et al., 2013).

4.4.6.3 Cross-sectional study 2: Foot placements and arm positions affect the Five Times Sit to Stand Test completion time of people with chronic stroke.

Although FTSTS have been widely used to assess the sit to stand performance in people with stroke, some shortcomings of the test still existed. Initial foot placement would affect the distance travelled by the body's centre of gravity (CoG) and leverage in rising from a seat (Cameron et al., 2003; Kawagoe et al., 2000; Shepherd & Koh, 1996). Kawagoe and colleagues (Kawagoe et al., 2000) demonstrated that forward displacement of CoG during standing-up was significantly longer in normal foot placement when compared to posterior foot placement, which was referred to 10cm behind the normal position. However, initial foot placement was not clearly mentioned in previous studies adopting FTSTS as an outcome measure (Annweiler et al., 2011; Belgen et al., 2006; Bohannon et al., 2007; Byl, 2012; Duncan et al., 2011b; McCarthy et al., 2004; Mong et al., 2010; Ng, 2010; Weiss et al., 2000; Wong et al., 2012; Zhang et al., 2013). The effect of normal and posterior foot placement on FTSTS times has not been investigated in previous studies.

The result of a previous biomechanical study demonstrated that arm position could influence the momentum of upper body generated during sit to stand, and restricted arm position would lead to the different strategy adopted by the participant when rising up from sitting (Carr & Gentile, 1994). However, arm position was not standardized across different clinical studies. People with stroke were sometimes instructed to cross their arms in front of the chest (Annweiler et al., 2011; Bohannon et al., 2007; Bohannon et al., 2010; Duncan et al., 2011b; McCarthy et al., 2004; Ng, 2010) or to put their hands on their thighs (Mong et al., 2010). In some published studies, the arm position was not even mentioned (Belgen et al., 2006; Byl, 2012; Weiss et al., 2000; Wong et al., 2012; Zhang et al., 2013). Augmented arm position, referred to the position of two hands gripping together with the shoulders flexed at 90^o and the elbows fully extended. Although augmented arm position was commonly used in clinical setting to facilitate sit to stand movement in people with stroke (Davies, 2000), the effect of different arm positions including augmented arm position on FTST times have not yet been investigated.

It was hypothesized that foot placements and arm positions during FTSTS would lead to a significant difference of the FTSTS times in people with stroke. The objectives of the present study were to investigate the effect of (1) 2 foot placements (normal and posterior placement) and (2) 3 arm positions (hands on thighs, arms crossed over chest, and augmented arm position with the elbow fully extended) on the FTSTS times of people with chronic stroke.

4.4.6.3.1 Methods

Participants

Forty-five community-dwelling people with chronic stroke were recruited from a local self-help group for stroke survivors. People with stroke were included in the study if they: (1) were aged 50 years or above, (2) had experienced a single stroke at least 1 year before the study, and (3) were able to stand up from a chair without any external support. People with stroke were excluded if they: (1) were unable to follow commands properly, (2) had an Abbreviated Mental Test score below 6 (Chu et al., 1995) , (3) were medically unstable, or (4) were suffering from other neurological or musculoskeletal disorders which could affect sit-to-stand performance. The Ethics Committee of the administrative institution approved the study protocol. The objectives and procedures of the study were clearly explained to all people with stroke, and they all signed written consent forms. The study procedure followed the guidelines set by the Declaration of Helsinki for human experiments.

Assessment procedure

This study was conducted in a university-based rehabilitation laboratory. An armless, height-adjustable chair was used in this study to ensure participants' hip were in 90 degrees flexion when seated. The people with stroke were instructed to stand up and sit down from a height-adjustable chair for 5 times as quickly as they could. The standardized instruction given for each trial was, “On the count of 3, please stand up and sit down 5 times as fast as you can.” The timing started when the participant’s back left the backrest and ended when their back touched the backrest after the 5th repetition. The time was recorded by hand using a digital stopwatch.

The effects of normal and posterior foot placement together with hands on thighs, arms crossed over chest and augmented arm position on FTSTS times were investigated in this study. Seat height was adjusted according to their lower leg length in all trials. The lower leg length was defined as the perpendicular distance between the fibular head and the floor when the participant sat on the chair with the knees in 90° of flexion and the ankles in the neutral position. This sitting position was also defined as the normal foot placement. Posterior foot placement was defined as having both heels positioned 10cm backwards from the normal foot placement. The setup was shown in Figure 4.1.

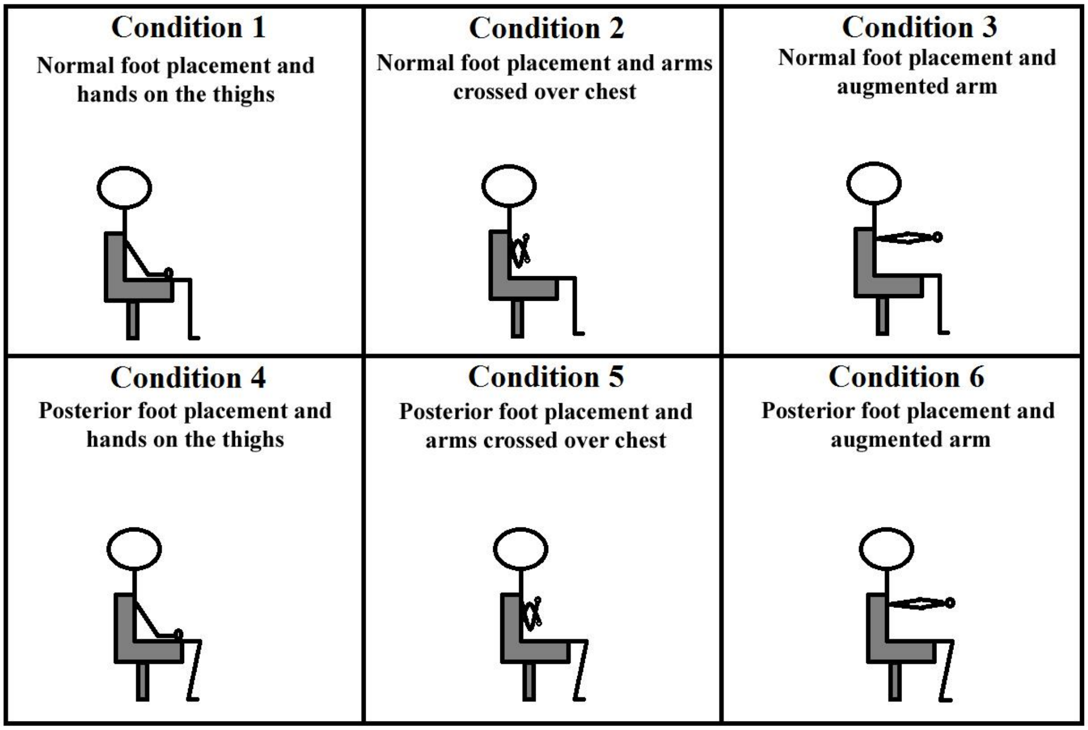


Figure 4.1. Diagram showing the 6 experimental conditions of sit to stand positions

Each participant was required to perform the FTSTS under 6 experimental conditions in a random sequence by drawing lots. Two trials were performed under each condition, with a 2 minutes rest between each trial to avoid fatigue. The 6 experimental conditions were as follows:

Condition 1: Normal foot placement and hands on the thighs.

Condition 2: Normal foot placement and arms crossed over chest.

Condition 3: Normal foot placement and augmented arm.

Condition 4: Posterior foot placement and hands on the thighs.

Condition 5: Posterior foot placement and arms crossed over chest.

Condition 6: Posterior foot placement and augmented arm.

Statistical analysis

Two-way repeated measures ANOVA were conducted to examine the significance of the observed relationship between 2 foot placements and 3 arm positions with FTSTS times. If the main effect of arm position were statistically significant, post hoc multiple comparison tests with Bonferroni adjustment would be used to evaluate the differences of FTSTS times between the 3 arm positions. The null hypothesis will be rejected if $p < 0.05$. All the statistical analysis was conducted with the help of version 16.0 of the SPSS for Windows software package.

4.4.6.3.2 Results

The demographic characteristics of the 45 people with stroke are shown in Table 4.6. Their mean age was 60 ± 5.6 years, with an average post-stroke duration of 7.1 ± 2.9 years. Table 4.6 shows the average FTSTS times with the different foot placements and arm positions. The mean FTSTS times for the 6 conditions ranged from 15.2 to 17.1 seconds.

Table 4.6. Demographic Characteristics of the Subjects of cross-sectional study 2 (n = 45).

Variables	n (%)
Gender (male/female)	32 (71)/13 (29)
Side of hemiplegia (Right/Left)	25 (56)/20 (44)
Cause of stroke (Ischemic/hemorrhagic)	28 (62)/17 (38)
	Mean ± SD (ranges)
Age (y)	60 ± 5.6 (50 - 70)
Height (m)	1.6 ± 6.8 (1.4 – 1.7)
Body weight (kg)	66.6 ± 10.1 (41 - 93)
BMI (kgm^{-2})	25.7 ± 3.1 (20.6 - 34.6)
Years poststroke (y)	7.1 ± 2.9 (2.4 - 16.9)

Remarks:
BMI: Body Mass Index

Two-way repeated measures ANOVA revealed no significant interaction between foot placement and arm position on the FTSTS times [$F_{2,88} = 0.632$, $p = 0.534$]. Both the main effect of foot placement and arm position were statistically significant with $F_{1,44} = 97.69$, $p < 0.001$ and $F_{2,88} = 3.873$, $p = 0.024$ respectively (Table 4.7). The significant main effect of foot placement indicated that the normal foot placement led to a significantly longer FTSTS time than the normal foot placement. Results of post hoc test showed that that the hands on thigh position led to significantly longer FTSTS times than the augmented arm position ($p = 0.014$).

Table 4.7: Average FTSTS times with different foot placements and arm positions.

Arm position	FTSTS times (s)			
	Normal foot placement	**Posterior foot placement**		
Arms on the thighs	17.1 ± 5.9	15.6 ± 5.9	#	†
Augmented arm position	16.8 ± 5.9	15.2 ± 5.9		
Arms crossed on the chest	17.1 ± 6.8	15.2 ± 5.5		
	*			

* Significant Main effect of foot placements ($p < 0.001$)
† Significant main effect of different arm positions ($p = 0.024$)
# Significant difference between arm positions ($p = 0.014$)

4.4.6.3.3 Discussion

This is the first published study to investigate the relationship between foot placement and arm position, and the FTSTS times of people with chronic stroke. Our results showed that both the foot placement and arm position could affect FTSTS times. Posterior foot placement in combination with augmented arm position, associated with faster FTSTS times in people with chronic stroke.

The average FTSTS times for the 6 conditions ranged from 15.2 to 17.1 seconds. These averages were comparable to those observed in previous studies that reported in people with chronic stroke (Belgen et al., 2006; Mong et al., 2010). Weiss and colleagues reported FTSTS times of 19.3 ± 2.4 seconds in people with chronic stroke (Weiss et al., 2000), but that study included only 7 participants with a mean age of 70 ± 2.4 years, whom were twenty years older than our participants.

Bohannon (Bohannon, 2006) had published a meta-analysis which demonstrated that the normal FTSTS times for healthy adults aged between 60 and 69 years was 11.4 seconds. It was expected that our participants with chronic stroke would take a longer duration to complete the FTSTS. It might be probably due to stroke-specific impairments such as muscle weakness, poor weight bearing on the paretic limb (Cameron et al., 2003), impaired balance (Cheng et al., 1998) and fear of falling (Aruin & Latash, 1995).

Consistent with the results of healthy adults that posterior foot placement could increase the speed of sit to stand (Kawagoe et al., 2000), our study also showed that posterior foot placement led to shorter FTSTS times with all 3 arm positions. Kawagoe and colleagues (Kawagoe et al., 2000) showed that placing the feet at 10 cm behind the normal foot placement was associated with significantly less anterior and abrupt displacement of the CoG, as well as a shorter distance between CoG and point of application at lift-off. The point of application was defined as the point where the compound vector of ground reaction force acting on. Shorter distance between CoG and point of application could reduce the demand on muscle forces required for a forward acceleration and backward braking. Posterior foot placement, therefore, could facilitate the sit to stand movement. In another study (Khemlani et al., 1999), posterior foot placement resulted in a significantly smaller hip flexion angle ($p < 0.05$) in the pre-extension phase of sit to stand. The smaller hip flexion angle implied a shorter distance that the trunk or upper body segment has to move forward to initiate the action of rising from a chair.

The reduced muscular effort required during rising from the seat when the feet are placed posteriorly could also explain shorter FTSTS times taken in posterior foot placement. Reduced tibialis anterior muscle activation during standing up had been found in posterior foot placement when compared with those of normal foot placement (Kawagoe et al., 2000). As tibialis anterior muscle activity provides an anterior rotatory force of shank on the ankle to bring the CoG forward and to stabilize the ankle (Khemlani et al., 1999), reduced tibialis anterior muscle activity reflected reduced muscular effort during standing up. In another study, maximum hip extension moment (32.7 ± 12.1 Nm) was found to be reduced when the feet were placed posteriorly by 10 cm when compared with the feet being placed by 10 cm forward (148.8 ± 7.5 Nm) during sit-to-stand.

The minimal detectable changes of FTSTS test was calculated according to published data from the study of Mong and colleagues (Mong et al., 2010). Using standard deviation of 7.5 seconds and mean ICC of 0.997 for test-retest reliability, 95% minimal detectable changes would be 1.14 seconds (Haley & Fragala-Pinkham, 2006). In average, FTSTS completion with posterior foot placement was 1.67 seconds shorter when compared with normal foot placement. Therefore, the change in FTSTS times was unlikely due to measuring error.

The present results revealed significantly shorter FTSTS times with the augmented arm position than the hands on the thighs position, There was, however, no significant interaction between foot placement and arm position. The augmented arm position might help to shift the CoG forward more efficiently, which could explain its association with faster FTSTS times. Carr and Gentile (Carr & Gentile, 1994) conducted a kinematic and kinetic analysis of arm position on sit-to-stand movements with force plate and videotaping on 6 healthy young males (Carr & Gentile, 1994). The augmented arm position similar to that of our study was shown to induce larger peak CoG momentum in both the horizontal and vertical directions than the restricted arm position. Carr and Gentile (Carr & Gentile, 1994) explained that the augmented arm position could generate greater propulsive force during a sit-to-stand manoeuvre (Carr & Gentile, 1994). As there is only one study examining the effects of arm positions on sit-to-stand manoeuvre, further biomechanical studies are warranted.

This study has several limitations. Only 2 foot placements and three arm positions were studied. A previous study (Camargos et al., 2009) has shown that different foot placement including spontaneous, asymmetric and symmetric foot placement would significantly affect the electromyographic activities of lower limb muscles. Whether other foot placements or arm positions could induce a greater effect on FTSTS times needs further investigation. Further study of the actual kinetics and kinematics of FTSTS with different arm positions is warranted. In view that our study design was cross-sectional, no causal relationships can be established. In addition, all people with stroke were required to perform FTSTS in 6 different conditions, certain degrees of learning and fatigue effects might affect our results. However, randomization of testing sequences by drawing lots and adoption of 2 minutes rest periods would help to minimize the learning and fatigue effects.

4.4.6.3.4 Conclusion

Posterior foot placement and augmented arm position were found to associate with shorter FTSTS times for people with chronic stroke. The study did not aim to identify an optimal starting position for the FTSTS test, but the results did highlight the fact that foot placement and arm position had a significant influence on the FTSTS times of stroke survivors. If the test is to be repeated with the same subject, standardizing the arm and foot positions in the test procedure is essential in clinical and research setting.

4.4.7 Walking capacity

4.4.7.1 Rationale of measurement

Walking dysfunction in people with stroke is characterized by slower walking speed (Bohannon et al., 1991; Dean et al., 2001; Dickstein, 2008; van de Port et al., 2008), lower walking endurance (Bohannon et al., 1991; Dean et al., 2001) and less stable in transitional movement such as sit to stand (Boukadida et al., 2015) and turning (Shiu et al., 2016). Using discriminate analysis, Perry and colleagues (Perry et al., 1995) reported that walking speed is the best parameter to classify the people with stroke having a different ambulatory ability.

Reduction of walking endurance might be due to inactivity (Michael et al., 2005) and poor cardiovascular fitness (Courbon et al., 2006; Salbach et al., 2014) in people with stroke. Bohannon and colleagues (Bohannon et al., 1991) have reported that approximately 50% of people with stroke considered walking distance was important or very important, which made walking distance the second important walking variable after independence in walking. A cross-sectional study conducted by Mayo and colleagues (Mayo et al., 1999) and our previous study (chapter 4) also reported that walking endurance was a significant predictor of the participation and level of community integration in people with stroke.

4.4.7.2 10-meters walk test (10mWT)

Participants' walking speed was measured by the 10mWT. After review of the literature, van Peppen and colleagues (van Peppen et al., 2007) suggested that 10mWT should be considered as a core outcome measure in stroke rehabilitation, as high-quality evidence has shown that 10mWT walking speed truly reflected the ability in mobility-related activities (van Peppen et al., 2007). Similarly, the Stroke Recovery and Rehabilitation Roundtable (Kwakkel et al., 2017) also recommended that the 10mWT should be one of the standardized measures to be used in every stroke recovery trial which concerning lower limb functions.

In this study, a 14 meters walkway was used to assess the comfortable walking speed. Two meters at the start and 2 meters at the end of the pathway were served for acceleration and deceleration (Ng et al., 2016a). Participants were instructed to walk at their comfortable walking speed. The travel duration was timed with a stopwatch. The test demonstrated excellent test-retest reliability (ICC = 0.94 to 0.99) (Collen et al., 1990; Flansbjer et al., 2005b), intra-rater reliability (ICC = 0.87 to 0.88) (Collen et al., 1990) and inter-rater reliability (ICC = 0.998) (Wolf et al., 1999) in assessing walking speed on people with chronic stroke. One practice trial was offered, and the averaged of three test trials were used for analysis.

4.4.7.3 6-meter Walk Test (6MWT)

The distance covered in a 6-Minute Walk Test (6MWT) (Eng et al., 2004) was used to assess walking endurance. The 6MWT was originally used to evaluate the exercise capacity of people with chronic heart failure (Guyatt et al., 1985) and respiratory diseases (Butland et al., 1982). The 6MWT distance demonstrated a strong correlation with maximal oxygen consumption in people with the chronic obstructive pulmonary disease (Wijkstra et al., 1994) and heart failure (Guyatt et al., 1985; Riley et al., 1992). After an extensive review of the literature, Solway and colleagues (Solway et al., 2001) concluded that the 6MWT is better tolerated and more reflective of ability in activities of daily living in people with cardiopulmonary diseases when compared with Shuttle Walk Test or 2-minute Walk Test.

The 6MWT has also been extensively used to measure the walking endurance in people with stroke (Dean et al., 2001; Eng et al., 2004; Mayo et al., 1999; Ng & Hui-Chan, 2009; Pohl et al., 2002; Pradon et al., 2013). Excellent test-retest reliability for the walking distance covered in 6MWT (ICC = 0.99) has been reported for the assessing walking endurance on people with chronic stroke (Eng et al., 2004). The 6MWT distance had also been demonstrated a strong association with level of stroke severity (Pohl et al., 2002), lower limb muscle strength (Pradon et al., 2013), balance performance (Pohl et al., 2002), level of participation (Mayo et al., 1999) and level of community integration (Kwong et al., 2017a).

In this study, participants were instructed to walk as much distance as possible at their own walking pace during the allotted time of 6 minutes on a 15-meter walkway. A colored tape was used to marked both ends and each 1-m increment of the walkway. Standardized verbal encouragements were given during the walk (Ng et al., 2011a). The assessment protocols followed those recommended by the American Thoracic Society (American Thoracic Society, 2002). A 15-meter walkway was used in the current study, instead of 30-meter walking, due to the restraint of space in our laboratory. The averaged of two test trials were used for analysis.

4.4.7.4 Timed Up and Go test (TUG)

The TUG was used to assess the functional mobility of subjects with stroke (Ng & Hui-Chan, 2005; Podsiadlo & Richardson, 1991). All subjects were required to stand up from a chair, walk forward 3 m, turn 180 degrees, walk back to the chair and sit down. Completion time of TUG was measured with a stopwatch. The TUG demonstrated excellent test-retest reliability in assessing subjects with stroke (ICC = 0.95) (Ng & Hui-Chan, 2005).One practice trial was offered, and the averaged of three test trials were used for analysis.

4.4.8 Community integration

4.4.8.1 Rationale of measurement

The residual physical and cognitive deficiency could result in a decrease in quality and quantity of physical participation and social interaction among stroke survivors (Santus et al., 1990; Trigg et al., 1999). Changed in social role, losing working ability as well as an unfriendly environment for could hinder the process of integration (Mukherjee et al., 2006). Promoting successful community integration after stroke should be the ultimate goal of rehabilitation. As Cott and colleagues (Cott et al., 2007) suggested, rehabilitation service should incorporate outcome that could examine the values of the service in enabling people to return to meaningful life. Thus, the assessment of the level of community integration was included in the current study.

4.4.8.2 ***Subjective Index of Physical and Social Outcome (SIPSO)***

The remarkable levels of physical impairment and functional limitation in people with stroke can affect their level of community integration. To provide a better understanding and record the level of community integration throughout the rehabilitation process in people with stroke, a comprehensive measure that evaluates rehabilitative outcomes from the perspective of those people with stroke is needed.

Divergent interpretations of community integration have led to the development of several instruments to measure the construct. Wilier and colleagues (Wilier et al., 1994) operationalised the inverse of “handicap” to develop the Community Integration Questionnaire. McColl and colleagues (McColl et al., 2001) developed the Community Integration Measure based on a model of community integration derived from groups of people with brain injuries. Finally, Wood-Dauphinee and colleagues (Wood-Dauphinee et al., 1988) developed the Reintegration to Normal Living Index based on the “Activity and Participation” component of the International Classification of Functioning Disability and Health model.

Although all of these instruments have been validated in populations with various neurological deficits, certain aspects relevant to the community integration of the stroke population have not been addressed. For example, the Community Integration Questionnaire neglected the subjective experience of the target population. In contrast, the Community Integration Measure fails to evaluate the level of engagement in the activities of daily living and social activities. For Reintegration to Normal Living Index, a previous study reported poor scoring agreement between people with stroke and persons knowledgeable about their condition (Tooth et al., 2003).

The Subjective Index of Physical and Social Outcome (SIPSO) questionnaire (Trigg et al., 1999; Trigg & Wood, 2000) was developed based on the normalisation approach (Wolfenberger, 1972). The normalisation approach advocates that people with disabilities should be able to enjoy patterns and conditions of life as close as possible to those that prevail in the wider community. The 10-item SIPSO have been reported as a valid and reliable tool for measuring the level of community integration in people with stroke (Kersten et al., 2004; Kersten et al., 2010; Trigg & Wood, 2000, 2003). Besides, the agreement of scoring between people with stroke and their carer was excellent (ICC = 0.95).

4.4.8.3 Cross-sectional study 3: An investigation of the psychometric properties of the Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome (SIPSO)

A growing body of clinical research in Europe and North America is adopting the SIPSO questionnaire as an outcome measure (Baseman et al., 2010; Fogg-Rogers et al., 2016; Harrington et al., 2010; Kersten et al., 2002; Kilbride et al., 2013; Lord et al., 2008; McKenna et al., 2015; Okoye et al., 2016; Plummer et al., 2014; Teale et al., 2013), but it is yet to be translated into Chinese, and neither has its reliability and validity been evaluated in a Chinese community. Culturally adaptation of the questionnaire is necessary as Chinese community might hold a different perspective on post-stroke care. For example, a recent study points out that post-discharge care and rehabilitation are tended to be neglected in policy in China (Chen et al., 2016).

The objectives of the current study were, therefore, to translate and culturally adapt the SIPSO questionnaire to develop a Chinese (Cantonese) version (SIPSO-C) and evaluate the psychometric properties of SIPSO-C for use in assessing the level of community integration amongst community-dwelling people with stroke in Hong Kong and southern China.

4.4.8.3.1 Methods

The standard forward-backwards translation procedure described by Beaton and colleagues (Beaton et al., 2000) was adopted to translate the original English version of the SIPSO questionnaire into Cantonese, the Chinese variety spoken in southern China and Hong Kong. Two independent bilingual translators whose mother tongue is Cantonese produced two translated Chinese version of SIPSO. One of the translators was a registered physiotherapist, and the other was a professional translator who had received no training in the fields of medicine or rehabilitation. Back-translation was conducted by another two independent professional translators who were blinded to the original (English) version of the SIPSO questionnaire.

An expert panel comprising five registered physiotherapists, with 3 to 20 years of clinical experiences, was established. This expert panel was tasked with reviewing, consolidating the meanings of items in and making cultural adaptations to the translated version of SIPSO. Equivalence between the translated and original versions in four areas, namely, semantic, idiomatic, experiential and conceptual, was examined by the panel. A pilot version of SIPSO-C was produced after consensus had been reached amongst the panel members. Finally, five community-dwelling people with chronic stroke were invited to complete the pilot version of SIPSO-C, with the aim of evaluating its fluency, clarity, and comprehensibility. The final version of SIPCO-C was then confirmed with reference to the feedback received from these 5 participants with stroke.

Assessment procedure

Eligible people with stroke were invited to come to the Balance and Neural Control Laboratory of The Hong Kong Polytechnic University for the first assessment (Day 1). All assessments were conducted by a registered physiotherapist (KWH). Twenty-five participants were randomly selected to revisit the laboratory after a one-week interval through the drawing of lots. The relatively short period (one-week interval) between 2 assessments were to minimize the chance that real changes of their condition or significant events in their life occurred. These 25 people with stroke completed the SIPSO-C questionnaire a second time (Day 2) to establish its test-retest reliability. The same rater (KWH) interviewed the people with stroke and filled out the SIPSO-C on both occasions (Day 1 and Day 2).

Participants

People with stroke were recruited from local self-help groups for individuals with cerebral vascular disease via a poster advertisement. People with stroke were eligible for this study if they 1) were aged > 55; 2) had received a stroke diagnosis at least 12 months previously; 3) were living in the community; and 4) had an Abbreviated Mental Test Score of 6 or above (Chu et al., 1995).

People with stroke were excluded if they were 1) medically unstable; 2) unable to give written informed consent; and/or 3) suffering from a comorbid neurological disease such as Parkinson’s disease, multiple sclerosis or traumatic brain injury. People with stroke who suffered from expressive dysphasia were not excluded given that they could give written consent.

The ethics committee of The Hong Kong Polytechnic University approved the study’s protocol, and the study was conducted in accordance with the principles of the Declaration of Helsinki for human experiments. The study’s objectives and procedures were explained to the participants, all of whom provided informed written consent before study commencement.

Outcome measures

Demographic characteristics, including age, sex, post-stroke duration, type of stroke, hemiplegic side and use of aids for outdoor ambulation were recorded. Participants' level of community integration was measured using the SIPSO-C questionnaire which was translated from the original SIPSO (Trigg et al., 1999; Trigg & Wood, 2000) as mentioned above (Appendix 4.4).

The SIPSO questionnaire was developed from the perspective of people with stroke. In the first phase of SIPSO's development, a qualitative study involving in-depth interviews with 30 community-dwelling people with stroke was conducted (Trigg et al., 1999), with the questionnaire items based on the results. Final item selection was then based on the comments and responses of another 100 community-dwelling people with chronic stroke (Trigg & Wood, 2000). These procedures ensured that all items were relevant to the concerns of the population with stroke. The SIPSO questionnaire comprises 10 items. Items 1-5 belong to the physical integration subscale, and items 6-10 to the social integration subscale (Kersten et al., 2004; Kersten et al., 2010; Trigg & Wood, 2000, 2003). Each item is rated on a 5-point scale (0-4). The maximum total score is 40, and higher scores indicate a better level of community integration.

Two studies (Kersten et al., 2004; Trigg & Wood, 2003) reported an excellent test-retest reliability of the English version of SIPSO (ICC = 0.96) in 128 (Trigg & Wood, 2003) and 32 (Kersten et al., 2004) people with chronic stroke, respectively. In addition, the degree of scoring agreement between 48 people with stroke and their caregivers was high (ICC = 0.962) (Kersten et al., 2004; Trigg & Wood, 2003). The construct validity of the SIPSO has been established by its significant correlation with Reintegration to Normal Living Index scores ($r = 0.651$ to 0.758) (Trigg & Wood, 2003) and the Barthel Index ($r = 0.730$) (Trigg & Wood, 2000), Frenchay Activities Index ($r = 0.801$) (Trigg & Wood, 2000) and Nottingham Health Profile ($r = 0.671$) (Trigg & Wood, 2000). The SIPSO questionnaire and its subscale scores have also been shown to be responsive to a change in status over time, with an effect size of 0.240 to 0.267 (Trigg & Wood, 2003).

Comfortable walking speed was also measured to quantify the mobility level of people with stroke using the 10-metre walk test. Please refer to section 4.4.7.2 for details.

Geriatric Depression Scale (GDS) was used to evaluate the level of depression symptoms. Please refer to section 4.4.9.2 for details.

Statistical analysis

Descriptive statistics (mean, median and frequency) were used to summarise the demographic characteristics and responses to each individual item of the SIPSO-C questionnaire. The internal consistency of the questionnaire and its subscales was assessed by Cronbach’s α coefficients, ICC was used to assess their test-retest reliability.

The statistical model $ICC_{3,1}$ was selected because this model is suitable to measure the consistency of scoring between two occasions when the rater is fixed (Shrout & Fleiss, 1979). The kappa statistic was adopted to evaluate the agreement in item scores between the two rating occasions for the 25 participants asked to complete the SIPSO-C questionnaire twice.

The factor structure was evaluated using principal component analysis (Abdi & Williams, 2010), with the number of factors to be retained determined by the eigenvalue > 1 rule and inspection of the scree plot (Abdi & Williams, 2010). The varimax rotation method was also used to facilitate interpretation of the factor structure by optimising the factor loadings and producing a simplified factor structure. After varimax rotation, items with large factor loadings in the same factor were considered measuring a similar construct , and items with small loadings were considered to be noise (Abdi & Williams, 2010).

The Mann-Whitney U test was performed to compare the SIPSO-C scores of people with stroke with different demographic characteristics, including sex, hemiplegic side, age group, walking speed and risk of minor depression (based on GDS score). A cut-off of 65 years was used to divide the people with stroke into two age groups, thus allowing the results of the current study to be compared with those of a previous study (Trigg & Wood, 2003). For the walking speed, a 10-meter Walk test speed of $0.8ms^{-1}$ was adopted as the cut-off speed, since a speed lower than $0.8\ ms^{-1}$ indicated a limited community ambulation ability in people with stroke (Bowden et al., 2008; Perry et al., 1995). SPSS (Version 22.0. Armonk, NY: IBM Corp.) was used to conduct all of the statistical analyses. *p* values ≤ 0.05 were considered to be statistically significant.

4.4.8.3.2 Results

Ninety-two community-dwelling people with stroke were recruited between May 2014 and December 2015. Demographic characteristics of the people with stroke were summarised in Table 4.8. Twelve participants were classified as household ambulators (≤ 0.4 ms^{-1}), 40 as limited community ambulators (0.4 to 0.8 ms^{-1}) and 40 as community ambulators (> 0.8 ms^{-1}) (Bowden et al., 2008; Perry et al., 1995). Thirty-eight of them had a GDS score higher than 10, indicating that they were at high risk of minor depression (Sivrioglu et al., 2009).

The median total SIPSO-C score was 28, 5 of the people with stroke scored the maximum of 40 (Table 4.8). With regard to individual item scoring, the mean score of item 9 was the lowest and item 2 was the highest. Distribution of Item 2,5,10 was highly skewed with the skewness value lower than -1.0 (Bulmer, 2012) (Table 4.9).

Table 4.8. Demographic characteristics of people with stroke of cross-sectional study 3 (n = 92).

Characteristics	Mean ± SD (range)
Age (yr)	62.3 ± 5.6 (55-79)
Post-stroke duration (yr)	6.6 ± 5.0 (1-24)
BMI (kgm^{-2})	24.2 ± 3.0 (18.0-32.4)
Comfortable walking speed (ms^{-1})	0.76 ± 0.32 (0.09-1.89)
	Median ± IQR (range)
SIPSO-C total score	28 ± 10 (10-40)
Physical functioning subscale score	17 ± 6 (3-20)
Social functioning subscale score	12 ± 7 (2-20)
Geriatric Depression Scale score	8 ± 8 (0-28)
	Number (%)
Sex	
Male/Female	59 (64.1)/33 (35.9)
Hemiplegic side	
Left/Right	41 (44.6)/51 (55.4)
Type of stroke	
Ischaemic	54 (58.7)
Haemorrhagic	35 (38.0)
Mixed/Unknown	3 (3.3)
Use of walking aid outdoors	
Unaided	36 (39.1)
Stick/quadripod	53 (57.6)
Wheelchair	3 (3.3)

Remarks:

BMI: Body Mass Index; IQR: interquartile range; SD: standard deviation; SIPSO-C: Chines (Cantonese) version of Subjective Index of Physical and Social Outcome.

Table 4.9. Central tendency, variation, skewness and floor and ceiling effects of SIPSO-C and its items score (n=92).

Item	Mean (SD)	Median (IQR)	Skewness	Number (%) of minimum score	Number (%) of maximum score
1	3.0 (0.9)	3 (2)	-0.76	2 (2.2)	36 (39.1)
2	3.5 (0.7)	4 (1)	-1.26	1 (1.1)	55 (59.8)
3	3.0 (0.9)	3 (2)	-0.59	0 (0.0)	29 (31.5)
4	3.0 (1.1)	3 (2)	-0.92	2 (2.2)	34 (37.0)
5	3.4 (1.0)	4 (1)	-1.66	1 (1.1)	47 (51.1)
6	2.8 (1.1)	3 (2)	-0.59	1 (1.1)	21 (22.8)
7	2.2 (1.1)	2 (2)	0.13	6 (6.5)	12 (13.0)
8	2.6 (0.9)	3 (1)	-0.06	0 (0.0)	13 (14.1)
9	1.7 (1.3)	1 (2)	0.53	18 (19.6)	10 (10.9)
10	3.1 (0.8)	3 (1)	-1.31	2 (2.2)	24 (26.1)
SIPSO-C total score	28.3 (6.6)	28 (10)	-0.30	0 (0)	4 (4.4)

Remarks:
CI: confidence interval; ICC: intra-class correlation coefficient; SIPSO-C: Chines (Cantonese) version of Subjective Index of Physical and Social Outcome.

The SIPSO-C questionnaire demonstrated a high level of internal consistency, (Cronbach’s α = 0.83) (Table 4.10). Both the SIPSO-C total score and physical and social integration subscale scores demonstrated excellent reliability (ICC > 0.8) (Portney & Watkins, 2000), The kappa statistic revealed that for all items, the level of agreement between the two assessment occasions was unlikely to be the result of chance ($p <$ 0.001) However, a fair level of agreement (kappa: 0.21 to 0.40) for item 8 was found (Viera & Garrett, 2005) (Table 4.11). The characteristics of the sub-sample were comparable to the total sample.

Principal component analysis revealed a two-factor solution, which explained 63.2% of the variance, to be preferred. The initial eigenvalues of the one-, two- and three-factor solutions were 4.91, 1.52 and 0.74, respectively. Items 1-5 loaded onto factor 1, and items 6-10 onto factor 2 (Table 4.12). Item 6 cross-loaded onto both with a factor loading > 0.32. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy confirmed the sample size to be adequate, with KMO = 0.76. This KMO value is higher than the recommended threshold value of 0.6 (Yong & Pearce, 2013).

Table 4.10. Internal consistency of SIPSO-C (n = 92).

	Item	Corrected item-total correlation	Cronbach's α if item deleted
1	How much difficulty do you have in dressing yourself fully?	0.45	0.82
2	How much difficulty do you have moving around all areas of the home?	0.45	0.82
3	How satisfied are you with your overall ability to perform daily activities in and around the home?	0.53	0.82
4	How much difficulty do you have shopping for and carrying a few items (1 bag of shopping or less) when at the shops?	0.50	0.82
5	How independent are you in your ability to move around your local neighbourhood?	0.50	0.82
6	How often do you feel bored in your free time at home?	0.64	0.80
7	How would you describe the amount of communication between you and your friends/associates?	0.63	0.81
8	How satisfied are you with the level of interests and activities you share with your friends/associates?	0.64	0.83
9	How often do you visit friends/others?	0.46	0.83
10	How do you feel about your appearance when out in public?	0.46	0.82

Scale	Cronbach's α
SIPSO-C	0.83
Physical integration subscale	0.76
Social integration subscale	0.80

Remarks:
SIPSO-C: Chines (Cantonese) version of Subjective Index of Physical and Social Outcome.

Table 4.11. Test-retest reliability of SIPSO-C (n = 25).

Item	Kappa statistic	*p*-value
1	0.63	< 0.001
2	0.78	< 0.001
3	0.71	< 0.001
4	0.47	< 0.001
5	0.53	< 0.001
6	0.53	< 0.001
7	0.57	< 0.001
8	0.38	< 0.001
9	0.60	< 0.001
10	0.68	< 0.001

	ICC (3,1)	95% CI	
		Upper	Lower
Total score	0.866	0.720	0.939
Physical functioning subscale	0.850	0.689	0.931
Social functioning subscale	0.898	0.782	0.954

Remarks:
CI: confidence interval; ICC: intra-class correlation coefficient.

Table 4.12. Rotated factor matrix of SIPSO-C based on principal components analysis with varimax rotation.

Item	Factor loading	
	1	2
1	0.67	
2	0.83	
3	0.76	
4	0.73	
5	0.68	
6	0.43	0.64
7		0.84
8		0.78
9		0.80
10		0.73
Variance explained (%)	31.6%	31.6%
Kaiser-Meyer-Olkin measure of sampling adequacy	0.76	

Factor loadings < 0.32 are suppressed.

The Mann-Whitney U test results revealed that the people with stroke at high risk of minor depression (GDS score > 10: $U = 555.0$; $p \leq 0.001$) and with limited community walking ability (10-metre Walk test speed ≤ 0.8: $U = 726.5$; $p = 0.012$) scored significantly lower on the SIPSO-C questionnaire. No significant differences in SIPSO-C scores were found amongst the different sex ($U = 861.5$; $p = 0.361$), hemiplegic side ($U = 957.5$; $p = 0.489$) and age groups (< 65 vs ≥ 65) ($U = 878$; $p = 0.765$) (Table 4.13).

Table 4.13. Results of Mann-Whitney U test: Comparison of SIPSO-C scores of people with different characteristics (n = 92).

Characteristics		Number of people with stroke	Median (IQR)	Mann-Whitney U	*Z*	*p* value
Sex	Male	49	28 (10)	861.5	-0.913	0.361
	Female	33	30 (10)			
Hemiplegic side	Left	41	29 (11)	957.5	-0.693	0.489
	Right	51	28 (9)			
Age	< 65	63	28 (10)	878	-0.299	0.765
	≥ 65	29	29 (11)			
Geriatric Depression Scale > 10	Yes	38	24 (9)	555.0	-3.742	>0.001†
	No	54	31 (9)			
Comfortable walking speed ≤ 0.8 ms^{-1}	Yes	52	25 (12)	726.5	-2.379	0.017 *
	No	40	30 (10)			

Remarks:
IQR: interquartile range.
* $p \leq 0.05$, †$p \leq 0.001$.

4.4.8.3.3 Discussion

This is the first study to translate and culturally adapt the Chinese (Cantonese) version of the SIPSO questionnaire. The satisfactory internal consistency and excellent test-retest reliability of SIPSO-C had been demonstrated. Subgroup comparison based on GDS score and walking speed indicated that, people with stroke at high risk of minor depression and with limited community ambulation ability, scored significantly lower on the SIPSO-C questionnaire. Results of this study suggest that the SIPSO-C questionnaire is a reliable instrument for measuring the level of community integration in Cantonese-speaking community-dwelling people with stroke.

The Cronbach α values for the SIPSO-C questionnaire and sub-scales fell within the acceptable range of 0.75 to 0.90 (Tavakol & Dennick, 2011). None of the Cronbach α value exceeded 0.9, indicating that none of the questionnaire items was likely to be redundant. The excellent test-retest reliability demonstrated by the SIPSO-C questionnaire and its subscales indicated that the questionnaire is a reliable instrument for recording the level of community integration throughout the rehabilitation process in people with stroke. Having the same raters conduct the assessment on two occasions within a week rendered the chances of a real change in condition very low.

The strength of the agreement amongst the item scores ranged from moderate to high (kappa = 0.47 to 0.78) for all items except item 8 (kappa = 0.38). Item 8 (How satisfied are you with the level of interests and activities you share with your friends/associates?) may be considered less concrete than the other items. Moreover, this item does not ask respondents to consider a specific time frame, and thus their responses may have been overly influenced by recent experiences. For example, a pleasurable social gathering within the one-week interval between assessments could have influenced their perception of the degree of satisfaction in question.

The median SIPSO-C questionnaire score in the present study (28 ± 10) was higher than those (19.8 to 26) reported in previous studies using SIPSO (Kersten et al., 2004; Kilbride et al., 2013; Lord et al., 2008; McKenna et al., 2015; Trigg & Wood, 2003). Lord and colleagues (Lord et al., 2008) reported a mean SIPSO questionnaire score of 21.0 to 21.5, whereas McKenna and colleagues (McKenna et al., 2015) reported a mean score of 19.82 to 23.69. These two studies (Lord et al., 2008; McKenna et al., 2015) investigated the efficacy of novel community rehabilitation services for people with stroke in the subacute phase, and their results indicated that people with stroke who were newly returned to the community exhibited lower levels of community integration. There were several explanations for the discrepancies in these findings. First, physical capacity was generally poorer within the first three months post-stroke for people with stroke with moderate to severe stroke (Jorgensen et al., 1995). Second, compensatory strategies for and confidence in independent living in the community might take time to develop.

Two studies with larger sample sizes (n = 261 (Trigg & Wood, 2003) and n = 315 (Kersten et al., 2004)) reported a median SIPSO questionnaire score of 26. Both of those studies (Kersten et al., 2004; Trigg & Wood, 2003) distributed the questionnaire to people with stroke in accordance with records provided by health service agencies. Thus, people with stroke who were isolated and had poor community ambulation ability could be recruited. For example, 24% of the 315 people with stroke examined by Kersten and colleagues were unable to walk independently in the 10-metre walk test (Kersten et al., 2004). In addition, some of those recruited by Trigg and Wood lived in residential care accommodation (Trigg & Wood, 2003). Subgroup analysis showed the participants receiving residential care service to score significantly lower on the SIPSO questionnaire (16.5 versus 27; $p = 0.03$) (Trigg & Wood, 2003) relative to those not receiving such care. In contrast, the majority of participants with stroke in our study were active members of local self-help groups, thus it is not surprising that they would exhibit better community integration.

The physical integration subscale scores in the current study were higher than those for the social integration sub-scale. Teale and colleagues (Teale et al., 2013) suggested that a sub-scale score higher than or equal to 15 is indicative of a good level of integration. Distribution of scoring was found to be negatively skewed in all items of the physical integration subscale. In addition, 60.9% had achieved a good level of physical integration. Of the five items in that subscale, four are partially influenced by respondents’ mobility, namely, item 2 (difficulties moving at home), item 3 (satisfaction in performing daily activities), item 4 (difficulties in shopping) and item 5 (independence in outdoor ambulation). Personal factors such as good mobility may explain the satisfactory levels of physical integration in this study. A disability-friendly community can also facilitate community integration in people with stroke. For example, metro stations in Hong Kong are all equipped with lifts, allowing people with stroke to move from the railway platform to street level with little difficulty.

In contrast to the generally positive physical integration results, only 22.8% of the people with stroke in this study reported a good level of social integration (social integration subscale score > 15), and the median score of item 9 (How often do you visit friends/others?) was 1 only. Most of the participants said that they were usually visited by friends or relatives, rather than vice versa, which may explain the low scores for this item.

The results of principal component analysis suggested that the SIPSO-C questionnaire has a two-factor structure, with items 1 to 5 loading onto factor 1 and items 6 to 10 onto factor 2. This factor structure and item-loading pattern agreed with those reported in previous studies on the SIPSO questionnaire (Kersten et al., 2010; Trigg & Wood, 2000, 2003). The first factor, namely, *physical integration*, assesses the ability to perform physical activities which are important to daily activities and functioning in the community, such as dressing (item 1), the ability to ambulate at home (item 2) and in the community (items 3 and 4), and the ability to shop (item 5). On the other hand, the second, *social integration*, assesses the three distinct areas of boredom (item 6), social interaction (items 7-9) and self-image (item 10) (Trigg & Wood, 2000).

Consistent with Trigg and Woods' findings (Trigg & Wood, 2003), item 6 (How often do you feel bored with your free time at home?) cross-loaded onto both factors in this study. Trigg and Woods reported item 6 in the original SIPSO questionnaire to have a factor loading of 0.449 for factor 1 (physical integration) and of 0.578 for factor 2 (social integration) (Trigg & Wood, 2003). These results indicate that in addition to reducing social interaction, impaired physical capacity may also contribute to boredom in people with stroke. Indeed, a qualitative study involved 8 Hong Kong older adults (age > 60 years) reported that these participants considered assisting in household chores and taking care of their grandchildren to constitute their family role in Hong Kong (Cheng et al., 2008). Inability to fulfil that role was thus likely to induce a sense of boredom.

With regard to between-group differences, people with stroke at high risk of minor depression (GDS score > 10) were found to score significantly lower on the SIPSO-C questionnaire when compared with those who have a GDS score lower than 10. Several cross-sectional studies have also reported depression levels to be significantly associated with or able to predict the level of community integration in people with stroke (Chau et al., 2009; Obembe et al., 2013; Pang et al., 2007). For example, GDS score was reported to be a predictor of London Handicap Scale, in 188 chronic people with stroke ($\beta = -0.27$; $p < 0.001$) (Chau et al., 2009). The Hamilton Depression Scale score was also shown to be significantly correlated with Reintegration to Normal Living Index score ($r = -0.373$; $p = 0.006$) and to be one of its independent predictors ($\beta = -0.255$; $p = 0.008$) in 90 community-dwelling people with chronic stroke

(Obembe et al., 2013). Finally, a study of 63 community-dwelling people with chronic stroke showed GDS score to be an independent predictor of Reintegration to Normal Living Index score (β = -0.404; $p \leq 0.001$) (Pang et al., 2007).

People with stroke who walked slower than 0.8ms^{-1} were also found to score significantly lower on the SIPSO-C questionnaire. The selection of the cut-off speed of 0.8ms^{-1} was based on Perry and colleagues (Perry et al., 1995) showed that the people with stroke with an average walking speed above 0.8ms^{-1} were predicted to be independent community ambulators. Only a few studies (Liu et al., 2015; Mayo et al., 1999) had reported the influence of walking capacity on the level of community integration in people with stroke. A previous study had reported that walking endurance measured with distance covered by the 6-minute walk test predicted the level of community integration measured with Return to Normal Living Index (Mayo et al., 1999). However, neither the strength of association nor the R^2 value of the model was reported (Mayo et al., 1999). Results of the current study revealed that comfortable walking speed has an influence on the level of community integration in community-dwelling people with stroke. The high predictive power of walking speed in community ambulation ability might explain the result.

No significant differences in SIPSO-C scores were found amongst the people with stroke in the different sex, hemiplegic side and age groups. Amongst the 315 people with chronic stroke involved in Trigg and Wood's study (Trigg & Wood, 2003), no significant differences in SIPSO questionnaire or subscale scores were found in the different sex and age groups (< 65 or 65-74; $p > 0.05$). Similarly, Kersten and colleagues also reported no difference between the SIPSO questionnaire scores of men and women amongst 372 people with chronic stroke ($p = 0.29$).

The results of this study should be considered in light of several limitations. First, the participants were recruited from self-help groups for people with stroke. The sample was thus self-selecting and likely to have a higher level of community integration. It is recommended that relatively isolated people with stroke be recruited in future studies using the SIPSO-C questionnaire. Second, the convergent and predictive validity of SIPSO-C has not been established. Finally, the test-retest reliability of SIPSO-C was evaluated with only a one-week interval between the assessments. This relatively short interval minimised the chances of a real change in the participant's status, but it is possible that the memory effect influenced the results.

4.4.8.3.4 Conclusions

This is the first study to translate and culturally adapt the Chinese (Cantonese) version of the SIPSO questionnaire. The satisfactory internal consistency and excellent test-retest reliability of SIPSO-C had been demonstrated. A two-factor structure has been identified, which is comparable to the structure of the original SIPSO. Results of this study suggest that the SIPSO-C questionnaire is a reliable instrument for measuring the level of community integration in Cantonese-speaking community-dwelling people with stroke.

4.4.9 Psychological well-being

4.4.9.1 Geriatric Depression Scale

The Chinese version of the Geriatric Depression Scale (GDS) (Chan, 1996) was used to assess participants' level of depressive symptoms. The scale comprises 30 dichotomous (yes or no) questions, for a total score of 30, with a higher score indicating a higher level of depressive symptoms. A GDS score higher than 10 indicates a high risk of minor depression in people with stroke (sensitivity = 0.69; specificity = 0.75) (Sivrioglu et al., 2009). Good test-retest reliability has been demonstrated for the Chinese version of the GDS in a sample of 461 elderly participants (ICC = 0.85) (Chan, 1996).

4.4.9.2 Activities-specific Balance Confidence Scale

The Chinese version of the Activities-specific Balance Confidence Scale (ABC) (Mak et al., 2007) was used to assess the participants' confidence in balance during certain activities of daily living. The ABC consists of 16 items, each referring to a specific daily activity. The participants were asked to score their confidence level about maintaining their balance in each activity on a scale of 0 to 100. A score of 100 represented complete confidence in performing that activity without losing balance while a score of 0 represented no confidence at all (Mak et al., 2007). This instrument has been reported to have excellent test-retest reliability for participants with chronic stroke (ICC = 0.85) (Botner et al., 2005).

4.5 Ethical Considerations

The Ethics Committee of The Hong Kong Polytechnic University approved the protocol. All participants with stroke signed a written consent form before participation (Appendix 4.5, 4.6). All studies were conducted in accordance with the Declaration of Helsinki for human experiments. The study protocol of the RCT presented in chapter 5 and 6 was prospectively registered with ClinicalTrials.gov (Uniform Resource Locator: http://www.clinicaltrials.gov; unique identifier: NCT02152813).

4.6 Summary

This chapter describes the general methodology that will be adopted in the following chapters. Moreover, results of cross-sectional studies 1 and 2 presented in this chapter provide insight in how to standardise the assessment procedure of BBS and FTSTS test. Results of cross-sectional study 2 also showed that by selecting the paretic leg as the primary weight-bearing leg, the ceiling effect of BBS could be dampened. Results of cross-sectional study 3 reveal that SIPSO-C is reliability and valid instrument. Thus, these results support the use of SIPSO-C in assessing the level of community integration of people with stroke living in Hong Kong. Although the SIPSO-C was found to be valid and reliability, only a few studies have investigated the association between physical functions and level of community integration in people with stroke.

The following chapter will explore the relationship between mobility functions and level of community integration in people with stroke to justify the use of SIPSO-C in the subsequence randomised controlled trial.

Chapter 5

Relationship between motor functions and community integration in people with stroke

This chapter has been published by the author of this thesis.

Kwong P, Ng S, Chung R, Ng G. A structural equation model of the relationship between muscle strength, balance performance, walking endurance and community integration in stroke survivors. PLoS One. 2017;12(10):e0185807. (Appendix 5.1)

5.1 Abstract

Muscle weakness, impaired balance performance and reduced walking capacity are common physical impairments following a stroke. However, only a few studies have evaluated the relationship between lower-limb motor functions and level of community integration in people with stroke. The objectives of this study were to determine (1) the direct and indirect associations of strength of paretic lower limb muscles with the level of community integration, and (2) the direct association of walking endurance and balance performance, with the level of community integration in community-dwelling people with stroke.

In this cross-sectional study of 105 people with stroke, the Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome (SIPSO-C) was used to measure the level of community integration. Lower-limb strength measures included isometric paretic ankle muscle strength and isokinetic peak torque of knee extension and flexion. The Berg Balance Scale (BBS) and the 6-minute walk test (6MWT) were used to evaluate balance performance and walking endurance, respectively.

Structural equation model (SEM) analysis revealed that the distance covered in the 6MWT had the strongest direct association with the SIPSO-C scores ($\beta = 0.41$, $p < 0.001$). An increase of one standard deviation in the 6MWT distance resulted in an increase of 0.41 standard deviations in the SIPSO-C score. Moreover, paretic dorsiflexor

strength ($\beta = 0.18$, $p = 0.044$) and the BBS score ($\beta = 0.21$, $p = 0.021$) had direct associations with the SIPSO-C score.

The results of the proposed model suggest that rehabilitation training focusing on improving walking endurance and balance performance, as well as paretic ankle dorsiflexor muscle strengthening in community-dwelling people could optimize the level of community integration in people with stroke.

5.2 Introduction

Stroke is a major cause of motor impairment and disability worldwide (Walsh et al., 2015b). The residual physical and cognitive deficiencies after stroke can reduce both the quality and the quantity of the survivor’s social participation and interaction (Santus et al., 1990; Trigg et al., 1999). Impaired physical and cognitive functions, changes in social roles, the inability to work and poor adaptability to the physical environment can hinder the process of community integration for people with stroke, which in turn can lead to social isolation (Mukherjee et al., 2006). A previous study reported that only 11% of community-dwelling people with stroke were completely satisfied with their level of community integration (Pang et al., 2007).

Promoting successful community integration after a stroke is one of the ultimate goals of stroke rehabilitation. Identification of predictors for community integration can help researchers and clinicians to develop new treatment strategies to enhance the process of community integration after hospital discharge. Obembe et al. (Obembe et al., 2013) reported that age, the geriatric depression scale (GDS) score and the motor assessment scale score were significant predictors of stroke survivors’ scores on the return to normal living index (Return to Normal Living Index; $R^2 = 41.0\%$). Chau et al. (Chau et al., 2009) showed that GDS score ($\beta = -0.41$), gender ($\beta = 0.11$), age ($\beta = -0.13$) and living in a residential care institute ($\beta = -0.11$) significantly predicted the London handicap scale score ($R^2 = 71.0\%$). Physical functioning, such as balance performance measured with the Berg Balance Scale (BBS), was an independent predictor of the Return to Normal Living Index score ($\beta = 0.36$) (Pang et al., 2007). Although walking endurance measured with the 6-minute walk test (6MWT) predicted the level of community integration as measured by the Return to Normal Living Index, neither the strength of the association nor the R^2 value of the model was reported (Mayo et al., 1999).

Muscle weakness is a common physical impairment following a stroke (Bohannon, 2007). The concentric paretic knee extension torque measured with an isokinetic dynamometer has been shown to be significantly correlated with self-paced sit-to-stand duration ($r = -0.72$) (Lomaglio & Eng, 2005), comfortable walking speed ($r = 0.61$) (Flansbjer et al., 2006), maximum walking speed ($r = 0.65$ to 0.85) (Flansbjer et al., 2006; Suzuki et al., 1990) and speed of walking up stairs ($r = -0.58$) (Flansbjer et al., 2006). Isometric paretic ankle dorsiflexor and plantarflexor strength were significantly correlated with the comfortable walking speed ($r = 0.77$ and 0.83, respectively) and maximum walking distance ($r = 0.68$ and 0.76, respectively), which measures the distance the subject is able to walk before stopping due to fatigue (Bohannon, 1989). Moreover, paretic ankle dorsiflexor strength was found to be an independent predictor of the timed up and go test completion time ($R^2 = 27.5\%$)(Ng & Hui-Chan, 2013) and the 6MWT distance covered ($R^2 = 48.4\%$) (Ng & Hui-Chan, 2012). The strength of the paretic lower limb muscles was a strong predictor of functional performance (Ng & Hui-Chan, 2012; Ng & Hui-Chan, 2013), including walking endurance (Mayo et al., 1999) and balance (Pang et al., 2007), which were identified as independent predictors of the level of community integration. Thus, muscle strength might have a strong influence on the level of community integration, as mediated by the level of functional performance. However, no studies have evaluated the relationship between paretic lower-limb muscle strength and level of community integration in people with stroke.

In accordance with the International Classification of Functioning, Disability and Health model (World Health Organization, 2001), it was hypothesised that paretic lower-limb muscle strength would have a direct association with balance performance and walking endurance, and thus be indirectly associated with the level of community integration in people with stroke. The objectives of this study were to determine (1) the direct and indirect associations of the muscle strength of the paretic lower limb with the level of community integration, and (2) the direct associations of balance performance and walking endurance with the level of community integration in community-dwelling people with stroke.

5.3 Methods

5.3.1 Procedure

Eligible people with stroke were invited to come to the Balance and Neural Control Laboratory of The Hong Kong Polytechnic University for the assessment. All assessments were conducted by a registered physiotherapist (KWH). All of the assessments were conducted by the same physical therapist in one session. Please refer to section 4.5 for the details on ethical consideration.

5.3.2 Participants

Please refer to section 4.3 for details.

5.3.3 Outcome measures

5.3.3.1 Level of community integration

The SIPSO-C questionnaire was used to measure the level of community integration. Please refer to section 4.4.8.2 for details.

5.3.3.2 Isokinetic knee muscle strength

Isokinetic knee muscle strength was measured with the isokinetic dynamometer. Please refer to section 4.4.2.2 for details.

5.3.3.3 Isometric ankle muscle strength

Isometric ankle muscle strength was assessed with the hand-held dynamometer. Please refer to section 4.4.2.3 for details.

5.3.3.4 Balance performance

Balance performance was assessed with the Berg Balance Scale (BBS). Please refer to section 4.4.5.4 for details.

5.3.3.5 Walking endurance

Walking endurance was assessed with the 6-minute walk test. Please refer to section 4.4.7.3 for details.

5.3.3.6 Depression symptoms

The level of depression symptoms was quantified using the geriatric depression scale (GDS). Please refer to section 4.4.9.1 for details.

5.3.4 Statistical analysis

Statistical analyses were conducted with SPSS (version 22.0. Armonk, NY: IBM Corp.) in conjunction with AMOS (version 23.0, Chicago: IBM SPSS). A *p* value of 0.05 or less was considered to indicate statistical significance. The participants' demographic characteristics are summarised with descriptive statistics.

The statistical analyses of the relationship between the SIPSO-C and the functional outcomes were conducted in two stages. In the first stage, partial correlation analysis was used to evaluate the strength of associations between the SIPSO-C score and other physical outcomes after controlling for the effects of age, gender and the GDS score. The variables that demonstrated a significant correlation with the SIPSO-C score were further analysed with multiple linear regression with a stepwise approach. To avoid the inflation of type 1 errors, a Bonferroni correction was applied in the partial correlation analyses. Regression analysis was used to identify the set of variables that could independently explain part of the variance of the SIPSO-C score. Similarly, paretic lower-limb muscle strength demonstrated a significant partial correlation with functional performance and was further analysed by multiple linear regression, with functional performance as the dependent variable. The variance inflation factor was used to assess the degree of multicollinearity in the regression models. A variance inflation factor greater than 10 indicated that a particular predictor demonstrated a strong linear relationship with other predictors in the model (Myers, 1990).

The second stage of the statistical analysis involved the development of a hypothesised model based on the results of the multiple regression analysis. It was hypothesised that muscle strength would directly influence functional performance and that functional performance would directly influence the SIPSO-C scores. The variables that were found to be significant predictors in the multiple regression analysis were selected to construct the model. Structural equation modelling (SEM) is a multivariate statistical analysis technique that estimates the strength of the direct and indirect relationships between sets of variables. The SEM was used to estimate the strength and significance of the hypothesised causal connections between the paretic lower-limb muscle strength, balance performance, walking endurance and SIPSO-C score. The SIPSO-C score and outcome measures at the functional level were considered to be *endogenous* variables. Paretic lower-limb muscle strength was considered to be an *exogenous* variable. An *endogenous* variable referred to the dependent variables which its value can be predicted by other variables in a causal model. An *endogenous* variable referred to the independent variable that its values are causally independent from other variables in the model.

A path diagram was used to represent the interconnections of each variable in the model. In the path diagram, a single-headed arrow indicates a direct association, with the arrowhead pointing to the dependent variable and its tail from the independent variable. A curved arrow indicates a correlation between two variables. An indirect association signifies that an independent variable could influence the dependent variable, mediated by another variable.

The model fit was assessed with the comparative fit index (CFI) and the standardised root mean square residual (SRMR) (Hu & Bentler, 1999). If either index showed a poor fit of the data to the hypothesised model, the model would be revised according to the recommendations given by the modification index, which estimates the effect on the chi-square statistic of adding an additional path to the model (Whittaker, 2012). A modification index value larger than 3.84 for a specific path indicates that adding the path to the model could significantly improve the model fit (Whittaker, 2012). The minimal sample size for the SEM was suggested to be at least 15 cases per predictor in the hypothesised model. Thus, a sample of 105 stroke survivors was sufficient to conduct SEM, as 7 predictors were adopted in this study.

5.4 Results

One-hundred and five community-dwelling stroke survivors (60% male) were recruited for this study. The mean time since stroke was 6.2 years, and the subjects' mean age was 61.0 years. The majority were living with family or friends (87.6%), and only eight (7.6%) were still in the workforce (Table 5.1).

Table 5.1. Demographic characteristics of the participants and results of the physical assessments (n = 105).

Variable	Frequency (%)
Gender (male/female)	63 (60.0)/42 (40.0)
Side of hemiplegia (right/left)	57 (54.3)/48 (45.7)
Type of stroke (ischaemic/haemorrhagic/mixed)	59 (56.1)/43 (41.0)/3 (2.9)
Living with care giver (yes/no)	92 (87.6)/13 (12.4)
Working (yes/no)	8 (7.6)/97 (92.4)
Education level (primary or below/secondary/college or above)	31 (29.5)/60 (57.1)/14 (13.3)
Using walking aid (yes/no)	69 (65.8)/36 (34.2)
Using ankle-foot orthosis (yes/no)	6 (5.7)/99 (94.3)
	Mean ± SD (range)
Age (y)	61.0 ± 6.9 (50.0 to 79.0)
Time since stroke (y)	6.2 ± 4.9 (1.0 to 24.0)
Paretic ankle dorsiflexor strength (kg)	8.5 ± 5.0 (0.6 to 23.7)
Paretic ankle plantarflexor strength (kg)	13.4 ± 5.6 (2.3 to 28.4)
Paretic knee extension torque (Nm)	23.7 ± 14.2 (4.0 to 85.0)
Paretic knee flexion torque (Nm)	7.53 ± 6.2 (0.0 to 26.0)
6MWT (m)	219.7 ± 84.4 (35.0 to 452.8)
	Median, IQR (range)
AMT	10, 1 (7 to 10)
BBS	48, 7 (17 to 56)
GDS	9, 8 (0 to 28)
SIPSO-C	28, 10 (10 to 40)

6MWT: 6-minute walk test; AMT: Abbreviated Mental Test; BBS: Berg Balance Scale; GDS: Geriatric Depression Score; IQR: interquartile range; SD: standard deviation; SIPSO-C: Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome

After controlling for the effects of age, gender and GDS score, isometric paretic ankle dorsiflexor strength, isokinetic paretic knee flexion torque, BBS scores and the distance covered in the 6MWT were found to demonstrate significant correlations with the SIPSO-C score. In addition, isometric paretic ankle dorsiflexor strength, isokinetic paretic knee extension torque and isokinetic paretic knee flexion torque, showed significant correlations with BBS scores and distance covered in the 6MWT, but isometric paretic ankle plantarflexor strength did not show such a correlation (Table 5.2).

Table 5.2. Partial correlation coefficients (controlling for GDS score, gender and age) between SIPSO-C score, functional performance and muscle strength (n = 105).

		Correlation coefficient						
Variable		1	2	3	4	5	6	7
1.	SIPSO-C	1						
2.	Paretic dorsiflexor strength	0.447**	1					
3.	Paretic plantarflexor strength	0.218	0.234	1				
4.	Paretic knee extension torque	0.235	0.249	0.005	1			
5.	Paretic knee flexion torque	0.287	0.310*	0.054	0.598**	1		
6.	6-minute walk test	0.545**	0.413**	0.092	0.401*	0.458**	1	
7.	Berg Balance Scale	0.429**	0.402**	0.212	0.306*	0.249	0.464**	1

**p* <0.05; ***p* <0.001
GDS: Geriatric Depression Score; SIPSO-C: Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome.
p value was adjusted with Bonferroni correction.

Multiple linear regression analyses showed that isometric ankle dorsiflexor strength, BBS score and distance covered in 6MWT were significant predictors of the SIPSO-C score, with the whole model explaining 43.1% of the variance of the SIPSO-C score (Table 5.3). Isometric ankle dorsiflexor strength and isokinetic paretic knee flexion torque were significant predictors of the distance covered in the 6MWT (R^2 = 32.5%). Isometric ankle dorsiflexor strength and isokinetic paretic knee extension torque were significant predictors of the BBS score (R^2 = 25.0%). The variance inflation factors ranged from 1.07 to 1.55, indicating that some correlations exist between the predictors, though it may not affect the whole model.

Table 5.3. Hierarchical multiple regression analyses for the hypothesised model (n = 105).

Dependent variable	R^2	Independent variable	Standardised coefficient β	*p*
SIPSO-C score	0.431	DF strength	0.17	0.048*
		6MWT	0.41	<0.001**
		BBS	0.21	0.029*
6MWT	0.325	DF strength	0.30	0.001*
		Knee F torque	0.39	<0.001**
BBS	0.250	DF strength	0.40	<0.001**
		Knee Ext torque	0.21	0.018

6MWT: 6-meter walk test; BBS: Berg Balance Score; DF: dorsiflexor; Ext: extensor; F: flexion; SIPSO-C: Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome
**p* <0.05; ***p* <0.001

The hypothesised model was constructed based on the results of the hierarchical multiple regression analysis. The SEM supported the hypothesis that BBS score and the 6MWT distance would have a direct association with the SIPSO-C score. Isometric ankle dorsiflexor strength also had an indirect association with the SIPSO-C score, which was mediated by its influences on the BBS score and 6MWT distance covered.

Isokinetic paretic knee flexion torque had an indirect association with the SIPSO-C score mediated by the 6MWT distance. Isokinetic paretic knee extension torque had an indirect association with the SIPSO-C score mediated by the BBS score. The relationships between muscle strength, balance performance, walking endurance and level of community integration are illustrated in a path diagram (Figure 5.1). The regression coefficient shows that the 6MWT distance demonstrated the largest direct association with the SIPSO-C score ($\beta = 0.41$, $p < 0.001$), with every increase of one standard deviation in the 6MWT distance leading to an increase of 0.41 standard deviations in the SIPSO-C score. The results also show that the BBS score ($\beta = 0.21$, $p = 0.021$) and isometric dorsiflexor strength ($\beta = 0.18$, $p = 0.044$) had significant direct associations with the SIPSO-C score. Initially, the fit indices indicated that the model was a poor fit to the observed data, with CFI and SRMR values of 0.918 and 0.076, respectively. A modification index value of 14.37 indicated that correlation of the residual terms of BBS and 6MWT could significantly improve the model fit. The model fit became satisfactory after the model modification, with CFI and SRMR values of 0.993 and 0.031, respectively.

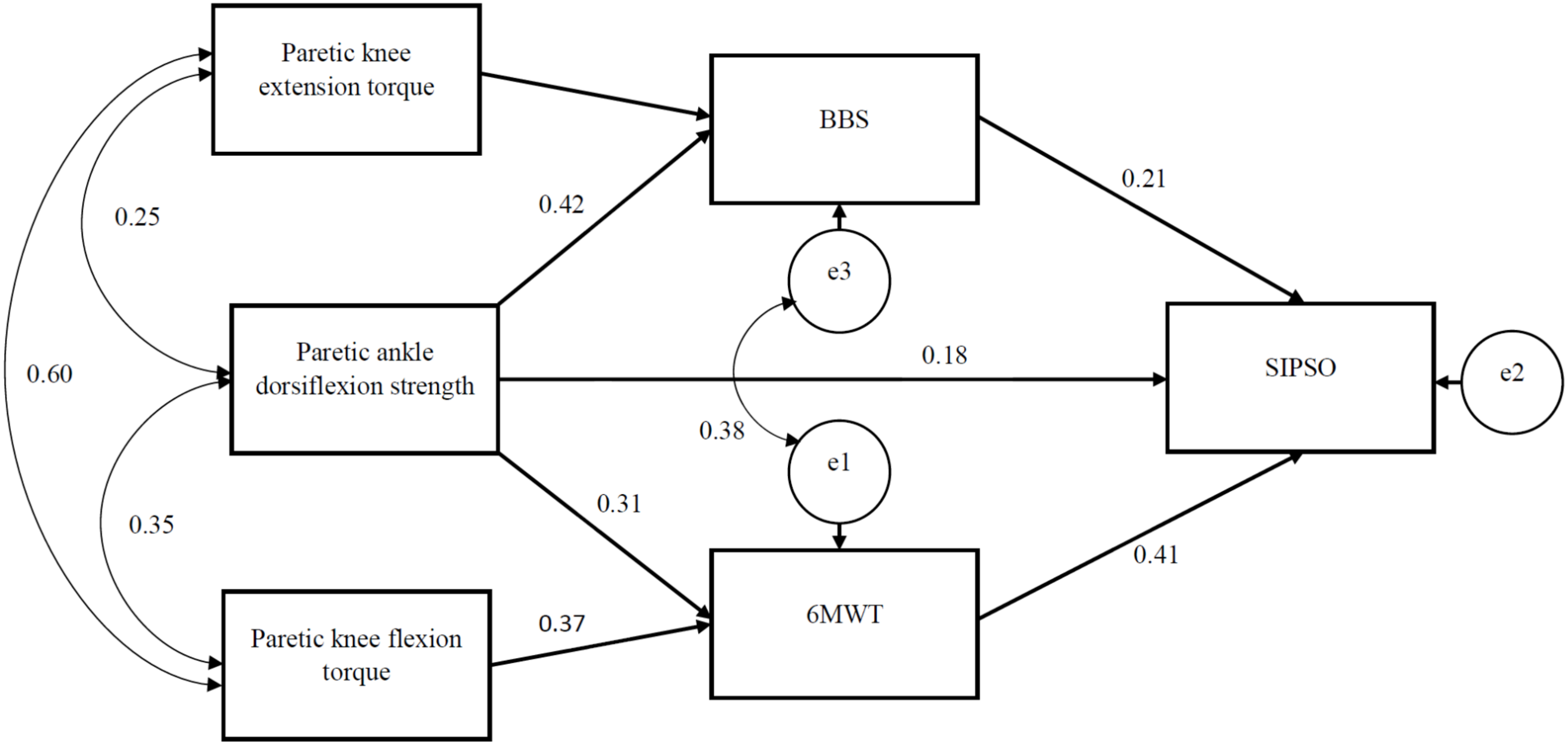


Figure 5.1. Path diagram shows the relationship between paretic lower-limb muscle strength, walking endurance, balance performance and level of community integration.

The values shown next to the single-headed arrows and double-headed curved arrows are the estimated standardised regression coefficients and estimated correlation coefficients, respectively. All coefficients are statistically significant ($p \leq 0.05$). e1, e2 and e3 represent the residual of predictions of 6MWT, SIPSO-C and BBS, respectively. 6MWT: 6-metre walk test; BBS: Berg Balance Scale; SIPSO-C: Subjective Index of Physical and Social Outcome.

5.5 Discussion

This study is the first to evaluate the relationship between paretic lower-limb muscle strength and the level of community integration in community-dwelling people with chronic stroke using structural equation modelling. Community integration is the ability to live in a usual setting, interact with different people, such as friends and neighbours, and participate in daily activities (Trigg et al., 1999). A meta-synthesis of the results of 18 qualitative studies revealed that the primary effects of stroke, such as limited mobility, impaired hand functioning and impaired communication ability, remain the major barriers to community integration in people with stroke (Walsh et al., 2015a). In this study, it was found that isometric paretic ankle dorsiflexor strength and isokinetic paretic knee flexion torque indirectly influenced the SIPSO-C score, mediated by the BBS score and the 6MWT distance. Moreover, isometric paretic ankle dorsiflexor strength demonstrated a significant direct association with the SIPSO-C score.

In this study, knee muscle strength was measured with an isokinetic dynamometer. A previous study reported that isokinetic training of the knee extensor and flexor in 15 people with chronic stroke resulted in higher levels of perceived participation, as measured by the participation domain of the Stroke Impact Scale, than in the no-treatment control group 5 months after training (Flansbjer et al., 2008). Those results suggested a causal relationship between isokinetic knee muscle strength and the level of participation in people with stroke. However, maximum isometric strength was used to measure ankle muscle strength in this study because some of the participants demonstrated severe ankle plantarflexor spasticity, which made measurement of the isokinetic strength of the ankle muscles difficult, due to the limited range of motion in the ankle. The maximum isometric ankle muscle strength was therefore measured instead of the isokinetic peak torque.

5.5.1 Influence of isometric ankle dorsiflexor strength

In this study, paretic dorsiflexor strength had been shown to have a direct positive association with the level of community integration in people with chronic stroke. This result indicates that paretic ankle dorsiflexor strength could have a strong influence on physical functions other than walking endurance and balance performance. Weak paretic ankle dorsiflexor is common after stroke. Isometric paretic ankle dorsiflexor strength of the paretic leg in 60 people with chronic stroke was reported to be only 35% of that of age-matched healthy control subjects (Dorsch et al., 2015).

During walking, ankle dorsiflexor weakness results in insufficient ankle clearance from the floor during the swing phase, and reduces the weight-bearing ability of the paretic leg in the mid-stance phase (Lin et al., 2006). Based on a sample of 68 people with chronic stroke, Lin et al. identified that isometric paretic ankle dorsiflexor strength was the primary predictor of comfortable walking speed ($R^2 = 0.30$) and the temporal asymmetry index, which measured the reduction of the single-leg support time on the paretic leg ($R^2 = 0.38$) (Lin et al., 2006). Shiu et al. (Shiu et al., 2016) also reported a significant correlation between isometric paretic ankle dorsiflexor strength and 360° turning time in people with chronic stroke ($r = -0.505$). Ankle dorsiflexor strength has been suggested to enhance the foot clearance from the ground during turning, thus shortening the completion time for 360° turning (Shiu et al., 2016).

Based on a sample of 73 community-dwelling people with chronic stroke, Ng and Hui-Chan identified that isometric paretic ankle dorsiflexor strength was the strongest predictor of the timed up and go performance ($R^2 = 27.5\%$) (Ng & Hui-Chan, 2013), which measures the participants' level of functional mobility. In this study, four of the five items (items 2 to 5) in the SIPSO-C questionnaire were found to be related to ambulatory ability (item 2: the ability to ambulate at home; items 3 and 4: satisfaction and independence of community ambulation; and item 5: shopping). This might explain why paretic ankle dorsiflexor strength contributes significantly to a higher level of community integration as measured by SIPSO-C in people with stroke.

5.5.2 Influence of BBS and indirect associations mediated by BBS

Balance performance measured with the BBS was found to have a direct positive association with the level of community integration. The BBS measures an individual's stability in performing functional tasks, such as sit-to-stand or stepping up and down. The results consistent with those of a previous study which demonstrated that the BBS score was an independent predictor of the Return to Normal Living Index score in a sample of 63 community-dwelling people with chronic stroke (Pang et al., 2007). Satisfactory balance performance probably augments the level of self-efficacy in carrying out daily activities and participating in social life, as demonstrated in a previous study (French et al., 2016). Fear of falling (Liu et al., 2015) and balance-related self-efficacy (Pang et al., 2007) were also found to be independent predictors of community integration in people with stroke. Both factors were strongly associated with balance performance (Belgen et al., 2006; Kim & Park, 2014). As fear of falling and balance-related self-efficacy measures were not included in this prediction model, the influence of balance performance in predicting the level of community integration might have been overestimated.

Paretic ankle dorsiflexor strength was found to have a significant direct association with the balance performance measured by BBS, and was indirectly associated with the SIPSO-C score. In contrast, one study reported that isometric ankle dorsiflexor strength was not significantly correlated with the balance performance measured with the functional reach test ($r = 0.06$) in a sample of 30 people with stroke (Kligyte et al., 2003). The functional reach test measures an individual’s ability to reach forward while standing, thus testing the limit of stability of the participants. However, another study found that compensatory movements, such as trunk movements, had a stronger influence on the functional reach test results than that of the actual forward displacement of the centre of pressure in healthy elderly subjects (Jonsson et al., 2003). The BBS assesses the stability of a participant in performing multiple functional movements, such as sit-to-stand, turning, stepping up and down, reaching and standing on one leg. BBS can be regarded as a more comprehensive tool for measuring balance performance. It is reasonable to suggest that paretic ankle dorsiflexor strength has a strong influence on balance performance because it plays an important role in maintaining ankle stability (Gefen, 2001) and facilitating foot clearance during walking (Lin et al., 2006).

Isokinetic peak knee extension torque was also found to be a significant predictor of balance performance measured by BBS. This result is consistent with the findings of Gerrits et al. (Gerrits et al., 2009) and Kobayashi et al. (Kobayashi et al., 2011) that isometric paretic knee strength had a moderate correlation with the BBS score (r = 0.64 to 0.76) in 17 and 10 people with chronic stroke, respectively. Weiss et al. (Weiss et al., 2000) also reported that 12 weeks of resistance training to strengthen the knee extensor and hip muscles led to significant improvement in the BBS score in seven people with chronic stroke.

5.5.3 Influence of 6MWT and indirect associations mediated by the 6MWT

The results of this study are consistent with other reports that walking endurance measured by the distance covered in the 6MWT is a significant predictor of the level of community integration (R^2 = 0.326) as measured by the social participation domain of the stroke impact scale in people with chronic stroke (Danielsson et al., 2011). It is not surprising that walking endurance has a significant association with the level of community integration. As stated earlier, four of the items in the SIPSO-C questionnaire assess the participants' abilities in outdoor ambulation. Satisfactory walking endurance could help a stroke survivor to attend social gatherings and visit friends or others (item

9). A randomised controlled trial on 15 people with chronic stroke demonstrated that 10 weeks of progressive resistance training of the knee extensors and flexors led to a 10% increase in the 6MWT distance (p <0.05). More importantly, the percentage changes in the 6MWT distance and the participation domain of the Stroke Impact Scale were strongly correlated (r = 0.74, p <0.01) (Flansbjer et al., 2008). These results (Flansbjer et al., 2008) further support the finding of the current study that isokinetic peak paretic knee flexion torque has a direct association with the 6MWT distance.

Despite having similar inclusion criteria, the results of this study are not consistent with the findings of Liu et al. (Liu et al., 2015). They reported that walking endurance measured by the 6MWT was not a significant predictor of the level of community integration (β = 0.083, p = 0.469) in a sample of 57 people with chronic stroke (Liu et al., 2015). The differences between the findings of the two studies may be partly explained by the different outcome measures. The community integration measure mainly assesses the subjective feelings of being accommodated in the community, whereas SIPSO-C evaluates the quality and level of engagement in the activities of daily living and social activities.

Paretic isometric ankle dorsiflexor strength was found to be a significant predictor of walking endurance measured by the 6MWT. This result is consistent with Ng and Hui-Chan's (Ng & Hui-Chan, 2012) finding that paretic isometric ankle dorsiflexor strength was the strongest independent predictor of the distance covered in the 6MWT, and that it could explain up to 48.8% of the variance (β = 0.75, p <0.001).

Isokinetic peak knee flexion torque was also found to be a significant predictor of walking endurance, as measured by 6MWT. This result is consistent with the findings of Flansbjer et al. (Flansbjer et al., 2006) that the paretic peak isokinetic knee flexion and extension torques were independent predictors of walking endurance measured by 6MWT (R^2 = 50% and 49%, respectively; $p < 0.05$) in a sample of 50 people with chronic stroke. In contrast, non-paretic peak knee flexion and extension torque were not significant predictors of walking endurance. A study of the influence of muscle weakness on the walking load of the weakened muscle (Krogt et al., 2012) revealed that weakness of lower limb muscles, including the tibialis anterior and hamstring, would lead to greater loading on the weakened muscles. The increased muscle loading could result in higher energy costs during walking and thus reduce the level of walking endurance (Krogt et al., 2012). It should be noted that the prediction model was based on the gait patterns of healthy participants (Krogt et al., 2012) and may not be applicable to people with stroke who walk with a pathological gait or with walking aids.

5.5.4 Model fitting

The modification index revealed that correlating the residual term of the prediction of the BBS score and the 6MWT distance could improve the model's fit. The result suggests the possible existence of *extraneous* variables that have not been specified in the model that influence both the BBS score and the 6MWT distance (Hermida, 2015). The presence of such *extraneous* variables is plausible because only paretic lower-limb muscle strength was used to predict the BBS score and the 6MWT distance in the current model. Other *extraneous* variables such as the strength of the non-paretic lower limb and severity of stroke might explain a significant portion of the variances of the BBS score and the 6MWT distance. However, further identification of the predictors of the BBS score and the 6MWT distance in people with stroke was beyond the scope of this study.

5.5.5 Limitations

This study has several limitations. First, the results may have limited generalisability because the subjects were recruited from local patient self-help groups and most of them were active members who participated in various social and volunteer activities. People with stroke over 80 years of age were not recruited. To improve the generalisability of the findings, relatively isolated and older people with stroke should be recruited in future studies. Second, isometric ankle muscle strength and isokinetic peak knee muscle torque were not measured in a functional position, and the measures might not adequately represent muscle strength during functional activities. Third, subgroup analysis for people with stroke with a low level of community integration has not been conducted. Understanding the barriers and facilitators of community integration in isolated people with stroke might provide more insights for formulation of rehabilitation programmes to facilitate integration. Fourth, the model only explained 43.1% of the variance of the SIPSO-C score. Given the multi-dimensional nature of community integration, muscle strength, walking endurance and balance performance are likely to be just some of many factors that influence community integration. Moreover, it is possible that other functional measures apart from walking endurance and balance performance could have a strong influence on the SIPSO-C score. The significant direct association of paretic isometric ankle dorsiflexor strength may reflect the absence from the model of other functional measures that are also strongly influenced by isometric ankle dorsiflexor strength. Lastly, this was a cross-sectional study, and thus causal relationships could not be established between the variables.

5.6 Conclusions

Paretic ankle dorsiflexor strength, walking endurance and balance performance were found to be significant predictors of the level of community integration in community-dwelling people with chronic stroke. Paretic ankle dorsiflexor strength influenced the level of community integration indirectly, mediated by walking endurance and balance performance. Although the hypothesised model explained only 43.1% of the variance in the level of community integration, results of this study have implications for facilitating the community integration of people with stroke. Hence, results of this chapter have justified the use of SIPSO-C in the randomised controlled trial which will be presented in the next chapter.

Chapter 6

Bilateral transcutaneous electrical nerve stimulation (TENS) improves lower-limb motor impairments in people with chronic stroke: a randomised controlled trial

This chapter has been published by the author of this thesis.

Kwong PW, Ng GY, Chung RC, Ng SS. Bilateral transcutaneous electrical nerve stimulation (TENS) improves lower-limb motor function in subjects with chronic stroke: a randomised controlled trial. Journal of the American Heart Association. 2018; 7(4), e007341. (Appendix 6.1)

6.1 Abstract

Transcutaneous electrical nerve stimulation (TENS) has been used to augment the efficacy of task-oriented training (TOT) after stroke. Bilateral intervention approaches have also been shown to be effective in augmenting motor function after stroke. The purpose of this chapter was to compare the efficacy of bilateral TENS (Bi-TENS) combined with TOT versus unilateral TENS (Uni-TENS) combined with TOT in improving lower-limb motor impairments in people with chronic stroke.

Eighty people with chronic stroke were randomly assigned into a Bi-TENS+TOT or a Uni-TENS+TOT group and they all underwent 20 sessions of training over a 10-week period. Outcome measures included the paretic limb muscle strength, Lower Extremity Motor Coordination Test (LEMCOT), limit of stability (LOS) and Berg Balance Scale (BBS). Each participant was assessed at baseline, after 5 and 10 weeks of training and 3 months after cessation of the training. The people in the Bi-TENS+TOT group showed greater improvement in paretic ankle dorsiflexor strength ($\beta = 1.32$; $p = 0.008$) as indicated by the significant interaction effects.

The application of Bi-TENS over the common peroneal nerve combined with TOT was superior to the application of Uni-TENS combined with TOT in improving paretic ankle dorsiflexor strength after 5 weeks of training.

6.2 Introduction

Results of the systematic review and meta-analysis which was presented in chapter 3 suggested that transcutaneous electrical nerve stimulation (TENS) is an effective adjunct treatment to enhance paretic lower-limb muscle strength (Jung et al., 2017; Tyson et al., 2013b; Yan & Hui-Chan, 2009), walking speed (Hussain & Mohammad, 2013; Ng & Hui-Chan, 2007, 2009; Tyson et al., 2013b), balance performance (Jung et al., 2017; Ng et al., 2016b; Tyson et al., 2013b) and functional mobility (Ng & Hui-Chan, 2009; Ng et al., 2016b; Park et al., 2014; Yan & Hui-Chan, 2009) in subjects with acute (Yan & Hui-Chan, 2009), subacute (Hussain & Mohammad, 2013; Ng et al., 2016b) and chronic (Jung et al., 2017; Ng & Hui-Chan, 2007, 2009) stroke. The therapeutic effects of TENS may be mediated via peripheral (Chen et al., 2005b; Hui-Chan & Levin, 1993; Levin & Hui-Chan, 1992) and central mechanisms (Celnik et al., 2007; Lai et al., 2016). At the peripheral level, TENS applied over paretic legs reduced the amplitude of the H-reflex (Levin & Hui-Chan, 1992) and lengthened the stretch reflex latency (Hui-Chan & Levin, 1993) and H-reflex latency (Chen et al., 2005b) in subjects with chronic stroke. At the cortical level, a single session of cutaneous electrical stimulation applied over a paretic hand reduced short-interval intracortical inhibition (Celnik et al., 2007) and enhanced cortical-muscular coupling during paretic thumb contraction (Lai et al., 2016). Previous studies from our laboratory (Ng & Hui-Chan, 2007, 2009) showed that 20 sessions of unilateral TENS (Uni-TENS) applied over the paretic legs combined with task-oriented training (TOT) led to greater improvement in lower-limb muscle strength and walking performance than placebo-TENS combined with TOT in subjects with chronic stroke.

Clinical studies have consistently demonstrated that bilateral motor training is beneficial (Sasaki et al., 2017) and superior to unilateral or conventional training for the recovery of motor control (Lin et al., 2010; Pandian et al., 2015), muscle strength (Pandian et al., 2015), the kinematics of upper limb movement (Lin et al., 2010; McCombe Waller et al., 2008; Summers et al., 2007), hand dexterity (Pandian et al., 2015) and upper-limb function (Sethy et al., 2016; Summers et al., 2007) after stroke. In addition, Sasaki and colleagues (Sasaki et al., 2017) reported that high-frequency transcranial magnetic stimulation over the cortical motor areas that represent both legs led to significantly greater improvement in the Brunnstrom Recovery Stage score than sham stimulation in subjects with acute stroke.

The mechanisms that mediate the effects of bilateral intervention in subjects with stroke include re-balancing interhemispheric inhibition (Stinear et al., 2014; Stinear & Byblow, 2004a, 2004b), activating the homologous neural networks in both hemispheres (Grefkes et al., 2010; Renner et al., 2005) and recruiting the neural networks of the contralesional hemisphere (Grefkes et al., 2010; Luft et al., 2004a; Summers et al., 2007). The use of transcranial magnetic stimulation on subjects with stroke, in which the maximum voluntary contraction of the non-paretic hand was combined with less-forceful contraction of the paretic hand, increased the cortical excitability of ipsilesional motor representation area of the hand when compared with contraction of the paretic hand alone (Renner et al., 2005). Grefkes and colleagues (Grefkes et al., 2010) used fMRI and dynamic causal modelling to demonstrate positive neural coupling between the ipsilesional primary motor cortex (M1) and the contralesional motor-related areas in bilateral synchronised hand movements in subjects with stroke (Grefkes et al., 2010). Similarly, Luft and colleagues (Luft et al., 2004a) reported that activation of the contralesional cerebrum and ipsilesional cerebellum had increased after 6 weeks of bilateral arm training, but not after dose-matched training based on the neuro-developmental principles that focused on the paretic upper limb in subjects with stroke. In the same study (Luft et al., 2004a), after exclusion of subjects without cortical activation changes from the analyses, the group with bilateral arm training also demonstrated greater improvement in hand function than the group with dose-matched exercises.

Clinical trials investigating the effects of bilateral lower-limb motor training in subjects with stroke are sparse. Johannsen and colleagues (Johannsen et al., 2010) reported that a 10-session bilateral lower limb training program with rhythmic auditory cueing led to greater improvement in step length and in the accuracy of the paretic foot-aiming task in subjects with chronic stroke when compared with a control group of patients who underwent upper limb training (Johannsen et al., 2010).

Current evidence shows that bilateral intervention could recruit spare neural substrates to enhance motor recovery (Grefkes et al., 2010; Luft et al., 2004a; Renner et al., 2005; Stinear et al., 2014; Stinear & Byblow, 2004a, 2004b; Summers et al., 2007). We thus hypothesised that the application of TENS over both paretic and non-paretic legs (Bi-TENS) might induce greater and earlier improvement in lower limb motor function than the use of Uni-TENS in subjects with stroke. A literature search revealed that no study has compared the efficacy of Bi-TENS+TOT and Uni-TENS+TOT on motor recovery after stroke. Therefore, this study aimed to compare the efficacy of a Bi-TENS+TOT program versus a Uni-TENS+TOT program for improving paretic muscle strength, lower- limb coordination, and balance performance in subjects with chronic stroke. The efficacy of Bi-TENS in improving lower limb motor functions will be discussed in chapter 6.

6.3 Methods

6.3.1 Participants

Please refer to section 4.3 for details.

6.3.2 Sample size estimation

The sample size was estimated prospectively using G*power v3.1.0 (Franz Faul, University of Kiel, Germany) with an α level of 0.05 and power of 0.8. As no previous study has compared the effects of bilateral electrical stimulation with those of unilateral stimulation on lower-limb motor function in this population, the estimation is based on a recent systematic review and meta-analysis (Stewart et al., 2006) that showed a medium to large effect size (Cohen’s d = 0.73) for bilateral movement training in the improvement of upper limb motor function after stroke. We selected a more conservative effect size of 0.6 in our model, so the total sample size was estimated to be 72 subjects (36 per group) to detect significant between-group differences. To allow for dropouts, we planned to recruit an additional eight participants. Thus, the planned sample size was 80 (40 subjects per group).

6.3.3 Randomization procedure

The people with stroke were stratified and randomly allocated into either a Bi-TENS group or a Uni-TENS group using Minimize computer software (Jensen, 1991). The stratification was based on age (55 to 70 years or 71 to 85 years), gender, the type of stroke (ischaemic or haemorrhagic) and the side of hemiplegia. The stratification procedure served to avoid an imbalance in the distribution of the major demographic characteristics between the two groups. Randomisation was performed immediately after the collection of demographic data. These procedures were conducted by an independent research assistant who was not involved in the assessment or treatment of these patients.

These stratification factors were selected since they had known effects on outcome variables. First, older people have poorer muscle strength and functional mobility (Frontera et al., 1991; Oberg et al., 1993). A previous review suggested that older people with stroke demonstrated less motor recovery than their younger fellows (Jongbloed, 1986). On the other hand, gender was found to be a significant predictor of muscle strength (Frontera et al., 1991) and walking speed (Oberg et al., 1993), where male generally had greater muscle strength (Frontera et al., 1991) and walked faster than female (Oberg et al., 1993). Besides, people suffered an ischemic stroke was reported to demonstrate better ability in activities and daily living up to 26 weeks post stroke when comparing to the people suffered a hemorrhagic stroke (Schepers et al., 2008). In addition, people with ischemic stroke also demonstrated better motor recovery (odds ratio = 1.98) when compared to the people with hemorrhagic stroke at 1-year post stroke, as measured by modified Rankin Scale score (Wei et al., 2010). For the side of hemiplegia, people with right side hemiplegia but not left side hemiplegia showed improvement in hand function and paretic upper limbs strength after 6 weeks of bilateral arm training with rhythmic auditory cueing (McCombe Waller & Whitall, 2005). Lastly, it has also been reported that people with right side hemiplegia showed significantly greater ipsilesional sensorimotor cortex activation during finger tapping when compared with people with left side hemiplegia (Zemke et al., 2003).

6.3.4 Interventions

6.3.4.1 Transcutaneous electrical nerve (TENS) stimulation

The training program comprised 20 sessions of TENS or placebo-TENS with simultaneous TOT, twice per week for 60 min per session. In Bi-TENS group, TENS was applied on both paretic and nonparetic leg over the common peroneal nerve innervation area. In Uni-TENS group, TENS was applied on the paretic leg only, and the placebo stimulation was applied on the nonparetic leg. The placebo-stimulation was applied by an identical-looking TENS unit with the electrical circuit disconnected inside.

6.3.4.2 Transcutaneous Electrical Nerve Stimulation parameters

The 120Z Dual-Channel TENS Unit (EMSphysio Ltd, Wantage, UK; Figure 6.1) was used to stimulate the nerve trunk of the common peroneal nerve. The stimulation frequency was set at 100 Hz, with a pulse width of 0.2 ms. The stimulation frequency and pulse width were regularly calibrated with an oscilloscope (MSO6014A, Agilent Technologies, California, US; Figure 6.2). The stimulation intensity was set at double of the sensory threshold and below the motor threshold, which was confirmed by the absence of muscle twitching. The sensory threshold was defined as the minimum intensity that provoked a tingling sensation (Ng & Hui-Chan, 2009). Sensory stimulation was used in this study because it could enhance the neuronal activity and/or cortical excitability of the motor cortex via the corticocortical connections between S1 and M1 (Kaneko et al., 1994a, 1994b). In addition, the cutaneous sensory stimulation was applied simultaneously with the TOT, which comprised a series of functional tasks. Electrical stimulation that was above the motor threshold induced muscle twitching; this uncontrolled muscle twitching would produce conflicting afferent inputs during the performance of TOT. For instance, contraction of the ankle dorsiflexor induced by a high-intensity stimulation during push-off phase of gait could interfere with the normal gait pattern.

Figure 6.1. Photo of the 120Z Dual-Channel TENS Unit.

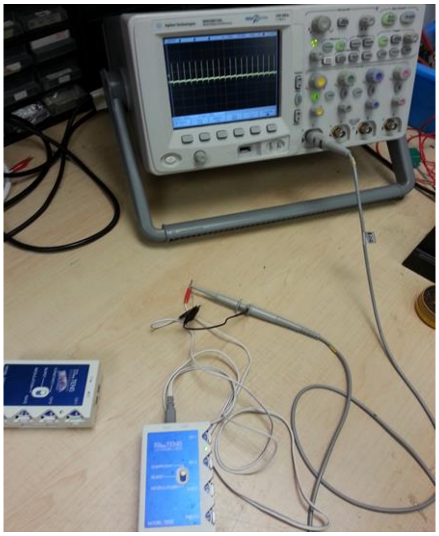


Figure 6.2. Calibration of the TENS unit with an oscilloscope.

6.3.4.3 Location and rationale of electrodes placement

A pair of electrodes (ITO Co. Ltd., Tokyo, Japan: rubber electrodes 40 × 41 mm and gel pad 40 × 41 mm) were applied over the trunk of the common peroneal nerve of the lower leg (Figure 6.3). The cathode (black) electrode was placed proximally on the popliteal fossa, whilst the anode (red) electrode was placed on the neck of fibula. The cathode electrode was placed proximal to the anode electrode to avoid the anodal block of the nerve impulse (Johnson, 2014).

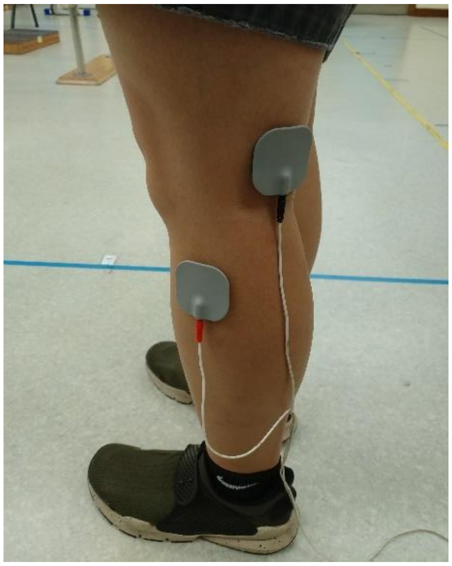


Figure 6.3. Placement of the electrodes for stimulation.

Kaelin-Lang and colleagues (Kaelin-Lang et al., 2002) reported that a 2-hour cutaneous electrical stimulation (1Hz, pulse width 1ms) applied over the ulnar nerve at palmar aspect of wrist increased the MEPs amplitude recorded from abductor digiti minimi in response to focal TMS. On the contrary, MEPs amplitudes recorded from abductor pollicis brevis, which is innervated by median nerve, demonstrated no significant change. The results suggested that cutaneous electrical stimulation on peripheral nerve specifically increased the excitability of the muscles that innervated by the stimulated nerve. The common peroneal nerve divides into deep peroneal nerve and superficial peroneal nerve which mainly innervates muscles that control ankle movements. The dorsiflexors and invertors of the ankle, including the tibialis anterior, extensor hallucis longus and extensor digitorum longus are innervated by the deep peroneal nerve. The plantarflexors and evertors of the ankle, including the peroneus longus and peroneus brevis, are innervated by the superficial peroneal nerve (Moore, 2006). Thus, it was hypothesized that the TENS could enhance the excitability of the neural substrates that innervated these muscles and subsequently enhanced the motor output of these muscles.

6.3.4.4 Simultaneous TENS and TOT protocol

In the current study, TENS was applied simultaneously with the TOT. This was different from Ng and Hui-Chan studies (Ng & Hui-Chan, 2007, 2009) and Yan and Hui-Chan study (Yan & Hui-Chan, 2009), where TENS was applied to the lower limb for 60 min in prior to the exercise training. Using TMS, Khaslavskaia and colleagues (Khaslavskaia et al., 2002) reported that cutaneous electrical stimulation over the common peroneal nerve for 30 min enhanced corticospinal excitability up to 110 min in healthy adults, which could support the application of TENS before TOT. In a later study, Khaslavskaia and Sinkjaer (Khaslavskaia & Sinkjaer, 2005) also reported that cutaneous electrical stimulation applied over the common peroneal nerve combined with simultaneous active ankle dorsiflexion exercise for 30 min increased the motor evoked potentials recorded from the tibialis anterior by 66% in eight healthy adults, whilst cutaneous electrical stimulation alone increased the motor evoked potentials by only 38% (Khaslavskaia & Sinkjaer, 2005). One of the advantages of the current TENS+TOT protocol is that it significantly reduces the treatment duration, thus enhancing the cost-effectiveness of the program and the compliance of the participants.

6.3.4.5 Task-oriented training (TOT) protocol

The TOT protocol comprised of 6 exercises which were modified from previous studies (Ng & Hui-Chan, 2009, 2010). Each TOT session lasted for 60 min, including 30 min of strengthening exercise, 10 min of balance exercise, 10 min of gait training and 10 min of transitional movement practice.

The TOT protocol comprised exercises that aimed to strengthen lower limb muscles in a functional position, improved anti-gravity muscles endurance, augment postural control and smoothen transition between functional positions. These exercises were:

(1) Stepping up and down exercises was used to strengthen the muscles of bilateral lower limb muscles. This exercise aimed to strengthen the knee extensors and improve the lower limb control in weight shifting. This exercise is commonly used to improve the weight-bearing ability of the paretic lower limb in people with stroke. Inability in weight-bearing on the paretic leg could lead to impaired walking gait, such as hyperextension of the knee during mid-stance phase (Davies, 2000). Participants were instructed to place the paretic leg on a 5 cm height wooden step, and then step up and place the nonparetic leg on the step. Afterwards, participants were instructed to step down by putting the nonparetic leg back to the floor, and then followed by the paretic leg. Participants were encouraged

to perform the movements as slow as possible in order to improve the eccentric control of knee extensors.

(2) Heel-raising exercises on an inclined wedge was used to strengthen the bilateral ankle plantarflexors. This exercise aimed to strengthen the plantarflexors in a functional position. The plantarflexors serves to generate a propulsive force, to stabilize ankle and knee and to restrain the forward rotation of tibia in normal walking gait (Sutherland et al., 1980). When participants were standing on the wedge, their ankles were placed in 10 degree of dorsiflexion. Contraction of plantarflexor occurs during mid-stance phase to propel the body forward, in which the ankle is in approximately 10 degrees of dorsiflexion (Ayyappa, 1997). During the heel-raising exercise, participants were instructed to raise both ankles simultaneously and held for 5 s. Participants were encouraged to perform the movements as slow as possible in order to improve the eccentric control of plantarflexors.

(3) The semi-squatting exercise was used to improve the endurance of anti-gravity muscles and proprioception of the knees and ankles. In this exercise, participants were instructed to maintain a semi-squatting position with the knees in approximately 30 degree of flexion.

(4) Standing on a dura disc to improve dynamic standing balance. This exercise aimed to enhance the postural control, ankle control, and the weight shifting ability. In this exercise, participants were instructed to stand on a dura disc (33 cm in diameter; AOK Health, Newcastle,

Australia) and maintain an upright standing posture. For the safety reason, this exercise was conducted inside a parallel bar, participants were encouraged not to hold on the handrail unless they were unable to maintain balance.

(5) Walking on level ground and across obstacles was used to improve the hip flexor strength, increase the awareness of ankle clearance as well as lengthen the step length of the paretic leg. In this exercise, five 10 cm height wooden blocks were evenly placed on a 10 m walkway. Participants were required to lift up the legs in order to avoid tipping over the obstacles. Participants could use a stick or quadripod as necessary.

(6) Exercise including standing up from a chair, walking a short distance, and returning to the chair was used to promote a smooth transition between sitting, standing and walking. In this exercise, a 45 cm height chair and 3 m walkway were used. Participants could use a stick or quadripod as necessary.

Each exercise lasted for 10 min, the total exercise time for one training session was 60 min. An additional 10 min of stretching exercise would be conducted before training in order to enhance muscle flexibility and reduce the risk of injury. The TOT protocol involved various tasks which could strengthen multiple muscle groups and could induce muscle hypertrophy. The TOT protocol also comprised sit-to-stand, stepping and walking training which was functionally relevant. These exercises could augment motor control and facilitate functional neuroadaptation. Using TMS, Yen and colleagues (Yen et al., 2008) have reported that additional gait training (30 min/session for 12 sessions) augmented the corticospinal excitability of the motor representation area of tibialis anterior muscle in 14 people with chronic stroke (Yen et al., 2008). Results of the study showed that the resting motor threshold of non-paretic tibialis anterior muscle reduced, and the mapping area of both paretic and non-paretic tibialis anterior muscle enlarged in the gait training group but not after control therapy. Results of this study demonstrated that functional training could increase the corticospinal excitability in people with chronic stroke (Yen et al., 2008).

6.3.4.6 Progression of exercises

The physical therapist in charge was not blinded from the group allocation. Progression of the exercise was directed according to the pre-set criteria as listed in Table 6.1.

Table 6.1 Progression criteria of the task-oriented training.

Exercise	Progression criteria	Progression
1. Stepping up and down exercises	Able to complete 50 times without loss of balance	Increase the height of the wooden step by 5cm
2. Heel-raising exercises	Able to complete 30 repetitions of heel raise	Increase the height of the wooden wedge
3. Semi squatting	Able to maintain the semi-squatting position for 1 minute without obvious body shaking	Decrease the resting period in between trials of semi-squatting
4. Standing on dura disc	Able to stand without external assistance for at least 1 minute (hold on handrail or support by other)	Decrease the base of support

5. Walking across obstacles	Able to complete the task within pre-set duration (20 seconds in the beginning) without knocking down the obstacles	Shorten the pre-set duration and increase the number of obstacles
6. Standing up, walking and sitting down	Able to complete the task within pre-set duration (30 seconds in the beginning)	Shorten the pre-set duration.

6.3.4.7 Safety considerations

The following strategies were used to ensure the safety of the participants

1. Blood pressure and heart rate were measured before starting of training. The training session would be terminated if the resting systolic blood pressure is greater than 200mmHg or if the resting diastolic blood pressure greater than 115mmHg as suggested by the American College of Sports Medicine (American College of Sports Medicine, 2013). Besides, the therapist in charge would screen the general condition of the participant in every session to ensure they were fit for exercise.
2. Participants were instructed to terminate the exercise if they experienced dizziness, chest discomfort or any unusual pain and reported to the therapist in charge immediately.
3. Participants were asked to report their level of exertion with the Modified Borg Scale (Wilson & Jones, 1989) regularly in order to avoid overexertion.

4. The therapist in charge and research assistants would stay close to participants when they were performing the balance training (exercise 4) and gait training (exercise 5 and 6) to prevent fall.

5. The level of fatigue and delayed onset muscle soreness was closely monitored to avoid overstressing the cardiopulmonary system and muscles. The exercise intensity would be reduced, and duration of resting would be lengthened if there were signs of prolonged fatigue or muscle soreness.

6.3.5 Outcome measures

6.3.5.1 Assessment procedure

Participants were assessed on 4 different occasions for all outcome measures. These occasions were: Baseline assessment before training (A0); after 10 sessions (mid-training) (A1); after 20 sessions (end of training) (A2); and at 3 months after cessation of training (A3). The participants were assessed by a trained research assistant who was blinded from the group allocation.

6.3.5.2 Measurement Battery

Demographic characteristics of participants were collected via interview. Past medical history was retrieved from participant's discharge summary issued by hospitals. The level of lower limb motor recovery was evaluated by the lower extremity motor subscale of the Fugl-Meyer Assessment (FMA-LE). Please refer to section 4.4.2 for details.

Outcome measures in this chapter included the measurements of:

Muscle strength in terms of peak paretic knee extension and flexion torque, and maximum isometric voluntary contraction strength of ankle dorsiflexor and plantarflexor;

Coordination of lower-limb in terms of Lower Extremity Motor Coordination Test (LEMOCOT) score;

Balance performance in terms of the limit of stability (LOS) maximal excursion and Berg Balance Scale (BBS) score;

6.3.5.3 Lower Limbs muscles strength

6.3.5.3.1 Rationale of measurement

Please refer to section 4.4.3.1 for details.

6.3.5.3.2 Isokinetic peak torque

Please refer to section 4.4.3.2 for details.

6.3.5.3.3 Maximum isokinetic voluntary contraction

Please refer to section 4.4.3.3 for details.

6.3.5.4 Lower Limb coordination

6.3.5.4.1 Rationale of measurement

Please refer to section 4.4.4.1 for details.

6.3.5.4.2 Lower Extremity Motor Coordination Test (LEMOCOT)

Please refer to section 4.4.3.2 for details.

6.3.5.5 Balance performance

6.3.5.5.1 Rationale of measurement

Please refer to section 4.4.5.1 for details.

6.3.5.5.2 Limit of Stability (LOS)

Please refer to section 4.4.5.2 for details.

6.3.5.5.3 Berg Balance Scale (BBS)

Please refer to section 4.4.5.4 for details.

6.3.6 Statistical analysis

Intention-to-treat analysis was adopted, and SPSS (version 23.0; Armonk, NY: IBM Corp.) was used for all statistical analyses. A *p* value of 0.05 or lower was considered as significant statistically. The Bonferroni correction was applied to post-hoc analyses to prevent type 1 error inflation.

The demographic characteristics and outcome measures were summarised with descriptive statistics. The baseline characteristics of the two groups were compared with a chi-square test, independent *t*-test or Mann-Whitney U test, as appropriate. A linear mixed model (LMM) was used to compare the differential changes in the outcomes over time between the two groups because it accounts well for intra-correlated repeated-measures data (Gueorguieva & Krystal, 2004). The groups, time points and group by time interaction were included as fixed effects. The random intercept and random slope of change in the outcome variables over time were included as the random effects. Maximum likelihood was chosen as the estimation method, and the first order autoregressive covariance structure was selected to estimate the model parameters.

A significant group by time interaction effect indicated that the variables changed at different rates between the two groups. Where the group by time interaction effect was significant, the between-group and within-group differences were evaluated by dividing the data into three time-points and two groups, respectively. The LMM was then repeated with the interaction effect, and either the time or the group effect was removed and followed by post-hoc analysis. With the absence of a significant group by time interaction, a significant time effect indicated that the variables changed significantly with a similar trend in both groups. Post-hoc analysis was conducted to determine at which time point the outcome variable had significantly changed from the baseline. The carry-over effects were analysed by comparing the results between A2 and A3 with the same model specifications mentioned above. For the analyses of between-group differences and a carry-over effect, missing data were handled with the last observation carried forward method.

6.3.7 Ethical Considerations

Please refer to section 4.5 for details.

6.4 Results

6.4.1 Participants

The selection criteria of participants were stated in section 4.3. One hundred and two people with chronic stroke were screened between February 2014 and April 2016. Eighty of them fulfilled the inclusion criteria were recruited for this study. Their mean age was 62.0 years, and time since the stroke was 5.2 years. Their mean walking speed was 0.77 ms^{-1}, which indicated limited ambulatory ability (Fulk et al., 2017) (Table 6.2).

No significant differences existed between the two groups at baseline (Table 6.2). Six people (three in each group) did not complete the training. Another five (two in the Bi-TENS group and three in the Uni-TENS group) were lost to follow-up (Figure 6.4). The results of outcome measures on motor impairments of the 4 assessment occasions were summarised in Table 6.3.

Table 6.2. Demographic characteristics and results of baseline assessment of the people with stroke shown by group (n=80).

Variables	Total Sample (n = 80)	Bi-TENS + TOT (n = 40)	Uni-TENS + TOT (n = 40)	Between groups comparison
	Frequency (%)			Chi-square test χ^2; *p*
Gender (male/female)	50 (62.5)/30 (47.5)	26 (65)/14 (35)	24 (60)/16 (40)	0.21; 0.821
Side of hemiplegia (right/left)	46 (57.5)/34 (42.5)	24 (60)/16 (40)	22 (55)/18 (45)	0.21; 0.651
Type of stroke (ischemic/hemorrhagic/mixed)	49 (61.3)/30 (37.5)/1 (1.3)	22 (55)/17 (42.5)/1 (2.5)	27 (67.5)/13 (32.5)/0 (0.0)	2.04; 0.360
Living with care giver (yes/no)	70 (87.5)/10 (12.5)	35 (87.5)/5 (12.5)	35 (87.5)/5 (12.5)	0.00; 1.000
Employed/Working (yes/no)	6 (7.5)/74 (92.5)	4 (10)/36 (90)	4 (10)/36 (90)	0.00; 1.000
Education level (primary or below /secondary/college or above)	25 (31.3)/44 (55.0)/11 (13.8)	13 (32.5)/21 (52.5)/6 (15)	12 (30.0)/23 (57.5)/5 (12.5)	0.22; 0.895
Using walking aid (yes/no)	53 (66.2)/27 (33.8)	25 (62.5)/15 (47.5)	28 (70)/12 (30)	0.50; 0.478
	Mean ± SD (ranges)			Independent t-test t_{78}; *p*
Age (yr)	62.0 ± 5.4 (55.0 – 73.1)	61.8 ± 5.7 (55.0 – 73.1)	62.2 ± 5.1 (55.0 – 72.1)	-0.37; 0.715

BMI (kgm^{-2})	24.2 ± 3.1 (18.0 – 32.2)	24.6 ± 3.4 (18.0 – 32.2)	23.8 ± 2.8 (18.0 – 30.0)	-0.77; 0.443

Variables	Total Sample (n = 80)	Bi-TENS (n = 40)	Uni-TENS (n = 40)	Between groups comparison
	Mean ± SD (ranges)	Independent t-test t_{78}; *p*	Mean ± SD (ranges)	Independent t-test t_{78}; *p*
Post-stroke duration (yr)	5.2 ± 3.1 (1.0 – 10)	5.2 ± 3.1 (1.0 – 10.0)	5.7 ± 2.8 (1.0 – 10)	1.14; 0.256
Paretic ankle dorsiflexor strength (kg)	7.6 ± 5.2(0.0-23.7)	7.9 ± 4.9 (0.0-18.5)	7.3 ± 5.6 (0.0-23.7)	0.50; 0.616
Paretic ankle plantarflexor strength (kg)	12.2 ± 5.5 (0.0-28.4)	12.6 ± 5.7 (0.0-25.7)	11.9 ± 5.4 (2.3-28.4)	0.74; 0.460
Peak paretic knee extension torque (Nm)	20.8 ± 14.4 (4.0-85.0)	20.8 ± 13.1 (4.0-54.0)	20.7 ± 12.4 (6.0-70.0)	0.35; 0.972
Peak paretic knee flexion torque (Nm)	7.6 ± 6.3 (0.0-26.0)	8.5 ± 6.7 (0.0-26.0)	6.8 ± 5.9 (1.0-26.0)	1.19; 0.239
LEMOCOT	11.9 ± 10.4 (0.0-40.0)	12.9 ± 12.4 (0.0-40.0)	10.8 ± 7.7 (0.0-28.0)	0.94; 0.363
LOS composite excursion	61.3 ± 15.3(28.0-89.0)	60.0 ± 14.4(28.0-84.0)	62.6 ± 16.1(32.0-89.0)	-0.75; 0.454
10mWT (ms^{-1})	0.77 ± 0.31(0.22-1.89)	0.79 ± 0.34(0.22-1.89)	0.75 ± 0.29(0.29-1.89)	0.61; 0.543

	Median ± IQR (ranges)			Mann-Whitney U test *Z; p*
AMT	10 ± 1 (7-10)	10 ± 1(7-10)	10 ± 0.8(8-10)	-1.34; 0.180
FMA-LE	23 ± 11 (10-33)	23 ± 12.8(10-33)	21.5 ± 9.8(10-32)	-1.23; 0.219
BBS	49 ± 5 (35-56)	48 ± 5.8(36-56)	49 ± 5(35-56)	-0.12; 0.908

Remarks:
10mWT: 10-meter Walk Test; AMT: Abbreviated Mental Test; BBS: Berg Balance Scale; Bi: bilateral; BMI: Body Mass Index; FMA-LE: lower extremity motor subscale of the Fugl-Meyer Assessment; IQR: interquartile range; LEMOCOT; Lower Extremity Motor Coordination Test; LOS: limit of stability; SD: standard deviation; TENS: transcutaneous electrical nerve stimulation; TOT: task-oriented training; Uni: unilateral.

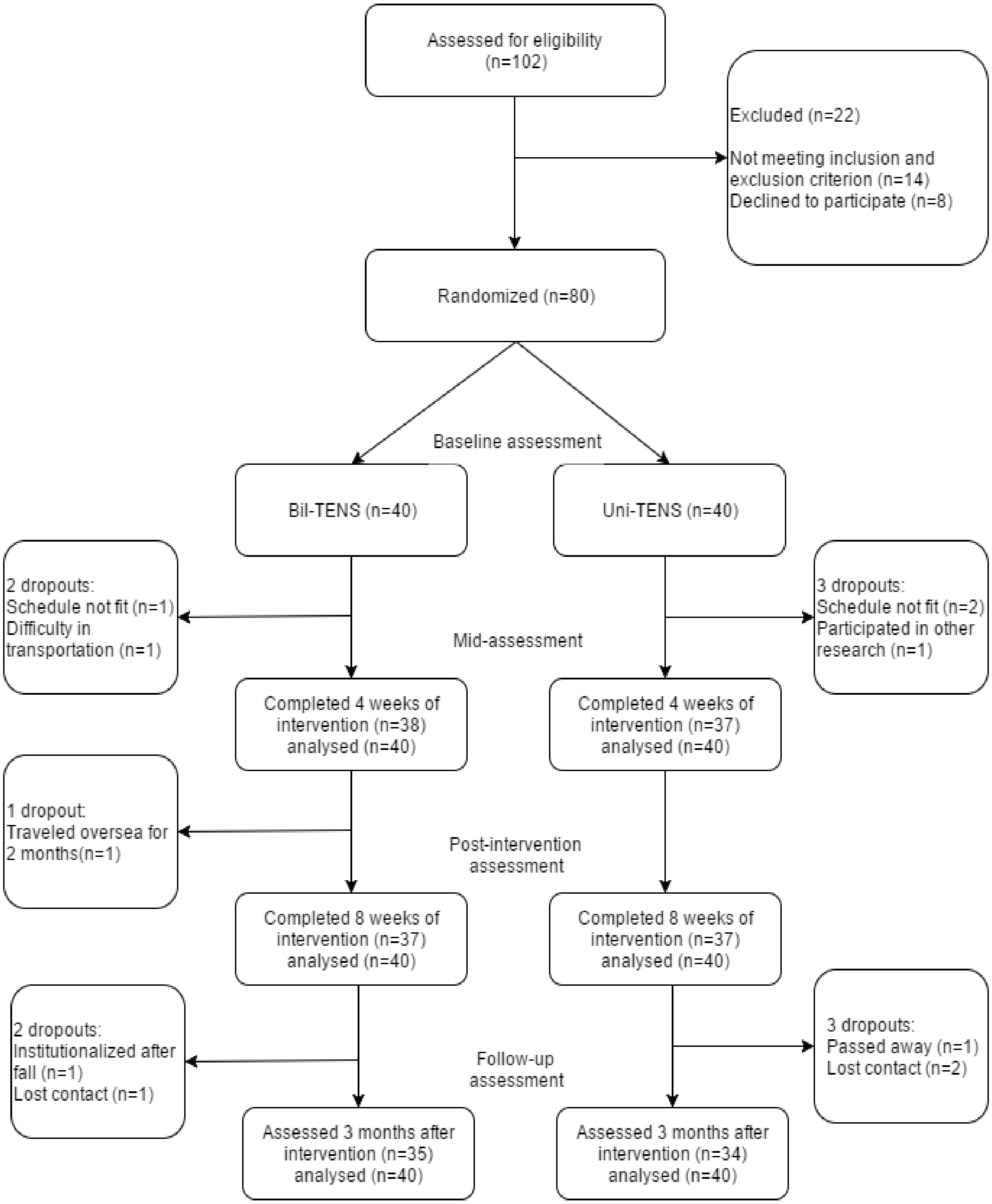


Figure 6.4. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study.

Table 6.3A. Summarized results of the outcome measures of the bilateral TENS + TOT group.

	Bilateral TENS + TOT (n = 40)							
	A0		A1		A2		A3	
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Paretic ankle dorsiflexor strength (kg)	7.9	4.9	10.6	5.4	12.4	6.5	10.6	5.7
Paretic ankle plantarflexor strength (kg)	12.6	5.7	14.5	6.2	15.9	7.3	13.5	6.2
Peak paretic knee extension torque (Nm)	20.8	14.4	28.9	19.1	28.2	15.4	28.5	16.9
Peak paretic knee flexion torque (Nm)	8.5	6.7	15.10	13.7	15.6	12.6	12.2	9.2
LEMOCOT	12.9	12.4	14.8	13.7	17.0	15.1	17.3	16.7
LOS composite excursion (%)	60.0	14.4	65.5	15.6	65.6	15.4	65.5	14.1
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
BBS	48	6	50	5	50	4	51	6

Table 6.3B. Summarized results of the outcome measures of the unilateral TENS + TOT group.

	Unilateral TENS + TOT (n = 40)							
	A0		A1		A2		A3	
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Paretic ankle dorsiflexor strength (kg)	7.3	5.6	8.0	5.5	9.2	6.9	8.3	6.5
Paretic ankle plantarflexor strength (kg)	11.9	5.4	11.9	5.6	13.9	6.8	12.1	6.3
Peak paretic knee extension torque (Nm)	20.7	12.4	24.6	14.3	25.1	15.8	25.4	14.8
Peak paretic knee flexion torque (Nm)	6.8	5.9	10.5	7.5	12.2	8.2	12.5	6.3
LEMOCOT	10.8	7.7	13.5	9.9	15.0	12.2	14.7	11.8
LOS composite excursion (%)	62.6	16.1	68.4	14.0	68.7	12.4	67.9	14.1
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
BBS	49	5	51	5	51	4	51	4

Remarks:
BBS: Berg Balance Scale; TENS: transcutaneous electrical nerve stimulation; IQR: interquartile range; LEMOCOT; Lower Extremity Motor Coordination Test; LOS: limit of stability; SD: standard deviation; Uni-TENS: unilateral transcutaneous electrical nerve stimulation; TOT: Task-oriented training.

6.4.2 Effects of the two treatment protocols on muscle strength

6.4.2.1 Maximal isometric voluntary paretic ankle dorsiflexor strength

The LMM showed that the time effects ($\beta = 0.90$; 95% confidence interval (CI), 0.22 to 1.59; $p = 0.010$) and group by time interaction effects ($\beta = 1.32$; 95% CI, 0.36 to 2.29; $p = 0.008$) were significant for the paretic ankle dorsiflexor strength (Table 6.4; Figure 6.5). The results suggested that for every 5 weeks of training, the Bi-TENS group demonstrated an additional 1.32-kg increase in paretic ankle dorsiflexor strength when compared with the Uni-TENS group.

Post-hoc analyses showed that the Bi-TENS group demonstrated greater improvement than the Uni-TENS group in the paretic ankle dorsiflexor strength at A1 (mean differences, 2.62; 95% CI, 0.18 to 5.06; $p = 0.036$) and A2 (mean differences, 3.23; 95% CI, 0.25 to 6.22; $p = 0.034$). When compared with baseline, the Bi-TENS group showed improvement in the paretic ankle dorsiflexor strength at A1 (mean differences, 2.67; 95% CI, 1.61 to 3.73; $p < 0.001$) and A2 (mean differences, 4.46; 95% CI, 3.14 to 5.78; $p < 0.001$). However, the Uni-TENS group showed improvement in the paretic ankle dorsiflexor strength (mean differences, 1.81; 95% CI, 0.56 to 3.07; $p = 0.005$) only at A2.

For the analyses of carry-over effects, both the time effect and group by time interaction effects were not statistically significant. While the group effect was significant (*β* = 4.19; 95% CI, 0.21 to 8.16; *p* = 0.025; Table 6.5), which was likely resulted from the between-groups difference of the paretic ankle dorsiflexor strength at A2.

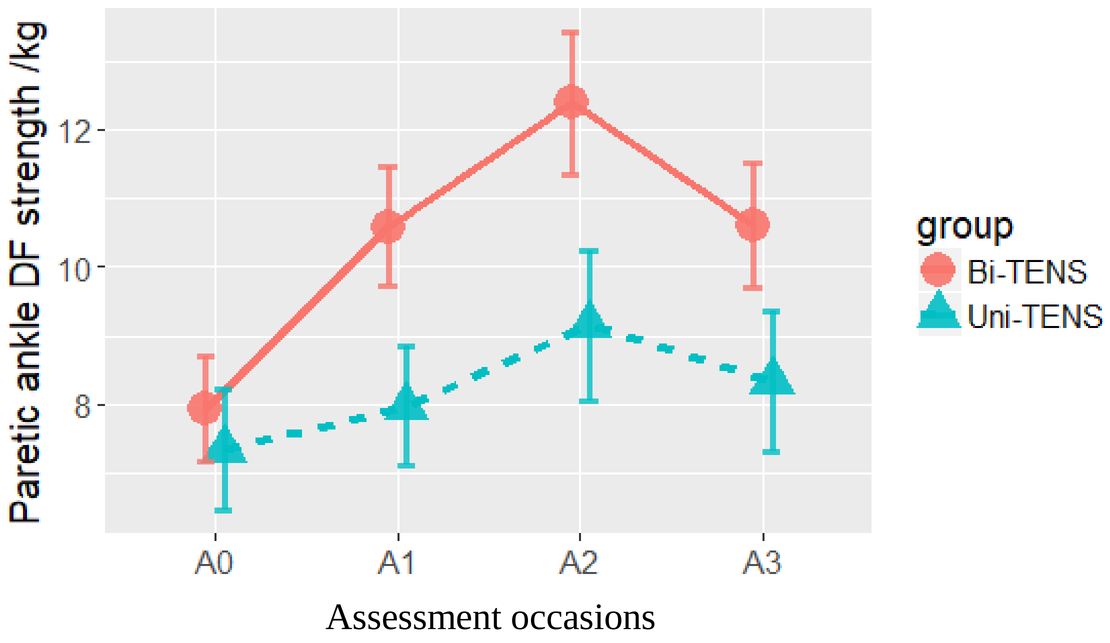


Figure 6.5. Mean change of the paretic ankle DF strength over time of the 2 groups.
Remarks:
Error bars represented the standard error of the mean.
Bi-TENS: bilateral transcutaneous electrical stimulation; DF: dorsiflexion; Uni-TENS: unilateral transcutaneous electrical stimulation.

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6.4.2.2 Maximal isometric voluntary paretic ankle plantarflexor strength

The LMM showed that the time effects ($\beta = 0.99$; 95% CI, 0.11 to 1.88; $p = 0.029$), but not the group by time interaction effects was significant for the paretic ankle plantarflexor strength. (Table 6.4; Figure 6.6). The results suggested that the paretic ankle plantarflexor strength improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the paretic ankle plantarflexor strength were demonstrated only at A2 (mean differences, 4.12; 95% CI, 2.30 to 5.94; $p < 0.001$) when compared to A0.

For the analyses of carry-over effects, the time effects ($\beta = -1.75$; 95% CI, −3.21 to −0.29; $p = 0.021$; Table 6.5) but not the group by time interaction effects were significant for paretic ankle plantarflexion (Table 6.5).

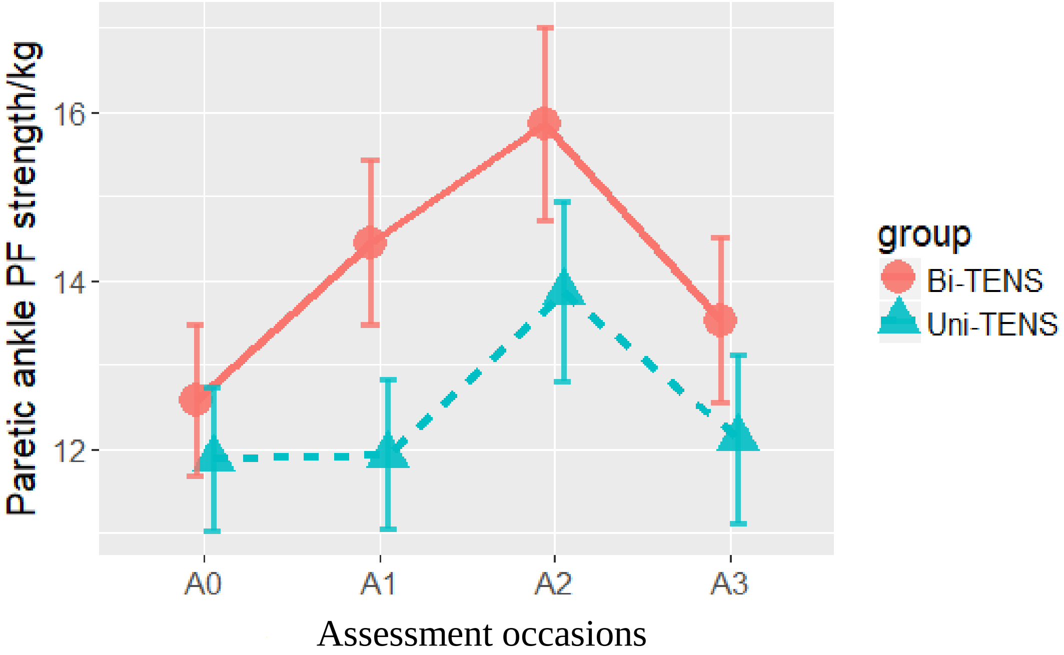

Figure 6.6. Mean change of the paretic ankle PF strength over time of the 2 groups.
Remarks:
Error bars represented the standard error of the mean.
Bi-TENS: bilateral transcutaneous electrical stimulation; PF: plantarflexion; Uni-TENS: unilateral transcutaneous electrical stimulation.

6.4.2.3 Peak paretic knee extension torque

The LMM showed that the time effects ($\beta = 2.20$; 95% CI, 0.34 to 4.06; $p = 0.021$) were significant for the peak paretic knee extension torque, but not the group by time interaction effects. (Table 6.4; Figure 6.7). The results suggested that the peak paretic knee extension torque improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the peak paretic knee extension torque were demonstrated at A1 (mean differences, 4.07; 95% CI, 0.71 to 7.37; $p = 0.012$) and A2 (mean differences, 3.43; 95% CI, 0.07 to 6.78; $p = 0.044$) when compared to A0.

For the analyses of carry-over effects, neither time effects nor the group by time interaction effects were significant for the peak paretic knee extension torque (Table 6.5).

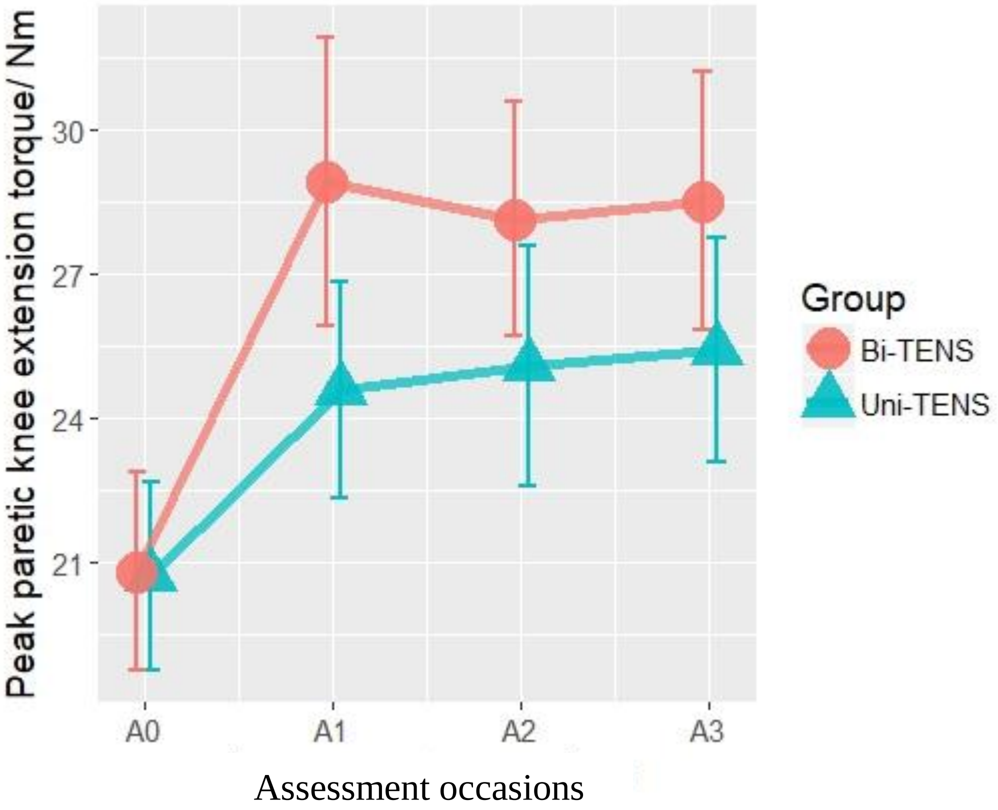

Figure 6.7. Mean change of the peak paretic knee extension torque over time of the 2 groups.
Remarks:
Error bars represented the standard error of the mean.
Bi-TENS: bilateral transcutaneous electrical stimulation; Uni-TENS: unilateral transcutaneous electrical stimulation.

6.4.2.4 Peak paretic knee flexion torque

The LMM showed that the time effects ($\beta = 2.69$; 95% CI, 1.31 to 4.06; $p < 0.001$), but not the group by time interaction effects, was significant for the peak paretic knee flexion torque. (Table 6.4; Figure 6.8). The results suggested that the peak paretic knee flexion torque improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the peak paretic knee flexion torque were demonstrated at A1 (mean differences, 5.16; 95% CI, 3.02 to 7.31; $p < 0.001$) and A2 (mean differences, 6.26; 95% CI, 4.19 to 8.33; $p < 0.001$) when compared to A0.

For the analyses of carry-over effects, the group by time interaction effects were significant for the peak paretic knee flexion torque ($\beta = -3.25$; 95% CI, -6.94 to -0.56; $p = 0.021$). The results suggest that the Bi-TENS group demonstrated an additional 3.75 Nm decrease in peak paretic knee flexion torque when compared with the Uni-TENS group (Table 6.5).

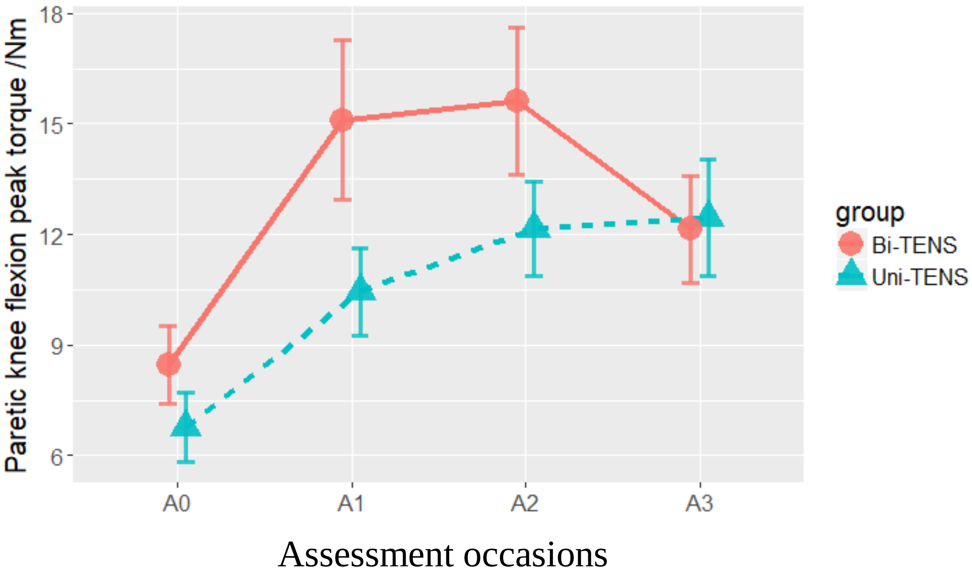

Figure 6.8. Mean change of the peak paretic knee flexion torque over time of the 2 groups.
Remarks:
Error bars represented the standard error of the mean.
Bi-TENS: bilateral transcutaneous electrical stimulation; Uni-TENS: unilateral transcutaneous electrical stimulation.

6.4.3 Effects of the two treatment protocols on lower limb coordination

6.4.3.1 LEOMCOT score

The LMM showed that the time effects ($\beta = 2.08$; 95% CI, 1.34 to 4.06; $p < 0.001$), but not the group by time interaction effects, was significant for the LEMOCOT score. (Table 6.4; Figure 6.9). The results suggested that the LEMOCOT score improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the LEMOCOT score were demonstrated at A1 (mean differences, 2.31; 95% CI, 0.77 to 3.85; $p = 0.001$) and A2 (mean differences, 4.11; 95% CI, 2.24 to 5.99; $p < 0.001$) when compared to A0.

For the analyses of carry-over effects, neither time effects nor the group by time interaction effects were significant for the LEMOCOT score (Table 6.5).

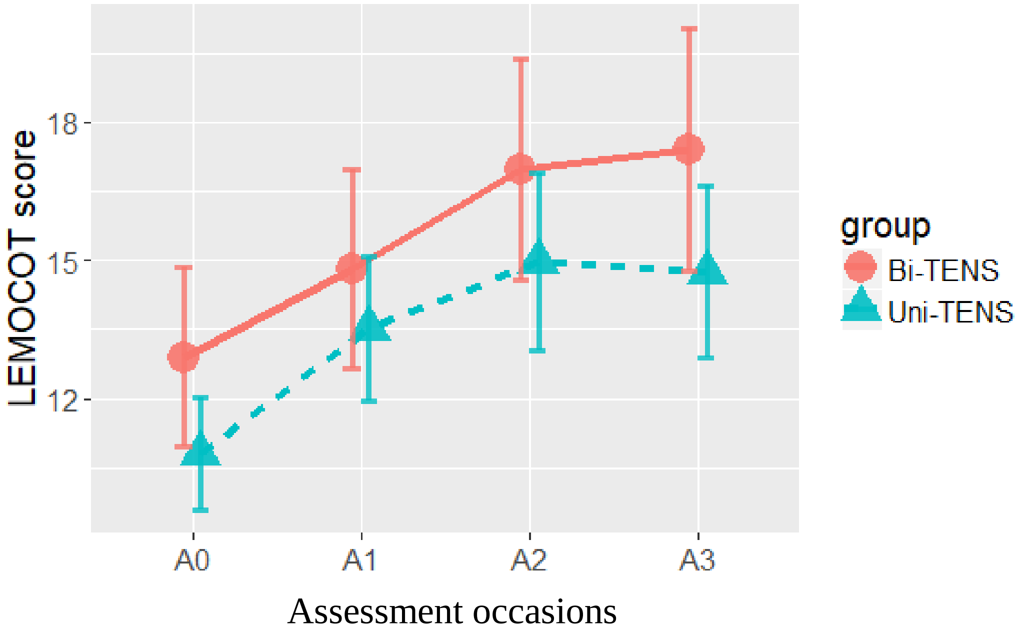

Figure 6.9. Mean change of the LEMOCOT score over time of the 2 groups.
Remarks:
Error bars represented the standard error of the mean.
Bi-TENS: bilateral transcutaneous electrical stimulation; LEMOCOT: Lower Extremity Motor Coordination Test; Uni-TENS: unilateral transcutaneous electrical stimulation.

6.4.4 Effects of the two treatment protocols on balance performance

6.4.4.1 LOS composite excursion score

The LMM showed that the time effects ($\beta = 3.04$; 95% CI, 1.67to 4.40; $p < 0.001$), but not the group by time interaction effects, was significant for the LOS composite excursion score. (Table 6.4; Figure 6.10). The results suggested that the LOS composite excursion score improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the LOS composite excursion score were demonstrated at A1 (mean differences, 5.63; 95% CI, 3.37 to 7.88; $p < 0.001$) and A2 (mean differences, 5.81; 95% CI, 3.63 to 7.92; $p < 0.001$) when compared to A0.

For the analyses of carry-over effects, neither time effects nor the group by time interaction effects was significant for the LOS composite excursion score (Table 6.5).

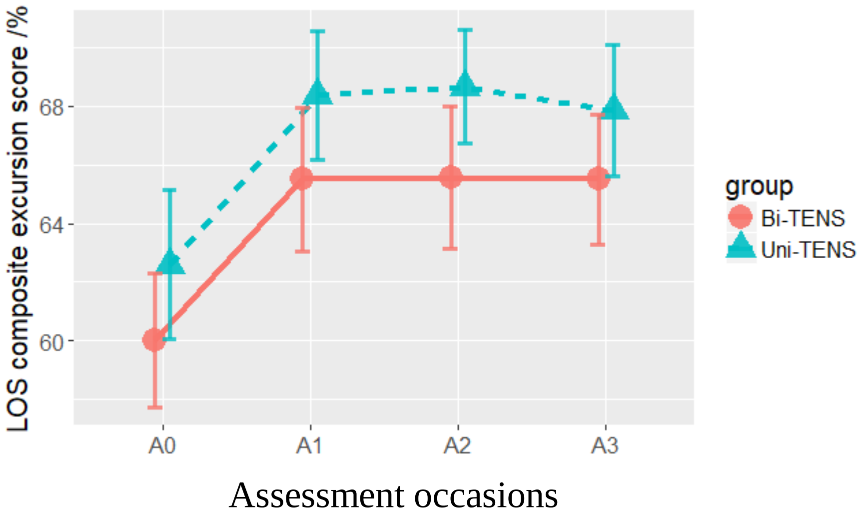

Figure 6.10. Mean change of the LOS composite excursion score over time of the 2 groups.
Remarks:
Error bars represented the standard error of the mean.
Bi-TENS: bilateral transcutaneous electrical stimulation; LOS: limit of stability; Uni-TENS: unilateral transcutaneous electrical stimulation.

6.4.4.2 BBS score

The LMM showed that the time effects ($\beta = 1.23$; 95% CI, 0.69 to 1.78; $p < 0.001$), but not the group by time interaction effects, was significant for the BBS score. (Table 6.4; Figure 6.11). The results suggested that the BBS score improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the BBS score were demonstrated at A1 (mean differences, 1.50; 95% CI, 0.69 to 2.36; $p < 0.001$) and A2 (mean differences, 2.30; 95% CI, 1.29 to 3.32; $p < 0.001$) when compared to A0.

For the analyses of carry-over effects, neither time effects nor the group by time interaction effects were significant for the BBS score (Table 6.5).

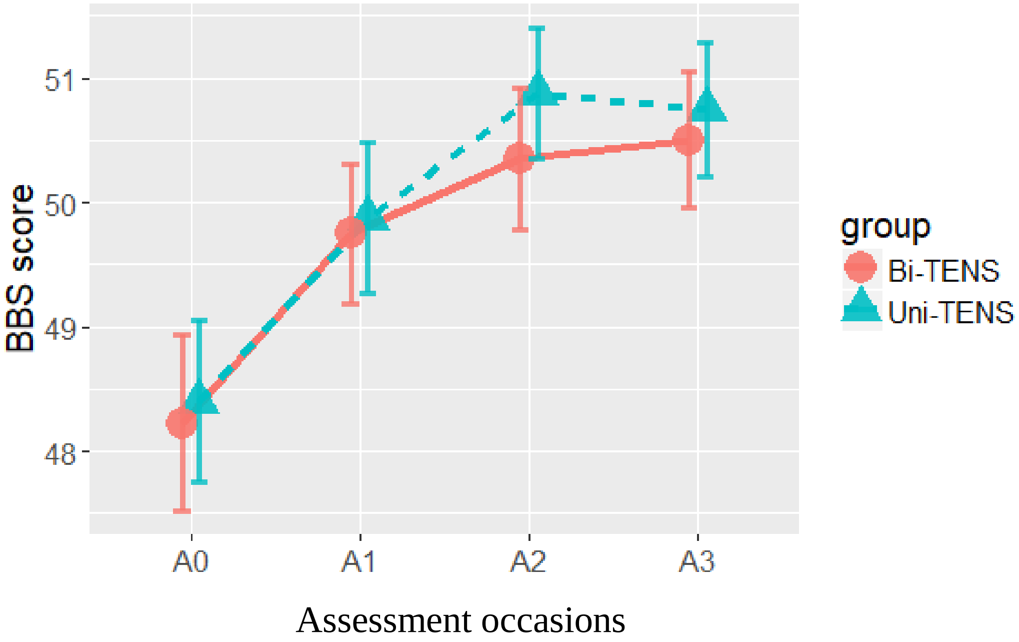

Figure 6.11. Mean change of the BBS score over time of the 2 groups.

Remarks:

Error bars represented the standard error of the mean.

BBS: Berg Balance Scale; Bi-TENS: bilateral transcutaneous electrical stimulation; Uni-TENS: unilateral transcutaneous electrical stimulation.

Table 6.4. Results of linear mixed models for people in the Bi-TENS group compared to those in the Uni-TENS group across A0 to A2 (n = 80; Uni-TENS = reference).

	Fixed effects		
	Time	Group	Group by time interaction
	Estimate; 95% CI; *p*	Estimate; 95% CI; *p*	Estimate; 95% CI; *p*
Paretic ankle dorsiflexor strength (kg)	0.90; 0.22 – 1.59; 0.010*	-0.50; -2.86 – 1.86; 0.675	1.32; 0.36 – 2.29; 0.008 *
Paretic ankle plantarflexor strength (kg)	0.99; 0.11 – 1.88; 0.029*	0.44; -2.49 – 3.36; 0.766	0.65; -0.61 – 1.9; 0.308
Peak paretic knee extension torque (Nm)	2.20 0.34 – 4.06; 0.021*	-0.46 -7.57 – 6.65; 0.898	1.48 -1.89 – 4.84; 0.335
Peak paretic knee flexion torque (Nm)	2.69 1.31 – 4.06; ≤ 0.001†	1.48 -2.10 – 5.07; 0.415	0.89 -1.05 – 2.83; 0.369
LEMOCOT	2.08; 0.99 – 3.17; ≤ 0.001†	1.90; -2.47 – 6.28; 0.389	-0.04; -1.59 – 1.5; 0.955
LOS composite excursion	3.04 1.67 – 4.40; ≤ 0.001†	-2.33 -9.98 – 5.33; 0.547	-2.63 -2.20 – 1.67; 0.788
BBS	1.23; 0.69 – 1.78; ≤ 0.001†	0.08; -2.25 – 2.40; 0.950	-0.18; -0.94 – 0.59; 0.652

Remarks:
BBS: Berg Balance Scale; CI: confidence interval; LEMOCOT: Lower Extremity Motor Coordination; LOS: limit of stability Test.
* $p \leq 0.05$, †$p \leq 0.001$.

Table 6.5. Results of linear mixed models for people in the Bi-TENS group compared to those in the Uni-TENS group across A2 to A3 (n = 80; Uni-TENS = reference).

	Fixed effects		
	Time	Group	Group by time interaction
	Estimate; 95% CI; *p*	Estimate; *p* 95% CI; *p*	Estimate; 95% CI; *p*
Paretic ankle dorsiflexor strength (kg)	-0.82; -2.01 – 0.38; 0.177	4.19; 0.21 – 8.16; 0.025*	-0.95; -2.64 – 0.73; 0.263
Paretic ankle plantarflexor strength (kg)	-1.75; -3.21 – -0.29; 0.021*	2.57; -1.91 – 7.04; 0.264	-0.58; -2.64 – 1.49; 0.585
Peak paretic knee extension torque (Nm)	0.33; -2.51 – 3.17; 0.821	3.00; -5.80 – 11.80; 0.499	0.05; -5.12 – 5.22; 0.913
Peak paretic knee flexion torque (Nm)	0.30; -1.93 – 2.53; 0.281	7.20; -0.44 – 13.96; 0.037*	-3.75; -7.79 – 0.30 0.020*
LEMOCOT	-0.22; -2.75 – 2.31; 0.863	1.38; -6.24 – 9.00; 0.735	0.64; -2.93 – 4.22; 0.725
LOS composite excursion	1.25; -4.80 – 7.30; 0.684	-7.10; -23.17 – 37.37; 0.644	-3.40; -11.96 – 5.16; 0.434
BBS	-0.13; -0.82 – 0.57; 0.724	-0.80; -2.87 – 1.27; 0.451	0.28; -0.70 – 1.25; 0.583

Remarks:
BBS: Berg Balance Scale; CI: confidence interval; LEMOCOT: Lower Extremity Motor Coordination Test.
* $p \leq 0.05$.

6.5 Discussion

This is the first study to compare the efficacy of Bi-TENS+TOT and Uni-TENS+TOT in the improvement of lower limb motor function after stroke. The notion of Bi-TENS was inspired by the success of bilateral motor training (Lin et al., 2010; McCombe Waller et al., 2008; Pandian et al., 2015; Sethy et al., 2016; Summers et al., 2007), and positive findings (Johannsen et al., 2010) have also been reported with bilateral leg training after stroke. In addition, training of the non-paretic limb has also been reported to enhance motor recovery in paretic limbs (Dragert & Zehr, 2013; Pandian et al., 2015). Results of this study demonstrated that Bi-TENS+TOT induced greater and earlier improvement in the paretic ankle dorsiflexor strength than Uni-TENS+TOT. Both treatments demonstrated significant improvements in the LEMOCOT score and BBS score after 10 training sessions and significant improvements in paretic ankle plantarflexor strength after 20 training sessions. In general, the training effects on all outcome measures could be maintained 3 months after training ended, except for the maximum isometric voluntary contraction of paretic ankle plantarflexion and peak paretic knee flexion torque of the Bi-TENS group.

6.5.1 Unilateral TENS and motor recovery

Consistent with previous results (Ng & Hui-Chan, 2007, 2009), our results demonstrate significant within-group improvement in paretic ankle dorsiflexor strength in both the Bi-TENS and Uni-TENS groups after 20 sessions of intervention. The mechanism that underlies the improved motor function in paretic limbs after TENS treatment is multifactorial; it involves alleviation of the hyperexcitability of alpha motor neurons (Chen et al., 2005b; Levin & Hui-Chan, 1992), reduction of intracortical inhibition (Celnik et al., 2007) and enhancement of cortico-muscular functional connectivity (Lai et al., 2016). Several clinical studies have demonstrated that the hyperexcitability of the alpha motor neurons that innervate the spastic ankle plantarflexor could be reduced by an increase in pre-synaptic inhibition after repetitive TENS (Chen et al., 2005b; Levin & Hui-Chan, 1992). Levin and Hui-Chan reported that the ankle plantarflexor stretch reflex amplitude, as measured by the magnitude of integrated electromyography (EMG), was reduced significantly after a 3-week regimen of repetitive application of TENS over the common peroneal nerve, but not after placebo-TENS stimulation (Levin & Hui-Chan, 1992). Chen and colleagues demonstrated that the H-reflex latency of paretic ankle plantarflexor was lengthened significantly after 6 weeks of TENS stimulation over the Achilles muscle–tendon junction, but not after placebo-TENS stimulation (Chen et al., 2005b).

Other neurophysiological studies have demonstrated that repetitive cutaneous electrical stimulation could lead to a reduction in intracortical inhibition (Celnik et al., 2007) and enhancement of cortical and neuromuscular coupling (Lai et al., 2016) at the cortical level, which might explain the improvement of motor function after TENS combined with TOT. Lai and colleagues (Lai et al., 2016) reported that 40 min of cutaneous electrical stimulation applied over the median nerve on the paretic hand could augment electroencephalography (EEG)–EMG coherence in nine subjects with chronic stroke. The EEG-EMG coherence, which refers to the synchronisation of the oscillatory activities of the EMG and EEG signals, was used to assess the level of cortical and neuromuscular coupling. It has been reported that a low-to-high shift of the EEG-EMG coherence frequency is a clinical indicator of motor recovery after stroke (von Carlowitz-Ghori et al., 2014). Lai and colleagues (Lai et al., 2016) showed that the EEG-EMG coherence in the high-frequency band (>30 Hz) had increased significantly after repetitive TENS. Moreover, motor control, as measured by the percentage of force deviation in maintaining a steady force output, was also improved after cutaneous electrical stimulation (Lai et al., 2016).

In addition, it has been suggested that the occurrence of motor cortex reorganisation is suppressed by intra-cortical inhibition and that the release of intra-cortical inhibition might facilitate motor learning (Jacobs & Donoghue, 1991; Smyth et al., 2010). This notion was supported by the fact that reorganisation of the motor representation area can be induced rapidly in rats when intra-cortical inhibition is blocked with drugs (Jacobs & Donoghue, 1991). Celnik and colleagues (Celnik et al., 2007) used transcranial magnetic stimulation to investigate the effects of cutaneous electrical stimulation on the level of corticospinal excitability in subjects with stroke. In this crossover-designed study, subjects with stroke received 2 h of sub–motor threshold cutaneous electrical stimulation on both ulnar and radial nerves or received placebo stimulation before 1 h of hand function training. Cutaneous electrical stimulation did not lead to any change in the resting motor threshold from the first dorsal interosseous muscle, but it did reduce the short-interval intracortical inhibition in nine subjects with subacute stroke (Celnik et al., 2007). The reduction of intracortical inhibition has been demonstrated during motor skill acquisition of a wrist flexion-extension waveform-tracking task in healthy adults (Smyth et al., 2010), and the enhanced cortical and neuromuscular coupling after TENS led to better motor control (Lai et al., 2016). Thus, repetitive TENS potentially optimizes the participants' motor performance and augments the training effects of TOT.

The stimulation protocol in the current study was based on the findings of our previous studies that had effectively demonstrated improvement in lower limb motor function in subjects with stroke (Hui-Chan & Levin, 1993; Laddha et al., 2016; Levin & Hui-Chan, 1992; Ng & Hui-Chan, 2007, 2009; Yan & Hui-Chan, 2009). The 100-Hz stimulation frequency was chosen because previous studies have demonstrated that this frequency reduces the amplitude of the H-reflex (Levin & Hui-Chan, 1992), lengthens the stretch reflex latencies (Hui-Chan & Levin, 1993) and enhances walking capacity (Laddha et al., 2016; Ng & Hui-Chan, 2007, 2009) in subjects with stroke.

The TOT program adopted the specificity of training principles by ensuring that the force generated by the muscles is directly related to functional movement (Ng & Hui-Chan, 2007). The TOT protocol for this study was adopted from that in our previous studies (Ng & Hui-Chan, 2007, 2009). It demonstrated that a combination of placebo-TENS and TOT was superior to control group with no active treatment in isometric paretic ankle dorsiflexor and plantarflexor strength (Ng & Hui-Chan, 2007) and TUG completion time (Ng & Hui-Chan, 2009). The improvement in muscle strength after

TOT could be attributed to an increase in muscle volume (Ryan et al., 2011) and neuroadaptation (Luft et al., 2008). Ryan and colleagues reported that 12 weeks of resistive training of the knee extensors increased the paretic thigh’s cross-sectional area and volume by approximately 15%, and increased the knee extension strength by 56% (Ryan et al., 2011). Luft and colleagues (Luft et al., 2008) reported that 6 months of treadmill exercise induced greater activation in multiple brain regions when compared with those having passive stretching in subjects with stroke. These brain areas included the posterior cerebellar lobe, the midbrain and the ipsilesional postcentral and superior frontal gyri, which were the brain areas that potentially mediated the walking-related activities. In addition, ambulation functions could be facilitated because TOT exercises required the subjects to activate the muscle in the position in which the muscles normally functioned.

Unlike our previous studies (Ng & Hui-Chan, 2007, 2009) in which TENS was applied before TOT, the TENS treatment in this study was applied concurrently with TOT. Two studies have reported that simultaneous TENS and TOT augment balance performance (Ng et al., 2016b) and trunk control (Chan et al., 2015) in subjects with stroke. Khaslavskaia and colleagues (Khaslavskaia et al., 2002) reported that cutaneous electrical stimulation over the common peroneal nerve for 30 min enhanced corticospinal excitability for up to 110 min in healthy adults, which supported the application of TENS before TOT. However, Khaslavskaia and Sinkjaer (Khaslavskaia & Sinkjaer, 2005) reported that cutaneous electrical stimulation applied over the common peroneal nerve combined with simultaneous active ankle dorsiflexion exercise for 30 min increased the motor evoked potentials recorded from the tibialis anterior muscle by 66% in eight healthy adults, whilst cutaneous electrical stimulation alone increased the motor evoked potentials by only 38% (Khaslavskaia & Sinkjaer, 2005). One of the advantages of the current TENS+TOT protocol is that it can significantly reduce the treatment duration, thus enhancing the cost-effectiveness of the program and the compliance of the participants.

6.5.2 Bilateral TENS and motor recovery

Based on the findings of neuroanatomical (Wahl et al., 2007) and clinical (Grefkes et al., 2010; Renner et al., 2005) studies, the underlying mechanisms that mediate the effects of Bi-TENS might include the enhancement of interhemispheric interaction, possibly via the corpus callosum, which is the white matter in the human brain that connects the two hemispheres via more than 200 million axonal connections (Wahl et al., 2007). The motor areas of the two hemispheres have been shown with functional magnetic resonance imaging (fMRI) and diffusion tensor imaging to be connected via the posterior body of the corpus callosum (Wahl et al., 2007). Results of clinical studies have demonstrated that bilateral pinch gripping could enhance ipsilesional M1 excitability when compared to unilateral pinch gripping with either hand in subjects with stroke (Renner et al., 2005), which was shown by an increase in the motor evoked potential amplitude recorded from the first dorsal interosseous of the paretic hand (Renner et al., 2005). Moreover, Grefkes and colleagues (Grefkes et al., 2010) demonstrated in a sample of 11 subjects with subacute and subcortical stroke that bilateral hand movements resulted in facilitatory neural coupling between the M1 and supplementary motor areas of the two cerebral hemispheres. Simultaneous activation of bilateral sensorimotor cortices via TENS might exert a similar effect of enhancing the interhemispheric interaction in both hemispheres via the corpus callosum, thus enhancing the effects of motor training.

The neural networks of the contralesional hemisphere could also contribute to the motor recovery of the paretic limb after repetitive application of TENS over both legs. Dragert and Zehr (Dragert & Zehr, 2013) reported that high-intensity ankle dorsiflexion resistance training on the non-paretic ankle resulted in a 34% increase in non-paretic ankle dorsiflexor strength and a 31% increase in paretic ankle dorsiflexor strength in 19 subjects with chronic stroke (Dragert & Zehr, 2013). It is plausible that the application of TENS over the non-paretic leg activated the contralesional hemisphere and enhanced the paretic ankle strength by recruiting the contralesional neural networks. The Bi-TENS+TOT group showed earlier and greater improvement in paretic ankle dorsiflexor strength with as little as 10 sessions of training, probably due to the enhanced descending input to the alpha-motor neurons that innervate the paretic ankle dorsiflexor.

Although significant within-group improvement was shown in paretic ankle plantarflexor strength, lower limb coordination, dynamic standing balance and balance performance, no significant between-group differences was shown in these outcomes. Kaelin-Lang and colleagues (Kaelin-Lang et al., 2002) demonstrated that 2 h of cutaneous electrical stimulation over the ulnar nerve at the wrist level increased the motor evoked potentials measured from the abductor digiti minimi muscle in response to focal transcranial magnetic stimulation in healthy adults (Kaelin-Lang et al., 2002). However, no significant change in motor evoked potentials was recorded from the abductor pollicis brevis, which is innervated by the median nerve. The result indicated that cutaneous electrical stimulation over a peripheral nerve increased the focal corticospinal excitability of the muscles innervated by the nerve being stimulated. The ankle plantarflexors are predominantly innervated by the tibial nerve, and LEMOCOT involved the coordinated movement of the knee flexor and extensor, which were predominantly innervated by the femoral and sciatic nerves respectively. The LOS and BBS evaluated trunk control and anticipatory postural adjustment, and the muscles involved are innervated by nerves other than common peroneal nerves.

Application of Bi-TENS to the common peroneal nerve might only improve the motor outputs of muscles that are innervated by the superficial and deep peroneal nerves, including the ankle dorsiflexors and evertors. This might explain the lack of between-group difference in plantarflexor strength, LEMOCOT, LOS composite excursion and BBS scores.

6.5.3 Carry-over effects

The peak paretic ankle dorsiflexor strength and peak paretic knee extension torque, paretic lower limb coordination and balance performance showed no significant deterioration at 3 months after training in either group. Surprisingly, the peak paretic knee flexion torque showed a significantly greater reduction in the Bi-TENS group when compared to the Uni-TENS group. However, it should be noted that the value of peak paretic knee flexion torque was still comparable between the two group at A3 even though the Bi-TENS group demonstrated a greater reduction between A2 and A3.

The paretic ankle plantarflexor strength was reduced significantly in follow-up assessment in both groups. These findings demonstrated that the detraining effect had a strong influence on muscle strength, but not on functional performance. Häkkinen and colleagues (Hakkinen et al., 2000) reported a significant reduction in the cross-sectional area of the quadriceps and reduction in the isometric strength of knee extensors up to 6% after 3 weeks, and 12% after 24 weeks of detraining in healthy adults. However, the functional outcomes, including walking speed and jumping height, showed no significant change (Hakkinen et al., 2000) . The improved motor control of knee was maintained even after detraining (Hakkinen et al., 2000) .

6.6 Conclusions

This study demonstrates that Bi-TENS applied on the common peroneal nerves combined with lower-limb TOT would induce greater improvement in paretic ankle dorsiflexor strength at 5 weeks, when compared with those of the Uni-TENS combined with TOT. Both Bi-TENS+TOT and Uni-TENS+TOT induced significant within-group improvements in paretic ankle strength, lower limb coordination and balance performance in people with chronic stroke after 20 training sessions. The training effects in both groups were maintained for 3 months, except for the paretic ankle plantarflexor strength. The results of this study suggest that Bi-TENS+TOT is superior to Uni-TENS+TOT for augmentation of maximal isometric contracture strength of paretic ankle dorsiflexion in people with chronic stroke. The following chapter will further evaluate the effects of the two treatment protocols on lower-limb functions and level of community integration in people with stroke.

Chapter 7

Bilateral transcutaneous electrical nerve stimulation (TENS) improves lower limb motor function in people with chronic stroke: a randomised controlled trial

7.1 Abstract

The results presented in Chapter 5 show that both bilateral TENS (Bi-TENS) and unilateral TENS (Uni-TENS) combined with task-oriented training (TOT) led to significant improvements in ankle and knee muscle strength, lower limb coordination, and balance performance. Bi-TENS+TOT resulted in greater improvement in paretic ankle dorsiflexor strength. The primary objective of the study presented in this chapter was to compare the efficacy of Bi-TENS+TOT with Uni-TENS+TOT in improving lower limb motor function in people with chronic stroke. The secondary objective of this investigation was to identify the predictors of a more favourable response to Bi-TENS.

Eighty people with chronic stroke were randomly assigned to a Bi-TENS+TOT or a Uni-TENS+TOT group and underwent 20 sessions of training over a 10-week period. Outcome measures included the Step Test (ST), Five Times Sit-to-Stand Test (FTSTS), 10-Metre Walk Test (10mWT), 6-Minute Walk Test (6MWT) and Timed Up and Go Test (TUG). Each participant was assessed at baseline, after 5 and 10 weeks of training and 3 months after cessation of the training. Regression tree analysis was used to identify the characteristics that can predict greater improvement in TUG completion after Bi-TENS+TOT training.

The people in the Bi-TENS+TOT group showed greater improvement in TUG times (β = -1.54; p = 0.004) as indicated by significant interaction effects. The post-

stroke duration and level of motor recovery were able to identify those people with stroke who could benefit the most from Bi-TENS+TOT.

The results of the regression tree analysis showed that the participants with a shorter post-stroke duration (<1.9 years) showed the greatest improvement in TUG completion time, followed by those with an FMA-LE score between 16 and 22. The group with a post-stroke duration of less than 1.9 years showed an average of 36% reduction in TUG completion time after training. Those with a post-stroke duration greater than 1.9 years *and* an FMA-LE score between 16 and 22 had an average reduction of 26% in TUG completion time.

The application of Bi-TENS over the common peroneal nerve combined with TOT was superior to the application of Uni-TENS combined with TOT in improving the completion time for the TUG test after 10 weeks of training. A shorter post-stroke duration predicted a better treatment outcome in the Bi-TENS+TOT group. For those with a longer post-stroke duration, an FMA-LE score between 16 and 22, indicating an intermediate level of motor recovery, predicted a better outcome.

7.2 Introduction

Residual motor impairments following a stroke can result in functional limitations. Unsteadiness in self-initiated limb movements on standing (Tyson et al., 2006), unsteadiness in sit-to-stand movements (Cheng et al., 1998; Tyson et al., 2006) and reduction of mobility (please refer to section 1.6 for details) are common functional limitations following stroke.

Previous studies have reported that lower-limb strengthening programs improved cadence (Teixeira-Salmela et al., 2001), stride length (Teixeira-Salmela et al., 2001), walking speed (Kim et al., 2001; Ouellette et al., 2004; Teixeira-Salmela et al., 1999), TUG completion time (Son et al., 2014) and speed of stair climbing (Teixeira-Salmela et al., 1999) in people with stroke. In addition, a meta-analysis conducted by Ada and colleagues (Ada et al., 2006a) which pooled the results from 12 clinical trials with 367 people showed that muscle strengthening had a positive effect on both upper and lower limb functions (standardised effect size = 0.32) in people with stroke.

The results presented in Chapter 6 show that both Bi-TENS and Uni-TENS combined with TOT led to significant improvements in knee and ankle muscle strength, lower limb coordination, and balance performance. In addition, Bi-TENS+TOT demonstrated greater effects in improving the paretic ankle dorsiflexor strength. Previous studies have demonstrated that paretic ankle dorsiflexor strength is a strong predictor of 6WMT distance (Ng & Hui-Chan, 2012) and TUG completion time (Ng & Hui-Chan, 2013) in people with stroke. Improvements in lower limb motor impairments could lead to improvement in lower limb motor functions. The TOT protocol of the current study was designed to improve walking performance in people with stroke, based on the training principle of specificity. For example, strengthening exercises were conducted in functional positions, and walking related tasks were included in the training protocol. Therefore, it was hypothesised that both Bi-TENS+TOT and Uni-TENS+TOT could induce within-group improvements in lower limb motor functions in people with stroke.

Mayo and colleagues (Mayo et al., 1999) reported that walking endurance measured with 6MWT predicted the level of community integration in people with stroke. The results presented in Chapter 4 lead to the similar conclusion that paretic ankle dorsiflexor strength, balance performance, and walking endurance are significant predictors of the level of community integration in community-dwelling people with stroke. Thus, it was also hypothesised that the investigated training program could increase the level of community integration in participants with stroke.

Previous studies have suggested that demographic characteristics of participants, such as age (Barbeau & Visintin, 2003) and severity of stroke (Barbeau & Visintin, 2003; Morone et al., 2011; Morone et al., 2012) can identify people who could obtain greater benefits from a rehabilitation program. Barbeau and Visintin (Barbeau & Visintin, 2003) reported that more severely impaired and older people with stroke got the greatest benefits from body-weight supported treadmill training, in terms of a greater improvement in walking speed. Similarly, Morone and colleagues (Morone et al., 2011; Morone et al., 2012) reported that people with lower Motricity Index scores showed greater improvement in walking performance and daily living function after robotic-assisted walking training. In contrast, Fritz and colleagues (Fritz et al., 2005) reported that better voluntary control of finger extension predicted a greater improvement in hand function after constraint-induced movement therapy training in people with stroke. Likewise, participants with different demographic characteristics might benefit differently from the experimental intervention in the current study. It was hypothesised that demographic characteristics and level of motor function at baseline could identify the people who would get the most benefit from Bi-TENS+TOT.

As no study has compared the efficacy of Bi-TENS+TOT and Uni-TENS+TOT in augmenting lower limb motor function in people with stroke, the objective of this study was to compare the efficacy of Bi-TENS+TOT with Uni-TENS+TOT in the improvement of lower limb motor functions, including dynamic standing balance, sit-to-stand performance and walking performance, as well as the level of community integration in people with stroke. The secondary objective was to identify which group of participants could get the greatest benefit from Bi-TENS+TOT, as defined by a greater within-group improvement of TUG completion time.

7.3 Methods

The methodology adopted in this study, including the selection of participants, sample size estimation, randomisation procedure, interventions, data analysis, and ethical considerations have been presented in Chapters 4 and 6.

7.3.1 Participants

Please refer to section 4.3 for details.

7.3.2 Sample size estimation

Please refer to section 6.3.2 for details.

7.3.3 Randomisation procedure

Please refer to section 6.3.3 for details.

7.3.4 Interventions

Please refer to section 6.3.4 for details.

7.3.5 Outcome measures

7.3.5.1 Assessment procedure

Please refer to section 6.3.5.1 for details.

7.3.5.2 Measurement battery

Outcome measures in this study include the following:

1. Dynamic standing balance in terms of paretic and non-paretic Step Test (ST) score;

2. Sit-to-stand performance in terms of Five Times Sit-to-stand Test (FTSTS) completion time;

3. Walking performance in terms of comfortable walking speed measured by 10mWT, 6MWT distance and TUG completion time.

7.3.5.3 Dynamic standing balance

7.3.5.3.1 Rationale of measurement

Please refer to section 4.4.5.1 for details.

7.3.5.3.2 Step Test (ST)

Please refer to section 4.4.5.3 for details.

7.3.5.4 Performance of sit-to-stand

7.3.5.4.1 Rationale of measurement

Please refer to section 4.4.6.1 for details.

7.3.5.4.2 Five Times Sit-to-Stand Test (FTSTS)

Please refer to section 4.4.6.2 for details. The posterior foot placement and arm crossover chest position were selected as the standardised positions in this study.

7.3.5.5 Walking performance

7.3.5.5.1 Rationale of measurement

Please refer to section 4.4.7.1 for details.

7.3.5.5.2 10-Metre Walk Test (10mWT)

Please refer to section 4.4.7.2 for details.

7.3.5.5.3 6-Minute Walk Test (6MWT)

Please refer to section 4.4.7.3 for details.

7.3.5.5.4 Timed Up and Go test (TUG)

Please refer to section 4.4.7.4 for details.

7.3.5.6 Community integration

7.3.5.6.1 Rationale of measurement

Please refer to section 4.4.8.1 for details.

7.3.5.6.2 Subjective Index of Physical and Social Outcome (SIPSO)

The Chinese version of the SIPSO questionnaire was adopted in the study (Kwong et al., 2017b). Please refer to section 4.4.8.3 for details.

7.3.6 Statistical analysis

The method of statistical analysis is presented in Chapter 6 (section 6.3.6). In addition, regression tree analysis was used to explore which characteristics could predict a more favourable outcome in the Bi-TENS group. A regression tree is a supervised machine learning technique for constructing a prediction model from data. This technique classifies the dependent variable using the recursive partitioning algorithm. Initially, the whole set of the dependent variable is grouped into the same partition. The algorithm then splits the dependent variable into two partitions by selecting the split that minimises within-group variance in the two partitions. This splitting algorithm is then applied to create a new partition until no split can produce two partitions that significantly reduce the total variance of the whole model (Loh, 2008). Demographic characteristics including age, gender, side of hemiplegia, type of stroke, post-stroke duration and baseline lower extremity domain of FMA-LE score are used as the independent variables to construct the model. The percentage changes of the TUG completion time between A0 and A2 are used as the dependent variable.

7.3.7 Ethical considerations

Please refer to section. 4.3.7.

7.4 Results

7.4.1 Participants

The demographic characteristics of the participants are presented in Table 7.2. No significant differences in functional outcome measures existed between the two groups at baseline (Table 7.1). The results of outcome measures on motor functions on the four assessment occasions are summarised in Table 7.2.

Table 7.1. Results of outcome measures of lower limb motor functions of the people with stroke shown by group (n = 80).

Variable	Total sample (n = 80)	Bi-TENS (n = 40)	Uni-TENS (n = 40)	Between groups comparison
	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	Independent *t*-test t_{78}; *p*
Paretic Step test score	7.4 ± 3. (0.0–16.7)	7.5 ± 3.7 (0.0–15.0)	7.3 ± 3.4 (0.0–16.7)	0.31; 0.761
Non-paretic Step test score	9.2 ± 3.8 (0.0–27.3)	9.1 ± 3.6 (0.0–14.3)	9.2 ± 4.0 (0.0–27.3)	-0.02; 0.981
FTSTS (s)	20.8 ± 8.8 (11.0–64.9)	20.4 ± 8.0 (11.1–45.0)	21.2 ± 9.6 (11.0-64.9)	-0.40; 0.688
10mWT (ms^{-1})	0.77 ± 0.31 (0.22–1.89)	0.79 ± 0.34 (0.22–1.89)	0.75 ± 0.29 (0.29–1.89)	0.61; 0.543
6-Minute Walk Test (m)	226.8 ± 82.7 (78.7–452.8)	232.8 ± 88.5 (78.8–452.8)	220.9 ± 77.1 (84.5–441.3)	0.65; 0.521
TUG (s)	19.2 ± 8.1 (4.4–43.3)	19.2 ± 8.3 (4.4–40.9)	19.2 ± 8.0 (8.9–43.3)	-0.01; 0.992
	Median ± IQR (range)			Mann-Whitney U test *Z; p*
SIPSO	28 ± 8 (16–40)	28.5 ± 10.5 (17–37)	28.5 ± 7.5 (16–40)	-0.49; 0.491

6MWT: 6-minute Walk Test; 10mWT: 10-metre Walk Test; Bi: bilateral; FTSTS: Five Times Sit-to-Stand Test; SD: standard deviation; SIPSO: Subjective Index of Physical and Social Outcome; TENS: transcutaneous electrical nerve stimulation; TUG: Timed Up and Go test; Uni: unilateral.

Table 7.2A. Outcome measures of the bilateral TENS+TOT group.

	Bilateral TENS+TOT (n = 40)							
	A0		A1		A2		A3	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Paretic Step Test	7.5	3.7	8.6	3.7	9.5	4.1	9.1	4.2
Non-paretic Step Test	9.1	3.6	10.5	3.7	11.2	4.3	10.8	4.3
FTSTS (s)	20.4	8.0	17.2	6.0	18.0	7.3	17.5	6.1
10mWT (ms^{-1})	0.79	0.34	0.82	0.31	0.85	0.36	0.84	0.30
6MWT (m)	232.83	88.52	247.21	87.67	257.43	99.99	252.7	91.1
TUG (s)	19.2	8.3	17.2	7.6	14.5	6.34	15.6	7.3
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
SIPSO	29	10	29	8	28	6	31	8

Table 7.2B. Outcome measures of the unilateral TENS+TOT group.

	Unilateral TENS+TOT (n = 40)							
	A0		A1		A2		A3	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Paretic Step Test	7.3	3.4	8.0	2.7	9.2	4.2	8.9	3.6
Non-paretic Step Test	9.2	4.0	9.6	2.9	10.9	4.9	10.4	3.0
FTSTS (s)	21.2	9.6	19.1	6.7	17.5	5.5	18.1	5.8
10mWT (ms^{-1})	0.75	0.29	0.79	0.30	0.84	0.34	0.85	0.30
6MWT (m)	220.9	77.1	229.0	80.5	232.2	85.5	235.8	73.1
TUG (s)	19.2	8.0	18.8	8.0	17.5	7.3	18.0	8.1
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
SIPSO	29	10	29	8	28	6	31	8

6MWT: 6-minute Walk Test; 10mWT: 10-metre Walk Test; FTSTS: Five Times Sit-to-Stand Test; IQR: interquartile range; SD: standard deviation; SIPSO: Subjective Index of Physical and Social Outcome; TENS: transcutaneous electrical nerve stimulation; TOT: task-oriented training; TUG: Timed Up and Go test.

7.4.2 Effects of the two treatment protocols on dynamic standing balance

7.4.2.1 Paretic Step Test (ST)

The linear mixed model (LMM) showed that the time effect ($\beta = 0.96$; 95% CI, 0.43 to 1.50; $p = 0.001$), but not the group by time interaction effect, was significant for the paretic ST score (Table 7.3; Figure 7.1). This result shows that the paretic ST score improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the paretic ST score were demonstrated at A1 (mean differences, 0.93; 95% CI, 0.19 to 1.67; $p = 0.009$) and A2 (mean differences, 1.95; 95% CI, 1.11 to 2.80; $p < 0.001$) when compared to A0.

In the analyses of carry-over effects, neither time effects nor the group by time interaction effects were significant for the paretic ST score (Table 7.4).

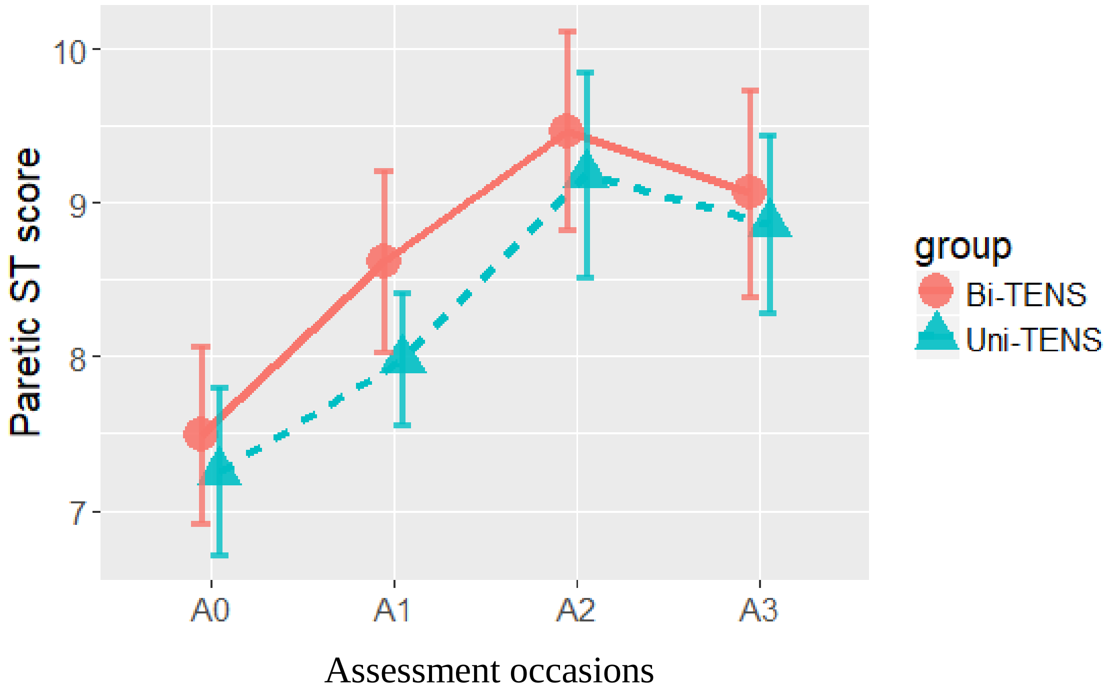

Figure 7.1. Mean change of the paretic Step Test score over time in the two groups. Error bars represent the standard error of the mean. Bi-TENS: bilateral transcutaneous electrical stimulation; ST: Step Test; Uni-TENS: unilateral transcutaneous electrical stimulation.

7.4.2.2 Non-paretic Step Test

The LMM showed that the time effect ($\beta = 0.87$; 95% CI, 0.15 to 1.60; $p = 0.019$), but not the group by time interaction effect, was significant for the non-paretic ST score (Table 7.3; Figure 7.2). The results suggest that the non-paretic ST score improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the non-paretic ST score were demonstrated at A1 (mean difference, 0.88; 95% CI, 0.10 to 1.65; $p = 0.021$) and A2 (mean difference, 1.92; 95% CI, 0.82 to 3.02; $p < 0.001$) when compared to A0.

In the analyses of carry-over effects, neither time effects nor the group by time interaction effects were significant for the non-paretic ST score (Table 7.4).

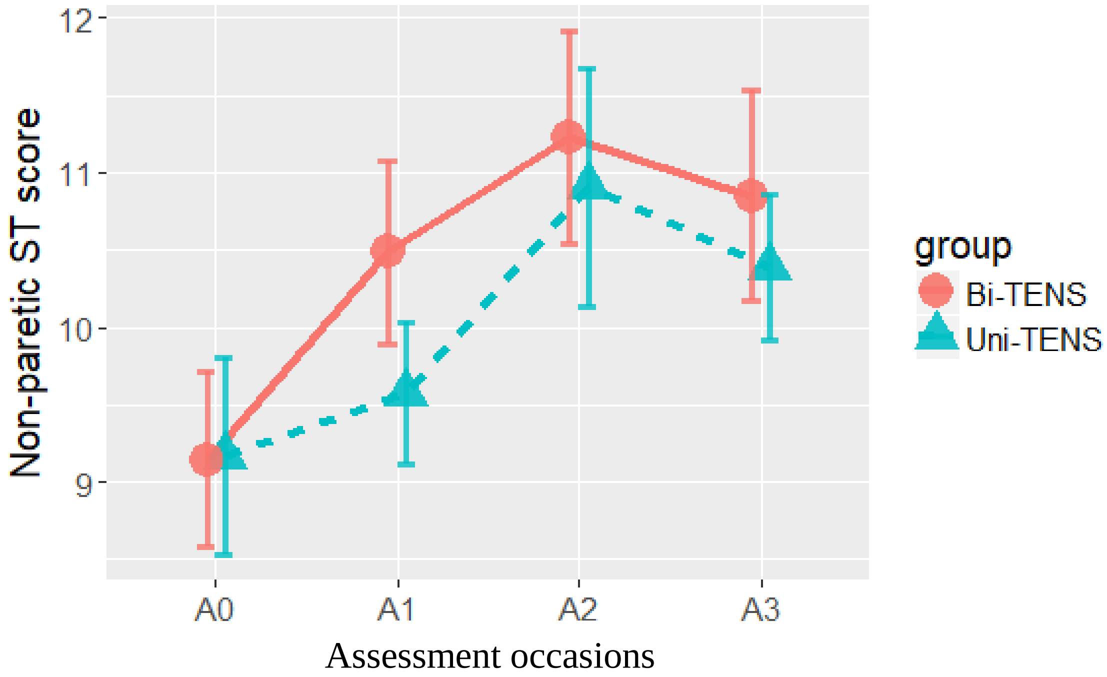

Figure 7.2. Mean change of the non-paretic Step Test score over time in the two groups. Error bars represent the standard error of the mean.

Bi-TENS: bilateral transcutaneous electrical stimulation; ST: Step Test; Uni-TENS: unilateral transcutaneous electrical stimulation.

7.4.3 Effects of the two treatment protocols on functional muscle strength

7.4.3.1 Five Times Sit-to-stand Test (FTSTS)

The LMM showed that the time effect (β = -1.83; 95% CI, -2.88 to -0.79; p = 0.001), but not the group by time interaction effect, was significant for the FTSTS completion time (Table 7.3; Figure 7.3). The results suggest that the FTSTS completion time improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvements in the FTSTS completion time were demonstrated at A1 (mean difference, -2.65; 95% CI, -4.23 to -1.08; $p < 0.001$) and A2 (mean difference, -3.04; 95% CI, -4.85 to -1.23; $p < 0.001$) when compared to A0.

In the analyses of carry-over effects, neither time effects nor the group by time interaction effects were significant for the FTSTS completion time (Table 7.4).

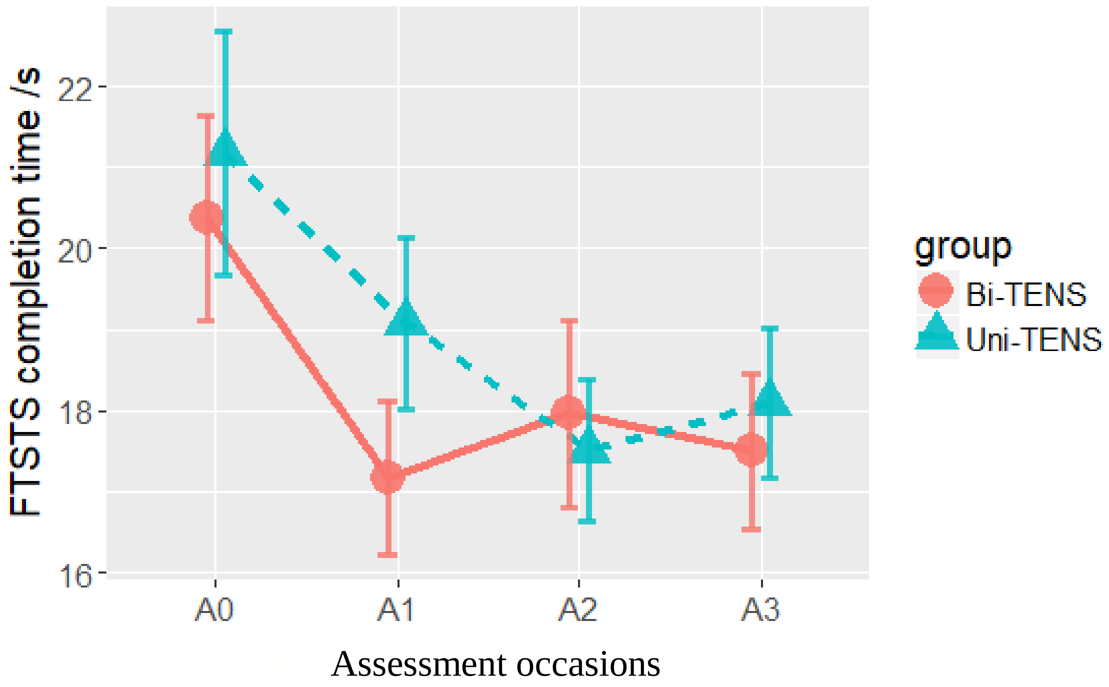

Figure 7.3. Mean change of the FTSTS completion time over time in the two groups. Error bars represent the standard error of the mean.
Bi-TENS: bilateral transcutaneous electrical stimulation; FTSTS: Five Times Sit-to-Stand Test. Uni-TENS: unilateral transcutaneous electrical stimulation.

7.4.4 Effects of the two treatment protocols on walking performance

7.4.4.1 10-Metre Walk Test (10mWT)

The LMM showed that the time effect ($\beta = 0.045$; 95% CI, 0.017 to 0.071; $p = 0.001$), but not the group by time interaction effect, was significant for the 10mWT walking speed (Table 7.3; Figure 7.4). The results suggest that the 10mWT walking speed improved over time in both groups at a similar rate. Post-hoc analyses of the significant time effects showed that improvement in the 10mWT walking speed was demonstrated at A2 only (mean difference, 0.075; 95% CI, 0.030 to 0.119; $p < 0.001$) when compared to A0.

In the analyses of carry-over effects, neither time effects nor the group by time interaction effects were significant for the 10mWT walking speed (Table 7.4).

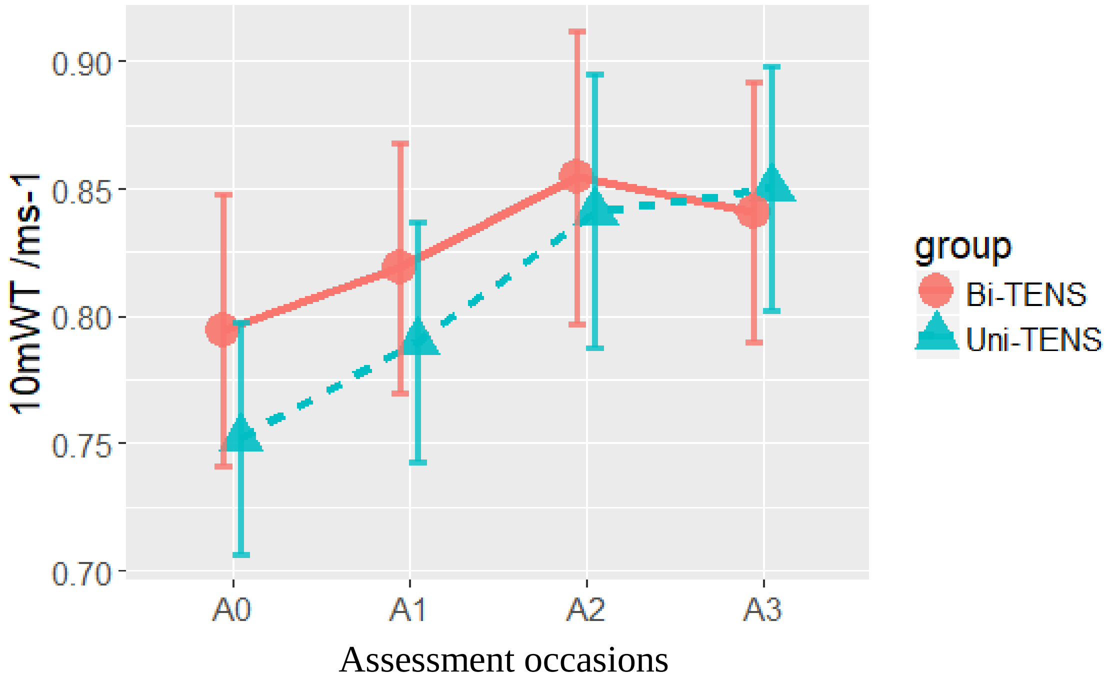

Figure 7.4. Mean change of the 10-metre walking speed over time in the two groups. Error bars represent the standard error of the mean. 10mWT: 10-Metre Walk Test. Bi-TENS: bilateral transcutaneous electrical stimulation; Uni-TENS: unilateral transcutaneous electrical stimulation.

7.4.4.2 6-Minute Walk Test (6MWT)

The LMM showed that neither the time effect nor the group by time interaction effect was significant for the 6MWT distance (Table 7.3; Figure 7.5). The results suggest that the 6MWT distance showed no improvement over time in both groups.

In the analyses of carry-over effects, neither time effects nor the group by time interaction effects were significant for the 6MWT distance (Table 7.4).

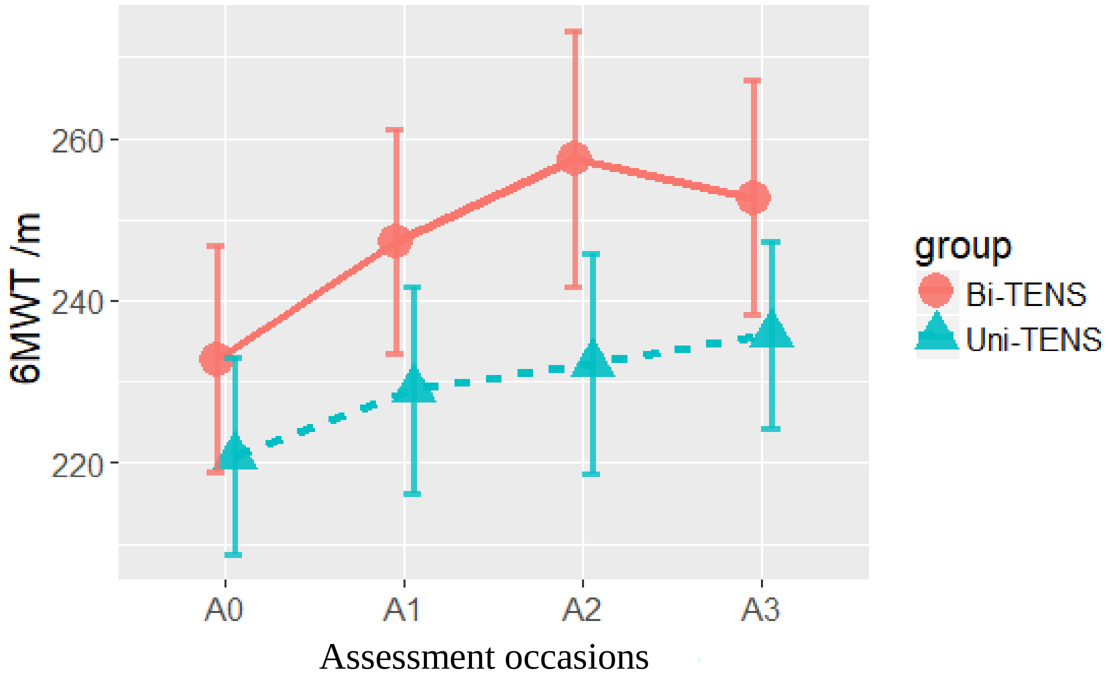

Figure 7.5. Mean change of 6MWT distance over time in the two groups.
Error bars represent the standard error of the mean.
6MWT: 6-Minute Walk Test; Bi-TENS: bilateral transcutaneous electrical stimulation; Uni-TENS: unilateral transcutaneous electrical stimulation.

7.4.4.3 Timed Up and Go test (TUG)

The LMM showed that the time effect (β = -0.82; 95% CI, -1.54 to -0.10; p = 0.010) and group by time interaction effect (β = -1.54; 95% CI, -2.55 to -0.52; p = 0.004) were significant for the TUG completion time (Table 7.3; Figure 7.6). The results suggest that for every 5 weeks of training, the Bi-TENS group demonstrated a further reduction of 1.54 s in the TUG completion time when compared to the Uni-TENS group.

Post-hoc analyses showed that the Bi-TENS group demonstrated greater improvement than the Uni-TENS group in the TUG completion time at A2 (mean difference, −3.09; 95% CI, −0.49 to −6.13; p = 0.047). When compared to the baseline, the Bi-TENS group showed improvement in the TUG completion time at A1 (mean difference, −2.01; 95% CI, −3.18 to −0.84; p = 0.001) and at A2 (mean difference, −3.76; 95% CI, −5.18 to −2.34; p < 0.001). However, the Uni-TENS group showed improvement in the TUG completion time (mean difference: −1.64; 95% CI: −0.40 to −2.87; p = 0.01) at A2 only.

In the analyses of carry-over effects, neither the time effect nor the group by time interaction effect was statistically significant. The group effect was significant (β = -3.80; 95% CI, -7.31 to -0.28; p = 0.037; Table 7.4), which is likely to be due to the between-group difference in the TUG completion time at A2.

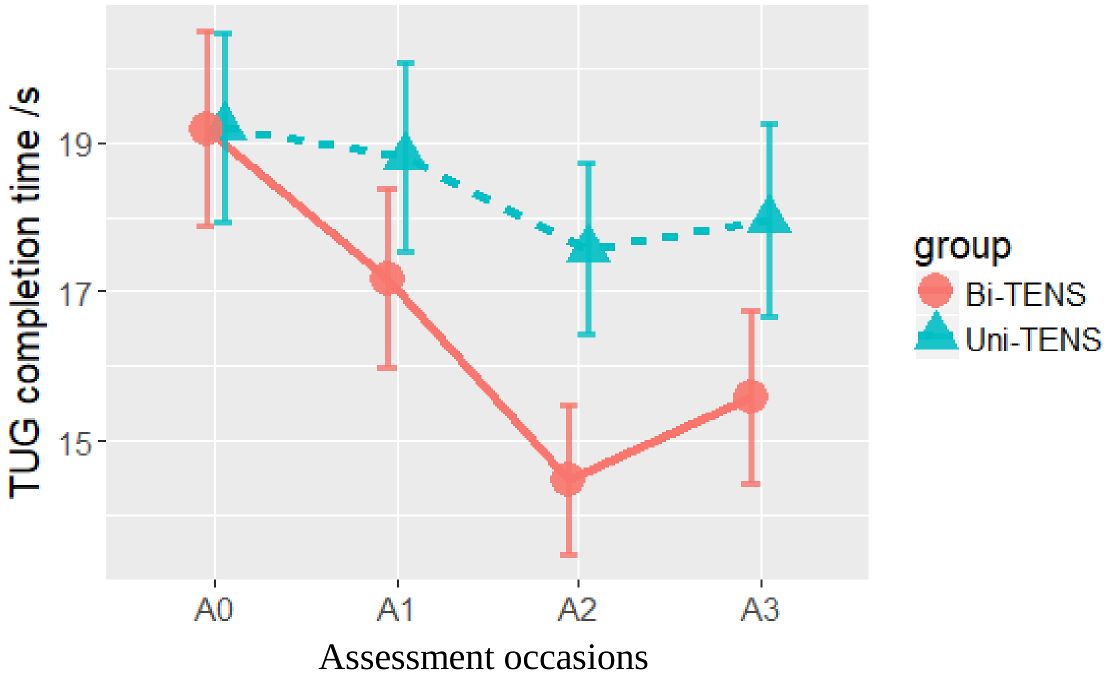

Figure 7.6. Mean change in the TUG completion time over time in the two groups. Error bars represent the standard error of the mean.

Bi-TENS: bilateral transcutaneous electrical stimulation; TUG: Timed Up and Go Test; Uni-TENS: unilateral transcutaneous electrical stimulation.

7.4.5 Effects of the two treatment protocols on the level of community integration

7.4.5.1 Subjective Index of Physical and Social Outcome (SIPSO)

The LMM showed that neither the time effect nor the group by time interaction effect was significant for the SIPSO score (Table 7.3; Figure 7.7). The results suggest that the SIPSO score showed no improvement over time in both groups.

In the analyses of carry-over effects, the time effect ($\beta = 1.45$; 95% CI, 0.03 to 2.87; $p = 0.049$; Table 7.4) but not the group by time interaction effect was significant for the SIPSO score.

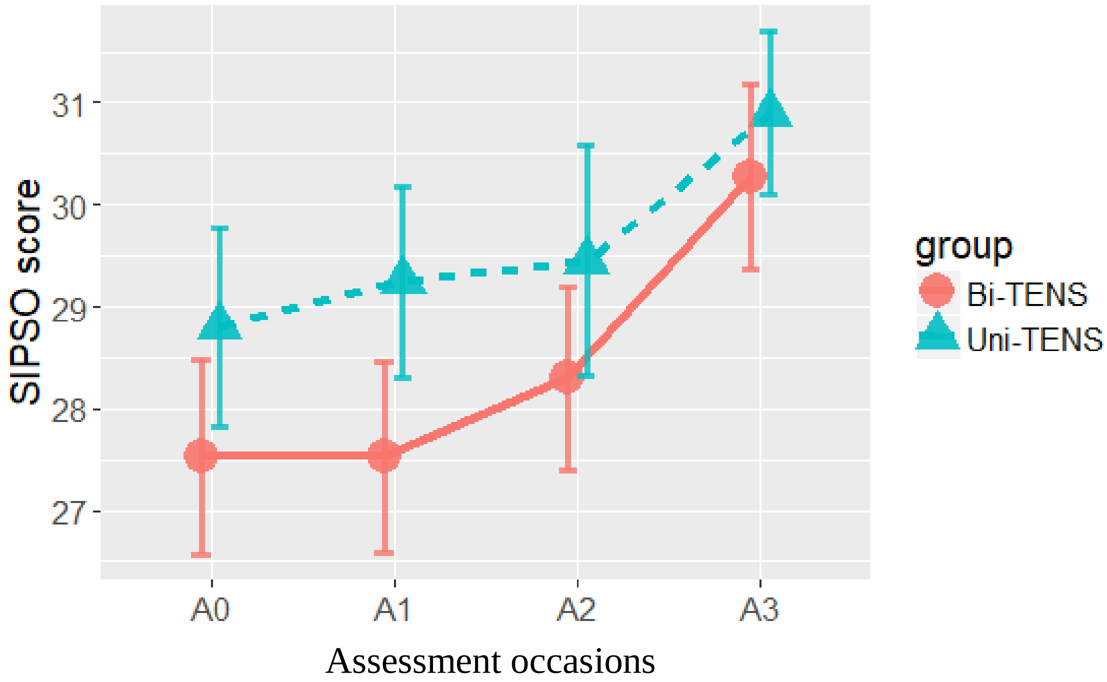

Figure 7.7. Mean change in the SIPSO score over time in the two groups.
Error bars represent the standard error of the mean.
Bi-TENS: bilateral transcutaneous electrical stimulation; SIPSO: Subjective Index of Physical and Social Outcome; Uni-TENS: unilateral transcutaneous electrical stimulation.

Table 7.3. Results of linear mixed models for people in the Bi-TENS group compared to those in the Uni-TENS group from A0 to A2 (n = 80; Uni-TENS = reference).

	Fixed effects		
	Time	Group	Group by time interaction
	Estimate; 95% CI; *P*	Estimate; 95% CI; *p*	Estimate; 95% CI; *P*
Paretic Step Test	0.96; 0.43 – 1.50; 0.001*	0.34; -1.52 – 2.21; 0.716	0.02; -0.74 – 0.78; 0.954
Non-paretic Step Test	0.87; 0.15 – 1.60; 0.019*	0.07; -2.16 – 2.29; 0.954	0.17; -0.85 – 1.2; 0.745
FTSTS (s)	-1.83; -2.88 – -0.79; 0.001*	-2.00 -6.80 – 2.81; 0.411	0.62 -0.86 – 2.11; 0.407
10mWT (ms^{-1})	0.045 0.017 – 0.071; 0.001*	0.058 -0.079 – 0.195; 0.404	-0.015 -0.053 – 0.023; 0.443
6MWT (m)	5.67; -0.92 – 12.27; 0.091	5.21 -31.85 – 42.26; 0.780	6.62 -2.71 – 15.95; 0.162
TUG (s)	-0.82; -1.54 – -0.10; 0.026*	1.49 -1.32 – 4.30; 0.485	-1.54 -2.55 – -0.52; 0.004*
SIPSO	0.33; -0.51 – 1.16; 0.442	-1.51; -5.03 – 2.02; 0.397	0.06; -1.12 – 1.25; 0.917

6MWT: 6-minute Walk Test; 10mWT: 10-Metre Walk Test; CI: confidence interval; FTSTS: Five Times Sit-to-Stand Test; SIPSO: Subjective Index of Physical and Social Outcome; TUG: Timed Up and Go test.

* $p \leq 0.05$

Table 7.4. Results of linear mixed models for people in the Bi-TENS group compared to those in the Uni-TENS group across A2 to A3 (n = 80; Uni-TENS = reference).

	Fixed effects		
	Time	Group	Group by time interaction
	Estimate; 95% CI; *p*	Estimate; *p* 95% CI; *p*	Estimate; 95% CI; *p*
Paretic Step Test	-0.32; -0.97 – 0.34; 0.342	0.38; -1.94 – 2.69; 0.747	-0.09; -1.02 – 0.84; 0.850
Non-paretic Step Test	-0.52; -1.66 – 0.61; 0.363	0.18; -3.11 – 3.46; 0.916	0.14; -1.46 – 1.75; 0.858
FTSTS (s)	0.58; -1.01– 2.16 0.472	3.58; -4.19 – 11.34 0.362	-1.04; -3.28 – 1.20 0.359
10mWT (ms^{-1})	0.009; -0.050 – 0.069; 0.760	0.083; -0.201 – 0.366; 0.564	-0.023; -0.108 – 0.062; 0.591
6MWT (m)	3.54 -11.60 – 18.69 0.644	49.89 -21.18 – 120.96 0.166	-8.22 -29.65 – 13.19 0.448
TUG	0.40; -0.81 – 1.61; 0.514	-3.80; -7.31 – -0.28; 0.036*	0.71; -1.00–2.42; 0.431
SIPSO	1.45; 0.03 – 2.87; 0.049*	-1.68; -5.97 – 2.62; 0.396	0.53; -1.49 – 2.54; 0.610

6MWT: 6-Minute Walk Test; 10mWT: 10-Metre Walk Test; CI: confidence interval; FTSTS: Five Times Sit-to-Stand Test; SIPSO: Subjective Index of Physical and Social Outcome; TUG: Timed Up and Go test.

* $p \leq 0.05$.

7.4.6 Predictor of more favourable outcomes in Bi-TENS group

The regression tree analysis showed that separating the people in the Bi-TENS+TOT group with the splitting criterion of having a post-stroke duration of less than 1.9 years led to the greatest reduction in the total variance of improvement in TUG completion time. Those participants who had a shorter post-stroke duration (<1.9 years) had the greatest improvement in TUG completion time after the Bi-TENS+TOT training. On average, the TUG completion time reduced by 36% in this group of participants. For those with a longer post-stroke duration (≥ 1.9 years), having an FMA-LE score between 16 and 22 predicted a more favourable outcome. On average, the TUG completion time reduced by 26% in the group of participants with FMA-LE scores between 16 and 22. Those participants with a longer post-stroke duration *and* an FMA-LE score greater than 22 showed an average of 20% reduction in TUG completion time. Those participants with a longer post-stroke duration *and* an FMA-LE score less than 16 showed the least improvement. On average, the TUG completion time reduced by 16% in the group of participants with FMA-LE scores less than 16 (Figure 7.8).

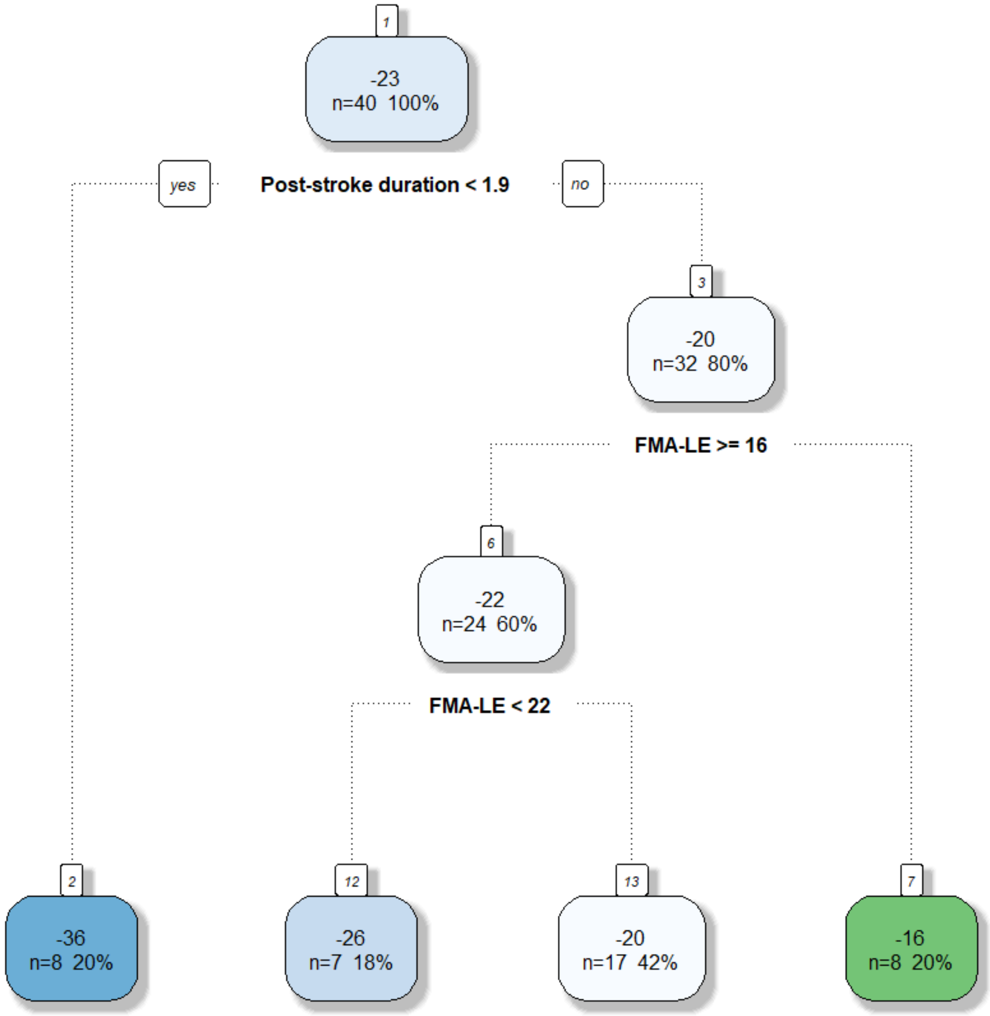

Figure 7.8. Regression tree showing the predictor and corresponding cut-off score to classify participant in different groups according to the percentage of reduction in TUG completion time.

The number in the middle of each node indicates the average percentage of reduction in TUG completion time in that subgroup. The subgroup on the left side of each cut-off criterion fulfilled the criterion.

FMA-LE: lower extremity domain of Fugl-Meyer assessment.

7.5 Discussion

The results of this study demonstrate that Bi-TENS+TOT induced greater and earlier improvement in TUG completion time when compared to Uni-TENS+TOT. Both groups demonstrated significant improvements in the paretic and non-paretic Step Test score and FTSTS completion time after 10 training sessions. Both groups also demonstrated significant improvements in 10-metre walking speed after 20 training sessions. The 6MWT distance and SIPSO score showed no significant changes in either group after the training. In general, the training effects on all outcome measures were maintained for 3 months after the training had ended. The SIPSO score improved at 3 months after the training.

The results of the regression tree analysis showed that the participants with the shorter post-stroke duration benefited the most from the Bi-TENS+TOT training. For those with a longer post-stroke duration, an intermediate level of motor recovery predicted a greater improvement in TUG after Bi-TENS training.

7.5.1 Effects on ST score

Paretic and non-paretic ST scores improved over time in both the Bi-TENS+TOT and Uni-TENS+TOT groups, without any between-group differences. This result is consistent with those presented in Chapter 6 (section 7.4.4), which show that additional

TENS applied over the non-paretic side offered no additional benefit in improving balance performance and postural control in people with stroke. Bi-TENS applied over the common peroneal nerve enhanced the motor output of ankle dorsiflexors but not trunk and other major antigravity muscles, such as the quadriceps and ankle plantarflexor.

The results also show that Bi-TENS was not superior to Uni-TENS in improving the FTSTS completion time. Ng (Ng, 2010) reported that balance performance measured on the Berg Balance Scale, but not lower limb muscle strength, predicted FTSTS completion time in people with stroke. Efficient postural control is critical for adjusting the centre of gravity during sit-to-stand movement (Ng, 2010). As there were no significant differences in the improvement of the Berg Balance Scale score and maximal excursion in the limit of stability test in the Bi-TENS+TOT group when compared to the Uni-TENS+TOT group, as shown in Chapter 5, it is not surprising that the improvement in FTSTS completion time was comparable in both groups.

7.5.2 Effects on TUG completion time

The Bi-TENS+TOT group demonstrated greater improvement in the TUG completion time when compared to the Uni-TENS+TOT group at week 10. The greater improvement in the Bi-TENS+TOT group could be mediated by improved paretic dorsiflexor strength (discussed in Chapter 6), as paretic ankle dorsiflexor strength has been identified as a significant predictor of TUG completion time (Ng & Hui-Chan, 2013). In addition, the muscles of the non-paretic leg are also known to be weakened in people with stroke (Andrews & Bohannon, 2000). It is possible that Bi-TENS also augmented the training effects on the non-paretic leg and thus enhanced overall walking performance. Moreover, TUG is not merely a walking task. It includes a series of transitional movements that are relevant to daily activity such as sit-to-stand and turning. Satisfactory muscle strength, balance control and movement coordination are prerequisites for completion of this complex functional task. In addition to ankle dorsiflexor strength, the Bi-TENS may have improved the proprioception and sensation of the non-paretic lower limbs and thus led to a greater improvement in TUG completion time. However, as the lower-limb sensation was not assessed in the current study the effect of Bi-TENS on lower-limb sensation remains unknown.

7.5.3 Effects on walking speed

Surprisingly, there was no significant difference in 10mWT walking speed between the two experimental groups, even though the Bi-TENS+TOT group showed significantly greater improvement in TUG completion time (see section 7.5.2). The improvement in walking speed was only apparent after 10 weeks of training, which was relatively slow when compared to the other physical outcomes, such as TUG and FTSTS. It should be noted that comfortable walking speed rather than maximum walking speed was assessed in the current study. For TUG and other outcome measures, the participants were assessed on their maximum capacity to perform the task. It is plausible that the comfortable walking speed measured may underestimate walking capacity because it may have been influenced by the walking habits of the participants.

7.5.4 Effects on 6MWT distance

The 6MWT distance showed no significant improvement in either group over time. This result is inconsistent with those reported by Ng and Hui-Chan (Ng & Hui-Chan, 2009), which showed that TENS+TOT improved the 6-minute walking distance by 29.3% after 20 sessions of training. Differences in training frequency might partly explain this discrepancy. In Ng and Hui-Chan’s study (Ng & Hui-Chan, 2009), people with stroke performed the exercise 5 times per week for 4 weeks. In contrast, the participants in the current study performed the exercise 2 times per week for 10 weeks. The exercise protocol in both studies included high-repetition exercises that involved large muscles and thus could be considered aerobic training (American College of Sports Medicine, 2013). It is well documented that increased exercise frequency is necessary to promote cardiopulmonary fitness (Billinger et al., 2014; Pang et al., 2006). A previous meta-analysis (Pang et al., 2006) that pooled results from 4 studies that involved 258 people with stroke revealed that aerobic exercise 3 to 5 times per week demonstrated a positive effect (standardised effect size = 0.30) in improving walking endurance. The American Heart Association also recommends that the frequency of aerobic exercise should be 3 to 5 times per week to improve exercise tolerance in people with stroke (Billinger et al., 2014). The lack of obvious improvement in the 6MWT distance seen in the current study might be because the relatively low exercise frequency adopted did not induce sufficient stimulus to improve cardiovascular fitness.

Another possible explanation is that the study by Ng and Hui-Chan (Ng & Hui-Chan, 2009) only recruited participants with moderate plantarflexor spasticity. Evidence suggests that TENS applied over the paretic leg can reduce ankle plantarflexor spasticity (Chen et al., 2005b; Hui-Chan & Levin, 1993). As TENS is effective in enhancing walking efficiency in patients with ankle plantarflexor spasticity, this might explain why a greater improvement in walking endurance was shown in the Ng and Hui-Chan study when compared with our study.

7.5.5 Effects on SIPSO score

There was no significant increase in SIPSO score in either group after 10 weeks of training. However, the SIPSO score was significantly improved at follow-up assessment when compared to A2 in both groups. Flansbjer and colleagues (Flansbjer et al., 2008) demonstrated that a 10-week resistance training programme led to a greater improvement in the level of participation, compared to usual care in 24 people with chronic stroke. Similarly, the differences existed at 5 months follow-up but not immediately after training.

The results of the current study show that walking speed and functional mobility improved in both groups after 10 weeks of training. It is plausible that this improved walking performance facilitated community ambulation and subsequently enhanced the participants' level of community integration. As self-efficacy in reintegration requires an extended period of time to develop, this might explain why the increases of the SIPSO score were observed at 3 months after training.

7.5.6 Predictor of more favourable outcome in the Bi-TENS group

The regression tree analysis showed that people with a post-stroke duration of less than 1.9 years showed the greatest improvement after the 10 weeks of Bi-TENS+TOT training. This result might suggest that people with shorter post-stroke duration have a higher degree of neuroplasticity even in the chronic phase of stroke. Another possible explanation is that people with a shorter post-stroke duration are more motivated than those with a longer post-stroke duration.

For those people with stroke who had a post-stroke duration of more than 1.9 years, FMA-LE was a significant predictor of training outcome. The results show that people with an intermediate level of motor recovery (FMA-LE score between 16 and 22) demonstrated a greater reduction in TUG completion time. Some exercises in the training protocol, such as practising transitional movement, could be challenging for people in this subgroup but not for those with a satisfactory level of motor recovery

(FMA-LE greater than 22). In contrast, people with a poor level of motor recovery could find the exercises too challenging. This result might suggest that the TOT protocol adopted in the current study met the physical capacity of those with moderate motor impairment and needed to be adjusted for those with mild or severe motor impairments.

7.5.7 Limitations

This study has several limitations that must be considered. First, because the primary objective of the study was to compare Bi-TENS and Uni-TENS in improving motor function in stroke survivors, there was no *pure* TOT group or control group without active treatment to delineate the treatment effects of TENS and TOT. Nevertheless, previous studies or our research group demonstrated that Uni-TENS+ TOT was superior to TENS alone, placebo-TENS+TOT and control without active treatment, in improving lower limb motor functions in people with stroke. Second, the neurophysiological mechanisms that mediate the effects of Bi-TENS and Uni-TENS remain unclear. Future studies are necessary to investigate the differential effects of Bi-TENS and Uni-TENS on cortical function. Third, the therapist who supervised the training was not blinded to the group allocations, although the standardised treatment protocol could have minimised the bias. Fourth, selection bias might have existed because all of the participants in this study were community-dwelling and self-selected to participate. Thus, they were likely to be more motivated and to have a better mobility level than those who declined to participate. Recruitment of subjects with poor mobility should be considered in a future study. Fifth, we did not measure the number of movement repetitions accomplished by the subjects in each exercise. Thus, the actual amount of exercise could have varied considerably among the subjects. The number of repetitions, rather than exercise duration, could be used as an indicator of exercise dosage in a future study. Sixth, the follow-up period was limited to 3 months after training due to resource limitations. Thus, a longer-term carry-over effect cannot be determined. Seventh, the TENS has been applied to the lower-limb only in the current study. Previous studies have suggested that applying the TENS as adjunct therapy augmented the upper-limb function (Peurala et al., 2002) and trunk control (Chan et al., 2015) in people with stroke. Application of Bi-TENS on other body part as an adjunct therapy could also be beneficial. Besides applying TENS on multiple body part, for example, on both upper and lower-limb may further augment the training effects. It is because this approach could have activated the entire motor cortex. The global functions may be further enhanced with this approach, since both the upper limb and lower limb function are expected to improve. Future studies evaluating the effectiveness of these approach are warranted.

Finally, it should be noted that limited demographic characteristics were used as independent variables in the regression tree analysis. The area of the lesion site could be a stronger predictor of responsiveness to treatment. Enhancement of interhemispheric interaction is hypothesised as one of the neural mechanisms by which motor control of paretic limbs can be enhanced. Thus, the intactness of the M1 and corpus callosum might have a strong influence on the efficacy of Bi-TENS. Due to limited resources, this hypothesis could not be verified in this study.

7.6 Conclusions

This study demonstrates that Bi-TENS applied on the common peroneal nerves combined with lower limb TOT induced greater improvement in TUG completion time at 5 weeks when compared with Uni-TENS combined with TOT. Both Bi-TENS+TOT and Uni-TENS+TOT induced significant within-group improvements in dynamic standing balance, sit-to-stand performance, walking speed and functional mobility in people with chronic stroke after 20 training sessions, but had no effects on walking endurance and level of community integration. The training effects in both groups were maintained for 3 months, and the level of community integration was improved at 3 months after the training. The results of this study suggest that Bi-TENS+TOT is superior to Uni-TENS+TOT in improving functional mobility in people with chronic stroke. A shorter post-stroke duration predicted a greater improvement in TUG completion time in the Bi-TENS+TOT group. For people with a longer post-stroke duration, the FMA-LE score could identify those who could benefit the most from Bi-TENS+TOT.

Since the neurophysiological mechanisms that mediate the effects of Bi-TOT remained unclear, a pilot study presented in the following chapter will explore the potential mechanism using the functional near-infrared spectroscopy (fNIRS).

Chapter 8

Influence of bilateral and unilateral transcutaneous electrical nerve stimulation (TENS) on the level of cortical perfusion: A pilot study with functional near-infrared spectroscopy (fNIRS)

8.1 Abstract

Results from the clinical study described in Chapters 6 and 7 show that Bi-TENS applied over the common peroneal nerve concurrent with TOT led to greater improvement in motor performance than Uni-TENS + TOT. However, the neurophysiological mechanisms remain unclear. It was hypothesised that Bi-TENS would more strongly influence cortical perfusion than Uni-TENS and placebo stimulation. As no study has compared the changes in cortical perfusion after Bi-TENS and Uni-TENS, the objective of this pilot study was to evaluate the effects of Bi-TENS and Uni-TENS on cortical perfusion in the motor representation area representing the lower limb in healthy older adults. This study also aimed to evaluate the effects of Bi-TENS and Uni-TENS on EMG amplitude, maximum ankle dorsiflexion torque and the ability to maintain a steady force output.

Ten healthy older adults were recruited for this pilot crossover study. Participants attended three experiment sessions at 1-week intervals and received either Bi-TENS, Uni-TENS or placebo stimulation on their lower limbs in each session. Functional near-infrared spectroscopy (fNIRS) was used to measure the change in maximum oxyhaemoglobin (HbO_2) concentration *before* and *after* stimulation. The EMG amplitude of the tibialis anterior muscle, maximum isometric dorsiflexion torque and coefficient of variation of ankle dorsiflexor force output were measured as secondary outcomes.

The results of a Wilcoxon Signed-Rank Tests showed that Bi-TENS reduced maximum HbO_2 concentration changes to a significantly greater extent than Uni-TENS ($Z = -2.14$; $p = 0.032$) and placebo stimulation ($Z = -2.45$; $p = 0.014$). There was, however, no significant difference in the change in maximum HbO2 concentration between the placebo stimulation and Uni-TENS groups ($Z = -1.58$; $p = 0.131$).

For the secondary outcomes, the results of the Wilcoxon signed-rank test showed that no between-group comparisons were significant for the EMG amplitude of the tibialis anterior, maximum ankle dorsiflexion torque and coefficient of variation of the ankle dorsiflexor force output.

The results of this pilot study show that Bi-TENS applied over the area innervated by the peroneal nerve reduced the maximum change in HbO_2 concentration of the contralateral motor representation area of the lower limb during isometric ankle dorsiflexion compared with Uni-TENS and placebo stimulation. This study provided preliminary evidence that Bi-TENS had a stronger influence on the cortical perfusion of the contralateral motor representation area. However, since there were no significant between-group differences in the secondary outcomes, it remains unclear if the observed reduction in the change indicates better processing efficiency in the contralateral motor representation area. The results nevertheless show that using fNIRS to assess changes in cortical perfusion during ankle dorsiflexion is feasible. This pilot study's preliminary results can be used to estimate the relative effect size of Bi-TENS versus Uni-TENS in modulating cortical perfusion

8.2 Introduction

Neuroimaging studies have demonstrated that cutaneous electrical stimulation modulates cortical perfusion in healthy adults (Golaszewski et al., 2004; Jang et al., 2014; Toma et al., 2003; Wu et al., 2005), but the results have been inconsistent. Using fMRI, Golaszewski and his colleagues investigated the effect of whole-hand stimulation at intensities below the motor threshold (50Hz, pulse width 0.25ms) on cortical activation in 10 healthy adults (Golaszewski et al., 2004). The blood-oxygenation-level-dependent signal in the bilateral M1, primary sensory cortex and medial frontal gyrus and the ipsilateral supplementary motor area increased during a finger-tapping task after 30 minutes of stimulation (Golaszewski et al., 2004). In addition, Wu and colleagues reported that 2 hours of sub-motor threshold electrical cutaneous stimulation on the median nerve at the wrist level (1 Hz, pulse width 1 ms) increased the contralateral M1, primary sensory cortex and premotor cortex cortical activation during a thumb flexion and extension task, as assessed with fMRI. The augmented cortical activation lasted for over an hour (Wu et al., 2005).

In contrast, Toma and colleagues (Toma et al., 2003) found that 15 minutes of TENS applied over the thenar area of the right hand reduced the activation of left M1 during the right thumb opposition task, as assessed with fMRI. Similarly, Jang and colleagues (Jang et al., 2014) reported that the 5 minutes of electrical stimulation applied over the wrist extensor reduced the oxyhaemoglobin (HbO_2) concentration change in the corresponding sensorimotor cortex, as measured with fNIRS.

The results from the clinical study described in Chapters 6 and 7 showed that Bi-TENS applied over the common peroneal nerve concurrent with physical training led to greater improvement in motor performance such as increased paretic ankle dorsiflexor strength and shortened Timed Up and Go test completion times compared with Uni-TENS + TOT. However, the mechanisms leading to these improvements in motor functions remain unclear. Understanding the mechanisms that mediate the therapeutic effects of Bi-TENS should provide insight into how to optimize rehabilitation protocols using Bi-TENS.

Up to now, no published study has compared the effect of Bi-TENS with that of Uni-TENS in terms of cortical perfusion in human subjects. Healthy participants were recruited in the current study, since understanding the effect of Bi-TENS and Uni-TENS on cortical perfusion in healthy persons should provide information useful for estimating their effects on cortical activity in people with brain lesions.

Studies have reported that the location of a brain lesion influences the neuroplastic change of the M1 in response to intervention in people with stroke (Ameli et al., 2009; Luft et al., 2004b). For example, Ameli and colleagues (Ameli et al., 2009) demonstrated that facilitatory TMS enhanced the finger-tapping frequency in people with subcortical stroke, but not in people with combined subcortical and cortical stroke.

The results of the study also showed that facilitatory TMS applied to the ipsilesional M1 led to a reduction in neural activities of the contralesional M1 in people with subcortical stroke measured with fMRI. In contrast, increased activation of the bilateral motor-related areas was demonstrated after facilitatory TMS in people combined subcortical and cortical stroke (Ameli et al., 2009). Luft and colleagues (Luft et al., 2004b) also reported that people with subcortical stroke demonstrated a different pattern of functional cortical reorganisation than did people with cortical stroke. The results of their study (Luft et al., 2004b) showed that *standard* physiological motor circuitry, which involved the ipsilesional M1 and contralesional cerebellum, was activated during paretic arm movement in people with *subcortical stroke*. On the contrary, there has been minimal activation of the ipsilesional M1 in people with cortical stroke. The loss of cortical tissue secondary to cortical stroke may explain the reduction of activation in the M1. However, the cortical area adjacent to the ipsilesional M1 has shown increased activation during paretic hand movement in people with cortical stroke, which may represent a compensatory cortical reorganisation (Luft et al., 2004b).

The results of these studies (Ameli et al., 2009; Luft et al., 2004b) suggested that the location of a brain lesion has a strong influence on the reorganisation of the motor representation area during spontaneous recovery and in response to non-invasive stimulation. Thus, Luft and colleagues (Luft et al., 2004b) suggested that stratification of participants according to lesion location was necessary when investigating the neurophysiological mechanisms of motor recovery. Recruiting a group of people with stroke, a *homogenous* pathology and the same level of motor functions to evaluate the influences of Bi-TENS versus Uni-TENS on cortical perfusion was impractical in the current study due to resource constraints. Thus, this pilot study aimed to investigate the effects of electrical stimulation on cortical perfusion in healthy older adults.

In this study, cortical perfusion was assessed via functional near-infrared spectroscopy (fNIRS). fNIRS provides continuous information about cortical perfusion and is more robust against motion-induced artefacts than other imaging techniques (Cooper et al., 2012). fNIRS has been extensively used to study the level of cortical perfusion during walking in healthy adults (An et al., 2013; Holtzer et al., 2011; Kurz et al., 2012; Maidan et al., 2016), people with Parkinson's disease (Maidan et al., 2016) and people with stroke (Mihara et al., 2007; Miyai et al., 2003; Rea et al., 2014). In general, those studies have found that cortical perfusion increased when subjects performed a more difficult task, such as talking while walking (Holtzer et al., 2011; Maidan et al., 2016) or walking backwards (Kurz et al., 2012). Miyai has reported (Miyai et al., 2003) that perfusion of the ipsilesional sensorimotor cortex and premotor cortex was increased after 2 months of stroke rehabilitation. The increase of perfusion the sensorimotor cortex correlated with improvements in the symmetry of the swing phase during walking. Rea and colleagues (Rea et al., 2014) demonstrated that fNIRS could capture brain activity associated with pedalling movements. Koenraadt' and colleagues (Koenraadt et al., 2012) have demonstrated that the locations of HbO_2 concentration changes differ between voluntary wrist movement and ankle movement in healthy adults.

This pilot study applied fNIRS to assess the level of cortical perfusion after 60 minutes of cutaneous stimulation during isometric ankle dorsiflexion in healthy older adults. It was hypothesized that both Bi- and Uni-TENS would modulate the perfusion of the contralateral motor areas representing the tested lower limb. Bi-TENS was expected to generate greater perfusion changes than Uni-TENS or placebo stimulation. Both Bi- and Uni-TENS were expected to increase the ankle dorsiflexor activities, the maximum isometric strength of the dorsiflexors, and to improve the ability to maintain a steady force output, but Bi-TENS was expected to be superior in improving those outcomes in healthy older adults.

The objectives of this study were to: (1) compare the effects of Bi- and Uni-TENS on the cortical perfusion of contralateral motor representation areas of the lower limb in healthy older adults and (2) compare the effects of Bi- and Uni-TENS on the EMG amplitude of the tibialis anterior during isometric contraction, dorsiflexor strength and the ability to maintain a steady force output in healthy older adults.

8.3 Methods

8.3.1 Assessment procedure

The study was conducted in the clinical research laboratory of the Hong Kong Polytechnic University. Participants were invited to visit the laboratory three times, with a 1-week interval between each visit. During each session, the participants received 60 minutes of either Uni-TENS, Bi-TENS or placebo stimulation over the common peroneal nerve in a random order based on drawn lots. fNIRS measurements were performed before and after stimulation. All of the participants signed written consent forms before participating (Appendix 8.1).

8.3.2 Participants

Participants were eligible to join the study if they (1) were between 55 and 85 years of age and (2) were right-leg dominant. Each participant's leg dominance was assessed using the three tasks suggested by de Ruiter (de Ruiter et al., 2010): the leg used to kick a ball, to step up a 40cm step and to step forward in response to a sudden perturbation was considered the dominant leg. If the three results were inconsistent, the leg used in two of the tests was considered the dominant leg. Participants were excluded if they (1) had any additional medical, cardiovascular or orthopaedic condition that would hinder assessment, (2) had a cardiac pacemaker implanted or (3) were unable to give informed consent.

8.3.3 TENS protocol

The TENS stimulation was delivered with a 120Z dual-channel TENS unit (EMSphysio Ltd, Wantage, UK) at 100 Hz (0.2 ms square pulses). Stimulation was delivered at an intensity twice the sensory threshold (the minimum intensity to provoke a tingling sensation) and below the motor threshold (identified by the absence of muscle twisting). A pair of self-adhesive electrodes (ITO Co. Ltd., Tokyo, Japan: rubber electrodes 40X41 mm and gel pad 40X41 mm) were applied to the common peroneal nerve of the lower limbs. The cathode electrode was placed on the popliteal fossa, and the anode electrode was placed on the head of the fibula (Wu et al., 2006). Participants received 60 minutes of either Uni-TENS, Bi-TENS or placebo stimulation in each session (Table 8.1).

Table 8.1. Type of stimulation applied in each stimulation condition.

Condition	Non-dominant leg	Dominant leg
Placebo stimulation	Placebo-TENS	Placebo-TENS
Uni-TENS	TENS	Placebo-TENS
Bi-TENS	TENS	TENS

8.3.4 Outcome measures

8.3.4.1 Level of cortical perfusion

Functional near-infrared spectroscopy (fNIRS) is a non-invasive tool to investigate the hemodynamic responses of the cortex. Many biological materials such as brain and cardiac tissue are nearly transparent to near-infrared (NIR) radiation (Boas et al., 2001). At the same time, the optical absorption features of HbO_2 and deoxyhaemoglobin differ within the NIR spectrum, which is between 650 and 900 nm (Boas et al., 2001) (Figure 8.1).

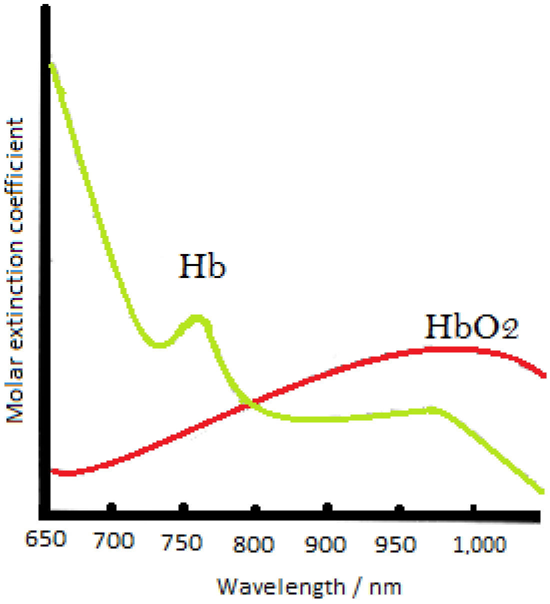

Figure 8.1. Optical-absorption features of oxyhaemoglobin (HbO2) and deoxyhaemoglobin (Hb). Modified from Boas and colleagues (Boas et al., 2001).

Series of metabolic and haemodynamic responses occur when the cortex is activated (Ferrari & Quaresima, 2012). Typically, local arterial vasodilation in the activated cortical area increases the focal cerebral blood flow and focal blood volume. The elevated cerebral blood volume in both arterial and venous compartments usually provides an extra oxygen supply that exceeds the actual oxygen usage rate of the activated region. This results in an increase in HbO_2 and a relative decrease in deoxyhaemoglobin concentration in the activated cortical region (Ferrari & Quaresima, 2012). These haemodynamic responses can be detected by fNIRS.

Plichta and colleagues (Plichta et al., 2006) reported a good test-retest reliability of fNIRS (ETG-4000, Hitachi Medical Co., Japan) in measuring the cortical activity of the occipital lobe in response to visual stimulation in 12 healthy young adults (ICC = 0.78) for the active channels. Bhambhani and colleagues (Bhambhani et al., 2006) also reported satisfactory test-retest reliability of fNIRS (MRM91, MicroRunman, NIM Inc, Philadelphia, Pennsylvania) in measuring prefrontal lobe haemodynamic response during a rhythmic hand-gripping exercise in 13 healthy young adults (ICC = 0.83) and in 25 patients with a moderate to severe degree of traumatic brain injury (ICC = 0.76).

8.3.4.2 fNIRS data acquisition and processing

In this study, the NIRSport system (NIRx Medical Technologies, Berlin, Germany) was used to measure the level of cortical activation of the contralateral M1 in conjunction with the NIRStar software (version 14.2, NIRx Medical Technologies, Berlin, Germany). The NIRSport system is equipped with a silicon photodiode sensor and an LED light emitter and uses two different wavelengths (760 and 850 nm) to measure the change in HbO_2 concentration relative to the baseline concentration. The HbO_2 concentration was used to estimate the focal cortical activation level. Studies have shown that a significant increase in HbO_2 concentration but no decrease in deoxyhaemoglobin concentration may be observed during lower-limb motor tasks such as pedalling (Miyai et al., 2001), stepping (Nishiyori et al., 2016) and walking (Suzuki et al., 2004).

The system's sampling frequency was 7.8Hz. Eight light emitters and seven light detectors (22 channels in total) were used (Figure. 8.2). The distance between each emitter-detector pair was fixed as 3.0cm. Signals were recorded while the subjects were completely at rest and during isometric dorsiflexion of the non-dominant ankle at 50% of peak torque (please refer to section 8.3.5.5 for the determination of peak torque). The first 1 minute of the recording while the subject was resting was set as the baseline.

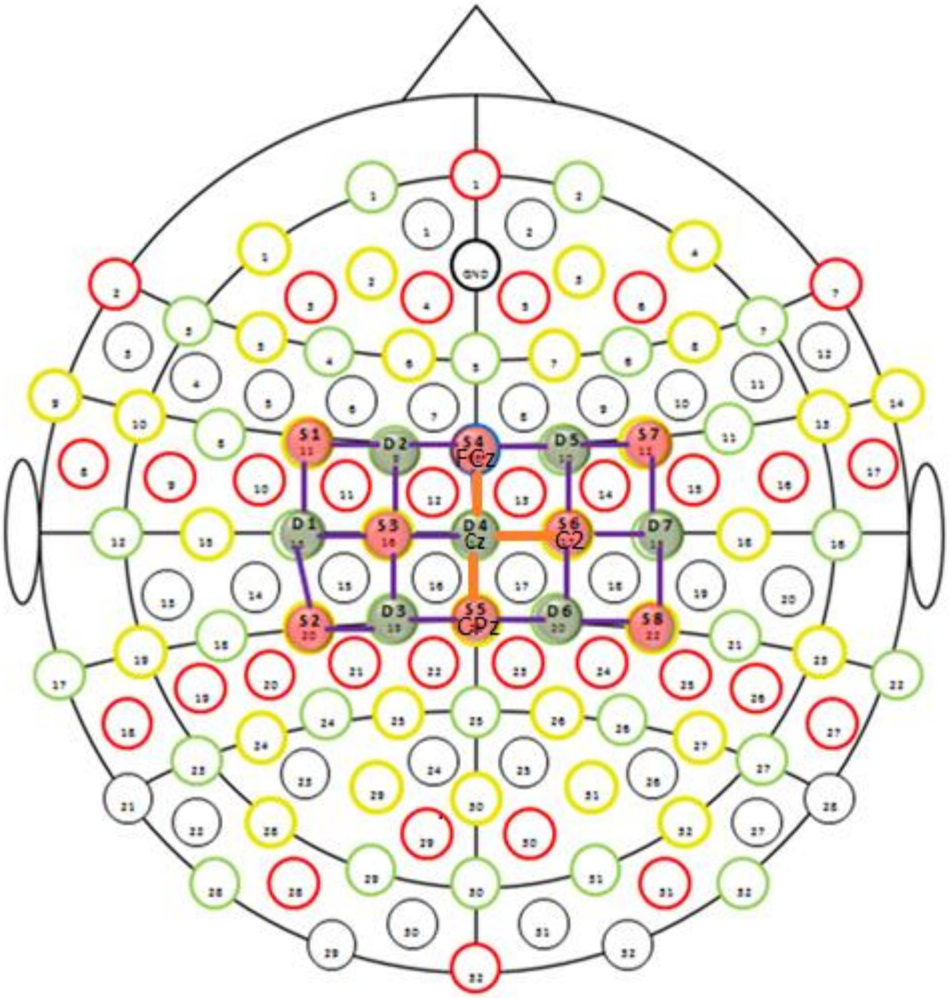

Figure 7.2. Montage used for the fNIRS assessment.
Notes: The solid green circles indicate light detectors and the solid red circles indicate the signal source. The purple line indicates the detector–signal source pair (channel). The three channels labelled in orange were used to capture the signal change for the motor representation areas of the left lower limb.

Data processing was conducted with the nirsLAB software (version 201605, NIRx Medical Technologies, Berlin, Germany). A bandpass filter (high pass frequency: 0.01 Hz; low pass frequency: 0.2 Hz) was applied. The high pass filter is typically used to remove long-term fluctuations, such as long-term drifting. The low pass filter is typically used to remove more rapid fluctuations, such as motion artefacts. The relative

HbO_2 concentration (ΔC) was calculated based on the modified Beer-Lambert law using the following equation (Bakker et al., 2012):

$$\Delta A = \Delta C \cdot \varepsilon \cdot d \cdot DPF$$

The relative light attenuation (ΔA) was measured by the NIRSport system. It was assumed that the background haemoglobin concentration in tissues was 75 µM, that the mean venous SaO_2 was 70% and that the molar extinction coefficients (ε) were equal to 1,486.6 and 2,526.4 for the two wavelengths, respectively (SUNY Downstate Medical Center Optical Tomography Group, 2016). Moreover, the mean distance travelled by the light beam in tissue (d) was 3.0 cm, and the differential path-length factors (DPFs) were equal to 7.25 and 6.38 for the two wavelengths, respectively (SUNY Downstate Medical Center Optical Tomography Group, 2016).

The averaged signal from three channels, which comprised the areas between the locations of Cz, FCz, CPz and C2 on the international 10–20 system (Figure 8.2), was used to represent the cortical perfusion of the lower-limb representation area. Selection of these channels was based on the results of two previous fNIRS studies (Koenraadt et al., 2012; Koenraadt et al., 2014). Work by Koenraadt and his colleagues (Koenraadt et al., 2012) has shown that the HbO_2 changes during active ankle movement is located approximately 2.2cm lateral to Cz with a standard deviation of 1cm in both the anteroposterior and mediolateral directions. In another study, Koenraadt and his colleagues (Koenraadt et al., 2014) reported that a significant increase in HbO_2

concentration during attempted right foot tapping movements was recorded from the channel on Cz when seven people with spinal cord injury attempted to perform ankle tapping.

The *maximum HbO_2 concentration change* was used to represent the change in cortical perfusion. The maximum HbO_2 concentration change was calculated by subtracting the maximum HbO_2 concentration recorded after stimulation from the maximum HbO_2 concentration recorded before stimulation. The maximum HbO2 concentration change was sensitive in detecting a change in cortical activities during cognitive tasks and motor tasks (Colier et al., 1999; Leff et al., 2008). Previous studies have suggested that the change in level of cortical perfusion when conducting the same task indeed reflected a change of processing efficiency of the area of interest (Toma et al., 2003).

8.3.4.3 Ankle isometric contraction paradigm

This study adopted an ankle isometric contraction paradigm, in which the participant maintained an isometric contraction at 50% of the peak torque in accordance with real-time numeric feedback displayed on a computer monitor. This level of torque was selected instead of the maximum peak torque because the force output could remain relatively stable within the 15-second measurement period. Two events, namely resting and isometric ankle contraction, were performed alternatively. Each isometric ankle contraction event last for 15 seconds and the resting event last for 30 seconds. Both events repeated five times (Figure 8.3). The participants were instructed to look at a computer monitor placed 1 meter in front of them. A text reminder showing either ‘Ankle’ or ‘Resting’ appeared 5 seconds before the start of each event. Following the text reminder showing ‘Ankle start!’, the participants were instructed to maintain an isometric dorsiflexion contraction at 50% of the peak torque until the cue ‘Resting’ appeared. The level of cortical activation was assessed before and after 60 minutes of stimulation (Figure 8.4). The participants practised the isometric contraction before starting the experiment until they were familiar with the task.

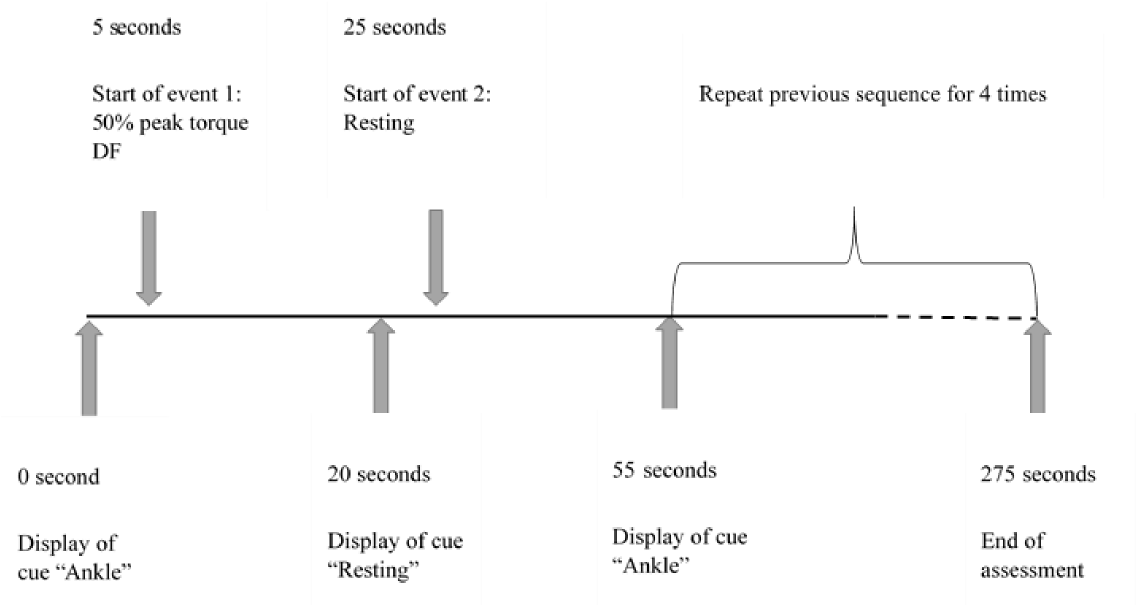

Figure 8.3. Timeline illustrating the sequence of events in the ankle movement paradigm.

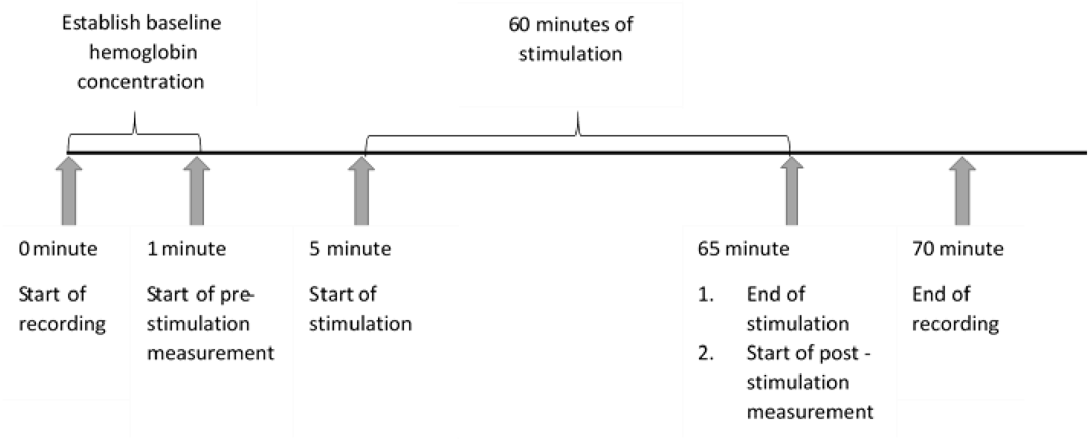

Figure 8.4. Timeline illustrating the overall assessment protocol.

8.3.4.4 Electromyography acquisition and processing

EMG was used to quantify the level of tibias anterior muscle activities. EMG signals were recorded from the non-dominant tibialis anterior (TA) during isometric ankle dorsiflexion in the position as mentioned. The SX230FW EMG Amplifier (Biometrics Ltd., Newport, UK) and disposable Ag/AgCl electrodes (Ambu® BlueSensor, Ambu, Denmark) with an interelectrode distance of 2 cm were used for signal acquisition. The optimal electrode placement for EMG of the TA is 1/6 of the way on the line between the tibial tuberosity and inter-malleoli line (Rainoldi et al., 2004). The hair over the areas of interest was shaved, and dead skin was removed with sandpaper to minimise the skin impedance. The skin impedance was then checked after the placement of the electrodes. The impedance of less than 10kΩ was considered acceptable. The EMG signal was acquired at 1.0 kHz with a custom program written in LabVIEW (version 2013; National Instruments, Austin, Texas, US). The EMG signals were stored for off-line analysis with the biosignalEMG package (version 2.0.0) and custom scripts in R (version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria).

The off-line data processing involved direct current offset removal, full-wave rectification and bandpass filtering (high-pass filter frequency: 5 Hz; low-pass filter frequency: 500 Hz) with a fourth-order digital Butterworth filter (roll-off rate: -24 dB/octave) as suggested by the International Society of Electrophysiology and Kinesiology (Merletti & Di Torino, 1999).

To calculate the maximum EMG amplitude during maximum contraction of the tibialis anterior muscle, the root mean square (RMS) of the EMG signals was calculated over a 500-ms window. The beginning of the window was set at 250 ms before the peak force output and ended at 250 ms after the peak output (Figure 8.5).

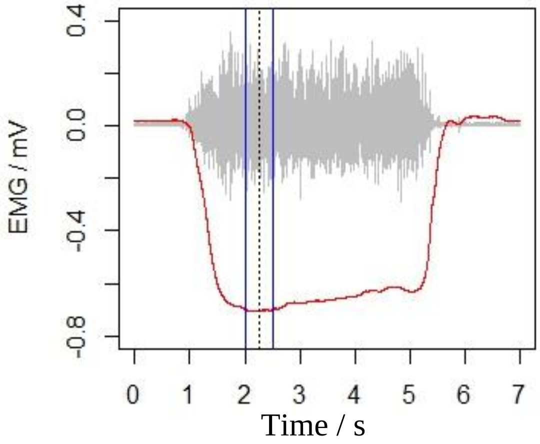

Figure 8.5. The time window used to calculate the maximum RMS of the EMG traces. The grey lines are the EMG signals; the red line represents the force output. The dotted black line locates the maximum force output. The blue lines define the window used to calculate the RMS maximum.

The RMS EMG of the isometric ankle dorsiflexion task (50% force output) was calculated over a 5-second window. The beginning of the window was set at 5 seconds after the start of the contraction. The force output and EMG signal were visually checked to ensure that the signals were stable. This EMG signal was then normalised by the RMS EMG recorded during maximum contraction and denoted as normalised RMS EMG (nrmsEMG).

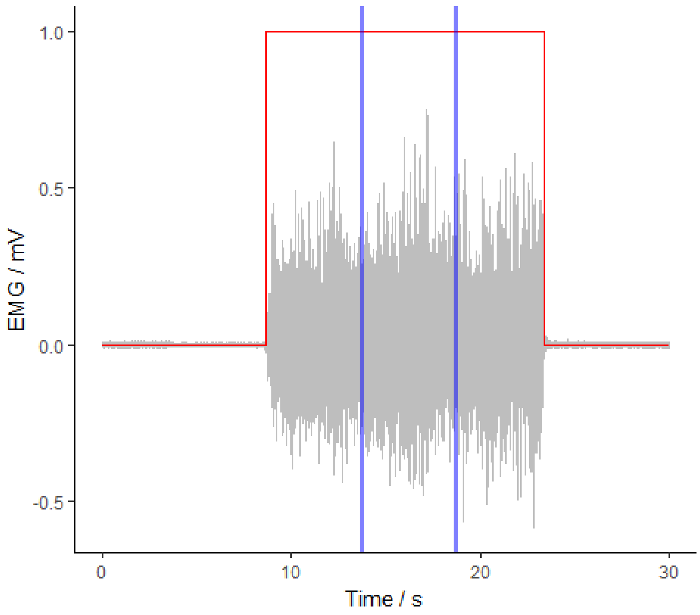

Figure 8.6. Illustration of the time window used to calculate the RMS EMG at 50% of the maximum isometric ankle dorsiflexion force. The grey lines are the EMG signal; the red line with a value of 1 indicates the dorsiflexor contraction phase. The on and off phases of dorsiflexor contraction were detected with the onoff_bonato() function from the R software’s BiosignalEMG package. The time window between the blue lines was used to calculate the maximum RMS of the EMG signal

8.3.4.5 Isometric ankle dorsiflexion torque

The isometric ankle dorsiflexion torque was measured with the participants in a sitting position. Each participant’s non-dominant leg was secured to a custom foot frame by strips. The knee of the tested leg was placed at 45° of flexion, and the ankle was placed at 0° of dorsiflexion (Figure 8.7). A load cell (YZC-516 S-Type, Guangzhou Electrical Measuring Instruments Factory, China) was mounted underneath a wooden footplate, and the participant’s foot and toes were attached to the footplate with strips (Siddiqi et al., 2015). Thus, the pulling force generated from ankle dorsiflexion was transmitted to the load cell. The load cell was calibrated using known weights before the study started.

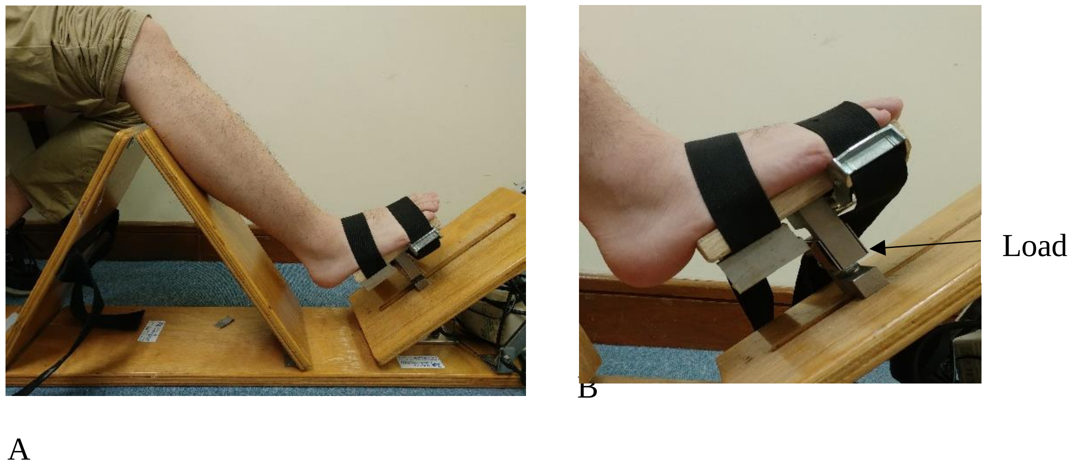

Figure 8.7. (A) The setup and joint positions during the isometric ankle dorsiflexion assessment. (B) A closeup showing the location of the load cell.

The ankle dorsiflexion torque was calculated by multiplying the generated force measured with the load cell by the lever arm. The lever arm was the length measured from the centre of the heel to the metatarsal heads. The participants were asked to hold the maximum isometric ankle dorsiflexor contraction for 3 seconds three times to estimate the maximum isometric torque. At least 1 minute of rest was offered in between each trial of maximum isometric contraction to minimise muscle fatigue. Signal acquisition and real-time joint torque calculation were conducted with a custom program written in LabVIEW (version 2013; National Instruments, Austin, TX, US).

8.3.4.6 Coefficient of variation (CV) of force output

Each participant’s ability to maintain a steady force output was quantified using a coefficient of variation (CV) using the following equation (Lai et al., 2016).

$$\text{Coefficient of deviation} = \sqrt{\left(\frac{\sum(y-y_{50})^2}{n}\right)}/\text{mean force}$$

where y equals the observed force output; y_{50} equals the targeted force output, which is 50% of the peak force output; and n is the total number of data points.

CV has been used to evaluate the ability to control steady force output in healthy older adults (Enoka et al., 2003; Galganski et al., 1993), healthy young adults (Enoka et al., 2003; Lai et al., 2016; Madsen, 1996), people with back pain (Luoto et al., 1996) and people with stroke (Lai et al., 2016). Lai and colleagues (Lai et al., 2016) used this method to investigate the effects of cutaneous electrical stimulation on EEG–EMG coherence and motor performance in healthy adults, as well as in people with stroke. In this study the middle 5 seconds of the force output was used to calculate the CV to ensure that the force output was stable and to minimize any effect of fatigue on the force control (Figure. 8.8). Lower CV values represent better control of the force output.

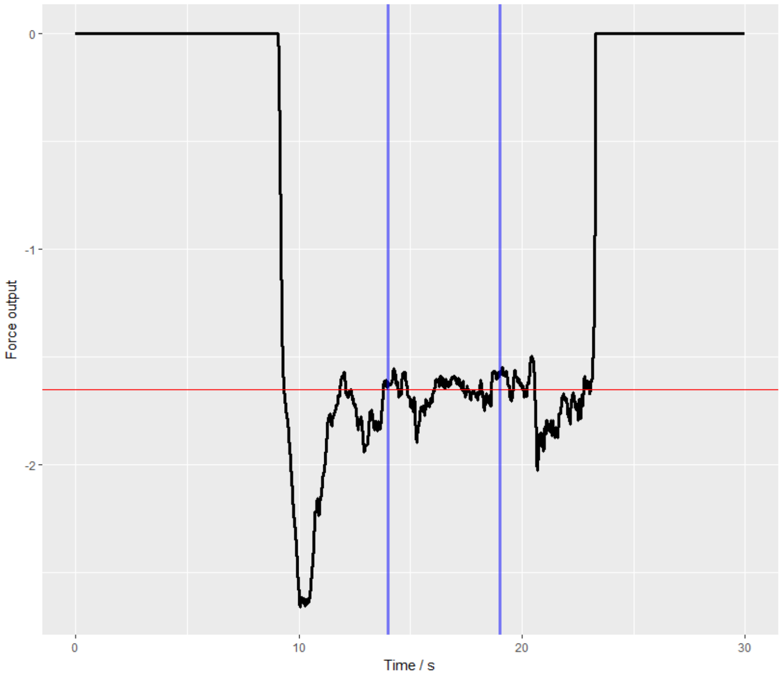

Figure 8.8. Illustration of the time window used to calculate the CVs. The black line represents the force output. The red line is the target output, which was 50% of the maximum obtainable. Data between the blue lines were used to calculate the CV.

8.3.5 Statistical analysis

The nirsLAB software (version 201605) was used to analyse the fNIRS data. The maximum HbO_2 concentration changes were used to represent the change in cortical perfusion before and after the assigned stimulation. Due to the small sample size of the pilot study, the between-group differences in the maximum HbO_2 concentration changes in the contralateral motor representation area of the lower limb and secondary outcome measures (nrmsEMG, maximum ankle dorsiflexion torque and CV) were examined based on non-parametric statistics. A Wilcoxon signed-rank test was conducted to compare the change scores of the outcome measures. The change scores were computed by subtracting the maximum HbO_2 concentration changes of the pre-stimulation measurements from the maximum HbO_2 concentration changes of the post-stimulation measurements. A *p*-value ≤ 0.05 was considered as statistically significant for all of the statistical analyses.

8.4 Results

Ten healthy older adults were recruited to evaluate the effects of TENS on cortical perfusion of the contralateral motor representation area. This cohort comprised seven males and three females. Their mean age was 63.4 years. For the analyses of maximum HbO_2 concentration changes, results of a Wilcoxon signed-rank test showed that Bi-TENS induced a greater, statistically significant reduction of maximum HbO_2 concentration changes than Uni-TENS ($Z = -2.14$; $p = 0.032$) and placebo stimulation ($Z = -2.45$; $p = 0.014$) (Figure 8.9). However, no significant differences in maximum HbO_2 concentration changes existed between the placebo stimulation and Uni-TENS groups ($Z = -1.58$; $p = 0.131$).

For the secondary outcomes, the results of the Wilcoxon Signed-Rank Test showed that none of the between-group comparisons was significant for nrmsEMG, maximum ankle dorsiflexion torque and CV (Table 8.2; Figure 8.9).

Table 8.2. Summarised outcome measures

	Pre-stimulation Mean (SD)	Post-stimulation Mean (SD)
maximum HbO_2 concentration change/µM		
Bi-TENS	0.697 (0.326)	0.584 (0.223)
Uni-TENS	0.614 (0.374)	0.564 (0.305)
Placebo	0.581 (0.260)	0.587 (0.327)
nrmsEMG/%		
Bi-TENS	58.0 (16.7)	55.6 (11.9)
Uni-TENS	51.4 (15.6)	53.4 (16.0)
Placebo	60.8 (10.8)	59.5 (10.7)
Maximum ankle dorsiflexion torque/Nm		
Bi-TENS	35.3 (8.4)	35.5 (6.5)
Uni-TENS	32.3 (6.4)	32.3 (3.4)
Placebo	34.0 (6.1)	33.5 (5.5)
Coefficient of variation of ankle dorsiflexor force output		
Bi-TENS	0.22 (0.114)	0.19 (0.93)
Uni-TENS	0.26 (0.10)	0.22(0.87)
Placebo	0.25 (0.13)	0.20 (0.83)

Remarks: HbO2: Oxyhemoglobin; SD: standard deviation; TENS: transcutaneous electrical nerve stimulation; nrmsEMG: normalized root mean square of the EMG readings

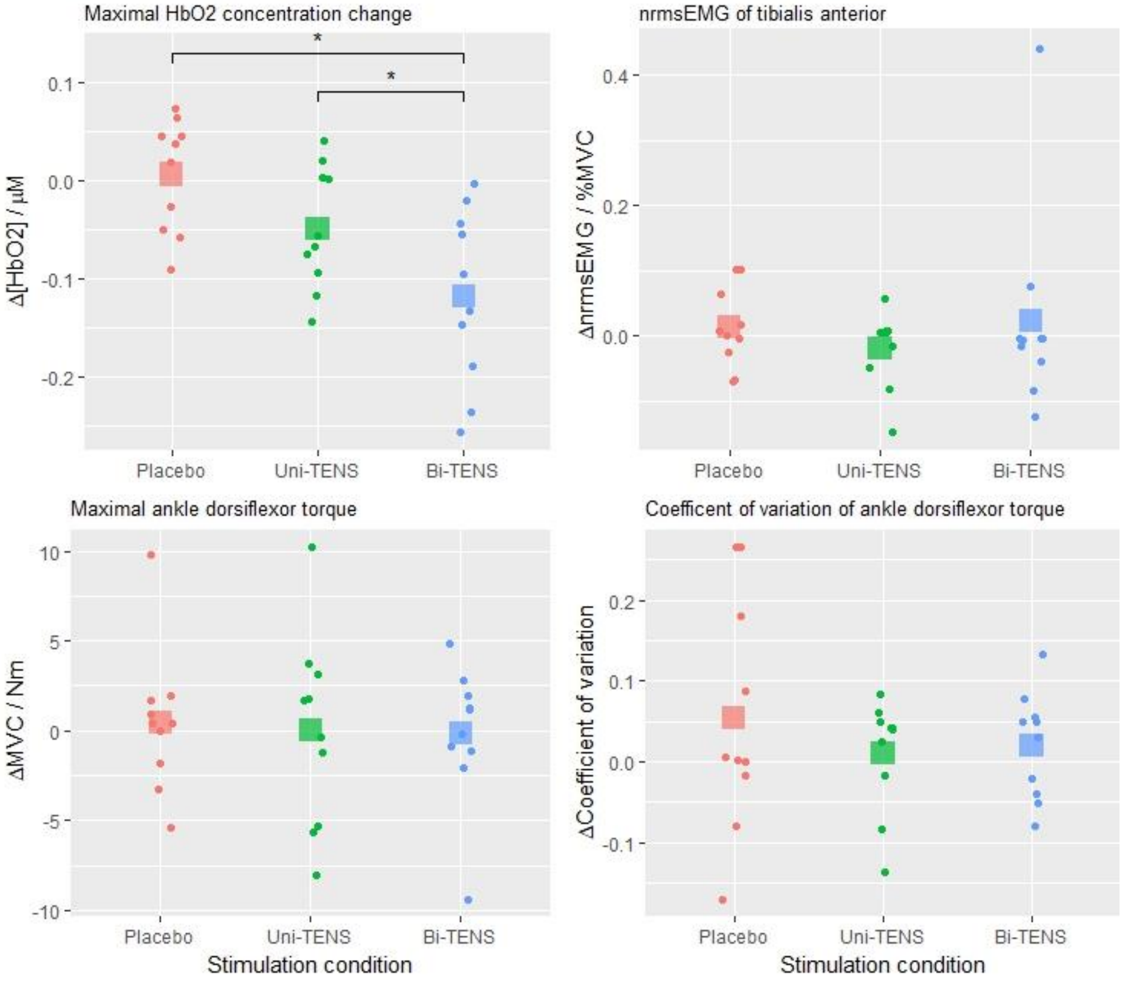

Figure 8.8. Group means (■) and individual participant data for the change score for maximum HbO2 concentration change, nrmsEMG of tibialis anterior, maximum ankle dorsiflexion torque and the coefficient of variation of ankle dorsiflexion torque across the three groups.
* indicates significant differences ($p \leq 0.05$) between the groups.

8.5 Discussion

The results of this pilot study show that an hour of Bi-TENS over the common peroneal nerve can reduce the maximum change in HbO_2 concentration in the areas around the contralateral motor areas representing the lower limb during exercise more effectively than Uni-TENS or placebo stimulation, at least in healthy older adults. The nrmsEMG recorded form tibialis anterior, the maximum ankle dorsiflexion torque, and CV of the ankle dorsiflexors' force output showed no significant changes regardless of the stimulation conditions.

8.5.1 Effect of TENS on maximum HbO_2 concentration changes

The significant reduction of change in HbO_2 after Bi-TENS indicated that Bi-TENS had a strong influence on the contralateral motor representation areas of the left lower limb. Several studies have investigated the neurophysiological effects of cutaneous electrical stimulation (Hamdy et al., 1998; Lai et al., 2016; Murakami et al., 2010; Toma et al., 2003) and electrical neuromuscular stimulation (Jang et al., 2014) in healthy adults. Using fMRI, Toma and colleagues (Toma et al., 2003) reported that 15 minutes of TENS applied over the thenar area of the right hand reduced the activated volume of the left M1 during a right thumb opposition task, and the effects lasted for 30 minutes after TENS in 11 healthy adults. Toma and colleagues (Toma et al., 2003) suggested that the reduction of the activated volume of left M1 indeed indicated that the *efficiency of information processing* in the M1 improved after TENS, as fewer resources were used to achieve the same action. Similarly, Jang and colleagues (Jang et al., 2014) reported a reduction in the activated volume of M1. Using fNIRS, Jang and colleagues (Jang et al., 2014) reported that 5 minutes of 35-Hz motor-threshold electrical neuromuscular stimulation applied over the wrist extensor led to a significant reduction of change in HbO_2 concentration in the sensorimotor cortex during a rhythmic grasp-and-release movement of healthy young adults. In contrast, HbO_2 concentration did not change significantly after placebo stimulation.

Using magnetoencephalogram, Murakami and colleagues (Murakami et al., 2010) reported that 15 minutes of TENS applied over the right extensor digitorum muscle reduced the amplitude of magnetic fields recorded from M1 during a self-paced right middle finger movement in nine healthy young adults, perhaps indicating that the level of activation in the left M1 during the movement decreased after TENS.

However, Toma (Toma et al., 2003), Jang (Jang et al., 2014) and Murakami (Murakami et al., 2010) did not assess the performance or quality of the movement. Thus, it is uncertain whether the reduction of activation volume (Toma et al., 2003), change in HbO_2 concentration (Jang et al., 2014) and amplitude of motor field of M1 (Murakami et al., 2010) are correlated with the change in performance. The results of the current study show that Bi-TENS led to a significant reduction of change in HbO_2 concentration compared with Uni-TENS and placebo stimulation. However, neither the nrmsEMG recorded from the tibialis anterior muscle, nor the maximum ankle dorsiflexion torque, nor the CV of the ankle dorsiflexor force output showed significant change between the two assessment time points across the three conditions. These results confirm that the change in HbO2 is not due to any change in actual performance of the motor task. While it also remains unclear if the observed reduction in the change of HbO2 concentration indicates better processing efficiency in the contralateral M1.

Also, it should be noted that there was no significant difference in the change in HbO2 concentration between the placebo stimulation and Uni-TENS. The small sample size probably had insufficient power to detect any differences. Post-hoc power analysis showed that the estimated effect size (Cohen's d) was 0.48 in favour of Uni-TENS. It was estimated that a total sample size of 36 healthy adults would have been needed to achieve sufficient statistical power to detect any differences between placebo stimulation and Uni-TENS in terms of changes in HbO2 concentration.

8.5.2 Effect of TENS on secondary outcomes

There was no significant change in nrmsEMG recorded from the left tibialis anterior muscle and maximum ankle dorsiflexion torque after the assigned stimulations in the current study. These results were inconsistent with studies reporting that one session of cutaneous electrical stimulation influenced motor output (Dickstein & Kafri, 2008; Kafri et al., 2015). Dickstein and Kafri (Dickstein & Kafri, 2008) found that one 15-minute session of high-frequency TENS (100Hz) applied over the volar aspect of forearm induced increments in EMGs recorded from the finger flexors during gripping. That was true of both Bi-TENS and Uni-TENS, but not immediately after placebo stimulation. Those results might suggest that applying TENS over the upper limb could have a greater effect in augmenting muscle activity than lower-limb stimulation, except that grip strength also increased in the placebo stimulation group 15min after the sham-stimulation. So the increases in grip strength cannot be totally attributed to the effect of

TENS. Indeed, the well-known placebo effect could have had a strong influence on the participants’ performance (Dickstein & Kafri, 2008).

In another study, Kafri and colleagues reported that the burst mode TENS, but not high-frequency TENS, enhanced the within-group EMG amplitude recorded from finger flexors and the maximum grip strength after 1 hour of stimulation in five healthy participants (Kafri et al., 2015). Their results suggest that the mode of stimulation was also critical in modulating the muscles activities and motor output. However, although not significant, the EMG amplitude also showed a trend of increase after high-frequency TENS (0.0723 to 0.0888 mV) (Kafri et al., 2015). The insignificant finding could be mainly attributed to the lack of statistical power resulting from the small sample size (Kafri et al., 2015).

The lack of any significant improvement in CV is consistent with the results of a study reported by Lai et al (Lai et al., 2016). In that study, 40 minutes of cutaneous electrical stimulation improved the ability to maintain steady force output among stroke survivors, but not among healthy young adults. Lai et al. concluded that the cutaneous electrical stimulation improved sensorimotor integration in the stroke survivors as evidenced by the augmented coherence of EMG and gramma band electroencephalogram signals observed after the stimulation (Lai et al., 2016). The healthy subjects may not have needed greater coherence because his thumb flexion task was too simple for them.

8.5.3 Limitations

In this study, the averaged fNIRS signals from three channels were used to estimate the signal change on the contralateral motor representation area of the lower limb. Selection of these channels was based on the results of previous studies (Koenraadt et al., 2012; Koenraadt et al., 2014) and an understanding of neuro-anatomy, while the location of the motor representation area could vary between individuals (Brett et al., 2002). Future studies should co-register the anatomical location of M1 with MRI to enhance the precision of the results. In addition, the small sample size of the current study probably led to insufficient statistical power to detect the true difference. Conducting this study with a larger sample is warranted.

8.6 Conclusions

The results of this pilot study show that Bi-TENS applied over the area innervated by the common peroneal nerve reduced the maximum change of HbO_2 concentration in the contralateral motor representation area of the lower limb during isometric ankle dorsiflexion compared with Uni-TENS and placebo stimulation. This provides preliminary evidence that Bi-TENS has a stronger influence on the activity of contralateral M1 during maximum ankle dorsiflexion. No significant between-group difference in the change of EMG amplitude, maximum ankle dorsiflexion torque and CV across the three groups was found.

This pilot study provides important data that could be used to estimate the effect size of the intervention with cutaneous electrical stimulation. Assessing the influence of Bi-TENS and Uni-TENS on the level of cortical perfusion and related changes in motor functions in people with stroke is warranted.

Chapter 9

Summary and Conclusions

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9.1 Summary and conclusions of the thesis

The review reported in chapter 3 demonstrated that TENS could reduce spasticity and improve walking capacity after a stroke. The results of the 11 randomised and controlled trials reviewed support the use of repeated applications of TENS as an adjunct therapy for improving walking capacity and reducing spasticity. The use of TENS as an adjunct therapy in both clinical and home-based settings is recommended, as TENS is non-invasive and safe. Stimulation for 60 minutes in each session appeared more effective than 20- or 30-minute sessions. Most of the studies included in the meta-analysis adopted a stimulation frequency of 100Hz, a plausible choice in clinical practice. Muscle strength and balance measures were not meta-analysed. Further studies of TENS that include muscle strength and balance outcome measures and subjects other than stroke survivors are warranted.

Chapter 4 reported on 3 cross-sectional studies which evaluated the assessment procedures of the BBS and the FTSTS test, and that chapter also discussed the translation and cultural adaptation of the SIPSO questionnaire into Chinese and assessed its psychometric properties.

In the first study, 63 hemiplegic stroke survivors demonstrated significantly lower BBS scores if they placed their paretic leg posteriorly in item 13 and when they tried to stand on their paretic leg in item 14. The result indicates that a BBS total score developed in that formulation dampens the ceiling effect of the scale. Moreover, their BBS total scores demonstrated stronger correlation with FTSTS completion time, walking speed and ABC score than alternative formulations. These findings provide a rationale for amending the BBS administration procedure.

In the second study, posterior foot placement and augmented arm position were found to associate with shorter FTSTS completion times after a stroke. The results highlight the fact that foot placement and arm position significantly influence FTSTS completion times. If the test is to be repeated with the same subject, standardizing the arm and foot positions in the test procedure is essential in both clinical and research settings.

The psychometric properties of the Cantonese version of the Subjective Index of Physical and Social Outcome were then evaluated. Ninety-two community-dwelling stroke survivors were recruited to evaluate the index’s internal consistency and factor structure. Twenty-five of them were reassessed after a one-week interval to determine the instrument’s test-retest reliability. Satisfactory internal consistency and excellent test-retest reliability were demonstrated. The results suggest that the SIPSO-C questionnaire is a reliable instrument for measuring the community integration of Cantonese-speaking, community-dwelling stroke survivors.

Chapter 5 described how the SIPSO-C was used to measure the level of community integration of 105 hemiplegics. The isometric strength of the paretic ankle and the isokinetic torque developed at the paretic knee were assessed along with the Berg Balance Scale and the 6-minute walk test to evaluate their balance performance and walking endurance. Structural equation model revealed that the dorsiflexor strength of the paretic ankle, walking endurance and balance performance were all significant predictors of the subjects' level of community integration. Paretic ankle dorsiflexor strength also influences the level of community integration indirectly, mediated by walking endurance and balance. Although the hypothesised model explained only 43.1% of the variance in community integration, these findings should nevertheless be useful for facilitating the community integration of community dwelling chronic stroke survivors.

Chapter 6 described a randomised and controlled trial which demonstrated that Bi-TENS could improve the lower-limb motor function of community dwelling chronic stroke survivors. Eighty stroke survivors were randomly assigned to a Bi-TENS+TOT or a Uni-TENS+TOT group and underwent 20 sessions of stimulation and training over a 10-week period. Outcome measures included muscle strength in the paretic limb, a Lower Extremity Motor Coordination test, limits of stability measurements and evaluation using the Berg Balance Scale.

Our results demonstrate that Bi-TENS applied over the common peroneal nerves combined with lower limb TOT induce greater improvement in the dorsiflexor strength of the paretic ankle after 5 weeks of training than Uni-TENS combined with the same TOT. However, both Bi-TENS+TOT and Uni-TENS+TOT induced significant improvements in paretic ankle strength, lower limb coordination and balance performance after 20 training sessions. Apart from the plantarflexion strength, the training effects in both groups were maintained for 3 months. These results suggest that Bi-TENS+TOT is superior to Uni-TENS+TOT for building the strength of paretic ankle, and perhaps of other muscle groups as well.

Chapter 7 reported on another randomised and controlled trial which compared Bi-TENS combined with TOT against Uni-TENS combined with TOT in terms of their ability to improve motor functions in a paretic lower limb. The outcome measures were the step test, the Five Times Sit to Stand Test, the 10-metre Walk test, the 6-Minute Walk test and the Timed Up and Go test. A secondary objective was to identify predictors useful for sorting people who would respond favourably to Bi-TENS from those who would not.

Both Bi-TENS+TOT and Uni-TENS+TOT induced significant improvements in dynamic standing balance, sit-to-stand performance, walking speed and functional mobility after 20 training sessions but neither had a significant effect on walking endurance or the level of community integration. Bi-TENS applied on the common peroneal nerves combined with lower limb TOT induced greater improvement in TUG completion time beginning at 5 weeks than that of Uni-TENS combined with TOT. The training effects on physical performance in both groups were maintained for 3 months, and the level of community integration improved at 3 months after the training. The post-stroke duration and level of motor recovery appeared able to identify people who would be more likely to benefit from Bi-TENS + TOT.

Chapter 8 discussed TENS and cortical perfusion. Functional near-infrared spectroscopy was applied to ten healthy older adults in a pilot cross-over study, which showed that Bi-TENS applied over the area innervated by the peroneal nerve reduced the maximum change of HbO_2 concentration during isometric ankle dorsiflexion more than placebo stimulation or Uni-TENS. Those data constitute preliminary evidence that Bi-TENS has a stronger influence on activity in the contralateral M1. However, neither stimulation protocol produced a significant change in EMG amplitude, maximum ankle dorsiflexor torque or the variation in force production. It remains unknown whether the reduction in HbO_2 concentration after Bi-TENS indicates better M1 efficiency. The results are inconclusive due to the experiment's small sample size. The data can, however, be used to estimate the effect sizes involved, which can facilitate the formulation of future studies.

9.2 Limitation of studies and direction of future research

The systematic review and meta-analysis (Chapter 3) identified that most of the study adopted the high stimulation frequency of TENS (100Hz) showed positive effects. It is plausible that the 100Hz stimulation frequency could be preferable in clinical practice. However, a randomised controlled trial is warranted to compare the effects of different stimulation frequency. Besides, the ideal length of the intervention program remains unclear. Future study should aim at identifying the ideal length of the training program to enhance its cost-effectiveness.

Due to the limitation of time and resources, the effects of applying Bi-TENS on upper limb or applying TENS on multiple body parts have not been evaluated. It is possible that these approaches could induce greater improvement in motor and global functions in people with stroke. Further works evaluating this strategy is needed.

The pilot study presented in chapter 8 indicated that Bi-TENS induced a stronger influence on the level of cortical perfusion in healthy older adults than that of Uni-TENS. Future studies assessing the influence of Bi-TENS and Uni-TENS on the level of cortical perfusion and related changes in people with stroke is warranted. Moreover, these studies should also evaluate the association between level of cortical perfusion and performance of behavioural outcomes in people with stroke.

Appendix 3.1 Chapter 3 published on Clinical Rehabilitation (Final manuscript)

Transcutaneous electrical nerve stimulation (TENS) reduces spasticity and improves walking capacity and in stroke survivors – a systematic review and meta-analysis

Introduction

Previous studies have demonstrated that the application of TENS or somatosensory electrical stimulation to the paretic lower extremities of stroke survivors can reduce plantarflexor spasticity[1-7], increase muscle strength[1, 7-9] and improve motor function[3, 4, 6, 8, 10, 11]. The mechanisms behind motor recovery following the use of TENS include enhanced presynaptic inhibition of the hyperactive stretch reflexes in spastic muscles[1, 2, 12] and decreased co-contraction of the spastic antagonist muscles[7].

A previous meta-analysis conducted by Veerbeek and colleagues [13] found a positive effect (Hedges' g=0.56, 95%CI=0.27–0.84) in favour of TENS after pooling five randomised controlled trials that involved 195 stroke survivors[13]. However, it should be noted that 3 of the included studies reported results from the same research projects. The effect size estimates could have been overestimated. A recent systematic review [14] concluded that TENS is effective for treating limb spasticity in people with central nervous system lesions, including stroke, spinal cord lesions, multiple sclerosis, cerebral palsy and Strümpell-Lorrain disease.

Nevertheless, the effects of TENS on muscle strength were not clearly described in the previous meta-analysis and the effect of TENS on balance has not been systematically reviewed[13, 14]. Moreover, the influence of stimulation parameters, including frequency and duration, was not evaluated. Several randomised controlled trials on the effect of TENS on motor recovery including lower limb spasticity, muscle strength, balance and walking capacity in stroke survivors have been published in the last few year[15-18]. The existing body of knowledge on the effects of TENS on lower-extremity motor recovery in stroke survivors could be improved by conducting a systematic review that includes the most recent studies and that explores the influence of the stimulation parameters.

Therefore, the objective of this review was to evaluate the effects of TENS and its parameters on lower-extremity motor recovery in stroke survivors, including its effects on spasticity, muscle strength, balance and walking capacity by systematically reviewing the available randomised controlled trials.

Methods

The study protocol was prospectively registered with the PROSPERO database of systematic reviews (registration number: CRD42016039754). A systematic search was conducted in seven electronic databases, including CINAHL, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, the Physiotherapy Evidence Database (PEDro), and Web of Science. Articles written in English were selected for further assessment. The general search strategy combined the disease group search string (e.g. stroke), Intervention search string (eg.TENS), and Outcome variables search string (eg.muscle strength). The search strategy is presented in appendix 1.

Studies were included in the review if they: 1) used a randomised controlled trial design, 2) involved stroke survivors, 3) used repetitive TENS/ electrical somatosensory stimulation, 4) applied the stimulation to lower extremity and 5) included at least one outcome measure on lower extremity motor function. Studies were excluded if they: 1) did not include a placebo or no-treatment control group, 2) investigated the effect of electro-acupuncture, 3) did not report the central tendency and/or variability of the outcome of interest, and 4) reported that the stimulation intensity was above motor threshold.

There were no restrictions regarding the earliest publication date and the latest publication date was set at October 2017. The reference lists of the included studies were also reviewed (backward tracking), and literature which citing the included studies were tracked (forward tracking) to look for additional studies. Two investigators (PWK and TL) independently screened the retrieved records and reviewed the full-text articles of the relevant studies. Disagreements regarding eligibility were resolved by discussion with a third-party reviewer (SSN).

The PEDro scale[19] was used to evaluate the methodological quality of the included studies. Where possible, the PEDro score of each study was identified from the PEDro database, in cases where there was no PEDro score in the database, two reviewers (PWK and TL) independently rated the study using the scale. Disagreements regarding the PEDro scores were resolved by discussion with a third-party reviewer (SSN).

A standardized data extraction form was used to extract the data from the included studies. The extracted information included the study design, sample size, dropout rate, characteristics of participants (age, gender and post-stroke duration), TENS protocol (frequency, duration of each session and placement of electrodes), intervention protocol (type of rehabilitation exercise, length and frequency of intervention and follow-up period), outcomes (type of outcome measures and means and standard deviations of the outcomes) and occurrences of adverse events.

The primary outcome measures were measures of the participants’ walking capacity. The meta-analysis of walking capacity involved pooling the gait speed and timed Up & Go test results. Where a study reported both measures, the Timed Up & Go test results were used because this test provides a more comprehensive measure of the walking capacity of stroke survivors than gait speed[20]. For one study[2], the standard deviations of gait speed was estimated from the mean 10 meter walk test completion time and its standard deviations using the delta method[21]. The secondary outcome measures included the spasticity, muscle strength and balance.

The statistical analyses were carried out using the Comprehensive Meta-Analysis Software (Version 2, Biostat, Englewood NJ). Meta-analyses were conducted if three or more studies used the same outcome measure. The effect size estimate was calculated using the means and standard deviations of the pre- and post-intervention measurements. Hedges' g was selected to estimate the overall effect of TENS on spasticity and walking capacity as it is less biased than other measures when sample sizes are small[22]. To provide clinically relevant value, separate meta-analyses of walking capacity (gait speed, Timed Up & Go test completion times) and spasticity (Modified Ashworth Scale score and Composite Spasticity Scale score) were conducted with the mean differences as effect size estimate.

I^2 statistic was used to quantify the statistical heterogeneity. We intended to use a random effects model for each meta-analysis if the result of I^2 statistic was significant ($P< 0.05$) or if the I^2 value greater than 50%, which represented a substantial heterogeneity [23]. A fixed effects model would be used if I^2 statistic was non-significant.

A funnel plot and Egger's regression test were used to assess the degree of publication bias. In the funnel plot, the of each study the Hedges' g was plotted against its standard error[24]. Egger's regression test evaluates whether the intercept of the regression line of the precision (inverse of the standard error) of each study against the weighted effect size deviates significantly from 0. A statistically significant Egger's regression test indicates that the funnel plot is skewed[24].

The influence of the methodological quality of the studies on the effect size estimate associated with walking capacity was evaluated using a sensitivity analysis, which entailed repeating the meta-analysis without the studies that were rated as having fair or poor PEDro scores (< 6)[25]. A significant discrepancy between the effect size estimates from the two meta-analyses would reflect a strong influence of studies with fair to poor PEDro scores.

Subgroup analyses were conducted to evaluate whether the effectiveness of TENS depends on the chronicity of stroke (i.e., chronic versus acute/subacute) or the duration of stimulation per session (i.e., 60 min versus < 60 min). In addition, a fixed effects meta-regression analysis (in which the studies were weighted by the inverse of the within-study variance[26]) was conducted to evaluate the influence of the cumulative duration of stimulation on the overall heterogeneity. The cumulative duration of stimulation was calculated by multiplying the duration of stimulation per session by the total number of sessions.

All of the statistical tests were two-tailed, and $P< 0.05$ was considered to represent statistical significance, except in Egger's regression test, for which a statistical significance threshold of $P< 0.1$ was used[24].

Results

The search identified 1053 records after duplicates were removed. The abstracts of these records were reviewed. Twenty-six studies were considered to be relevant, and so the full-text of those articles were reviewed (Figure. 1). The list of excluded studies and the reasons of exclusion were provided in Appendix 2.

Finally, 11 randomised controlled trials [2, 7, 9-11, 15-18, 27, 28] were eligible for inclusion according to the inclusion and exclusion criteria. These studies were published between 2005 and 2017. Two studies [10, 11] allocated the participants to four groups (TENS + exercise, placebo TENS + exercise, TENS only and no-treatment control) and one study[7] allocated the participants to three groups (TENS + exercise, placebo TENS + exercise and exercise only). In these three studies, only the data on the TENS + exercise and placebo TENS + exercise groups were extracted.

A Previous review conducted by Veerbeek's group[13] with the search date of August 2011 included 6 studies which evaluated the effects of TENS on lower limb motor functions. All of those 6 studies have been identified by our search strategy, while only 4 of them [7, 10, 11, 27] have been included in the current review. The remaining 2 studies were excluded since one of them applied TENS on paretic arm[29] and one of them reported duplicate results[30] with a study which have already been included in the current review[10]. On the other hand, a more recent review conducted by Mills's group[14] with the search date of July 2015 have included 8 studies to evaluate the effectiveness of TENS in managing spasticity in stroke survivors. Whereas only 3 of them was included in the current review[10, 11, 17]. The remaining 5 studies have been identified by our searching strategy but were excluded from the current review since 2 studies applied TENS on paretic arm[31, 32], 2 studies adopted a cross-over[33] or partial cross-over[1] study design and 1 study did not involve repetitive use of TENS[3].

The eleven studies randomized 439 stroke survivors into TENS and control groups and 29 participants dropped out. Of the remaining 410 participants, 206 were allocated to the TENS groups, and 204 were in the control groups. The extracted numerical data of outcome measures which had been meta-analyses was provided in appendix 3.

The PEDro score of seven studies[2, 7, 10, 11, 15, 17, 27] were rated by the PEDro database. However, the item of participant blinding was rated as fulfilled for two of the studies[2, 17]. For this item, participants were considered blinded if they were unable to distinguish between the intervention applied to experimental and control groups. Since the stimulation intensity was above sensory threshold in both studies[2, 17], participants in the experimental group should be able distinguish the differences between the intervention in the two groups. Thus, this item should be rated as not fulfilled for the two studies[2, 17] (Table 1).

The characteristics of the included studies are summarized in Table 2. Six studies[7, 9-11, 18, 28] applied TENS to four acupuncture points (ST36, LV3, GB34, and UB60) on the participants' paretic lower limbs. In the four remaining studies, the electrodes were placed at the distal end of the Achilles tendon[2], the belly of tibialis anterior muscle[27], the quadriceps and gastrocnemius muscle[17], along the peroneal nerve[16] or along the course of the common peroneal and sural nerves[15].

All of the studies combined TENS with rehabilitation exercises except one[2]. Two used home-based task-related training[10, 11], which involved functional training such as sit-to-stand tasks and moving past obstacles. One used task-related balance training^{29}, which included standing on a balance board, kicking with alternate legs and heel raising.

Deshmukh[28] combined task-related training with conventional physiotherapy training, which was focused on promoting posture control. In Kumar and Kulkarni' study[18], the participants received passive stretching, resistive training, reaching exercises and gait re-education. Park and colleagues' study[17] involved supervised range of motion exercises, mat exercises and gait re-education. Hussain and colleagues[9] used the Bobath inhibitory technique, which aims to inhibit abnormal reflex patterns. Jung and colleagues[16] offered sit to stand training in conjunction with conventional therapy. The participants of the two remaining studies[7, 27] received physiotherapy and occupational therapy, but the type and focus of the training were not reported. Four studies arranged follow-up assessments to evaluate the long-term effect of TENS. The follow-up periods were 4[10, 11], 5[7] and 12 weeks[15] post-intervention. None of the studies reported any adverse events.

Eight studies[2, 7, 9, 11, 16-18, 28] used clinical scales to rate the plantarflexor spasticity of the participants' paretic ankles. These studies (involving 252 participants) were pooled in a meta-analysis. The effect of TENS on plantarflexor spasticity was significant (Hedges' g = -0.884, 95%CI = -1.140 – -0.629, $P< 0.001$) and homogeneous ($I^2 = 34.75\%$, $P= 0.151$) (Figure. 2). However, separated meta-analysis pooing data from the three studies[7, 11, 16] (involving 119 participants) showed that there is no evidence that TENS had an effect on Composite Spasticity Scale score (difference in means = -1.26, 95%CI = -2.73 – 0.21, $P = 0.093$; $I^2 = 74.71$ %, $P = 0.019$) (Figure. 3A). Five studies[2, 9, 17, 18, 28] (involving 133 participants) were pooled in a meta-analysis of Modified Ashworth Scale score. The effect of TENS on Modified Ashworth Scale score was significant (difference in means = -0.59, 95%CI = -0.77 – -0.41, $P< 0.001$) and homogeneous ($I^2=0.00\%$, $P=0.624$; Figure. 3B).

Chen and colleagues[2] quantified the degree of paretic ankle plantarflexor spasticity using electrophysiological measurements, i.e., the tibial F_{max}/M_{max} ratio, H-reflex latency and H-reflex recovery curve. There was a reduction in the F_{max}/M_{max} ratio, an increase in the H-reflex latency and a downward shift of the H-reflex recovery curve in the TENS group but not in the control group. These results indicated that TENS reduced the degree of plantarflexor spasticity.

Three studies[7, 9, 11] measured the dorsiflexion strength of the participants' paretic ankles. Two of these studies[7, 11] measured the maximum voluntary contraction of the paretic ankle dorsiflexion and the other study[9] used manual muscle testing to assess the paretic ankle dorsiflexion strength. Due to the heterogeneity of the assessment methods, the three studies were not pooled. Two of the studies[7, 9] reported a significant between-group difference in favour of TENS. One of the three studies[11] also assessed the maximum voluntary contraction of the paretic ankle plantarflexion but no between-group improvement in plantarflexion strength was found. Jung and colleagues[16] assessed the isometric paretic hip extension, knee extension, and ankle plantarflexion strength with handheld dynamometer. Significant between-group difference in favour of TENS was demonstrated in hip extension strength only.

Ten studies measured walking capacity using gait speed[2, 9-11, 17, 27] and/or Timed Up & Go test completion times[7, 10, 15, 17, 18, 28]. One of the studies that measured gait speed[11] was not included in the meta-analysis of walking capacity because a considerable number of participants of that study also participated in another study[10]. Therefore, nine studies (involving 324 participants) measuring either gait speed[2, 9, 27] or Timed Up & Go test[7, 10, 15, 17, 18, 28] were pooled in a meta-analysis of walking capacity. The effect of TENS on walking capacity was significant (Hedges' g= 0.392; 95%CI=0.178–0.606; P<0.001) and homogeneous (I^2 = 0.00%; P= 0.704) (Figure. 4). Five studies[2, 9, 10, 17, 27] (involving 165 participants) were pooled in a meta-analysis of gait speed. There is no evidence that TENS had an effect on walking speed (difference in means = 0.017, 95%CI = -0.004 – 0.037, P = 0.108; I^2 = 0.00%, P = 0.842) (Figure. 5A). Six studies[7, 10, 15, 17, 18, 28] (involving 245 participants) were pooled in a meta-analysis of Timed Up & Go test completion times. The effect of TENS on Timed Up & Go test completion times was significant (difference in means = 4.37, 95%CI=0.72 – 8.03), P< 0.001) and heterogeneous (I^2=64.70%; P=0.015). In average, stroke survivors in the TENS group improved 4.37s more in Timed Up & Go test completion time than those in control group (Figure. 5B).

Two studies[10, 15] assessed walking endurance using a 6-minute walk test. Neither of the studies reported a significant effect in the TENS group compared to the placebo-control group.

Three studies[15-17] assessed balance performance but they had used different methods. Ng and colleagues[15] used the Berg Balance Scale to assess balance performance. The Berg Balance Scale score was significantly greater in the TENS group compared to the placebo-control group at 4 weeks during the intervention period, at the end of the 8-week intervention period and 12 weeks after the intervention had completed.

Park and colleagues[17] used computerized posturography (i.e., the Good Balance system) to measure postural stability in eyes-open and eyes-closed conditions during static standing. There were greater reductions in the anterior-posterior and medial-lateral postural sway speeds as well as the speed moment in the TENS group than the placebo-control group. Jung and colleagues[16] used the Wii balance board to assess the postural sway distance during static standing in eyes open and eyes closed conditions. Results of the study showed that stroke survivors in the TENS group demonstrated significant greater reduction in the sway distances than those in the control group.

The funnel plot appeared symmetrical for the meta-analysis of walking capacity (Figure. 6). Egger's regression test revealed that the intercept of the regression line did not significantly deviate from 0 (intercept=0.83; P=0.291), indicating that there was no evidence of publication bias.

A second meta-analysis of walking capacity was carried out without the four studies that had PEDro scores of less than 6[7, 17, 18, 28]. The effect size estimate decreased but remained statistically significant (Hedges' g = 0.271, 95% CI = 0.005–0.536, P = 0.046) and homogeneous (I^2 = 0.00%, P = 0.969).

Regarding the duration of stimulation per session, the effect of TENS on walking capacity in studies involving 60 min sessions[7, 10, 15, 18, 28] was significant (Hedges' g = 0.468, 95%CI = 0.201– 0.734, P=0.001) and homogeneous (I^2 = 6.92%, P = 0.367). In contrast, the effect of TENS on walking capacity in studies involving shorter sessions (20 or 30 min)[2, 9, 17, 27] was non-significant (Hedges' g = 0.254, 95%CI = -106 – 0.614, P = 0.166) and homogeneous (I^2 = 0.00%, P = 0.943).

The meta-regression analysis indicated that there was no significant correlation between the cumulative duration of stimulation and the effect size estimate associated with walking capacity (slope=0.00015, P=0.699).

Among the 10 studies that assessed walking capacity, 6 [7, 9, 15, 18, 27, 28] recruited acute/subacute stroke survivors and 4 [2, 10, 11, 17] recruited chronic stroke survivors. The effect of TENS on walking capacity in the acute/subacute stroke survivors was significant (Hedges' g = 0.441, 95% CI = 0.181–0.702, P = 0.001) and homogeneous (I^2 = 0.00%, P = 0.432). In contrast, the effect of TENS on walking capacity in the chronic stroke survivors (after one study[11] was removed from the meta-analysis because many of the participants in this study also participated in another study that was included in the meta-analysis[10]) was non-significant (Hedges' g = 0.289, 95% CI = -0.087–0.665, P = 0.132) and homogeneous (I^2 = 0.00%, P = 0.896).

Discussion

This systematic review provides evidence that the repeated application of TENS is effective at improving walking capacity and reducing paretic ankle plantarflexor spasticity in stroke survivors.

The meta-analysis showed that stroke survivors who underwent TENS had greatly reduced paretic plantarflexor spasticity (0.59 Modified Ashworth Scale points in average), compared to those in the control groups. This result is consistent with Mills and colleagues' finding[14] which showed that TENS was effective in reducing spasticity measured with Modified Ashworth Scale, especially when used as an adjunct modality.

However, this finding should be interpreted with caution as the Modified Ashworth Scale was treated as an interval scale in the meta-analysis, (i.e., the distances between each level of the scale were treated as equal), which may not be appropriate. Moreover, the validity of using the Modified Ashworth Scale to assess spasticity of paretic extremities has been questioned since Modified Ashworth Scale assessment of spasticity is confounded by contracture, despite the fact that this assessment has commonly been used in clinical and research settings[34, 35]. A previous study[34] compared the H-reflex latency and the ratio of the maximum H-reflex (H_{max}) to the maximum motor evoked potential (M_{max}) of the paretic soleus of 24 stroke survivors with Modified Ashworth Scale scores of 1 or 2. The study found that the H-reflex latency and the H_{max}: M_{max} ratio were comparable between stroke survivors with different Modified Ashworth Scale scores.

The stroke survivors in the TENS groups had a significant greater improvement in walking capacity than those in the control groups. This result is consistent with Veerbeek and colleagues'[13] finding which showed that TENS was effective in improving walking capacity in stroke survivors. The overall effect size estimated in the current study was smaller than then reported by Veerbeek and colleagues[13] (Hedges' g: 0.40 vs. 0.56). However, the 95% confidence interval of the effect size estimate of the current meta-analysis was narrower than that reported by Veerbeek and colleagues[13], indicated that the estimation in the current study could be more robust.

In addition, TENS significantly reduced the Timed Up & Go test completion time by 4.37s, but did not increase the gait speed. The exact mechanisms by which TENS improve the walking capacity are unknown. A study that carried out a regression analysis using data from 73 chronic stroke survivors revealed that the maximum voluntary contraction of paretic ankle dorsiflexors was a significant predictor of Timed Up & Go test completion times (β=-6.13, P< 0.001) [36]. An additional study of 22 chronic stroke survivors found that isometric paretic ankle dorsiflexor strength was significantly correlated with self-paced sit-to-stand durations (r=-0.450, P< 0.05) [37]. The improvements in paretic ankle dorsiflexion strength may directly influence the Timed Up & Go test completion times and indirectly influence the Timed Up & Go test completion times via its effects on the Timed Up & Go test subtasks, such as the sit-to-stand and turning tasks.

Only three studies included measures of balance (Berg Balance Scale [15] and sway distance[16, 17]) and both have reported the application of TENS to paretic lower extremities would lead to improvements in balance. However, the lack of studies using balance-specific outcome measures makes it difficult to draw firm conclusions about the effect of TENS on the balance of stroke survivors as a meta-analysis could not be conducted.

In the first meta-analysis of walking capacity, the studies rated as being of fair methodological quality (i.e., PEDro scores of 4–5) were included. As the risk of bias is relatively high in these studies, overestimation of the effect size was possible in this meta-analysis. However, an additional meta-analysis showed that the effect of TENS on walking capacity remained statistically significant when studies rated as being of fair methodological quality were excluded. This result indicates that the major finding of this systemic review is robust to the inclusion of studies rated as being of fair methodological quality.

The optimal TENS frequency for motor recovery in stroke rehabilitation is unknown. Most of the studies used a high stimulation frequency of 100 Hz[7, 9-11, 15-18, 28] and favourable effects on walking capacity were consistently demonstrated. Whether high stimulation frequency is superior to low frequency could not be determined because of the small number of studies that used low frequency[2, 27]. A recent study conducted by Koyama and colleagues [38] might provide some insight into the effect of various stimulation frequencies of TENS. In that study, 30 minutes of TENS was applied over the areas innervated by deep peroneal nerve. Effects of 50 Hz, 100 Hz and 200 Hz of TENS on the presynaptic Ia inhibition of α-motor neuron of the paretic soleus in 20 stroke survivors was compared in the study. Results of the study showed that the 200 Hz but not 50 Hz or 100 Hz stimulation frequency led to a significant increase of presynaptic Ia inhibition. However, since no randomised controlled trial have adopted that high frequency stimulation, the effect of stimulation frequencies over 100 Hz remains uncertain.

The subgroup analysis revealed a duration of 60 min per session is more effective than a short session (20 or 30 min) at improving walking capacity in stroke survivors. This result was agreed with Laddha and colleagues' study [39] which compared the effects of 30 min versus 60 min of TENS over the common peroneal nerve combined with task-oriented training. Their results indicated that 60 min of TENS combined with task-oriented training was superior to 30 min of TENS combined with task-oriented training in reducing ankle clonus in subjects with stroke.

However, it should be noted that all of the studies that involved 60 min sessions had used Timed Up & Go test completion times as the measure of walking capacity. In contrast, three out of the four studies that involved short stimulation durations assessed walking capacity using gait speed. As our results showed that the effect of TENS on gait speed is small and non-significant (Figure. 4), it is possible that the difference in effect size estimates between the two subgroups resulted from the use of different outcome measures.

The results of the meta-regression show that the cumulative duration of stimulation did not significantly influence the effect of TENS on walking capacity. This phenomenon may be explained by the potential existence of a non-linear improvement rate, where there is a greater improvement at the beginning of intervention programmes than at the end. This may occur because the stimulation may induce more neuro-plasticity in the first few weeks and then gradually have less effect over time due to adaptation.

The subgroup analysis on the effect of the post-stroke duration revealed that TENS led to a significant improvement in walking capacity in the acute/subacute stroke survivors but not in the chronic stroke survivors. This result is inconsistent with the previous systematic review conducted by Veerbeek and colleagues,[13] which found that post-stroke phases were not associated with the effect of TENS. Veerbeek and colleagues' review presented a meta-analysis of three studies[10, 11, 30] that recruited chronic stroke survivors. However, these studies were conducted by the same research team and their authors reported that some of the data were used in all of the three studies. Pooling the results from the three studies may therefore have led to an overestimation of the effect size.

A previous study showed that motor recovery after stroke (as measured using the Fugl-Meyer assessment) is rapid during the first month and gradually plateaus at 3 months post-stroke[40]. Therefore, it was not surprising that TENS was found to have a greater effect in acute/subacute stroke survivors than in chronic stroke survivors.

Nevertheless, the non-significant effect of TENS on walking capacity in chronic stroke survivors should be interpreted with caution as only three studies were included in the meta-analysis. Of these three studies[2, 10, 17], two reported significantly greater improvements of Timed Up & Go test completion times in the TENS group compared to the placebo-control group[10, 17]. However, the small numbers of studies and participants included in this subgroup analysis led to a low statistical power to detect effects.

Apart from the reduction of spasticity, the improvement in walking capacity in stroke survivors could attributed to effects of TENS on neuronal plasticity. The neural connection between the primary sensory cortex and the primary motor cortex provides an anatomical substrate via which somatosensory stimulation could affect the neuronal activity of the motor cortex [41]. Neurophysiological studies have provided evidence that the applications of somatosensory electrical stimulation to extremities leads to neuroplastic changes in the central nervous system [42, 43]. Using transcranial magnetic stimulation, Veldman and colleagues[43] reported that 25 minutes of somatosensory electrical stimulation applied to elbow enhanced the corticospinal excitability of bilateral motor cortex in 8 healthy young adults. In addition, Lai and colleagues[42] reported that 40 minutes of somatosensory electrical stimulation applied over the median nerve on the paretic hand augmented the gamma band electroencephalography - electromyography coherence in 9 chronic stroke survivors. Their finding may indicate that application of somatosensory electrical stimulation could enhance the sensorimotor integration in stroke survivors [42]. Results of these studies might support the finding of current review since the neuronal plasticity changes induced by TENS could have augmented the effects of the subsequent motor training.

This review has several limitations. First, only eleven randomised controlled trials were included, and most of these randomised controlled trials had small sample sizes. Second, due to the heterogeneity of assessment methods and the small sample sizes, it was not possible to carry out meta-analyses of the effects of TENS on muscle strength and balance. Third, many of the included studies used the Modified Ashworth Scale to measure the level of spasticity of the paretic ankle plantarflexion despite the fact that the validity of using the Modified Ashworth Scale to measure spasticity has been questioned. moreover, the Modified Ashworth Scale was treated as interval scale in the current study, the result of that analysis may not be robust. Although the review shows that TENS significantly decreases Modified Ashworth Scale scores, the effect of TENS on paretic ankle plantarflexor spasticity need further investigation. Fourth, the long-term effect of TENS could not be determined as only four studies carried out follow-up assessments, with the longest follow-up period being 12 weeks. Lastly, studies which investigated the immediate effects of TENS by comparing the change of motor functions after 1 section of TENS were excluded. The immediate effects of TENS on motor functions, thus, could not be concluded from the results of this review.

Most of the studies included in the current meta-analysis adopted the stimulation frequency of 100Hz. It is plausible that the 100Hz stimulation frequency could be chosen in clinical practice. However, a randomised controlled trial is warranted to compare the effects of difference stimulation frequency. Besides, the optimal length of the intervention program could not be deduced from the current review. Future work should aim at identifying the optimal length of the training program to enhance its cost-effectiveness. Muscle strength, balance performance and neurophysiological measures of spasticity have not been meta-analysed. Further studies of TENS that use balance-specific outcome measures and electrophysiological assessments to evaluate the effects of TENS on spasticity in stroke survivors are warranted.

Clinical messages

- TENS is effective at enhancing walking capacity and reduce plantarflexor spasticity in stroke survivors.
- The stimulation duration of 60 min per session appeared more effective than a short session.
- Subgroup analysis showed that TENS is effective in acute/subacute stage of stroke but the effectiveness was uncertain in the chronic stage.

Acknowledgement

The authors wish to express their gratitude to Mr. Tai-Wa Liu for his assistance in searching and rating the methodological quality of studies.

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Appendix 3.2 Search strategy of randomised controlled trials

MEDLINE and EMBASE

1. Exp cerebrovascular disorder/
2. stroke$.mp
3. cerebrovasuclar$.mp
4. cerebral vascular$.mp
5. cva.mp.
6. hemiplegi$.mp.
7. paresis.mp
8. paretic.mp
9. (cerebral infarct$ OR brain infarct$).mp.
10. (cerebral ischemis$ OR brain ischemis$).mp.
11. (cerebral h?emorrhage OR brain h?emorrhage).mp.
12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7or 8 OR 9 OR 10 OR 11
13. exp transcutaneous electrical nerve stimulation/
14. TENS.mp.
15. Transcutaneous stimulation.mp.
16. Sensory stimulation.mp.
17. Somatosensory stimulation.mp.
18. Afferent stimulation.mp.
19. Electrical stimulation.mp.
20. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. Lower?extremit$.mp
22. Lower?limb$.mp
23. Leg$.mp
24. Strength$.mp
25. Muscle contraction$.mp.
26. Force$.mp
27. Spast$.mp
28. Muscle$ tone.mp
29. Hyperton$.mp.
30. Balance$.mp.
31. Stabilit$.mp.
32. Walk$.mp.
33. Mobilit$.mp.
34. Locomot$.mp.
35. Gait$.mp.
36. 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35

37. 13 AND 20 AND 36
38. limit 37 to humans

CINAHL

1. MH Cerebrovascular Disorders
2. TI (Stroke*) OR AB (Stroke*)
3. TI (cerebrovasuclar*) OR AB (cerebrovasuclar*)
4. TI (cerebral vascular*) OR AB (cerebral vasuclar*)
5. TI (cva) OR AB (cva)
6. TI (hemiplegi*) OR AB (hemiplegi*)
7. TI (paresis) OR AB (paresis)
8. TI (paretic) OR AB (paretic)
9. TI (cerebral infarct* OR brain infarct*) OR AB (cerebral infarct* OR brain infarct*)
10. TI (cerebral ischemis* OR brain ischemis*) OR AB (cerebral ischemis* OR brain ischemis*)
11. TI (cerebral h?emorrhage OR brain h?emorrhage) OR AB (cerebral h?emorrhage OR brain h?emorrhage)
12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7or 8 OR 9 OR 10 OR 11
13. MH transcutaneous electrical nerve stimulation
14. TI (TENS) OR AB (TENS)
15. TI (Transcutaneous stimulation) OR AB (Transcutaneous stimulation)
16. TI (Sensory stimulation) OR AB (Sensory stimulation)
17. TI (Somatosensory stimulation) OR AB (Somatosensory stimulation)
18. TI (Afferent stimulation) OR AB (Afferent stimulation)
19. TI (Electrical stimulation) OR AB (Electrical stimulation)
20. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. TI (Lower?extremit*) OR AB (Lower?extremit*)
22. TI (Lower?limb*) OR AB (Lower?limb*)
23. TI (Leg*) OR AB (Leg*)
24. TI (Strength*) OR AB (Strength*)
25. TI (Muscle contraction*) OR AB (Muscle contraction*)
26. TI (Force*) OR AB (Force*)
27. TI (Spast*) OR AB (Spast*)
28. TI (Muscle* tone) OR AB (Muscle* tone)
29. TI (Hyperton*) OR AB (Hyperton*)
30. TI (Balance*) OR AB (Balance*)
31. TI (Stabilit*) OR AB (Stabilit*)
32. TI (Walk*) OR AB (Walk*)
33. TI (Mobilit*) OR AB (Mobilit*)

34. TI (Locomot*) OR AB (Locomot*)
35. TI (Gait*) OR AB (Gait*

36. 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35
37. 13 AND 21 AND 36
38. limit 37 to humans

ClinicalTrials.gov

(Storke OR CVA OR hemiplegia) and (TENS OR Transcutaneous electrical nerve stimulation OR sensory stimulation)

Study status: Completed

Study type: Investigational study

Cochrane Central Register of Controlled Trials

(Storke OR CVA OR hemiplegia) and (TENS OR Transcutaneous electrical nerve stimulation OR sensory stimulation)

Limit search to trials

PEDro

Search strategy: Advanced

Abstract and Title: Stroke OR CVA

Title: Transcutaneous electrical nerve stimulation OR somatosensory stimulation

Method: Clinical trial

Web of Science

1. Cerebrovascular Disorders
2. Stroke*
3. cerebrovasuclar*
4. cerebral vascular*
5. cva
6. hemiplegi*
7. paresis
8. paretic
9. cerebral infarct* OR brain infarct*
10. cerebral ischemis* OR brain ischemis*
11. cerebral hemorrhage OR brain hemorrhage OR cerebral haemorrhage OR brain haemorrhage
12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7or 8 OR 9 OR 10 OR 11
13. Tanscutaneous electrical nerve stimulation

14. TENS
15. Transcutaneous stimulation
16. Sensory stimulation
17. Somatosensory stimulation
18. Afferent stimulation
19. Electrical stimulation
20. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21. Lower extremit* OR Lower-extremit*
22. Lower limb* OR Lower-limb*
23. Leg*
24. Strength*
25. Muscle contraction*
26. Force*
27. Spast*
28. Muscle* tone
29. Hyperton*
30. Balance*
31. Stabilit*
32. Walk*
33. Mobilit*
34. Locomot*
35. Gait*
36. 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35
37. 13 AND 21 AND 36

Appendix 3.3 List of excluded studies and reasons of exclusion

Study	Reason of exclusion					
	1	2	3	4	5	6
Burridge, Taylor et al. 1997	X					
Yan, Hui-Chan et al. 2005	X					
Tong, Ng et al. 2006	X					
Ng, Tong et al. 2008	X					
Embrey, Holtz et al. 2010	X					
Sabut, Sikdar et al. 2010	X					
Kesar, Reisman et al. 2011	X					
Johansson, Haker et al. 2001		X				
Tyson, Sadeghi-Demneh et al. 2013		X				
Levin and HuiChan 1992			X			
Peurala, Pitkänen et al. 2002			X			
Tekeoğlu et al. 1998				X		
Laddha, Ganesh et al. 2016					X	
HuiChan et al. 2009						X

Reason:
1 The stimulation intensity was above motor threshold.
2. Placebo or no-treatment control group not included.
3. The participants were not randomly allocated.
4. TENS was applied on the participants’ paretic arms.
5. Results were presented in graphs only and the numerical data could not be extracted.
6. Results reported in the study were duplication of another included study.

Appendix 3.4 Numeric data extracted from individual study.

CSS: Composite Spasticity Scale; MAS: Modified Ashworth Score; SD: standard deviation; TUG: Timed Up and Go test

Study	Outcome measure	TENS group				Control group			
		Pretest mean	Pretest SD	Posttest mean	Posttest SD	Pretest mean	Pretest SD	Posttest mean	Posttest SD
Jung 2017	CSS	11.5	1.7	8.9	1.7	11.9	1.8	10.8	1.8
Ng 2007	CSS	12.1	1.7	11	1.4	12.2	1.5	11.2	1.7
Yan 2009	CSS	4.5	5.8	7	2	4	5	10	3
Chen 2005	MAS	2.17	0.37	1.71	0.32	2.25	0.433	2.21	0.477
Deshmukh 2013	MAS	3.3	0.6	2.2	0.7	3	0.7	2.7	0.5
Hussain 2013	MAS	3.27	1.1	2	0.76	3	1.07	2.47	0.99
Kumar 2014	MAS	2.6	0.52	1.5	0.49	2.5	0.53	2	0.47
Park 2014	MAS	2.6	0.63	1.8	0.41	2.5	0.76	2.36	0.74
Chen 2005	Speed/ ms^{-1}	0.111	0.03	0.124	0.03	0.114	0.03	0.114	0.03
Hussain 2013	Speed/ ms^{-1}	0.4	0.16	0.46	0.16	0.45	0.17	0.476	0.17
Ng 2007	Speed/ ms^{-1}	0.506	0.283	0.682	0.345	0.49	0.25	0.577	0.3
Ng 2009	Speed/ ms^{-1}	0.479	0.268	0.666	0.325	0.507	0.245	0.606	0.297
Park 2014	Speed/ ms^{-1}	0.458	0.15	0.528	0.174	0.469	0.201	0.494	0.205
Yavuzer 2007	Speed/ ms^{-1}	0.31	0.18	0.34	0.11	0.36	0.22	0.37	0.2
Deshmukh 2013	TUG/ s	24.1	2.63	20.9	3.6	25.2	3.08	23.4	3.1
Kumar 2014	TUG/ s	37.09	3.15	32.6	2.96	36.24	4.57	34.32	3.91
Ng 2009	TUG/ s	25.5	17.4	18.7	9.7	29.4	22.1	26.2	21.7
Ng 2016	TUG/ s	42.89	27.06	22.82	10.75	45.6	23.67	31.68	22.08
Park 2014	TUG/ s	26.16	11.71	21.84	9.28	25.7	12.41	24.61	11.61
Yan 2009	TUG/ s	67.5	13.7	30	13.5	55.5	14.8	41.1	27.9

Appendix 4.1 Cross-sectional study 1 published on *Archive of Physical Medicine and Rehabilitation* (Final manuscript)

Effect of leg selection on the Berg Balance Scale scores of hemiparetic stroke survivors:
A cross sectional study

INTRODUCTION

The Berg Balance Scale (BBS) was first introduced in 1989[1]. The scale consists of 14 items, each rating a participant's ability to maintain stability in a specified functional task on a 5 point (0–4) scale[1,2]. The BBS has demonstrated excellent test-retest reliability (ICC 0.95–0.98)[3,4] and inter-rater reliability (ICC: 0.95)[5] for participants with stroke and been extensively used for measuring the functional balance performance of elderly participants[6,7], stroke survivors[5,8] and participants with Parkinson's disease[9]. It has also been used to evaluate risk of falling with participants who have suffered a stroke[10,11]. While one of the short comings of BBS is that BBS demonstrated a large ceiling effect in stroke survivors who had high physical function [12].

The last two items of BBS, 'Item 13- standing unsupported one foot in front' and 'Item 14- standing on one leg', are considered the most difficult because both items require narrowing the base of support during asymmetric weight bearing[13,14]. In item 13 of BBS the participant is asked to stand with one foot in front of the other. A score of 4 is given if the participant can maintain this tandem stance for at least 30 seconds with one foot placed directly anterior to the other and the longitudinal axis of the two feet aligned[15]. A biomechanical study with healthy adults has shown that body weight is loaded significantly more on the posterior leg in that tandem stance position[16]. Single leg stance (SLS) is an even more extreme form of asymmetrical weight bearing. SLS duration on a paretic leg after stroke is significantly shorter than on a non-paretic leg[8]. Previous studies have demonstrated that participants with stroke tended to bear more weight on their non-paretic leg when standing in order to better control postural stability[17,18].

The standard instructions for items 13 and 14 in a BBS assessment do not restrict the selection of the weight-bearing leg[1], but the choice is likely to affect the scores on those items and the total score, especially in patients with asymmetric motor control.

To our knowledge, effect of leg selection on performance of these 2 BBS items has not been studied. The primary purpose of this study was to investigate whether the total BBS score would differ when participants were required to use their more-involved leg in either weight bearing or non-weight bearing fashion for items 13 and 14. A secondary purpose was to examine the concurrent validity of the 4 BBS scoring strategies by considering correlation between the BBS performances and other measures of standing balance. We hypothesized that the item scores would be significantly lower when a participant stepped forward with the non-paretic leg in item 13, and stand on the paretic leg in item 14. We also hypothesized that The BBS total score with this formulation, thus, would be significantly lower than those alternative formulations. It had been reported that BBS demonstrated a large ceiling effect in stroke survivors who had high physical function [12]. By bring down the total score of BBS, This BBS formulation might also have less of a ceiling effect than the other formulations. Lastly, this BBS formulation might demonstrated stronger correlation with other outcome measures.

METHODS

Participants

Sixty-three community-dwelling chronic stroke survivors were recruited. Demographic characteristic of participants were shown in Table 2. Participants were recruited from local self-help groups by posting advertisement in local community centers. participants were eligible for this study if they: (1) were aged ≥ 50; (2) had been diagnosed as having had a stroke; (3) had suffered a single stroke at least 1 year previously; (4) were able to walk for 6 meters without assistance with or without walking aid. Participants were excluded if they were: (1) cognitively impaired (abbreviated mental test score below 6)[19]; (2) medically unstable; or (3) suffering from any other neurological or musculoskeletal condition that would affect mobility and balance performance. Sample size estimation was conducted with the aid of G*Power (version 3.1). A sample size of 62 participants would be adequate to detect significant difference ($\alpha=0.05$; power $= 0.8$) between the four formulations of BBS total scores, with a small effect size (Cohen's $f= 0.15$) and moderate correlation among repeated measures ($r=0.5$) were assumed.

The Ethics Committee of the administrating institution approved the study's assessment protocol. All of the participants gave written consent before starting the experiments. The study was conducted in accordance to the Declaration of Helsinki for human experiments.

Assessment Procedures

This was a cross sectional study. The experiment was conducted in the Balance and Neural Control Laboratory of The Hong Kong Polytechnic University. All of the participants completed the BBS and other assessments in a random order determined by drawing lots. Five minutes of rest was allowed in between each assessment in order to avoid fatigue.

Outcome measures

Fall History

Participants were asked whether they had any fall in the past 6 months, no matter the fall resulted in any injury or not. A fall was defined as “ an unexpected event in which the participants come to rest on the ground, floor, or lower level.” [20]. It had been reported that the accuracy of recalling of fall was satisfactory in elderly even for a 1 year period of time (sensitivity: 89% specificity: 95%)[21].

Berg Balance Scale Score

Items 1 to 12 of the assessments were conducted in accordance with the standard instructions. Items 13 (tandem stance) and 14 (SLS) were performed twice so that both legs could execute the weight bearing component of the item (i.e. for Item 13: the posterior leg was weight bearing; for Item 14: the stance leg was weight bearing). The sequence of performance was randomized for these 2 items. This produced 4 total BBS scores (Table 1).

Fugl- Meyer Assessment- Lower Extremity Score

The lower extremity motor subscale of the motor domain of the Fugl-Meyer assessment (FMA-LE) was used to measure the participants’ lower extremity motor recovery after stroke. Quality of reflexes, coordination and voluntary movements of the paretic leg were assessed using a 34-point scale[22]. Excellent inter-rater and intra-rater reliability[23] (ICC=0.959–0.963) and test-retest repeatability[3] (ICC=0.94) have previously been reported for the FMA-LE.

Five Times Sit-to-stand Time

The five times sit-to-stand test (FTSTS) was used to examine the functional muscle strength of the participants’ lower limbs[24]. The FTSTS has shown excellent test-retest reliability (ICC = 0.994–1.000) with chronic stroke participants[24]. The participants were asked to stand up and sit down for 5 times as fast as possible. A standard starting position was enforced with the heels 10 cm behind the neutral position when seated (posterior foot placement) and arms crossed in front of the chest[25]. The average completion time of 3 trials was used for analysis.

Ten Metre Walk Time

The participants’ walking speed was measured using the 10-metre walk test (10mWT). The participant was asked to walk at a comfortable speed along a 10-metre walkway with an extra 2 metres at the start and end to allow for acceleration and deceleration[26]. The time to cover the middle 10 metres was timed with a stopwatch. The test has previously been demonstrated to have, excellent intra-rater reliability (ICC=0.87–0.88)[27] for stroke survivors. The average walking speed of 3 trials was used for analysis.

Activities-specific Balance Confidence Scale Score

The Chinese version of the Activities-specific Balance Confidence Scale (ABC)[28] was used to assess the participants' confidence in balance during certain activities of daily living. The ABC consists of 16 items, each referring to a specific daily activity. The participants were asked to score their confidence level about maintaining their balance in each activity on a scale of 0 to 100. A score of 100 represented complete confidence in performing that activity without losing balance while a score of 0 represented no confidence at all[28]. This instrument has been reported to have excellent test-retest reliability for participants with chronic stroke (ICC=0.85)[29].

Statistical analysis

The frequency of scorings of the two conditions in items 13 and 14 of the BBS assessment and the percentage of participants who received the maximum score in the four BBS formations would be listed to evaluate the ceiling effect of the four formations. Wilcoxon's signed-rank test was used to compare the item scores of the two conditions in items 13 and 14. Friedman's analysis of variance (ANOVA) technique was used to compare the four BBS total scores (as defined in Table 1). Post-hoc analysis was done with Wilcoxon's signed-rank test. There were 4 BBS total scores included in the Friedman's ANOVA, and thus 6 pairs of comparisons in the Wilcoxon signed-rank tests. To avoid inflation of type 1 error, the critical level of confidence for significance was adjusted to be 0.05/6= 0.0083 in the post-hoc analysis with signed-rank tests. Internal consistency of the variation of the four BBS formations was measured by Cronbach's α. Receiver operating characteristics (ROC) analysis was adopted to exanimate the ability of the four BBS total scores in discriminating fallers from non-fallers.

Correlations between BBS total scores and other outcome measures were examined using Spearmen's rho. The strength of any correlation of the four BBS total scores with the other outcome measures for that participant was assessed using Steiger's Z test[30]. A p value ≤ 0.05 was considered as statistically significant. For Steiger's Z test, a critical z value larger than 1.96 indicated a significant difference between the strengths of the correlations with $p \leq 0.05$[30,31]. The Z test was conducted with the aid of FZT software[31]. All the other statistical analyses were conducted with version 20.0 of the SPSS software package. Any case with missing data was omitted from analysis.

RESULTS

In item 13, 35 participants received the maximum item score when they stepped forward with the non-paretic leg, while 18 of them received the maximum item score when stepped forward with the paretic leg. In item 14, 18 participants received the maximum item score when they were SLS on non-paretic leg, meanwhile only 9 of them received the maximum item score when SLS with the paretic leg (Table 3). Only 4.8% participants received the maximum total score in BBS_1, which was less than the other BBS formations (BBS_2: 6.3%; BBS_3: 12.6% and BBS_4:14.3%). There were significant differences in the scores for the 2 items (Item 13: mean difference = 0.4, Z=-3.10, p=0.002; Item 14: mean difference = 1.6, Z=-5.49, p≤0.001).

The BBS total scores ranged from 48.4 to 50.7. The BBS_1 total score was the lowest and BBS_4 was the highest on average. Mean FMA-LE score, FTSTS completion time, walking speed and ABC score were 23.9, 21.29, 0.837 and 72.8 respectively (Table 3). The Friedman's ANOVA revealed significant difference between four BBS total scores ($X^2(3) = 87.41$, $p \leq 0.001$). Post-hoc analysis showed that each model was significantly different from the others (Table 4). Cronbach's α value of BBS_1 was the highest (0.721) among the four formulations (BBS_2: 0.715; BBS_3:7.02; BBS_4:7.07).

Result of ROC analysis showed that total score of the 4 BBS formations unable to discriminate faller from non-faller in the current study (BBS_1: area under curve (AUC)= 0.52, p=0.85; BBS_2: AUC = 0.51, p=0.88; BBS_3: AUC = 0.53, p=0.74; BBS_3: AUC = 0.60, p=0.75).

The BBS total scores demonstrated significant correlation with the FMA-LE score, FTSTS completion times, walking speed and ABC scores ($p \leq 0.001$ in each case) (Table 5). The correlation coefficients of the BBS_1 total scores with the other outcome measures were larger than those of the other models. Steiger's Z test showed that the BBS_1 total scores had stronger correlations with the walking speeds and ABC scores than the BBS_3 or BBS_4. In addition, the BBS_1 total scores showed significantly stronger correlation with FTSTS completion times than the BBS_4 total scores. No significant difference in strength of correlation existed between the $BBS_1$and BBS_2 total scores (Table 6).

DISCUSSION

Results of the current study supported the hypotheses that the item scores were significantly lower when a participant stepped forward with the non-paretic leg in item 13, and stand on the paretic leg in item 14. The BBS_1 total score was significantly lower than those alternative formulations and demonstrated a smaller ceiling effect. This formulation also demonstrated marginally stronger correlations with other outcome measures.

Item 13 challenges a participant's postural control by reducing the lateral base of support[15]. In this study, the participants scored significantly lower on Item 13 when required to place their paretic leg posteriorly. A study led by Jonsson reported[16] that the rear leg is the primary weight-bearing leg in tandem stance. Jonsson demonstrated that with a healthy adult the body weight supported by the rear leg is double that of the forward leg[16]. In light of that, participants with chronic stroke have poorer postural stability when placing their paretic leg posteriorly during weight bearing activities.

As would be expected, the scores in item 14 were significantly lower when the participants stood on their paretic leg alone. Flansbjer has reported similar findings[8]. In another study by Goldie et al, they asked their participants to transfer as much of their body weight as possible onto one leg and found that the weight transfer transferred to the paretic leg was significantly less than that to the non-paretic leg[32].

Our results show that the selection of the weight-bearing leg in items 13 and 14 would affect the BBS total score. The BBS_1 formulation where the participant placed the non-paretic leg in front in item 13 and stood on the paretic leg in item 14 gave the lowest total score and less participants received the maximum item scores, confirming that these were the more challenging conditions of these two test items. It should also be noted that fewer participants achieved the maximum score with the BBS1 formulation,, indicated that the ceiling effect was dampened. Salbach’s group[12] reported that even in acute phase of stroke, 26% of the stroke survivors received the maximum score in BBS. By bringing down the items score with the more challenging conditions, BBS_1 might be more capable in detecting changes of balance ability over time in participates with high physical function.

In fact, when the BBS was first developed, it called for testing both legs alternately in items 13 and 14[1]. The protocol was later amended to testing the participant’s preferred leg only[1,2]. A Rasch analysis by Straube et al[33] found that Items 13 and 14 of the BBS showed a high level of variance in the item scores in participants with stroke, with infit mean square values of 2.0 and 1.6 respectively. An infit mean square value larger than 1.4 indicates an unusually high level of variance[33]. Straube hypothesized that the self-selection in items 13 and 14 caused item misfit in assessing participants with chronic stroke. He speculated that participants with poor balance would select their non-paretic legs, leading to higher item scores, while some with better balance might select their paretic leg, resulting in a lower item 13 and item 14 scores and greater variance, impairing the scale’s precision[33]. The results of the current study support Straube’s hypothesis and the need to standardize the testing procedures for items 13 and 14 of the BBS. Besides, analysis on internal consistency of the variation showed that BBS_1 demonstrated highest inter items correlation. However, the result was not conclusive since the differences between Cronbach’s α value were small.

The fall rate in the current study (22%) was lower than that reported in previous studies (36-50%)[10,34]. Our ROC analysis showed that none of the 4 BBS formulations was able to discriminate between fallers and non-fallers. Similar results have been reported by Harris and colleagues[34] who examined the relationship between falls and several outcome measures in a sample of 99 subjects with chronic stroke. They found no difference in BBS score between fallers and non-fallers and that a low BBS score was not a risk factor for multiple falls (OR=1.1, 95%CI: 1.1, 0.91).

A significant moderate correlation was found between all four BBS total scores and FMA-LE scores. Similar correlations between BBS total score and FMA-LE score have been reported previously for participants with stroke (e.g. r=0.661) [35]. However, Steiger's Z test did not reveal significant differences in the strength of correlations between the FMA-LE scores and any of four BBS total scores tested (Steiger's $Z > 1.96$). The FMA-LE assesses the quality of reflexes, coordination and voluntary movements. That could explain why the leg selected in items 13 and 14 did not significantly affect the strength of correlation between the BBS total scores and the FMA-LE score.

Significant correlations were found among the four BBS total score formulations and FTSTS completion times. This could be explained by the fact that there are several items in the BBS which assess a participant's ability to transit between sitting and standing (items 1, 4 and 5). The correlation between BBS_1 total score and FTSTS completion time was significantly stronger than that of the BBS_4 score (Steiger's $Z = -2.27$). This reflects the fact that the postural stability on the paretic leg affects the ability to sit down and stand up. Chou et al documented[36] that stroke survivors who took longer to rise from sitting also demonstrated greater asymmetry in weight bearing during the maneuver. Also, Lomaglio and Eng[37] have reported that weight bearing symmetry at lift off from a chair (defined as the ratio between the peak vertical forces applied through the paretic and non-paretic legs) is negatively correlated in stroke survivors with the time needed to complete the sit-to-stand movement ($r = -0.565$, $p \leq 0.01$).

Significant moderate correlations were shown between all four BBS total scores and walking speed. Patterson's group has reported[38] that BBS total score is a significant predictor of 30-foot walking velocity for participants with stroke who demonstrated moderate to severe motor deficits (adjusted $R^2 = 0.42$, $p \leq 0.001$). The strength of correlation between BBS_1 and walking speed was significantly stronger than those of BBS_3 and BBS_4 ($BBS_{3:}$ Steiger's $Z = 3.00$; BBS_4 Steiger's $Z = 1.98$), suggesting that the weight-bearing ability of paretic leg might affect walking speed. Aruin's group has previously demonstrated a 10.5% increase in walking speed after weight-bearing training in a study of 9 participants with chronic stroke[39]. Their results revealed that improving weight-bearing ability in the paretic leg could improve walking speed after stroke.

Significant correlation was found between all four BBS total score formulations and the ABC scores. Balance performance and subjective balance confidence are well known to be correlated in participants with stroke[29]. The BBS_1 formulation correlated more strongly with the ABC scores than either BBS_3 or BBS_4 ($BBS_{3:}$ Steiger's Z = 2.32; BBS_4 Steiger's Z = 3.00). To the best of our knowledge, no study has previously investigated the influence of the weight-bearing ability of a paretic leg on subjective balance confidence. These results suggested that subjective balance confidence is influenced by the weight-bearing ability of a paretic leg for stroke survivors.

Clinical implication

Result of the within subject comparison showed that leg selection could significantly affect the BBS total score. Although the mean differences between the four BBS formulation were small (0.5-2 points), It should be noted that the reliability of BBS is almost excellent in participants with chronic stroke. The standard error of mean of BBS for participants with chronic was ranging from 1.49 to 1.79 points [3,4,8]. Minimal detectable change was calculated to be 2.5 points according to Liston et.al.[4] study. The effect of leg selection could still influence the interpretation of the BBS total score. The results also shown that there were less participants receiving the maximum score in BBS_1 and standardizing the selection of weight bearing leg could effectively reduce the variation. Further research would be required to determine whether the improved standardization and a dampened of ceiling effect could improve the ability of BBS in categorizing patients and/or detecting change over time or not.

Limitations

It should be emphasized that the participants recruited in our study had relatively good functional mobility and balance ability. The results are only applicable to stroke survivors who fulfill the study's inclusion criteria and should not be directly applied to other participants with severe mobility deficits. Note too that several functional assessments were conducted within one assessment session, so fatigue might have influenced some participants' performance. Another limitation of this study was that it did not assess item 13 and item 14 performance with the participants' preferred legs, though they are usually tested in conducting a BBS assessment. Besides, it was speculated that challenging BBS formulation (i.e. BBS_1) might lead to greater test-retest variability. The reliability of the four formulations of BBS is worth further investigation.

CONCLUSION

The BBS total score is significantly lower for stroke survivors if they place the paretic legs posteriorly in item 13 and to stand on the paretic leg in item 14. The result indicated that standardization of the BBS protocol would be necessary. A BBS total score developed in that way (BBS_1) demonstrates a dampened ceiling effect and stronger correlation with FTSTS completion time, walking speed and ABC score than alternative formulations. Further research was required to investigate if the improved standardization and a dampened of ceiling effect could make BBS a more useful tool in assessing stroke survivors with high physical function.

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Appendix 4.2 Cross-sectional study 2 published on *BioMed Research International*

Foot and arm positions affect the five-times-sit-to-stand test time of individuals with chronic stroke

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INTRODUCTION

Stroke is a common disease that can cause severe impairment of survivors' mobility and ability to perform daily activity. Rehabilitation after stroke usually is a prolonged or even lifelong undertaking for the survivors.[1] In order to document the severity of impairment and to monitor progress in the course of rehabilitation, different outcome measures have been developed.

The five times sit to stand test (FTSTS) was designed by Csuka and McCarty in 1985.[2] It is used to assess the functional muscle strength of the lower limbs, especially with older adults. The subject is instructed to stand up from sitting for five times as quickly as possible without using the hands for support. The total duration is recorded in seconds. This protocol has shown excellent intra-rater reliability (intraclass correlation coefficient [$\mathrm{ICC}_{3,1}$] = .970–.976), inter-rater reliability ($\mathrm{ICC}_{3,2}$ = .999) and test-retest reliability ($\mathrm{ICC}_{2,1}$= .994–1.000) for subjects with chronic stroke.[3] In addition, good test-retest reliability has also been reported with healthy subjects of different ages.[4,5] The time for performing the FTSTS has also been found to be negatively correlated with Berg Balance Scale (BBS) scores (r = -.837, $P \leq .001$)[6] and with knee flexor strength in both the affected leg (ρ= -.753) and the unaffected leg (ρ= -.830) in subjects with chronic stroke.[3]

Indeed, BBS scores had been shown to be an independent predictor of FTSTS times, explaining 71 % of the variance in the FTSTS times in chronic stroke survivors.[6] The FTSTS times were also found to be negatively correlated with lower limb muscle strength among older women,[7] and an useful independent predictor of deterioration of ability in the activities of daily living over the subsequent 3 years for the elderly.[8]

Although FTSTS times were commonly used in stroke rehabilitation, the testing procedures were not well standardized, in particular the starting positions of feet and arms could vary widely among studies. Clearly, initial foot placement would affect the distance travelled by the body's centre of gravity (CoG) and leverage in rising from a seat.[9–11] However, initial foot placement was not clearly mentioned in previous studies.[3,7, 12–14] Arm position might also influence the body's CoG, and restricted arm movement would lead to a different strategy in rising from sitting.[14] Arm position was also not standardized in previous studies.[3,7, 12–14] Subjects were sometimes instructed to cross their arms in front of the chest[7, 12–14] or to put their hands on their thighs[3], and arm position was even not described at all in some studies.[16]

The objectives of the present study were to investigate the effect of (1) 2 foot placements (normal and posterior placement) and (2) 3 arm positions (hands on thighs, arms crossed over chest, and augmented arm position with elbow fully extended) on the FTSTS times of individuals with chronic stroke.

METHODS

Participants

Forty-five community-dwelling individuals with chronic stroke were recruited from a local self-help group for stroke survivors. Subjects were included in the study if they: (1) were aged 50 years or above, (2) had experienced a single stroke at least 1 year before the study, and (3) were able to stand up from a chair without any external support. Subjects were excluded if they: (1) were unable to follow commands properly, (2) had an abbreviated mental test score below 6, (3) were medically unstable, or (4) were suffering from other neurological or musculoskeletal disorders which could affect sit-to-stand performance.

The Ethics Committee of the administrative institution approved the study protocol. The objectives and procedures of the study were clearly explained to all subjects and they all signed written consent forms. The study procedure followed the guidelines set by the Declaration of Helsinki for human experiments.

Procedure

This study was conducted in a university-based rehabilitation clinic. An armless chair with an adjustable seat height was used in this study. The subjects were instructed to stand up and sit down from a height-adjustable chair 5 times as quickly as they could. The standardized instruction given for each trial was, "On the count of 3, please stand up and sit down 5 times as fast as you can." The timing started when the subject's back left the back rest and ended when their back touched the back rest after the 5th repetition. The time was recorded by hand using a digital stop watch.

The effects of normal and posterior foot placement together with hands on thighs, arms crossed over chest, and augmented arm position on FTSTS times were investigated in this study. Seat height was adjusted according to their lower leg length in all trials. The lower leg length was defined as the perpendicular distance between the fibular head and the floor, when the subject sat on the chair with the knees in 90° of flexion and the ankles in the neutral position. This sitting position was also defined as the normal foot placement. Posterior foot placement was defined as having both heels positioned 10cm backward from the normal foot placement. The augmented arm position was defined as the two hands gripping together with the shoulders flexed at 90° and the elbows fully extended.

Each subject was required to perform the FTSTS under 6 experimental conditions in a random sequence by drawing lots. Two trials were performed under each condition, with a 2-minute rest between each trial to avoid fatigue. The 6 experimental conditions were as follows:

Condition 1: Normal foot placement and hands on the thighs.
Condition 2: Normal foot placement and arms crossed over chest.
Condition 3: Normal foot placement, augmented arm position.
Condition 4: posterior foot placement, hands on the thighs.
Condition 5: posterior foot placement, arms crossed over chest.
Condition 6: posterior foot placement, augmented arm position.

Statistical Analysis

Paired t-tests were used to evaluate the significance to the time differences between the two foot placements. The differences between the three arm positions was evaluated using one-way repeated measures ANOVA followed by Bonferroni post hoc multiple comparison tests. Two-way repeated measures ANOVA were conducted to examine the significance of the observed relationship between arm and foot positions and FTSTS times. All the statistical analysis was conducted with the help of version 16.0 of the SPSS for Windows software package.

RESULTS

The demographic characteristics of the 45 subjects are shown in Table 1. Their mean age was 60 ± 5.6 years, with an average post-stroke duration of 7.1 ± 2.9 years. Table 2 shows the average FTSTS times with the different foot and arm positions. Two-way repeated measures ANOVA revealed no significant interaction between foot and arm position, and the FTSTS times.

There were, however, significant differences between the FTSTS times with normal and posterior foot placement in all the 3 arm positions ($P \leq .001$). With normal foot placement, no significant difference was found in the FTSTS times among the 3 arm positions. With posterior foot placement, the hands on the thighs position resulted in significantly longer FTSTS times than the augmented arm position ($P \leq .01$)

DISCUSSION

This is the first published study to investigate relationship between foot and arm position, and the FTSTS times of individuals with chronic stroke. Our results showed that both the foot and arm positions could affect FTSTS times. Posterior foot placement in combination with augmented arm position, predicts faster FTSTS times in individuals with chronic stroke.

The average FTSTS times for the 6 conditions ranged from 15.2 to 17.1 seconds. These averages were comparable to those observed in previous studies that reported on subjects with chronic stroke.[3,17] Weiss et at. reported FTSTS times of 19.3 ± 2.4 seconds in subjects with chronic stroke,[16] but that study included only 7 subjects with a mean age of 70 ± 2.4 years,[16] who were twenty years older than our subjects.

Bohannon and colleagues had published[18] a meta-analysis which demonstrated that the normal FTSTS time for healthy persons aged between 60 and 69 years was 11.4 seconds. It was expected that our subjects with chronic stroke would take longer to complete the FTSTS. After a stroke, survivors often needed more time to regain their balance in both rising and sitting down[19]. It was also well documented that individuals with stroke tended to have significantly less knee extensor strength, poorer BBS scores and less maximum weight bearing ability in their affected limbs.[11] All these stroke-specific impairments were strongly associated with lengthened sit-to-stand times.[11] Other intrinsic factors including impaired tactile sensation, poor proprioception and fear of falling in daily activities were commonly noted in people with stroke.[20]All these factors could hinder the sit-to-stand performance.

Foot Placement

Consistent with the results of healthy adults that posterior foot placement could increase the speed of sit to stand,[10] our study also showed that posterior foot placement led to shorter FTSTS times with all three arm positions. In the initial phase of sit to stand, flexion of trunk or upper body segment resulted in forward shifting of the CoG and brought the CoG close to the point of application (PoA) of ground reaction force at lift-off .[10]

The PoA was defined as the point where compound vector of ground reaction acted.[10] Kawagoe et.al. showed[10] that placing the feet at 10cm behind the normal foot placement was associated with significantly less anterior and abrupt displacement of the CoG, as well as shorter distance between CoG and PoA at lift-off. Shorter distance between CoG and PoA could reduce the demand on muscle forces required for forward acceleration and backward braking.[10] In another study,[21] posterior foot placement resulted in a significantly smaller hip flexion angle (*P*<.05) in the pre-extension phase of hip during sit to stand. The smaller hip flexion angle implied a shorter distance that the trunk or upper body segment has to move forward to initiate the action of rising from a chair.

Reduced muscular effort during rising when the feet are placed posteriorly could also explain shorter FTSTS times taken in posterior foot placement. Reduced tibialis anterior muscle (TA) activation during standing up had been found in posterior foot placement when compared with those of normal foot placement.[10] As TA muscle activity is necessary during rising from sitting because it would provide an anterior rotatory force of shank on ankle in order to bring the CoG forward and to stabilize the ankle ,[21] reduced TA activity is suggestive of less muscular effort and ankle stability during standing up. In another study, maximum hip extension moment (32.7 ± 12.1Nm) was found to be reduced when the feet were placed posteriorly by 10 cm than they being placed by 10 cm forward (148.8 ± 7.5Nm) during sit-to-stand.

Arm Position

The present results revealed significantly shorter FTSTS times with the augmented arm position than placing the hands on the thighs, when the feet were in the posterior placement. There was, however, no significant interaction between arm position and foot placement.

The augmented arm position might help to shift the CoG forward more efficiently, which could explain why it was associated with faster FTSTS times. Carr et al. conducted a kinetic and kinematic analysis of arm position on sit-to-stand movements with force plate and videotaping on 6 healthy young males.[15] The augmented arm position similar to that of our study, was shown to induce larger peak CoG momentum in both the horizontal and vertical directions than the restricted arm position. They explained that the augmented arm position had helped to generate greater propulsive force during a sit-to–stand maneuver.[15]As there is only one study examining the effects of arm positions on sit-to-stand maneuver, further biomechanical studies are warranted.

Limitations

This study has several limitations. The quality of FTSTS performance might have been overlooked because speed was the main focus of this study. Moreover, as the population studied was limited to stroke survivors, these results could not be generalized to other populations. Increased sample size and subjects with different degrees of stroke-specific impairment would improve the generalizability of the conclusions. In addition, only two foot placements and three arm positions were studied. A previous study[22] has shown that different foot placement including spontaneous, asymmetric and symmetric foot placement would significantly affect the electromyographic activities of lower limb muscles. Whether other foot or arm positions could induce a greater effect on FTSTS times needs further investigation. Further study of the actual kinetics and kinematics with different arm positions is warranted. In view that our study design was cross-sectional, no causal relationships can been established.

All subjects were required to perform FTSTS in 6 different conditions, certain degrees of learning and fatigue effects might affect our results. However, randomization of testing sequences by drawing lots and adoption of 2-minute rest periods would help to minimize the learning and fatigue effects.

CONCLUSIONS

Posterior foot placement and augmented arm position were found to associate with shorter FTSTS times for individuals with chronic stroke. The finding of this study suggests that foot placement and arm positions have a significant influence on the FTSTS times of stroke survivors thus it is necessary to standardize the arm and foot positions in the FTSTS test in the clinical situation.

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An investigation of the psychometric properties of the Chinese (Cantonese) version of Subjective Index of Physical and Social Outcome (SIPSO)

Appendix 4.3 Cross-sectional study 3 published on *Clinical Rehabilitation* (Final manuscript)

Introduction

The remarkable levels of physical impairment and functional limitation in patients with stroke can affect their level of community integration. To provide a better understanding and record the level of community integration throughout the rehabilitation process in stroke survivors, a comprehensive measure that evaluates rehabilitative outcomes from the perspective of those survivors is needed.

Divergent interpretations of community integration have led to the development of several instruments to measure the construct. Wilier et al.(1) operationalised the inverse of “handicap” to develop the Community Integration Questionnaire. McColl et al.(2) developed the Community Integration Measure based on a model of community integration derived from groups of survivors with brain injuries. Finally, Wood-Dauphinee et al.(3) developed the Reintegration to Normal Living Index based on the “Activity and Participation” component of the International Classification of Functioning Disability and Health model.

Although all of these instruments have been validated in populations with various neurological deficits, but certain aspects relevant to the community integration of the stroke population have not been addressed. For example, the Community Integration Questionnaire neglected the subjective experience of the target population. In contrast, the Community Integration Measure fails to evaluate the level of engagement in the activities of daily living and social activities. For Reintegration to Normal Living Index, a previous study reported poor scoring agreement between stroke survivors and persons knowledgeable about their condition.(4)

The Subjective Index of Physical and Social Outcome (SIPSO) questionnaire(5, 6) was developed based on the normalisation approach.(7) The normalisation approach advocates that people with disabilities should be able to enjoy patterns and conditions of life as close as possible to those that prevail in the wider community. The 10-item SIPSO have been reported as a valid and reliable tool for measuring the level of community integration in stroke survivors. (6, 8-10). Besides, the agreement of scoring between stroke survivors and their carer was excellent (ICC = 0.95).

A growing body of clinical research in the West is adopting the SIPSO questionnaire as an outcome measure,(11-20) but it is yet to be translated into Chinese, and neither has its reliability and validity been evaluated in a Chinese community. Culturally adaptation of the questionnaire is necessary as Chinese community might hold a different perspective on post-stroke care. For example, a recent study points out that post-discharge care and rehabilitation are tended to be neglected in policy in China (21). The objectives of the current study were, therefore, to translate and culturally adapt the SIPSO questionnaire to develop a Chinese (Cantonese) version (SIPSO-C) and evaluate the psychometric properties of SIPSO-C for use in assessing the level of community integration amongst community dwelling stroke survivors in Hong Kong and southern China.

Methodology

The standard forward-backward translation procedure described by Beaton et al.(22) was adopted to translate the original English version of the SIPSO questionnaire into Cantonese, the Chinese variety spoken in southern China and Hong Kong. Two bilingual translators whose mother tongue is Cantonese produced two independent translated the SIPSO. One of the translators was a registered physiotherapist, and the other was a professional translator who had received no training in the fields of medicine or rehabilitation. Back-translated was conducted by another two independent professional translators who were blinded to the original (English) version of the SIPSO questionnaire.

An expert panel comprising five registered physiotherapists was established. This expert panel was tasked with reviewing, consolidating the meanings of items in and making cultural adaptations to the translated version of SIPSO. Equivalence between the translated and original versions in four areas, namely, semantic, idiomatic, experiential and conceptual, was examined by the panel. A pilot version of SIPSO-C was produced after consensus had been reached amongst the panel members. Finally, five community-dwelling chronic stroke survivors were invited to complete the pilot version of SIPSO-C, with the aim of evaluating its fluency, clarity, and comprehensibility. The final version of SIPCO-C was then confirmed with reference to the feedback received from these stroke survivors.

Participants

Stroke survivors were recruited from local self-help groups for individuals with cerebral vascular disease via a poster advertisement. Stroke survivors were eligible for this study if they 1) were aged > 55; 2) had received a stroke diagnosis at least 12 months previously; 3) were living in the community; and 4) had an Abbreviated Mental Test Score of 7 or above.(23) Stroke survivors with cognitive impairment were excluded to ensure all participants could follow the study protocol.

Stroke survivors were excluded if they were 1) medically unstable; 2) unable to give written informed consent; and/or 3) suffering from a comorbid neurological disease such as Parkinson’s disease, multiple sclerosis or traumatic brain injury. Stroke survivors who suffered from expressive dysphasia were not excluded given that they could give written consent.

The ethics committee of The Hong Kong Polytechnic University approved the study's protocol, and the study was conducted in accordance with the principles of the Declaration of Helsinki for human experiments. The study's objectives and procedures were explained to the participating stroke survivors, all of whom provided informed written consent before study commencement.

Assessment procedure

Eligible stroke survivors were invited to come to the Balance and Neural Control Laboratory of The Hong Kong Polytechnic University for the first assessment. All assessments were conducted by a registered physiotherapist (KWH). Twenty-five participants were randomly selected to revisit the laboratory after a one-week interval through the drawing of lots. The relatively short period minimized the chance that real changes of the stroke survivors' condition or significant events in their life occurred. These 25 stroke survivors completed the SIPSO-C questionnaire a second time to establish its test-retest reliability. The same rater interviewed the stroke survivors and filled out the SIPSO on both occasions.

Outcome measures

Demographic characteristics, including age, sex, post-stroke duration, type of stroke, hemiplegic side and use of aids for outdoor ambulation were recorded. Participants' level of community integration was measured using the SIPSO-C questionnaire which was translated from the original SIPSO (5, 6) as mentioned above.

The SIPSO questionnaire was developed from the perspective of stroke survivors. In the first phase of SIPSO's development, a qualitative study involving in-depth interviews with 30 community-dwelling stroke survivors was conducted,(5) with the questionnaire items based on the results. Final item selection was then based on the comments and responses of another 100 community-dwelling chronic stroke survivors.(6) These procedures ensured that all items were relevant to the concerns of this population. The SIPSO questionnaire comprises 10 items. Items 1-5 belong to the physical integration subscale, and items 6-10 to the social integration subscale.(6, 8-10) Each item is rated on a 5-point scale (0-4). The maximum total score is 40, and higher scores indicate a better level of community integration. The SIPSO and SIPSO-C questionnaire are available in appendix 1.

Two studies (8, 9) reported an excellent test-retest reliability of the English version of SIPSO (ICC = 0.96) in 128(8) and 32(9) chronic stroke survivors, respectively. In addition, the degree of scoring agreement between 48 stroke survivors and their caregivers was high (ICC = 0.962).(8, 9) The construct validity of the SIPSO has been established by its significant correlation with Reintegration to Normal Living Index scores (*r* = 0.651-0.758)(8) and the Barthel Index (*r* = 0.730),(6) Frenchay Activities Index (*r* = 0.801)(6) and Nottingham Health Profile (*r* = 0.671).(6) The SIPSO questionnaire and its subscale scores have also been shown to be responsive to a change in chronic stroke survivor status over time, with an effect size of 0.240 to 0.267.(8)

Comfortable walking speed was also measured to quantify the mobility level of the participating stroke survivors using the 10-metre walk test. A 14-metre walkway was used, with 2 m allowed at the start and end of the 2-m test distance for acceleration and deceleration. Travel time was recorded with a stopwatch.(24)

The Chinese version of the Geriatric Depression Scale (25) was used to assess participants' level of depressive symptoms. The scale comprises 30 dichotomous (yes or no) questions, for a total score of 30, with a higher score indicating a higher level of depressive symptoms. A Geriatric Depression Scale score higher than 10 indicates a high risk of minor depression in stroke survivors (sensitivity = 0.69, specificity = 0.75).(26) Good test-retest reliability has been demonstrated for the Chinese version of the Geriatric Depression Scale in a sample of 461 elderly participants (ICC = 0.85).(25)

Statistical analysis

Descriptive statistics (mean, median and frequency) were used to summarise the participating stroke survivors' demographic characteristics and responses to each individual item of the SIPSO-C questionnaire. The internal consistency of the questionnaire and its subscales was assessed by Cronbach's α coefficients, ICC were used to assess their test-retest reliability. The statistical model $ICC_{3,1}$ was selected because this model is suitable to measure the consistency of scoring between two occasions when the rater is fixed.(27)The kappa statistic was adopted to evaluate the agreement in item scores between the two rating occasions for the 25 participants asked to complete the SIPSO-C questionnaire twice.

The Mann-Whitney U test was performed to compare the SIPSO-C scores of stroke survivors with different demographic characteristics, including sex, hemiplegic side, age group, walking speed and risk of minor depression (based on Geriatric Depression Scale score). A cut-off of 65 years was used to divide the stroke survivors into two age groups, thus allowing the results of the current study to be compared with those of a previous study.(8) For the walking speed, a 10-meter Walk test speed of $0.8ms^{-1}$ was adopted as the cut-off speed, since a speed lower than $0.8\ ms^{-1}$ indicated a limited community walking ability in stroke survivors.(28, 29) The Statistical Package for Social Science (SPSS version 22.0) was used to conduct all of the statistical analyses. P values ≤ 0.05 were considered to be statistically significant.

Results

Ninety-two community-dwelling stroke survivors were recruited between May 2014 and December 2015. Demographic characteristics of the stroke survivors were summarised in Table 1. Twelve participants were classified as household ambulators ($\leq 0.4\ ms^{-1}$), 40 as limited community ambulators ($0.4\text{-}0.8\ ms^{-1}$) and 40 as community ambulators ($> 0.8\ ms^{-1}$).(28, 29) Thirty-eight of the participating stroke survivors had a Geriatric Depression Scale score higher than 10, indicating that they were at high risk of minor depression.(26)

The median total SIPSO-C score was 28, 5 of the stroke survivors scored the maximum of 40 (Table 1). With regard to individual item scoring, the mean score of item 9 was the lowest and item 2 was the highest. Distribution of Item 2,5,10 was highly skewed with the skewness value lower than -1.0. (30) . (Table 2).

The SIPSO-C questionnaire demonstrated a high level of internal consistency, (Cronbach's $\alpha = 0.83$). (Table 3). Both the SIPSO-C total score and physical and social integration subscale scores demonstrated excellent reliability (ICC > 0.8),(31) The kappa statistic revealed that for all items, the level of agreement between the two assessment occasions was unlikely to be the result of chance ($P < 0.001$) However, a fair level of agreement (kappa: 0.21-0.40) for item 8 was found.(32) (Table 4). The characteristics of the sub-sample were comparable to the total sample. The summarized demographic characteristics are available in appendix 2.

The Mann-Whitney U test results revealed that the stroke survivors at high risk of minor depression (Geriatric Depression Scale > 10;$U = 555.0$, $P \leq 0.001$) and with limited community walking ability (10-metre Walk test speed ≤ 0.8; $U = 726.5$, $P = 0.012$) scored significantly lower on the SIPSO-C questionnaire. No significant differences in SIPSO-C scores were found amongst the different sex ($U = 861.5$, $P = 0.361$), hemiplegic side ($U = 957.5$, $p = 0.489$) and age groups (< 65 vs ≥ 65) ($U = 878$, $P = 0.765$) (Table 5).

Discussion

This is the first study to translate and culturally adapt the Chinese (Cantonese) version of the SIPSO questionnaire. The satisfactory internal consistency and excellent test-retest reliability of SIPSO-C had been demonstrated. Subgroup comparison based on Geriatric Depression Scale score and walking speed indicated that stroke survivors at high risk of minor depression and with limited community ambulation ability scored significantly lower on the SIPSO-C questionnaire. The study's results suggest that the SIPSO-C questionnaire is a reliable instrument for measuring the level of community integration in Cantonese-speaking community-dwelling stroke survivors.

The Cronbach α values for the SIPSO-C questionnaire and sub-scales fell within the acceptable range of 0.75 to 0.90.(33) None exceeded 0.9, indicating that none of the questionnaire items was likely to be redundant. The excellent test-retest reliability demonstrated by the SIPSO-C questionnaire and its subscales indicated that the questionnaire is a reliable instrument for recording stroke survivors' level of community integration throughout the rehabilitation process. Having the same raters conduct the assessment on two occasions within a week rendered the chances of a real change in condition very low.

The strength of the agreement amongst the item scores ranged from moderate to high (kappa = 0.47-0.78) for all items except item 8 (kappa = 0.38). Item 8 (How satisfied are you with the level of interests and activities you share with your friends/associates?) may be considered less concrete than the other items. Moreover, this item does not ask respondents to consider a specific time frame, and thus their responses may have been overly influenced by recent experiences. For example, a pleasurable social gathering within the one-week interval between assessments could have influenced their perception of the degree of satisfaction in question.

The median SIPSO-C questionnaire score in the present study (28 ± 10) was higher than those (19.8 to 26) reported in previous studies using SIPSO.(8, 9, 16, 18, 20) Lord et al.(18) reported a mean SIPSO questionnaire score of 21.0-21.5, whereas McKenna et al.(16) reported a mean score of 19.82-23.69. These two studies investigated the efficacy of novel community rehabilitation services for stroke survivors in the sub-acute phase, and their results indicate that stroke survivors who are newly returned to the community exhibit lower levels of community integration. There are several explanations for the discrepancies in these findings. First, physical capacity is generally poorer within the first three months post-stroke for stroke survivors with moderate to severe stroke.(34)Second, compensatory strategies for and confidence in independent living in the community may take time to develop.

Two studies with larger sample sizes (261(8) and 315(9) chronic stroke survivors) reported a median SIPSO questionnaire score of 26. Both of those studies distributed the questionnaire to stroke survivors in accordance with records provided by health service agencies. Thus, stroke survivors who were isolated and had poor community ambulation ability could be recruited. For example, 24% of the 315 stroke survivors examined by Kersten et al. were unable to walk independently in the 10-metre walk test.(9) In addition, some of those recruited by Trigg and Wood lived in residential care accommodation.(8) Sub-group analysis showed the participants receiving residential care service to score significantly lower on the SIPSO questionnaire (16.5 versus 27, $P = 0.03$) (8) relative to those not receiving such care. The stroke survivors in our study, in contrast, were active members of local self-help groups, and it thus not surprising that they would exhibit better community integration.

The physical integration subscale scores in the current study were higher than those for the social integration sub-scale. Teale et al.(12) suggested that a sub-scale score higher than or equal to 15 is indicative of a good level of integration. We found that distribution of scoring was negatively skewed in all items of the physical integration subscale. In addition, 60.9% had achieved a good level of physical integration. Of the five items in that subscale, four are partially influenced by respondents' mobility, namely, item 2 (difficulties moving at home), item 3 (satisfaction in performing daily activities), item 4 (difficulties in shopping) and item 5 (independence in outdoor ambulation). Personal factors such as good mobility may explain the satisfactory levels of physical integration in this study. A disability-friendly community can also facilitate community integration in stroke survivors. For example, metro stations in Hong Kong are all equipped with lifts, allowing stroke survivors to move from the railway platform to street level with little difficulty.

In contrast to the generally positive physical integration results, only 22.8% of the stroke survivors in this study reported a good level of social integration (social integration subscale score > 15), and the median score of item 9 (How often do you visit friends/others?) was 1 only. Most of the participants said that they were usually visited by friends or relatives, rather than vice versa, which may explain the low scores for this item.

With regard to between-group differences, stroke survivors at high risk of minor depression (Geriatric Depression Scale >10) were found to score significantly lower on the SIPSO-C questionnaire. Several cross-sectional studies have also reported depression levels to be significantly associated with or able to predict the level of community integration in stroke survivors.(35-37) For example, Geriatric Depression Scale score was reported to be a predictor of London Handicap Scale, in 188 chronic stroke survivors ($\beta = -0.27$, $P < 0.001$).(35) The Hamilton Depression Scale score was also shown to be significantly correlated with Reintegration to Normal Living Index score ($r = -0.373$, $P = 0.006$) and to be one of its independent predictors ($\beta = -0.255$, $P = 0.008$) in 90 community-dwelling chronic stroke survivors.(36) Finally, a study of 63 community-dwelling chronic stroke survivors showed Geriatric Depression Scale score to be an independent predictor of Reintegration to Normal Living Index score ($\beta = -0.404$, $P \leq 0.001$).(37)

Stroke survivors who walked slower than $0.8ms^{-1}$ were also found to were found to score significantly lower on the SIPSO-C questionnaire. The selection of the cut-off speed of $0.8ms^{-1}$ was based on Perry et.al. study (28) which showed that the stroke survivors with an average walking speed above $0.8ms^{-1}$ were predicted to be independent community ambulators. Only a few studies had reported the influence of walking capacity on the level of community integration in stroke survivors. A previous study had reported that walking endurance measured with distance covered by the 6-minute walk test predicted the level of community integration measured with Return to Normal Living Index.(38) However, neither the strength of association nor the R^2 value of the model was reported.(38) Results of the current study revealed that comfortable walking speed has an influence on the level of community integration in community-dwelling stroke survivors. The high predictive power of walking speed in community ambulation ability might explain the result.

No significant differences in SIPSO-C scores were found amongst the stroke survivors in the different sex, hemiplegic side and age groups. Amongst the 315 chronic stroke survivors involved in Trigg and Wood's study,(8) no significant differences in

SIPSO questionnaire or subscale scores were found in the different sex and age groups (< 65 or 65-74) (*P* > 0.05). Similarly, Kersten et al. also reported no difference between the SIPSO questionnaire scores of men and women amongst 372 chronic stroke survivors (*P* = 0.29).

The results of this study should be considered in light of several limitations. First, the participants were recruited from self-help groups for stroke survivors. The sample was thus self-selecting and likely to have a higher level of community integration. It is recommended that relatively isolated stroke survivors be recruited in future studies using the SIPSO-C questionnaire. Second, the convergent and predictive validity of SIPSO-C could not be established. Finally, the test-retest reliability of SIPSO-C was evaluated with only a one-week interval between the assessments. This relatively short interval minimised the chances of a real change in the participating stroke survivors' status, but it is possible that the memory effect influenced the results.

Clinical Messages

- The Chinese (Cantonese) version of SIPSO is a reliable instrument to measure the level of community integration in stroke survivors.
- Stroke survivors who scored more than 10 on the Geriatric Depression Scale and walked slower than 0.8 ms^{-1} were found to have a lower level of community integration.

Conflict of interest

The Authors declare that there is no conflict of interest.

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Table 1: Demographic characteristics of stroke survivors (n = 92)

Characteristics	Mean ± SD (range)
Age (yr)	62.3 ± 5.6 (55-79)
Post-stroke duration (yr)	6.6 ± 5.0 (1-24)
BMI (kg/m^2)	24.2 ± 3.0 (18.0-32.4)
Comfortable walking speed (ms^{-1})	0.76 ± 0.32 (0.09-1.89)
	Median ± IQR (range)
SIPSO total score	28 ± 10 (10-40)
Physical functioning subscale score	17 ± 6 (3-20)
Social functioning subscale score	12 ± 7 (2-20)
Geriatric Depression Scale score	8 ± 8 (0-28)
	Number (%)
Sex	
Male/Female	59 (64.1)/33 (35.9)
Hemiplegic side	
Left/Right	41 (44.6)/51 (55.4)
Type of stroke	
Ischaemic	54 (58.7)
Haemorrhagic	35 (38.0)
Mixed/Unknown	3 (3.3)
Use of walking aid outdoors	
Unaided	36 (39.1)
Stick/quadripod	53 (57.6)
Wheelchair	3 (3.3)

Table 2: Central tendency, variation, skewness and floor and ceiling effects of SIPSO-C and its items score (n=92).

Item	Mean (SD)	Median (IQR)	Skewness	Number (%) of minimum score	Number (%) of maximum score
1	3.0 (0.9)	3 (2)	-0.76	2 (2.2)	36 (39.1)
2	3.5 (0.7)	4 (1)	-1.26	1 (1.1)	55 (59.8)
3	3.0 (0.9)	3 (2)	-0.59	0 (0.0)	29 (31.5)
4	3.0 (1.1)	3 (2)	-0.92	2 (2.2)	34 (37.0)
5	3.4 (1.0)	4 (1)	-1.66	1 (1.1)	47 (51.1)
6	2.8 (1.1)	3 (2)	-0.59	1 (1.1)	21 (22.8)
7	2.2 (1.1)	2 (2)	0.13	6 (6.5)	12 (13.0)
8	2.6 (0.9)	3 (1)	-0.06	0 (0.0)	13 (14.1)
9	1.7 (1.3)	1 (2)	0.53	18 (19.6)	10 (10.9)
10	3.1 (0.8)	3 (1)	-1.31	2 (2.2)	24 (26.1)
SIPSO-C total score	28.3 (6.6)	28 (10)	-0.30	0 (0)	4 (4.4)

Table 3: Internal consistency of SIPSO-C (n = 92)

	Item	Corrected item-total correlation	Cronbach's alpha if item deleted
1	How much difficulty do you have in dressing yourself fully?	0.45	0.82
2	How much difficulty do you have moving around all areas of the home?	0.45	0.82
3	How satisfied are you with your overall ability to perform daily activities in and around the home?	0.53	0.82
4	How much difficulty do you have shopping for and carrying a few items (1 bag of shopping or less) when at the shops?	0.50	0.82
5	How independent are you in your ability to move around your local neighbourhood?	0.50	0.82
6	How often do you feel bored in your free time at home?	0.64	0.80
7	How would you describe the amount of communication between you and your friends/associates?	0.63	0.81
8	How satisfied are you with the level of interests and activities you share with your friends/associates?	0.64	0.83
9	How often do you visit friends/others?	0.46	0.83
10	How do you feel about your appearance when out in public?	0.46	0.82

Scale	Cronbach's alpha
SIPSO-C	0.83
Physical integration subscale	0.76
Social integration subscale	0.80

Table 4: Test-retest reliability of SIPSO-C (n = 25)

Item	Kappa statistic	*P*-value	
1	0.63	< 0.001	
2	0.78	< 0.001	
3	0.71	< 0.001	
4	0.47	< 0.001	
5	0.53	< 0.001	
6	0.53	< 0.001	
7	0.57	< 0.001	
8	0.38	< 0.001	
9	0.60	< 0.001	
10	0.68	< 0.001	
	ICC (3,1)	95% CI	
		Upper	Lower
Total score	0.866	0.720	0.939
Physical functioning subscale	0.850	0.689	0.931
Social functioning subscale	0.898	0.782	0.954

Note: ICC: intra-class correlation coefficient

Table 5: Results of Mann-Whitney U test: Comparison of SIPSO-C scores of subjects with different characteristics (n=92)

Characteristics		Number of stroke survivors	Median (IQR)	Mann-Whitney U	*Z*	*P* value
Sex	Male	49	28 (10)	861.5	-0.913	0.361
	Female	33	30 (10)			
Hemiplegic side	Left	41	29 (11)	957.5	-0.693	0.489
	Right	51	28 (9)			
Age	< 65	63	28 (10)	878	-0.299	0.765
	≥ 65	29	29 (11)			
Geriatric Depression Scale > 10	Yes	38	24 (9)	555.0	-3.742	> 0.001
	No	54	31 (9)			
Comfortable walking speed ≤ 0.8 ms^{-1}	Yes	52	25 (12)	726.5	-2.379	0.017
	No	40	30 (10)			

Appendix 4.4 Chinese version of the Subjective Index of Physical and Social Outcome.

體能與社交結果的主觀指數 **Subjective Index of Physical and Social Outcome (SIPSO; Trigg and Wood, 2007)**

Please answer all questions (Circle **One Number** for each question)
請回答以下的問題 (在每題問題,圈出**一個**合適的數字)

在中風後，你覺得自行穿衣、打扮自己有多困難？
1. Since your stroke, how much difficulty do you have dressing yourself fully?

完全沒有困難No difficulty at all	4
輕微困難Slight difficulty	3
一些困難Some difficulty	2
很多困難A lot of difficulty	1
完全不能I cannot dress myself fully	0

在中風後, 你覺得在家中的*全部*地方走動有多困難？
2. Since your stroke, how much difficulty do you have moving around *all* areas of the home?

完全沒有困難No difficulty at all	4
輕微困難Slight difficulty	3
一些困難Some difficulty	2
很多困難A lot of difficulty	1
我不能在家中的全部地方走動I cannot move around all areas of the home.	0

在中風後, 整體上,你滿意自己*在家中及家附近*之日常活動的能力嗎？
3. Since your stroke, how satisfied are you with your overall ability to perform daily activities *in and around the home*?

完全滿意Completely satisfied	4
大多感到滿意Mostly satisfied	3
還算滿意Fairly satisfied	2
不是很滿意Not very satisfied	1
完全不滿意Completely dissatisfied	0

在中風後, 你覺得去購物和拿*少量東西*(如一袋購物袋或更少)有多困難？

4. Since your stroke, how much difficulty do you have shopping for and carrying *a few items* (1 bag of shopping or less) when at the shops?

完全沒有困難No difficulty at all	4
輕微困難Slight difficulty	3
一些困難Some difficulty	2
很多困難A lot of difficulty	1
不能購物或 拿少量東西I cannot shop for and carry a few items	0

在中風後, 你覺得你可以獨立地在你的社區走動嗎?
5. Since your stroke, how independent are you in your ability to *move around your local neighborhood*?

我能夠完全獨立I am completely independent	4
我更喜歡有其他人與我一起I prefer to have someone else with me	3
我需要有人偶爾協助I need occasional assistance from someone	2
我需要有人經常協助I need assistance much of the time	1
我完全需要他人協助 I am completely dependent on others	0

在中風後, 你會否覺得在你空閒時間待在家中會無聊嗎？
6. Since your stroke, how often do you feel bored with your free time at home?

在我空閒的時間，我從來不覺得無聊 I am never bored with my free time	4
有少許時間我會覺得無聊 A little of my free time	3
有些時間我會覺得無聊 Some of my free time	2
在我大部分空閒的時間，我也覺得無聊 Most of my free time	1
在我全部空閒的時間，我都覺得無聊 All of my free time	0

在中風後, 你會如何描述你和你的朋友/同事之間的通信量？
7. Since your stroke, how would you describe the amount of communication between you and your friends/associates?

有很多的聯絡A great deal	4
有相當多的聯絡Quite a lot	3
有一些的聯絡Some	2
有少許的聯絡A little bit	1
沒有任何聯絡None	0

在中風後, 你與你與你的朋友/同事分享的興趣和活動的滿意程度如何？

8. Since your stroke, how satisfied are you with the level of interests and activities you share with your friends/associates?

完全滿意Completely satisfied 4
大多感到滿意Mostly satisfied 3
還算滿意Fairly satisfied 2
不是很滿意Not very satisfied 1
完全不滿意 Completely dissatisfied 0

在中風後, *你有多經常拜訪*你的朋友/其他人？
9. Since your stroke, how often do *you visit* friends/others?

經常Most days 4
最少一星期一次At least once a week 3
最少二星期一次At least once a fortnight 2
不多於一個月一次Once a month or less 1
完全沒有Never 0

在中風後，在公共環境裡，你對你自己的外表感覺如何？
10. Since your stroke, how do you feel about your appearance when out in public?

完全滿意 Perfectly happy 4
少許 不自然 Slightly self-conscious 3
相當不自然 Fairly self-conscious 2
非常不自然 Very self-conscious 1
我嘗試避免外出 I try to avoid going out in public 0

謝謝您完成這問題！ Thank you for completing this questionnaire.

Appendix 4.3 The consent form of cross-sectional studies

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project entitled:

Fear of falling: Its prevalence and correlation with stroke-specific impairments, motor functions, quality of life and community integration in patients with stroke in Hong Kong.

Investigator: Dr. Shamay Ng, Dr. Gabriel Ng, Mr. Tai-Wa Liu, Mr. Wai Hang Kwong, Ms Clara Shiu

Purpose: (1) investigate the prevalence of fear of falling and fear-related activity avoidance; (2) To investigate the relationships between fear of falling and stroke-specific impairments, motor functions and community integration in patients with stroke living in Hong Kong.

Methods:

All eligible subjects will be assessed on incidence of falls, muscle strength, lower limb coordination, balance ability, functional mobility, subjective balance confidence, fear-related activity avoidance, ability of independent living, level of community integration and health-related quality of life. Measurements include filling up falls calendar, questionnaires on subjective balance confidence, fear-related avoidance of activities, level of community integration, ability of independent living and health-related quality of life. Muscle strength, balance ability, lower limb coordination, and functional mobility are also assessed. The assessment will be conducted on two separate days, and each assessment will last for 2 hours, at least 15 minutes of resting period will be given in between each section to prevent fatigue.

Potential Risks and Benefits:

The major benefit from participating in this study is that you may have the opportunity to know your own level of balance confidence, fear-related avoidance of activities, stroke specific impairments, functional mobility, ability of independent living and community integration. The results may be beneficial for assessing the prevalence and correlates of fear of falling and fear-related activity avoidance in patients with chronic stroke.

The testing procedures have been well proved to be safe and used with negligible side effects, both clinically and experimentally. A few subjects may feel some exhaustion during assessment and therefore rest will be allowed between assessment procedures.

Informed Consent

I, ____, understand the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name will not appear on any publications resulted from this study.

I can contact the chief investigator, Dr. Shamay Ng, at telephone 2766-4889 for any questions regarding this study. If I have complaints related to the investigators, I can contact Ms. Man, secretary of Departmental Research Committee, at 2766-4394. I know I will be given a signed copy of this consent form.

Signature (subject): ______________________________ Date: ______________

Signature (Witness): ______________________________ Date: ______________

香港理工大學康復治療科學系研究同意書

項目名稱: 跌倒恐懼: 在香港慢性中風病人中的盛行率及其與中風相關的缺損、獨立生活能力、社區整合程度之間的關聯研究。

科研人員: 伍尚美博士, 吳賢發博士,廖泰華先生, 鄺偉恒先生, 蕭巧兒小姐

研究目的及內容:

1, 研究香港慢性中風病人跌倒恐懼及迴避活動的盛行率

2, 研究跌倒恐懼與中風相關的缺損、獨立生活能力、社區整合程度之間的關聯研究。

研究方法: 所有合適的研究參加者將會接受有關跌倒恐懼、因怕跌而避免活動程度、跌倒發生率、肌肉力量、下肢協調能力、平衡能力、活動功能、獨立生活能力、社區整合及健康有關之生活質素之檢查。檢查內容包括：填寫跌倒記錄月曆、跌倒恐懼之問卷、因怕跌而避免活動之問卷、健康有關之生活質素問卷、獨立生活能力之問卷、社區整合之問卷，並會一併評估平衡能力、活動能力及活動功能。整個檢查將分開兩天進行，每次需時約 2 小時，為避免過份疲勞, 每節檢查內會有最少 15 分鐘的休息時間。

潛在風險及得益:

參與此研究的好處是：參加者可以了解自己的跌倒恐懼程度、因有關怕跌而避免活動的程度、中風相關的缺損、活動功能、獨立生活能力的程度、社區整合的程度及健康有關之生活質素的程度，此外亦能提供重要數據幫助評估中風病人跌倒恐懼及有關怕跌而避免活動的程度。

整個檢查程序都經過驗證，證明過程十分安全，不論在臨床上或實驗上，其副作用都可以忽略，唯測試期間小部份參與人士可能會感到少許疲倦，參加者可按需要於測試期間作中段休息。

同意書:

本人 ________________________________ 已瞭解此次研究的具體情況。本人願意參加此次研究。本人有權在任何時候、無任何原因的情況下放棄參與此次研究，而此舉不會導致本人受到任何懲罰或不公平的對待。本人明白參加此研

究的潛在風險，以及本人的資料將不會泄露給與此研究無關的人員，我的名字或相片也不會出現在任何的出版物上。

本人可致電 2766 4889 與此研究的負責人伍尚美博士聯絡。若本人對研究人員有任何投訴，可聯絡文小姐 (部門科研委員會秘書)，電話：2766 4394。本人亦明白，參與此研究需要本人簽署一分同意書。

簽名 (參加者): ____ 日期: ____________

____

簽署 (見證人): ____ 日期: ____________

____

Appendix 4.4 The consent form of the randomised control trial.

The Hong Kong Polytechnic University
Department of Rehabilitation Sciences
Research Project Informed Consent Form

Project entitled: Efficacy of bilateral cutaneous electrical stimulation with task-orientated training in improving lower limb functions in subjects with chronic stroke: A randomized, controlled pilot trial

Investigator: Dr. Shamay S. M. Ng (RS)

Purpose:

To investigate whether bilateral cutaneous electrical stimulation over both paretic and non-paretic leg (bilateral ES) will be more superior to cutaneous electrical stimulation over affected leg (ipsilateral ES), when combined with task-orientated training (TOT) respectively.

Methods:

All eligible subjects will be randomly assigned into 2 groups: (1) bilateral cutaneous electrical stimulation over both paretic and non-paretic leg (bilateral ES) and (2) unilateral cutaneous electrical stimulation over affected leg (unilateral ES) combined with task-orientated training (TOT) respectively for 10 weeks, 2 times a week (total 20 treatment sessions). Subjects will be assessed on improvement of the muscle strength of bilateral lower limb muscle, step test scores, lower extremity motor coordination test (LEMCOT), walking speed and timed 'Up & Go' (TUG) scores.

Potential Risks and Benefits:

The major benefit from participating in this study is that subjects may have the opportunity to know their own level of muscle strength, lower limb functions and functional mobility. The results may also be beneficial for planning an intensive rehabilitation program for improving balance performance and functional mobility in elderly with stroke. The electrical stimulation and testing procedures have been well proved to be safe and used with negligible side effects, both clinically and experimentally. A few subjects may feel some exhaustion during assessment and therefore rest will be allowed between assessment procedures.

Informed Consent:

I, ____________________________, understand the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name will not appear on any publications resulted from this study.

I can contact the chief investigator, Dr. Shamay Ng at telephone 2766-4889 for any questions about this study. If I have complaints related to the investigators, I can contact Ms. Man, secretary of Departmental Research Committee, at 2766-4393. I know I will be given a signed copy of this consent form.

Signature (participant): _______________________ Date: ___________________

Signature (Witness): _________________________ Date: ___________________

香港理工大學康復治療科學系參加研究同意書

科研題目: 任務導向訓練配合兩邊經皮神經電刺激對改善慢性中風病人下肢功能之功效：隨機對照試驗。

科研人員: 伍尚美博士

科研目的及內容: 研究兩邊電刺激配合任務導向訓練是否比在患肢單邊電刺激配合任務導向訓練或安慰劑刺激配合任務導向訓練更有效。

研究方法: 所有合資格參加者會被隨機分為兩組，第一組：兩邊電刺激配合任務導向訓練，第二組：患肢單邊電刺激配合任務導向訓練，接受為期十星期，每星期兩次（共二十次治療）。參加者將會接受兩邊下肢肌肉力量測試、踏級測試、下肢活動協調測試(LEMCOT)、步行速度以及計時起身行走測試以評估進展。

潛在危險性及得益: 若參與此研究，參加者可以了解自己的下肢肌力、下肢功能及活動能力的表現，此外亦能提供重要數據幫助設計給中風長者改善平衡表現和活動能力的康復治療。電刺激治療和整個檢查程序都經過驗證，證明過程十分安全，不論在臨床上或實驗上，其副作用都可以忽略，唯期間小部份參與人士可能會感到少許疲倦，參加者可按需要於測試期間作中段休息。

同意書:

本人______________已瞭解此次研究的具體情況。本人願意參加此次研究, 本人有權在任何時候、無任何原因的情況下放棄參與此次研究, 而此舉不會導致本人受到任何懲罰或不公平的對待。本人明白參加此研究課題的潛在危險性以及本人的資料將不會洩露給與此研究無關的人員，我的名字或相片也不會出現在任何的出版物上。

本人可以用電話 2766 4889 來聯繫此次研究課題的負責人，伍尚美博士。若本人對研究人員有任何投訴，可以聯繫文小姐（部門科研委員會秘書），電話：2766 4393。本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參與者）：________________________ 日期：______________________

簽名（證人）：__________________________ 日期：______________________

Appendix 5.1 Chapter 5 published PLOS One(final manuscript)

A structural equation model of the relationship between muscle strength, balance performance, walking endurance and community integration in stroke survivors

Introduction

Stroke is a major cause of motor impairment and disability worldwide (Walsh et al., 2015b). The residual physical and cognitive deficiencies after stroke can reduce both the quality and the quantity of the survivor's social participation and interaction (Santus et al., 1990; Trigg et al., 1999). Impaired physical and cognitive functions, changes in social roles, the inability to work and poor adaptability to the physical environment can hinder the process of community integration for stroke survivors, which in turn can lead to social isolation (Mukherjee et al., 2006). One study reported that only 11% of community-dwelling stroke survivors were completely satisfied with their level of community integration (Pang et al., 2007).

Promoting successful community integration after a stroke is one of the ultimate goals of rehabilitation. Identification of predictors for community integration can help researchers and clinicians develop new treatment strategies and enhance the process of community integration after hospital discharge. Obembe et al. (Obembe et al., 2013) reported that age, the geriatric depression scale (GDS) score and the motor assessment scale score were significant predictors of stoke survivors' scores on the return to normal living index (RNLI; $R^2 = 41.0\%$). Chau et al. (Chau et al., 2009) showed that GDS score ($\beta = -0.41$), gender ($\beta = 0.11$), age ($\beta = -0.13$) and living in a residential care institute ($\beta = -0.11$) significantly predicted the London handicap scale (LHS) score ($R^2 = 71.0\%$). Physical functioning, such as balance performance measured with the Berg Balance Scale (BBS), was an independent predictor of the RNLI score ($\beta = 0.36$) (Pang et al., 2007). Although walking endurance measured with the 6-minute walk test (6MWT) predicted the level of community integration as measured by the RNLI, neither the strength of the association nor the R^2 value of the model was reported (Mayo et al., 1999).

Muscle weakness is a common physical impairment following a stroke (Bohannon, 2007). The concentric paretic knee extension torque measured with an isokinetic dynamometer has been shown to be significantly correlated with self-paced sit-to-stand duration ($r = -0.72$) (Lomaglio & Eng, 2005), comfortable walking speed ($r = 0.61$) (Flansbjer et al., 2006), maximum walking speed ($r = 0.65$ to 0.85) (Flansbjer et al., 2006; Suzuki et al., 1990) and speed of walking up stairs ($r = -0.58$) (Flansbjer et al., 2006). Isometric paretic ankle dorsiflexion and plantarflexion strength were significantly correlated with the comfortable walking speed ($r = 0.77$ and 0.83, respectively) and maximum walking distance ($r = 0.68$ and 0.76, respectively), which measures the distance the subject is able to walk before stopping due to fatigue (Bohannon, 1989). Moreover, paretic ankle dorsiflexion strength was found to be an independent predictor of the timed up and go test completion time ($R^2 = 27.5\%$) and the 6MWT distance ($R^2 =$ 48.4. The strength of the paretic lower limb muscles was a strong predictor of functional performance (Ng & Hui-Chan, 2012; Ng & Hui-Chan, 2013), including walking endurance (Mayo et al., 1999) and balance (Pang et al., 2007), which were identified as independent predictors of the level of community integration. Thus, it is plausible that muscle strength has a strong influence on the level of community integration, as mediated by the level of functional performance. However, no studies have evaluated the relationship between paretic lower-limb muscle strength and level of community integration in stroke survivors.

In accordance with the International Classification of Functioning, Disability and Health model (World Health Organization, 2001), we hypothesised that paretic lower-limb muscle strength would have a direct association with balance performance and walking endurance and thus be indirectly associated with the level of community integration in stroke survivors. Therefore, the aim of this study was to determine (1) the direct and indirect associations of the muscle strength of the paretic lower limb with the level of community integration, and (2) the direct associations of balance performance and walking endurance with the level of community integration in community-dwelling stroke survivors.

Methods

Procedure

Ethical approval has been obtained from The Hong Kong Polytechnic University. The study was conducted in accordance with the Declaration of Helsinki ethical principles for human experimentation, and written consent was obtained from all participants before the assessment. All of the assessments were conducted by the same physical therapist in one session.

Participants

The subjects were recruited via posters at local self-help group centres for stroke survivors. Subjects were included if they (1) were between 50 and 85 years of age; (2) had a stroke at least 1 year earlier; (3) received a diagnosis of ischaemic brain injury or intracerebral haemorrhage by magnetic resonance imaging or computed tomography; (4) were able to walk independently for 10 m with or without a walking aid; (5) were able to follow instructions and give informed consent; and (6) scored greater than 6 of 10 on the abbreviated mental test (AMT), which indicates normal cognitive function. Subjects were excluded if they (1) had any medical, cardiovascular or orthopaedic conditions that would hinder assessment or (2) were involved in drug studies or other clinical trials.

Outcome measures

Level of community integration

The Subjective Index of Physical and Social Outcome (SIPSO) is a 10-item questionnaire specifically designed to assess the level of community integration in stroke survivors and their satisfaction with their functioning status (Trigg et al., 1999; Trigg & Wood, 2000). Each item is rated on a five-point ordinal scale (0 to 4). SIPSO has demonstrated excellent test–retest reliability with an intraclass correlation coefficient (ICC) of 0.87 to 0.91 (Kwong et al.; Trigg & Wood, 2003). The total SIPSO score has been shown to be significantly correlated with the Barthel index, Frenchay activities index, Wakefield depression inventory and Nottingham health profile in chronic stroke survivors (Spearman’s ρ: 0.67 to 0.80) (Trigg & Wood, 2003). The Chinese version of SIPSO was used in this study (Kwong et al.).

Isometric ankle muscle strength

The maximum isometric dorsiflexion and plantarflexion strength of the paretic ankle were measured with a Nicholas handheld dynamometer (Lafayette Instrument Company, Lafayette, IN) in a supine lying position. Good to excellent reliability (ICC range, 0.84 to 0.99) has been reported when using the handheld dynamometer to assess lower-limb muscle strength in chronic stroke survivors (Bohannon & Andrews, 1987). At least 1 minute of rest was given between each set of isometric contractions of the ankle muscles to avoid muscle fatigue. The handheld dynamometer was placed on the dorsal and plantar surfaces across the first to fifth metatarsal-phalangeal joints with the ankle at 0 degrees of dorsiflexion.

Isokinetic knee muscle strength

The peak concentric isokinetic torque of the paretic knee extensor and flexor were measured at 90°/s in the sitting position with an isokinetic machine (Cybex 6000 dynamometer, Cybex, Henley, USA). An angular velocity of 90°/s was selected because good test–retest reliability was reported when measuring the peak isokinetic torque of the knee extensor (ICC, 0.81) in chronic stroke survivors using an angular velocity of 90°/s (Hsu et al., 2002), but not with a lower angular velocity of 30°/s (ICC, 0.42). Another study reported that most stroke survivors were able to achieve an angular velocity of 90°/s and that only 1.3% of the trials were discarded due to a mismatch between the actual movement speed and the criterion speed. In contrast, 5.2% of the trials in which an angular velocity of 120°/s was used were discarded due to mismatches (Clark et al., 2006).

Balance performance

The Berg Balance Scale (BBS) was used to measure functional balance performance. The scale consists of 14 items, each rating a participant’s ability to maintain stability while completing a specified functional task on a 5-point (0 to 4) scale (Berg et al., 1992). The BBS has excellent test–retest reliability (ICC, 0.95 to 0.98) (Hiengkaew et al., 2012) and inter-rater reliability (ICC, 0.95) (Mao et al., 2002) in assessing stroke survivors. Participants could wear an ankle/foot orthosis but were not allowed to use a walking aid in this assessment.

Walking endurance

The distance covered in a 6MWT (Eng et al., 2004) was used to assess walking endurance. The participants were instructed to walk as far as possible within 6 minutes. Excellent test–retest reliability for the walking distance covered (ICC, 0.99) was demonstrated in a previous study of chronic stroke survivors (Eng et al., 2004). The assessment protocols followed those recommended by the American Thoracic Society (American Thoracic Society, 2002), except that the walkway length was 15 m due to the space limitations of our laboratory. Participants were instructed to walk back and forth on the 15 m walkway, turning around as they reached either end of the walkway. The participants were allowed to wear ankle/foot orthosis and use a walking aid as necessary.

Statistical analysis

Statistical analyses were conducted with SPSS (version 22.0. Armonk, NY: IBM Corp.) in conjunction with AMOS (version 23.0, Chicago: IBM SPSS). A *p* value of 0.05 or less was considered to indicate statistical significance. The participants' demographic characteristics are summarised with descriptive statistics. The level of depression symptoms was quantified using the geriatric depression scale (GDS) (Chan, 1996).

The statistical analyses of the relationship between the SIPSO and the functional outcomes were conducted in two stages. In the first stage, partial correlation analysis was used to evaluate the strength of associations between the SIPSO score and other physical outcomes after controlling for the effects of age, gender and the GDS score. The variables that demonstrated a significant correlation with the SIPSO score were further analysed with multiple linear regression with a stepwise approach. To avoid the inflation of type 1 errors, a Bonferroni correction was applied in the partial correlation analyses. Regression analysis was used to identify the set of variables that could independently explain part of the variance of the SIPSO score. Similarly, paretic lower-limb muscle strength demonstrated a significant partial correlation with functional performance and was further analysed by multiple linear regression, with functional performance as the dependent variable. The variance inflation factor was used to assess the degree of multicollinearity in the regression models. A variance inflation factor greater than 10 indicated that a particular predictor demonstrated a strong linear relationship with other predictors in the model (Myers, 1990).

The second stage of the statistical analysis involved the development of a hypothesised model based on the results of the multiple regression analysis. We hypothesised that muscle strength would directly influence functional performance and that functional performance would directly influence the SIPSO scores. The variables that were found to be significant predictors in the multiple regression analysis were selected to construct the model. Structural equation modelling (SEM) is a multivariate statistical analysis technique that estimates the strength of the direct and indirect relationships between sets of variables. We used SEM to estimate the strength and significance of the hypothesised causal connections between the paretic lower-limb muscle strength, balance performance, walking endurance and SIPSO score. The SIPSO score and outcome measures at the functional level were considered to be endogenous variables. Paretic lower-limb muscle strength was considered to be an exogenous variable.

A path diagram was used to represent the interconnections of each variable in the model. In the path diagram, a single-headed arrow indicates a direct association, with the arrow head pointing to the dependent variable and its tail from the independent variable. A curved arrow indicates a correlation between two variables. An indirect association signifies that an independent variable could influence the dependent variable, mediated by another variable.

The model fit was assessed with the comparative fit index (CFI) and the standardised root mean square residual (SRMR) (Hu & Bentler, 1999). If either index showed a poor fit of the data to our hypothesised model, we would revise the entire model according to the recommendations given by the modification index, which estimates the effect on the chi-square statistic of adding an additional path to the model (Whittaker, 2012). A modification index value larger than 3.84 for a specific path indicates that adding the path to the model could significantly improve the model fit (Whittaker, 2012). The minimal sample size for the SEM was suggested to be at least 15 cases per predictor in the hypothesised model. Thus, our sample of 105 stroke survivors was sufficient to conduct SEM.

Results

One-hundred and five community-dwelling stroke survivors (60% male) were recruited for this study. The mean time since stroke was 6.2 years, and the subjects' mean age was 61.0 years. The majority were living with family or friends (87.6%), and only eight (7.6%) were still in the workforce (Table 1).

Table 1. Demographic characteristics of the participants and results of the physical assessments (n = 105).

Variable	Frequency (%)
Gender (male/female)	63 (60.0)/42 (40.0)
Side of hemiplegia (right/left)	57 (54.3)/48 (45.7)
Type of stroke (ischaemic/haemorrhagic/mixed)	59 (56.1)/43 (41.0)/3 (2.9)
Living with care giver (yes/no)	92 (87.6)/13 (12.4)
Working (yes/no)	8 (7.6)/97 (92.4)
Education level (primary or below/secondary/college or above)	31 (29.5)/60 (57.1)/14 (13.3)
Using walking aid (yes/no)	69 (65.8)/36 (34.2)
Using ankle foot orthosis (yes/no)	6 (5.7)/99 (94.3)
	Mean ± SD (range)
Age (y)	61.0 ± 6.9 (50.0 to 79.0)
Time since stroke (y)	6.2 ± 4.9 (1.0 to 24.0)
Paretic ankle dorsiflexion strength (kg)	8.5 ± 5.0 (0.6 to 23.7)
Paretic ankle plantarflexion strength (kg)	13.4 ± 5.6 (2.3 to 28.4)
Paretic knee extension torque (Nm)	23.7 ± 14.2 (4.0 to 85.0)
Paretic knee flexion torque (Nm)	7.53 ± 6.2 (0.0 to 26.0)

6MWT (m)	219.7 ± 84.4 (35.0 to 452.8)
	Median, IQR (range)
AMT	10, 1 (7 to 10)
BBS	48, 7 (17 to 56)
GDS	9, 8 (0 to 28)
SIPSO	28, 10 (10 to 40)

6MWT: 6-minute walk test; AMT: Abbreviated Mental Test; BBS: Berg Balance Scale; GDS: Geriatric Depression Score; IQR: interquartile range; SD: standard deviation; SIPSO: Subject Index of Physical and Social Outcome

After controlling for the effects of age, gender and GDS score, isometric paretic ankle dorsiflexion strength, isokinetic paretic knee flexion torque, BBS scores and the distance covered in the 6MWT were found to demonstrate significant correlations with the SIPSO score. In addition, isometric paretic ankle dorsiflexion strength, isokinetic paretic knee extension torque and isokinetic paretic knee flexion torque showed significant correlations with BBS scores and distance covered in the 6MWT, but isometric paretic ankle plantarflexion strength did not show such a correlation (Table 2).

Table 2. Partial correlation coefficients (controlling for GDS score, gender and age) between SIPSO score, functional performance and muscle strength (n = 105).

Variable		Correlation coefficient						
		1	2	3	4	5	6	7
8.	SIPSO	1						
9.	Paretic dorsiflexion strength	0.447**	1					
10.	Paretic plantarflexion strength	0.218	0.234	1				
11.	Paretic knee extension torque	0.235	0.249	0.005	1			
12.	Paretic knee flexion torque	0.287	0.310*	0.054	0.598**	1		
13.	6-minute walk test	0.545**	0.413**	0.092	0.401*	0.458**	1	
14.	Berg Balance Scale	0.429**	0.402**	0.212	0.306*	0.249	0.464**	1

*p <0.05; **p <0.001

GDS: Geriatric Depression Score; SIPSO: Subjective Index of Physical and Social Outcome.

p value was adjusted with Bonferroni correction.

Multiple linear regression analyses showed that isometric ankle dorsiflexion strength, BBS score and distance covered in 6MWT were significant predictors of SIPSO score, with the whole model explaining 43.1% of the variance of the SIPSO score (Table 3). Isometric ankle dorsiflexion strength and isokinetic paretic knee flexion torque were significant predictors of the distance covered in the 6MWT (R^2 = 32.5%). Isometric ankle dorsiflexion strength and isokinetic paretic knee extension torque were significant predictors of the BBS score (R^2 = 25.0%). The variance inflation factors ranged from 1.07 to 1.55, indicating that some correlations exist between the predictors but that they may not be problematic.

Table 3. Hierarchical multiple regression analyses for the hypothesised model (n = 105).

Dependent variable	R^2	Independent variable	Standardised coefficient β	p
SIPSO score	0.431	DF strength	0.17	0.048*
		6MWT	0.41	<0.001**
		BBS	0.21	0.029*
6MWT	0.325	DF strength	0.30	0.001*

BBS	0.250	Knee F torque	0.39	<0.001**
		DF strength	0.40	<0.001**
		Knee Ext torque	0.21	0.018

6MWT: 6-meter walk test; BBS: Berg Balance Score; DF: dorsiflexion; Ext: extension; F: flexion; SIPSO: Subjective Index of Physical and Social Outcome.

**p* <0.05; ***p* <0.001

The hypothesised model was constructed based on the results of the hierarchical multiple regression analysis. The SEM supported the hypothesis that BBS score and the 6MWT distance would have a direct association with the SIPSO score. Isometric ankle dorsiflexion strength also had an indirect association with the SIPSO score, which was mediated by its influences on the BBS score and 6MWT distance.

Isokinetic paretic knee flexion torque had an indirect association with the SIPSO score mediated by the 6MWT distance. Isokinetic paretic knee extension torque had an indirect association with the SIPSO score mediated by the BBS score. The relationships between muscle strength, balance performance, walking endurance and level of community integration are illustrated in a path diagram (Fig 1). The regression coefficient shows that the 6MWT distance demonstrated the largest direct association with the SIPSO score ($\beta = 0.41$, $p < 0.001$), with every increase of one standard deviation in the 6MWT distance leading to an increase of 0.41 standard deviations in the SIPSO score. The results also show that the BBS score ($\beta = 0.21$, $p = 0.021$) and isometric dorsiflexion strength ($\beta = 0.18$, $p = 0.044$) had significant direct associations with the SIPSO score.

Initially, the fit indices indicated that the model was a poor fit to the observed data, with CFI and SRMR values of 0.918 and 0.076, respectively. A modification index value of 14.37 indicated that correlation of the residual terms of BBS and 6MWT could significantly improve the model fit. The model fit became satisfactory after the model modification, with CFI and SRMR values of 0.993 and 0.031, respectively.

Discussion

To the best of our knowledge, this study is the first to evaluate the relationship between paretic lower-limb muscle strength and the level of community integration in community-dwelling chronic stroke survivors using structural equation modelling. Community integration is the ability to live in a usual setting, interact with different people, such as friends and neighbours, and participate in daily activities (Trigg et al., 1999). A meta-synthesis of the results of 18 qualitative studies revealed that the primary effects of stroke, such as limited mobility, impaired hand functioning and impaired communication ability, remain the major barriers to community integration in stroke survivors (Walsh et al., 2015a). In this study, we found that isometric paretic ankle dorsiflexion strength and isokinetic paretic knee flexion torque indirectly influenced the SIPSO score, mediated by the BBS score and the 6MWT distance. Moreover, isometric paretic ankle dorsiflexion strength demonstrated a significant direct association with the SIPSO score.

In this study, knee muscle strength was measured with an isokinetic dynamometer. A previous study reported that isokinetic training of the knee extensor and flexor in 15 people with chronic stroke resulted in higher levels of perceived participation, as measured by the participation domain of the stroke impact scale, than in the no-treatment control group 5 months after training (Flansbjer et al., 2008). Those results suggest a causal relationship between stroke survivors' isokinetic knee muscle strength and their level of participation.

In this study, isokinetic peak torque was used to measure knee muscle strength and maximum isometric strength was used to measure ankle muscle strength because some of the participants demonstrated severe ankle plantar flexor spasticity, which made measurement of the isokinetic strength of the ankle muscles difficult due to the limited range of motion in the ankle. The maximum isometric ankle muscle strength was therefore measured instead of the isokinetic peak torque.

SIPSO questionnaire scores

The median SIPSO questionnaire score (28 ± 10) was higher than the scores of 23.3 to 26 reported in previous studies (Kersten et al., 2004; Kilbride et al., 2013; Trigg & Wood, 2003). Despite using similar inclusion criteria and demographic characteristics of stroke survivors, Kilbride et al. (Kilbride et al., 2013) reported a SIPSO questionnaire score of 23.3, which is much lower than the median score in our study. The small sample size of only 22 in that study raises a concern about whether the obtained SIPSO questionnaire score could truly reflect the population mean. Two studies with larger sample sizes (261 (Trigg & Wood, 2003) and 315 (Kersten et al., 2004) chronic stroke survivors) reported a median SIPSO questionnaire score of 26. Both studies recruited stroke survivors from local health service agencies. The studies also included participants who demonstrated poor community ambulation and low levels of community integration (Kersten et al., 2004; Trigg & Wood, 2003).

In addition, stroke survivors who were receiving residential care services were included in the study by Trigg and Wood (Trigg & Wood, 2003). A subgroup analysis showed that this group scored significantly lower on the SIPSO questionnaire (16.5 vs. 27, $p = 0.03$) (Trigg & Wood, 2003). In contrast, we recruited members of local self-help groups, who were likely to be more socially active.

Influence of isometric ankle dorsiflexion strength

We found that paretic dorsiflexion strength had a direct positive association with the level of community integration in chronic stroke survivors. This result indicates that paretic ankle dorsiflexion strength could have a strong influence on physical functions other than walking endurance and balance performance. Weak paretic ankle dorsiflexion is common after stroke. Isometric paretic ankle dorsiflexion strength measured with a handheld dynamometer in the paretic leg in 60 chronic stroke survivors was reported to be only 35% of that of age-matched healthy control subjects (Dorsch et al., 2015).

Ankle dorsiflexion weakness results in insufficient ankle clearance from the floor during the swing phase and reduces the weight-bearing ability of the paretic leg in the mid-stance phase (Lin et al., 2006). Based on a sample of 68 chronic stroke survivors, Lin et al. identified that isometric paretic ankle dorsiflexion strength was the primary predictor of comfortable walking speed ($R^2 = 0.30$) and the temporal asymmetry index, which measured the decreased single-leg support time on the paretic leg ($R^2 = 0.38$) (Lin et al., 2006). Shiu et al. (Shiu et al., 2016) also reported a significant correlation between isometric paretic ankle dorsiflexion strength and 360° turning time in chronic stroke survivors ($r = -0.505$). Ankle dorsiflexion strength has been suggested to enhance the foot clearance from the ground during turning, thus shortening the completion time for 360° turning (Shiu et al., 2016).

Based on a sample of 73 community-dwelling chronic stroke survivors, Ng and Hui-Chan identified that isometric paretic ankle dorsiflexion strength was the strongest predictor of the timed up and go performance (R^2 = 27.5%) (Ng & Hui-Chan, 2013), which measures the participants' level of functional mobility. Four of the five items (items 2 to 5) in the questionnaire were found to be related to ambulatory ability to some extent (item 2: the ability to ambulate at home; items 3 and 4: satisfaction and independence of community ambulation; and item 5: shopping). This may explain why paretic ankle dorsiflexion strength contributes significantly to a higher level of community integration as measured by SIPSO in stroke survivors.

Influence of BBS and indirect associations mediated by BBS

Balance performance measured with the BBS was found to have a direct positive association with the level of community integration. The BBS measures an individual's stability in performing functional tasks, such as sit-to-stand or stepping up and down. The results agree with those of a previous study that demonstrated that the BBS score was an independent predictor of the RNLI score in a sample of 63 community-dwelling chronic stroke survivors (Pang et al., 2007). It is plausible that good balance performance augments the level of self-efficacy in carrying out daily activities and participating in social life, as demonstrated in a previous study (French et al., 2016). A fear of falling (Liu et al., 2015) and balance-related self-efficacy (Pang et al., 2007) were also found to be independent predictors of community integration in stroke survivors. Both factors were strongly associated with balance performance (Belgen et al., 2006; Kim & Park, 2014). If the fear of falling and balance-related self-efficacy measures were not included in the model, the influence of balance performance in predicting the level of community integration might have been magnified.

Paretic ankle dorsiflexion strength was found to have a significant direct association with the balance performance measured by BBS and was indirectly associated with the SIPSO score. In contrast, one study reported that isometric ankle dorsiflexion strength was not significantly correlated with the balance performance measured with the functional reach test (r = 0.06) in a sample of 30 stroke survivors (Kligyte et al., 2003). The functional reach test measures an individual's ability to reach forward while standing, thus testing the limit of the participant's stability. However, another study found that compensatory movements, such as trunk movements, had a stronger influence on the functional reach test results than that of the actual forward displacement of the centre of pressure in healthy elderly subjects (Jonsson et al., 2003). The BBS assesses the stability of a participant in performing multiple functional movements, such as sit-to-stand, turning, stepping up and down, reaching and standing on one leg. Therefore, BBS can be regarded as a more comprehensive tool for measuring balance performance. It is reasonable to suggest that paretic ankle dorsiflexion strength has a strong influence on balance performance because it plays an important role in maintaining ankle stability (Gefen, 2001) and facilitating foot clearance during walking (Lin et al., 2006).

Isokinetic knee extension peak torque was also found to be a significant predictor of balance performance measured by BBS. This result is consistent with the findings of Gerrits et al. (Gerrits et al., 2009) and Kobayashi et al. (Kobayashi et al., 2011) that isometric paretic knee strength had moderate correlation with the BBS score (r = 0.64 to 0.76) in 17 and 10 chronic stroke survivors, respectively. Weiss et al. (Weiss et al., 2000) also reported that 12 weeks of resistance training to strengthen the knee extensor and hip muscles led to significant improvement in the BBS score in seven chronic stroke survivors.

Influence of 6MWT and indirect associations mediated by the 6MWT

The results of this study are consistent with other reports that walking endurance measured by the distance covered in the 6MWT is a significant predictor of the level of community integration ($R^2 = 0.326$) as measured by the social participation domain of the stroke impact scale in chronic stroke survivors (Danielsson et al., 2011). It is not surprising that walking endurance has a significant association with the level of community integration. As stated earlier, four of the items in the SIPSO questionnaire assess the participants' abilities in outdoor ambulation. Satisfactory walking endurance could help a stroke survivor attend social gatherings and visit friends or others (item 9). A randomised control trial on 15 chronic stroke survivors demonstrated that 10 weeks of progressive resistance training of the knee extensors and flexors led to a 10% increase in the 6MWT distance ($p < 0.05$). More importantly, the percentage changes in the 6MWT distance and the participation domain of the stroke impact scale were strongly correlated ($r = 0.74$, $p < 0.01$) (Flansbjer et al., 2008). These results (Flansbjer et al., 2008) further support our finding that isokinetic paretic knee flexion peak torque has a direct association with the 6MWT distance.

Despite our studies having similar inclusion criteria, the results of this study are not consistent with the findings of Liu et al. (Liu et al., 2015). They reported that walking endurance measured by the 6MWT was not a significant predictor of the level of community integration ($\beta = 0.083$, $p = 0.469$) in a sample of 57 chronic stroke survivors (Liu et al., 2015). The differences between the findings of the two studies may be partly explained by the different outcome measures. The community integration measure mainly assesses the subjective feelings of being accommodated in the community, whereas SIPSO evaluates the quality and level of engagement in the activities of daily living and social activities.

Paretic isometric ankle dorsiflexion strength was found to be a significant predictor of walking endurance measured by the 6MWT. This result is consistent with Ng and Hui-Chan's (Ng & Hui-Chan, 2012) finding that paretic isometric ankle dorsiflexion strength was the strongest independent predictor of the distance covered in the 6MWT and that it could explain up to 48.8% of the variance ($\beta = 0.75$, $p < 0.001$).

Isokinetic knee flexion peak torque was also found to be a significant predictor of walking endurance measured by 6MWT. This result is consistent with the findings of Flansbjer et al. (Flansbjer et al., 2006) that the paretic isokinetic knee flexion and extension peak torque were independent predictors of walking endurance measured by 6MWT ($R^2 = 50\%$ and 49%, respectively; $p < 0.05$) in a sample of 50 chronic stroke survivors. In contrast, non-paretic knee flexion and extension peak torque were not significant predictors of walking endurance. A study of the influence of muscle weakness on the walking load of the weakened muscle revealed that weakness of lower limb muscles, including the tibialis anterior and hamstring, would lead to greater loading on the weakened muscles. The increased muscle loading could result in higher energy costs during walking and thus reduce the level of walking endurance (Krogt et al., 2012). Although the study indicated that muscle weakness could increase the energy costs during walking, it should be noted that the prediction model was based on the gait patterns of healthy participants (Krogt et al., 2012) and may not be applicable to stroke survivors who walk with a pathological gait.

Model fitting

The modification index revealed that correlating the residual term of the prediction of the BBS score and the 6MWT distance could improve the model's fit. The result suggests the possible existence of extraneous variables that have not been specified in the model that influence both the BBS score and the 6MWT distance (Hermida, 2015). The presence of such extraneous variables is plausible because only paretic lower-limb muscle strength was used to predict the BBS score and the 6MWT distance in the current model. Other extraneous variables such as the strength of the non-paretic lower limb and severity of stroke might explain a significant portion of the variances of the BBS score and the 6MWT distance. However, further identification of the predictors of the BBS score and the 6MWT distance in stroke survivors was not within the scope of this study.

Limitations

This study has several limitations. First, the results may have limited generalisability because the subjects were recruited from local patient self-help groups and most were active members who participated in various social and volunteer activities. Stroke survivors over 80 years of age were not recruited. To improve the generalisability of the findings, relatively isolated and older stroke survivors should be recruited in future studies. Second, isometric ankle muscle strength and isokinetic knee muscle peak torque were not measured in a functional position. Thus, the measures may not adequately represent muscle strength during functional activities. Third, we did not conduct a subgroup analysis for stroke survivors with a low level of community integration. Understanding the barriers and facilitators of community integration in isolated stroke survivors may provide more insights for formulation of rehabilitation programmes to facilitate integration. Fourth, the model only explained 43.1% of the variance of the SIPSO score. Given the multi-dimensional nature of community integration, muscle strength, walking endurance and balance performance are likely to be just some of many factors that influence community integration. Moreover, it is possible that other functional measures apart from walking endurance and balance performance could have a strong influence on the SIPSO score. The significant direct association of paretic isometric ankle dorsiflexion strength may reflect the absence from the model of other functional measures that are also strongly influenced by isometric dorsiflexion strength. Lastly, this was a cross-sectional study, and thus causal relationships could not be established between the variables.

Conclusions

Paretic ankle dorsiflexion strength, walking endurance and balance performance were found to be predictors of the level of community integration in community-dwelling chronic stroke survivors. Paretic ankle dorsiflexion strength influence the level of community integration indirectly, mediated by walking endurance and balance performance. Although the hypothesised model explained only 43.1% of the variance in the level of community integration, our findings nevertheless have implications for facilitating the community integration of stroke survivors.

Appendix 6.1 Chapter 6 and 7 published on the Journal of the American Heart Association (final manuscript)

Bilateral transcutaneous electrical nerve stimulation (TENS) improves lower-limb motor function in subjects with chronic stroke: a randomised controlled trial

Introduction

Transcutaneous electrical nerve stimulation (TENS) is used as an adjunct treatment to enhance paretic lower-limb muscle strength, [1-3] walking speed, [3-6] balance performance [2, 3, 7] and functional mobility [1, 5, 7, 8] in subjects with acute, [1] subacute [6, 7] and chronic [2, 4, 5] stroke. The therapeutic effects of TENS may be mediated via peripheral [9-11] and central mechanisms. [12, 13] At the peripheral level, TENS applied over paretic legs reduced the amplitude of the H-reflex [9] and lengthened the stretch reflex latency [10] and H-reflex latency [11] in subjects with chronic stroke. At the cortical level, a single session of cutaneous electrical stimulation applied over a paretic hand reduced short-interval intracortical inhibition [12] and enhanced cortical-muscular coupling during paretic thumb contraction. [13] Previous studies from our laboratory [4, 5] showed that 20 sessions of unilateral TENS (Uni-TENS) applied over the paretic legs combined with task-oriented training (TOT) led to greater improvement in lower-limb muscle strength and walking performance than placebo-TENS combined with TOT in subjects with chronic stroke.

Clinical studies have consistently demonstrated that bilateral motor training is beneficial [14] and superior to unilateral or conventional training for the recovery of motor control, [15, 16] muscle strength, [15] the kinematics of upper limb movement, [16-18] hand dexterity [15] and upper-limb function [17, 19] after stroke. In addition, Sasaki and colleagues [14] reported that high-frequency transcranial magnetic stimulation over the cortical motor areas that represent both legs led to significantly greater improvement in the Brunnstrom Recovery Stage score than sham stimulation in subjects with acute stroke.

The mechanisms that mediate the effects of bilateral intervention in subjects with stroke include rebalancing interhemispheric inhibition, [20-22] activating the homologous neural networks in both hemispheres [23, 24] and recruiting the neural networks of the contralesional hemisphere. [17, 23, 25] The use of transcranial magnetic stimulation on subjects with stroke, in which the maximum voluntary contraction of the non-paretic hand was combined with less-forceful contraction of the paretic hand, increased the cortical excitability of ipsilesional motor representation area of the hand when compared with contraction of the paretic hand alone. [24] Grefkes and colleagues [23] used functional magnetic resonance imaging and dynamic causal modelling to demonstrate positive neural coupling between the ipsilesional primary motor cortex (M1) and the contralesional motor-related areas in bilateral synchronised hand movements in subjects with stroke. [23] Similarly, Luft and colleagues [25] reported that activation of the contralesional cerebrum and ipsilesional cerebellum had increased after 6 weeks of bilateral arm training, but not after dose-matched training based on the neuro-developmental principles that focused on the paretic upper limb in subjects with stroke. In the same study, [25] after exclusion of subjects without cortical activation changes from the analyses, the group with bilateral arm training also demonstrated greater improvement in hand function than the group with dose-matched exercises.

Clinical trials of the effects of bilateral lower-limb motor training in subjects with stroke are sparse. Johannsen and colleagues [26] reported that a 10-session bilateral lower limb training program with rhythmic auditory cueing led to greater improvement in step length and in the accuracy of the paretic foot-aiming task in subjects with chronic stroke when compared with a control group of patients who underwent upper limb training. [26]

Current evidence shows that bilateral intervention recruits spare neural substrates to enhance motor recovery; [17, 20-25] we thus hypothesised that the application of TENS over both paretic and nonparetic legs (Bi-TENS) might induce greater and earlier improvement in lower limb motor function than the use of Uni-TENS in subjects with stroke. A literature search revealed that no study has compared the efficacy of Bi-TENS+TOT and Uni-TENS+TOT on motor recovery after stroke. Therefore, this study aimed to compare the efficacy of a Bi-TENS+TOT program versus a Uni-TENS+TOT program for improving lower-limb muscle strength, balance performance and functional mobility in subjects with chronic stroke.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Procedures

The study protocol was prospectively registered with ClinicalTrials.gov (identifier: NCT02152813). The study was conducted in a Balance and Neural Control Laboratory, and the Ethics Committee of the administrative institution approved the protocol. All participants gave written consent before participation. The study was conducted in accordance with the Declaration of Helsinki for human experiments.

Participants

The sample size was estimated prospectively using G*power v3.1.0 (Franz Faul, University of Kiel, Germany) with an α level of 0.05 and power of 0.8. Because no previous study has compared the effects of bilateral electrical stimulation with those of unilateral stimulation on lower-limb motor function in this population, the estimation is based on a recent systematic review and meta-analysis [27] that showed a medium to large effect size (Cohen's d = 0.73) for bilateral movement training in the improvement of upper limb motor function after stroke. We selected a more conservative effect size of 0.6 in our model, so the total sample size was estimated to be 72 subjects (36 per group) to detect significant between-groups differences. To allow for dropouts, we planned to recruit an additional eight participants. Thus, the planned sample size was 80 (40 subjects per group).

Subjects with stroke were recruited from local self-help groups via poster advertising. Subjects older than 85 years were excluded because old age frailty is commonly seen in this age group [28] and may have a strong influence on motor recovery after stroke. [29] Subjects were eligible to participate if they (1) were between 55 and 85 years of age; (2) had received a diagnosis of ischaemic or haemorrhagic stroke by magnetic resonance imaging or computed tomographic scan more than 1 year and less than 10 years earlier; (3) were able to walk 3 m independently; (4) were able to score greater than 6 out of 10 on the Abbreviated Mental Test; [30] (5) were able to follow instructions and give informed consent; and (6) had no skin allergy that would prevent the application of the TENS equipment. Subjects were excluded if they (1) had any additional medical, cardiovascular or orthopaedic condition that hindered training or assessment; (2) had a cardiac pacemaker; (3) had significant lower-limb peripheral neuropathy (e.g., diabetic polyneuropathy); or (4) had participated in other drug studies or clinical trials.

The subjects were stratified and randomly allocated into either a Bi-TENS group or a Uni-TENS group using Minimize computer software. [31] The stratification was based on age (55 to 70 years or 71 to 85 years), gender, the type of stroke (ischaemic or haemorrhagic) and the side of hemiplegia. The stratification procedure served to avoid an imbalance in the distribution of the major demographic characteristics between the two groups. Randomisation was performed immediately after the collection of demographic data. These procedures were conducted by an independent research assistant who was not involved in the assessment or treatment of these patients.

Training protocols

The training program comprised 20 sessions of TENS or placebo TENS with simultaneous TOT twice per week for 60 min per session.

TENS protocol

The 120Z Dual-Channel TENS Unit (EMSphysio Ltd, Wantage, UK) was used to stimulate the nerve trunk of the common peroneal nerve. The stimulation frequency was set at 100 Hz, with a pulse width of 0.2 ms. The stimulation intensity was set at double the sensory threshold and below the motor threshold, which was confirmed by the absence of muscle twitching. The sensory threshold was defined as the minimum intensity that provoked a tingling sensation. [5] Sensory stimulation was used in this study because it could enhance the neuronal activity and/or cortical excitability of the motor cortex via the corticocortical connections between S1 and M1. [32, 33] In addition, the cutaneous sensory stimulation was applied simultaneously with the TOT, which comprised a series of functional tasks. Electrical stimulation that was above the motor threshold induced muscle twitching; this uncontrolled muscle twitching would produce conflicting afferent inputs during the performance of TOT.

For the placement of electrodes, the cathode electrode (ITO Co. Ltd., Tokyo, Japan: rubber electrodes [40 × 41 mm] and gel pad [40 × 41 mm]) was placed on the popliteal fossa, whilst the anode electrode was placed on the neck of the fibula. For the Bi-TENS group, electrical stimulation was applied over the popliteal fossae of both legs. For the Uni-TENS group, electrical stimulation was only applied to the paretic leg. Placebo TENS was applied to the non-paretic leg with an identical-looking TENS device with the electrical circuit disconnected.

TOT protocol

During the application of TENS, all subjects performed 60 min of TOT under the supervision of a registered physical therapist. The TOT program was adopted from a previous study. [5] The TOT exercises included 1) stepping up and down to strengthen the muscles of both legs and to improve control in shifting the centre of gravity; 2) heel-raising exercises on an inclined wedge to strengthen both ankle plantarflexors; 3) assuming a semi-squatting position to improve lower-limb muscle endurance and proprioception in the knees and ankles; 4) standing on a dura disk to improve dynamic standing balance; 5) walking across obstacles to enhance anticipatory postural control; and 6) standing up from a chair, walking a short distance and returning to the chair to promote a smooth transition between sitting, standing and walking. Each exercise item lasted 10 min, so the total exercise time for each training session was 60 min. Guidelines for standardised exercise progression [5] were implemented to standardise the exercise intensity.

Outcome measures

The subjects were assessed by a trained research assistant who was blinded to group allocation. The assessments were performed at baseline (A0); after 10 sessions (5 weeks; mid-training; A1); after 20 sessions (10 weeks; after training; A2); and 3 months after the cessation of training (follow-up; A3). For all physical assessments, one practice trial was given, and the average of three test trials was used for data analysis. The muscle strength of paretic ankle dorsiflexors (pDF) and plantarflexors (pPF) and paretic knee extensors (pKE) and flexors (pKF) were selected as the primary outcome measures of this study. The ankle and knee muscle strength of the non-paretic ankle dorsiflexors (npDF) and plantarflexors (npPF) and the non-paretic knee extensors (npKE) and flexors (npKF), along with the results of the Step Test and the Lower Extremity Motor Coordination Test, were the secondary outcome measures. The Berg Balance Scale and the Timed Up and Go test were assessed to further capture the effects of the interventions on the subjects' functional mobility. These two outcome measures were not pre-specified in the clinical trial registration.

Maximum isometric voluntary contraction of ankle muscles

The maximum isometric voluntary contraction of the bilateral ankle dorsiflexors and plantarflexors were measured with a Nicholas handheld dynamometer (model 01,160, Lafayette Instrument Company, Lafayette, IN). The ankle muscle strength was assessed with a standardised position and placement of the dynamometer. [34] Good to excellent reliability (intraclass correlation coefficient [ICC], 0.84 to 0.99) has been reported for the use of a handheld dynamometer to assess leg muscle strength in subjects with chronic stroke [35].

Isokinetic peak torque

The strength of bilateral knee extension and flexion was measured with a Cybex 6000 Dynamometer (Lumex, Inc., Ronkonkoma, NY). Knee muscle strength was measured with an isokinetic dynamometer instead of a handheld dynamometer as specified in the clinical trial registration because the subjects of this study demonstrated good knee muscle strength, which made the measurement with a handheld dynamometer less accurate. [36] The peak concentric isokinetic torques of knee flexion and extension at 90 degrees per second were measured in a sitting position. The excellent test-retest reliability (ICC, 0.94) of the use of a Cybex 6000 Dynamometer to measure peak isokinetic torques in subjects with chronic stroke was reported in a previous study. [37]

Lower Extremity Motor Coordination Test (LEMOCOT)

The LEMOCOT was used to measure the intra-limb coordination of both legs. [38] Good test-retest reliability of the LEMOCOT (ICC, 0.83 to 0.88) has been reported for the assessment of subjects with stroke. [38] Two flat, circular targets were secured on the floor 30 cm apart in an anteroposterior direction. The participants were seated with their hips and knees in 90 degrees of flexion and were instructed to touch the two targets alternately with their big toe for 20 s. The total number of repetitions was counted.

Step Test (ST)

The ST was used to assess dynamic standing balance [39] by recording the number of times the subject could place one foot on a 7.5-cm step and back to the ground within 15 s. The ST scores have shown excellent intra-rater and inter-rater reliability in subjects with chronic stroke (ICC, 0.98 to 0.99). [39] The number of repetitions with the paretic and non-paretic legs were recorded.

Berg Balance Scale (BBS)

The BBS was used to measure functional balance performance. [40] The scale consists of 14 items in which a subject’s ability to maintain stability during a specified functional task is rated on a 5-point scale (0 to 4). The maximum score is 56, and a higher score indicates better balance performance. The BBS has shown excellent test-retest reliability (ICC, 0.95) [40] in the assessment of subjects with stroke. To dampen the ceiling effect, a standardised assessment procedure was implemented to challenge the paretic leg’s weight-bearing ability. [41]

Timed Up and Go (TUG) Test

The TUG test was used to assess functional mobility. [42] All subjects were asked to stand up from a chair, walk forward for 3 m, turn 180 degrees, walk back to the chair and sit down. The TUG has demonstrated excellent test-retest reliability in the assessment of subjects with stroke (ICC, 0.95). [42]

Statistical analysis

Intention-to-treat analysis was adopted, and SPSS (v23.0; IBM, Armonk, NY) was used for all statistical analyses. A *p*-value of 0.05 or lower was considered to indicate statistical significance.

The demographic characteristics and outcome measures were summarised with descriptive statistics. The baseline characteristics of the two groups were compared with a chi-square test, independent *t*-test or Mann-Whitney U test, as appropriate. A linear mixed model (LMM) was used to compare the differential changes in the outcomes between the two groups over time because it accounts well for intra-correlated repeated-measures data. [43] The groups, time points and group-by-time interaction were included as fixed effects. The random intercept and random slope of change in the outcome variables over time were included as random effects. Maximum likelihood was chosen as the estimation method, and the heterogeneous first-order autoregressive covariance structure was selected to estimate the model parameters. The group-by-time interaction term of the LLM is the focus of interest in the current study. Bonferroni correction was applied to adjust the *p*-value of the interaction term of primary outcomes and to *p*-value of post-hoc analyses, in order to prevent inflation of the type 1 error rate. The confidence intervals of the regression coefficients of the interaction terms were also adjusted accordingly. [44]

A significant group-by-time interaction effect indicated that the variables changed at different rates in the two groups. Where the group-by-time interaction effect was significant, the between-groups and within-group differences were evaluated by dividing the data into three time points and two groups, respectively. The LMM was then repeated with the interaction effect, and either the time or the group effect was removed and followed by post-hoc analysis. In the absence of a significant group-by-time interaction, a significant time effect indicated that the variables changed significantly with a similar trend in both groups. Post-hoc analysis was conducted to determine at which time point the outcome variable had changed significantly from the baseline. The carry-over effects were analysed by comparing the results between A2 and A3 with the same model specifications mentioned above. For the analyses of between-groups differences and a carry-over effect, the last observation carried forward method was used to handle missing data. The last observation carried forward method was chosen as it is a more conservative method to impute data with dropout in this study. A previous study suggested that the use of last observation carried forward method can introduce bias, especially when progressive diseases were studied or when adverse effects could be introduced by the intervention. [45] In the current study, all subjects were already in their chronic static phase of stroke, spontaneous improvement or rapid deterioration in physical functions should be unlikely to occur. In addition, none of the dropout case reported any adverse effect resulted from the training, thus it is unlikely that last observation carried forward method would overestimate the outcomes.

Results

One hundred and two subjects with chronic stroke were screened between February 2014 and April 2016. Eighty fulfilled the inclusion criteria for recruitment into this study. Their mean age was 62.0 years, and the mean time since the stroke was 5.2 years. Their mean walking speed was 0.77 ms^{-1}, which indicated limited ambulatory ability [46] (Table 1). No significant differences existed between the two groups at baseline (Table 1). Six subjects (three in each group) did not complete the training program. Another five (two in the Bi-TENS group and three in the Uni-TENS group) were lost to follow-up (Figure 1).

For the primary outcomes, the LMM showed that the group-by-time interaction effects were significant only for the pDF strength ($\beta = 1.32$; $p = 0.032$). The results suggest that for every 10 sessions of training, the Bi-TENS group demonstrated an additional 1.32-kg increase in pDF strength. Post-hoc analyses revealed that the Bi-TENS group had greater improvement than the Uni-TENS group in the pDF strength at A1 (mean difference, 2.62 ; $p = 0.036$) and at A2 (mean difference, 3.23; $p = 0.034$). When compared with baseline, the Bi-TENS group showed improvement in the pDF strength at A1 (mean difference, 2.67; $p < 0.001$) and at A2 (mean difference, 4.46; $p < 0.001$). However, the Uni-TENS group showed improvement in the pDF strength (mean difference, 1.81; $p = 0.005$). Results of LMM showed that none of the group effect was significant. The time effects were significant for pDF strength, pPF strength, pKE peak torque and pKF peak torque ($p \leq 0.05$; Table 2). Post-hoc analyses of the significant time effects showed that improvement in the pKE peak torque (mean difference, 6.01; $p < 0.001$) and pKF peak torque (mean difference, 5.16; $p < 0.001$) began at A1, but improvement in the pPF strength (mean difference, 2.63; $p < 0.001$) demonstrated in A2 only.

For the secondary outcomes, the LMM showed that none of the group effects were significant. The time effects were significant for all secondary outcomes except the npKE peak torque ($p \leq 0.05$; Table 2). The group-by-time interaction effects were significant only for the TUG completion times ($\beta = -1.54$; $p = 0.004$). The results suggest that for every 10 sessions of training, the Bi-TENS group demonstrated a further reduction of 1.54 s in the TUG completion time when compared with the Uni-TENS group.

Post-hoc analyses of the significant interaction effect reveal that the Bi-TENS group had greater improvement than the Uni-TENS group in the TUG completion time at A2 (mean difference, −3.09; $p = 0.047$). When compared with baseline, the Bi-TENS group showed improvement in the TUG completion time at A1 (mean difference, −2.01; $p = 0.001$) and at A2 (mean difference, −3.76; $p < 0.001$). However, the Uni-TENS group showed improvement in the TUG completion time (mean difference, −1.64; $p = 0.01$) only at A2.

Post-hoc analyses of the significant time effects showed that improvements in the npDF (mean difference, 2.48; $p < 0.001$), npKF peak torque (mean difference, 3.65; $p < 0.001$), paretic LEMOCOT score (mean difference, 2.31; $p = 0.001$), non-paretic LEMOCOT score (mean difference, 3.26; $p = 0.001$), paretic ST score (mean difference, 9.27; $p = 0.009$), non-paretic ST score (mean difference, 0.88; $p = 0.021$) and BBS score (mean difference, 1.50; $p < 0.001$) all began at A1. Improvement in npPF strength (mean difference; 3.40; $p < 0.001$) was demonstrated only at A2. In the analyses of carry-over effects, none of the group by time interaction effects was significant. The time effects were significant for pPF ($\beta = -1.75$; $p = 0.021$; Table 3).

Discussion

The results of this study demonstrate that Bi-TENS+TOT induced greater and earlier improvement in the pDF strength and greater improvement in the TUG completion time than Uni-TENS+TOT. Although there were no between-groups difference of other outcome measures, both treatments demonstrated significant improvements in the npDF strength, pKE, pKF and npKF peak torque, paretic and non-paretic LEMOCOT scores, paretic and non-paretic ST scores and BBS scores after 10 training sessions and significant improvements in pPF and npPF strength after 20 training sessions. In general, the training effects on all outcome measures could be maintained 3 months after training had ended, except for the pPF strength.

Primary outcomes

To the best of our knowledge, this is the first study to compare the efficacy of Bi-TENS+TOT and Uni-TENS+TOT in the improvement of lower limb motor function after stroke. The notion of Bi-TENS was inspired by the success of bilateral motor training, [15-19] and positive findings [26] have also been reported with bilateral leg training after stroke. In addition, training of the non-paretic limb has also been reported to enhance motor recovery in paretic limbs. [15, 47]

Based on the findings of neuroanatomical [48] and clinical [23, 24] studies, the underlying mechanisms that mediate the effects of Bi-TENS might include the enhancement of interhemispheric interaction, possibly via the corpus callosum, which is the white matter in the human brain that connects the two hemispheres via more than 200 million axonal connections. [48] The motor areas of the two hemispheres have been shown with functional magnetic resonance imaging and diffusion tensor imaging to be connected via the posterior body of the corpus callosum. [48] The results of clinical studies have demonstrated that bilateral pinch gripping could enhance ipsilesional M1 excitability when compared to unilateral pinch gripping with either hand in subjects with stroke, [24] which was shown by an increase in the motor evoked potential amplitude recorded from the first dorsal interosseous of the paretic hand [24]. Moreover, Grefkes and colleagues [23] demonstrated in a sample of 11 subjects with subacute and subcortical stroke that bilateral hand movements resulted in facilitatory neural coupling between the M1 and supplementary motor areas of the two cerebral hemispheres. Simultaneous activation of bilateral sensorimotor cortices via TENS might exert a similar effect of enhancing the interhemispheric interaction in both hemispheres via the corpus callosum, thus enhancing the effects of motor training.

The neural networks of the contralesional hemisphere might contribute to the motor recovery of the paretic limb after repetitive application of TENS over both legs. Dragert and Zehr [47] reported that high-intensity ankle dorsiflexion resistance training on the non-paretic ankle resulted in a 34% increase in npDF strength and a 31% increase in pDF strength in 19 subjects with chronic stroke. [47] It is plausible that the application of TENS over the non-paretic leg activated the contralesional hemisphere and enhanced the paretic ankle strength by recruiting the contralesional neural networks. The Bi-TENS+TOT group showed earlier and greater improvement in pDF strength with as little as 10 sessions of training, probably due to the enhanced descending input to the alpha-motor neurons that innervate the pDF.

However, it should be noted that among the 4 primary outcomes, the between-groups differences could only be shown in pDF strength. Bi-TENS + TOT was not superior to Uni-TENS + TOT in improving the pPF strength, pKE and pKF peak torque. This might be due to the fact that TENS was applied to stimulate the common peroneal nerve only. Kaelin-Lang and colleagues [49] demonstrated that 2 hours of cutaneous electrical stimulation over the ulnar nerve at the wrist level increased the motor evoked potentials of the abductor digiti minimi muscle in response to focal transcranial magnetic stimulation in healthy adults. [49] However, no significant change was shown in the motor evoked potentials of the abductor pollicis brevis muscle, which was innervated by the median nerve. Results of that study [49] indicated that cutaneous electrical stimulation over a peripheral nerve increases the focal corticospinal excitability of the muscles innervated by the nerve being stimulated. The ankle plantarflexor, knee flexor and extensor were predominantly innervated by the tibial nerve, sciatic and femoral nerves, respectively. The change in the pPF strength, pKF and pKE peak torque might be attributable to the effects of TOT, but not the effects of TENS.

Consistent with previous results, [4, 5] our results demonstrate significant within-group improvement in pDF strength in both the Bi-TENS and Uni-TENS groups after 20 sessions of intervention. The mechanism that underlies the improved motor function in paretic limbs after TENS treatment is multifactorial; it involves alleviation of the hyperexcitability of alpha motor neurons, [9, 11] reduction of intracortical inhibition [12] and enhancement of cortico-muscular functional connectivity. [13] Several clinical studies have demonstrated that the hyper-excitability of the alpha motor neurons that innervate the spastic ankle plantarflexor could be reduced by an increase in pre-synaptic inhibition after repetitive TENS. [9, 11] Levin and Hui-Chan reported that the ankle plantarflexor stretch reflex amplitude, as measured by the magnitude of integrated electromyography (EMG), was reduced significantly after a 3-week regimen of repetitive TENS over the common peroneal nerve but not after placebo-TENS stimulation. [9] Chen and colleagues demonstrated that the H-reflex latency of pPF was lengthened significantly after 6 weeks of TENS stimulation over the Achilles muscle–tendon junction but not after placebo-TENS stimulation. [11]

Other neurophysiological studies have demonstrated that repetitive cutaneous electrical stimulation could lead to a reduction in intracortical inhibition [12] and enhancement of cortical and neuromuscular coupling [13] at the cortical level, which might explain the improvement of motor function after TENS combined with TOT. Celnik and colleagues [12] applied cutaneous electrical stimulation on the ulnar and radial nerves of the paretic upper limb for 2 h before training of hand function. Their results showed a significant reduction of the short-interval intracortical inhibition and significant improvement in the Jebsen-Taylor Hand Function Test score in nine subjects with subacute stroke, [12] whilst no such change was seen after sham stimulation.

In addition, Lai and colleagues [13] reported that 40 min of cutaneous electrical stimulation applied over the median nerve on the paretic hand could augment electroencephalography (EEG)–EMG coherence in nine subjects with chronic stroke. The EEG-EMG coherence, which refers to the synchronisation of the oscillatory activities of the EMG and EEG signals, was used to assess the level of cortical and neuromuscular coupling. It has been reported that a low-to-high shift of the EEG-EMG coherence frequency is a clinical indicator of motor recovery after stroke. [50] Lai and colleagues [13] showed that the EEG-EMG coherence in the high-frequency band (>30 Hz) had increased significantly after repetitive TENS.

Moreover, motor control, as measured by the percentage of force deviation in maintaining a steady force output, was also improved after cutaneous electrical stimulation. [13] Studies have found that Uni-TENS augments the effects of TOT in subjects with stroke. [4, 5, 51] It has been suggested that the occurrence of motor cortex reorganisation is likely suppressed by inhibitory mechanisms under normal conditions and that the release of intra-cortical inhibition might facilitate motor learning. [52, 53] This notion was supported by the fact that reorganisation of the motor representation area can be induced rapidly in rats when intra-cortical inhibition is blocked with drugs. [52] Celnik and colleagues [12] used transcranial magnetic stimulation to investigate the effects of cutaneous electrical stimulation on the level of corticospinal excitability in subjects with stroke. In this crossover-designed study, subjects with stroke received 2 h of sub–motor threshold cutaneous electrical stimulation on both ulnar and radial nerves or received placebo stimulation before 1 h of hand function training. Cutaneous electrical stimulation led to no change in the resting motor threshold recorded from the first dorsal interosseous muscle, but it did reduce the short-interval intracortical inhibition in nine subjects with subacute stroke. [12] In addition, the reduction of intracortical inhibition has been demonstrated during motor skill acquisition of a wrist flexion-extension waveform-tracking task in healthy adults, [53] and the enhanced cortical and neuromuscular coupling after TENS led to better motor control. [13] Thus, repetitive TENS potentially optimises the participants' performance and augments the training effects of TOT.

Because a 'pure' TOT control group was not incorporated in this study, the therapeutic effects of TOT could not be determined. However, the effects of placebo-TENS+TOT and Uni-TENS+TOT have been investigated in our laboratory. [4, 5] With a training protocol and selection criteria similar to those for the participants with stroke, the results of our previous study [4, 5] showed that placebo-TENS+TOT led to greater improvement in paretic ankle dorsiflexion and plantarflexion strength [4] than that seen in a control group without active treatment. Moreover, Uni-TENS applied over the paretic limb combined with TOT was superior to TENS alone, placebo-TENS+TOT and control without any active treatment in improving ankle muscle strength [4] in subjects with stroke.

Our stimulation protocol was based on the findings of our previous studies that had effectively demonstrated improvement in lower limb motor function in subjects with stroke. [1, 4, 5, 9, 10, 54] The 100-Hz stimulation frequency was chosen because previous studies have demonstrated that this frequency reduces the amplitude of the H-reflex, [9] lengthens the stretch reflex latencies [10] and enhances walking capacity [4, 5, 54] in subjects with stroke. It has been reported that 30 min of TENS applied over the deep peroneal nerve of the paretic leg with a stimulation frequency of 200 Hz led to a greater increase of presynaptic Ia inhibition than 50 and 100 Hz in 20 subjects with chronic stroke. [55] However, no randomised controlled trial has supported the clinical efficacy of a 200-Hz stimulation frequency. As for the stimulation duration, Laddha and colleagues [54] compared the effects of 30 min versus 60 min of TENS applied over the common peroneal nerve combined with TOT. Although the pPF spasticity was reduced in both groups, their results indicated that 60 min of TENS combined with TOT was superior to 30 min of TENS combined with TOT in reducing ankle clonus in subjects with stroke.

The TOT program adopted the specificity of training principles by ensuring that the force generated by the muscles is directly related to functional movement. [4] The TOT protocol for this study was adopted from that in our previous study, [4, 5] which demonstrated that a combination of placebo-TENS and TOT outperformed a control group with no active treatment in isometric pDF and pPF strength [4] and TUG completion time. [5] The improvement in muscle strength after TOT could be attributed to an increase in muscle volume [56] and recruitment of alternative neural substrate. [57] Ryan and colleagues reported that 12 weeks of resistive training of the knee extensors increased the paretic thigh's cross-sectional area and volume by approximately 15% and increased the knee extension strength by 56%. [56] Luft and colleagues [57] reported that 6 months of treadmill exercise induced greater activation in multiple brain regions than passive stretching in subjects with stroke. These brain areas included the posterior cerebellar lobe, the midbrain and the ipsilesional postcentral and superior frontal gyri, which were the areas that potentially mediated the walking-related activities. In addition, ambulation functions could be facilitated because these exercises required the subjects to activate the muscle in the position in which the muscles normally functioned.

Unlike our previous studies [4, 5] in which TENS was applied before TOT, the TENS treatment in this study was applied concurrently with TOT. Two studies have reported that simultaneous TENS and TOT augment balance performance [7] and trunk control [51] in subjects with stroke. Khaslavskaia and colleagues [58] reported that cutaneous electrical stimulation over the common peroneal nerve for 30 min enhanced corticospinal excitability for up to 110 min in healthy adults, which supported the application of TENS before TOT. However, Khaslavskaia and Sinkjaer [59] reported that cutaneous electrical stimulation applied over the common peroneal nerve combined with simultaneous active ankle dorsiflexion exercise for 30 min increased the motor evoked potentials recorded from the tibialis anterior by 66% in eight healthy adults, whilst cutaneous electrical stimulation alone increased the motor evoked potentials by only 38%. [59] One of the advantages of the current TENS+TOT protocol is that it can significantly reduce the treatment duration, thus enhancing the cost-effectiveness of the program and the compliance of the participants.

Secondary outcomes

The greater improvement in the TUG completion time after completion of 20 sessions of training could have been mediated by the improved pDF strength, because pDF strength has been reported to be a significant predictor of the TUG completion time ($\beta = 0.750$). [60] Moreover, the muscles of the non-paretic leg are also weakened in subjects with stroke. [61] A previous study also reported that the non-paretic ankle contributed 55% to 89% to balance maintenance after perturbation, [62] and a simulation study reported that an increase in non-paretic knee extension strength could enhance clearance of the paretic ankle during the swing phase of the paretic leg in a model of subjects with stroke. [63] It is possible that Bi-TENS also augments the training effects on the non-paretic leg and thus enhances the overall walking capacity. However, results of the current study showed that there was no significant between-groups difference was seen on non-paretic lower limb muscle strength, lower limb coordination or dynamic standing balance after 20 sessions of training. Thus, it was unlikely that the improvement of non-paretic leg motor functions attributed to the improvement in walking capacity.

Although significant within-group improvement was shown in lower limb coordination, dynamic standing balance and balance performance, no significant between-groups difference was seen in these outcomes. The LEMCOT involves the coordinated movement of the knee flexor and extensor, which are predominantly innervated by the sciatic and femoral nerves. The ST and BBS evaluate trunk control, functional muscle strength in the legs and anticipatory postural adjustment. The application of Bi-TENS to the common peroneal nerve might only improve the motor outputs of muscles that are innervated by the superficial and deep peroneal nerves, including the ankle dorsiflexors and evertors. This finding might explain the lack of a between-groups difference in plantarflexor strength or in the LEMCOT, ST or BBS scores.

Carry-over effects

The paretic lower limb coordination, dynamic standing balance, functional mobility and balance performance showed no significant deterioration at 3 months after training in either group. The pPF strength was reduced significantly in follow-up assessment in both groups. These findings are suggestive of the detraining effect had a strong influence on muscle strength but not on functional performance. Häkkinen and colleagues [64] reported a significant reduction in the cross-sectional area of the quadriceps and reduction in the isometric strength of knee extensors up to 6% after 3 weeks and 12% after 24 weeks of detraining in healthy adults. However, the functional outcomes, including walking speed and jumping height, showed no significant change. Those results indicated that the improved neuromuscular control was maintained even after detraining, and partially compensated for the loss in muscle strength, which might explain the preservation of lower limb functions.

Limitations

This study has several limitations that must be considered. First, because the primary objective of this study is to compare Bi-TENS and Uni-TENS in improving motor function in stroke survivors, there was no pure TOT group or control group without active treatment to delineate the treatment effects of TENS and TOT. Second, the neurophysiological mechanisms that mediate the effects of Bi-TENS and Uni-TENS remain unclear. Future studies are necessary to investigate the differential effects of Bi-TENS and Uni-TENS on cortical function. Third, the therapist who supervised the training was not blinded to the group allocations, but the standardised treatment protocol could have minimised the bias. Fourth, selection bias might have existed because all participants in this study were community-dwelling and self-selected to participate. Thus, they were likely to be more motivated and to have a better mobility level than those who declined to participate. Recruitment of subjects with poor mobility should be considered in a future study. Fifth, we did not measure the actual repetition of movement accomplished by the subjects in each exercise. The actual dosage of exercise could vary considerably amongst subjects. The number of repetitions, instead of exercise duration, could be used as an indicator of exercise dosage in a future study. Finally, the follow-up period was limited to 3 months after training due to limitations in resources. A longer-term carry-over effect cannot be determined.

Conclusions and clinical implications

This study demonstrates that Bi-TENS applied on the common peroneal nerves combined with lower-limb TOT induces greater improvement in pDF strength beginning after 10 sessions and greater improvement in TUG completion time after 20 sessions than Uni-TENS combined with TOT, whilst Bi-TENS showed no additional advantage in improving pPF strength and knee muscle strength. Both Bi-TENS+TOT and Uni-TENS+TOT induced significant within-group improvements in paretic ankle strength, lower limb coordination, dynamic standing balance, functional mobility and balance performance in subjects with chronic stroke after 20 sessions of training. The training effects in both groups were maintained for 3 months. The results of this study suggest that Bi-TENS+TOT is superior to Uni-TENS+TOT for improving the TUG completion time in subjects with chronic stroke, but the two training protocols seem to demonstrate similar efficacy on the LEMOCOT score, ST score, and BBS score. The subjects who participated in this study had a relatively high level of motor function, so the results may not be applicable to subjects with limited motor function.

Funding Sources

This study was supported by the General Research Fund (reference number 562413) from the Research Grants Council, Hong Kong.

Disclosures

None.

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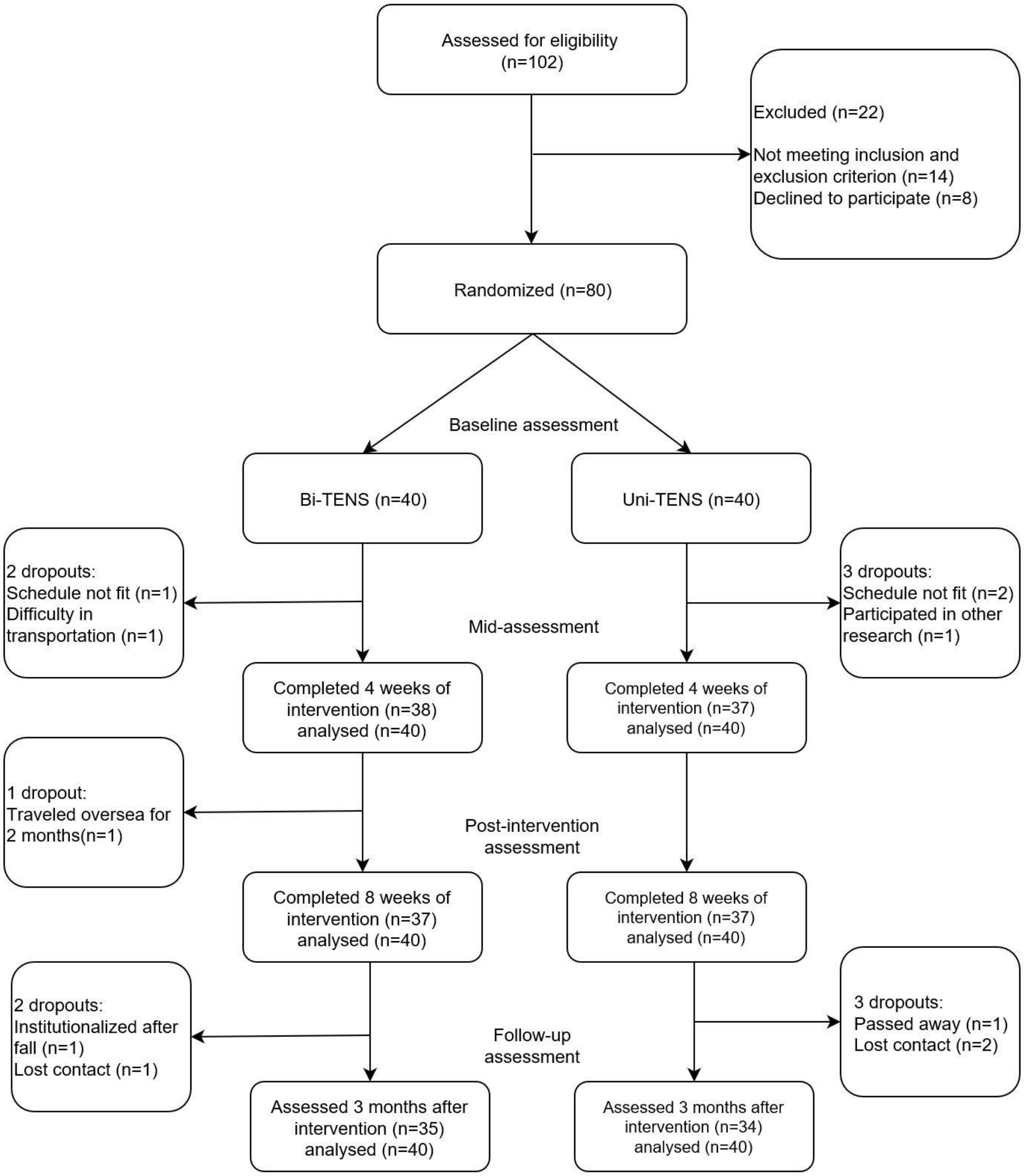

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study.

Appendix 8.1 Consent form of the fNIRS study.

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project entitled:

Influence of bilateral and unilateral transcutaneous electrical nerve stimulation (TENS) on the level of cortical activation: A functional near-infrared spectroscopy (fNIRS) study

Investigator: Dr. Shamay Ng, Mr. Kwong Wai Hang

Purpose: To investigate the effect of applying TENS on both legs versus on paretic or non-dominant leg on the level of brain activities in people with chronic stroke, as well as in healthy participant.

Methods:

The study will be conducted in the clinical research laboratory of The Hong Kong Polytechnic University. A non-invasive device named functional near-infrared spectroscopy will be used to assess brain activities before, during and after the application of TENS or sham stimulation. Electromyography (EMG) will be used to measure the level of muscular activation during the paretic or non-dominant ankle dorsiflexion/plantarflexion movement before, during and after the application of TENS or sham stimulation. Physical function, including ankle muscle strength and functional mobility will also be assessed. The assessments will be held on 3 days with a 1-week interval in between, and each session will last for 90 minutes.

Potential Risks and Benefits:

The major benefit from participating in this study is that you may know your level of physical functions including ankle muscle strength and functional mobility. The results may also be beneficial for developing new treatment protocol to augment the effectiveness of the traditional stroke rehabilitation program.

TNES protocols and testing procedures have been well proved to be safe and used with negligible side effects, both clinically and experimentally. Rest will be allowed between assessment procedures.

Informed Consent

I, ____, understand the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name will not appear on any publications resulted from this study.

I can contact the chief investigator, Dr. Shamay Ng, at telephone 2766-4889 for any questions regarding this study. If I have complaints related to the investigators, I can contact Ms. Chung, secretary of Departmental Research Committee, at 2766-4329. I know I will be given a signed copy of this consent form.

Signature (subject): ________________________________ Date: _______________

Signature (Witness): _______________________________ Date: _______________

香港理工大學康復治療科學系研究同意書

項目名稱: 兩側經皮神經電刺激與單側經皮神經電刺激對腦部活動的影響：功能性近紅外線光譜技術研究。

科研人員: 伍尚美博士, 鄺偉恒先生

研究目的及內容:

是項研究旨在比較兩側經皮神經電刺激與單側經皮神經電刺激對中風及健康人士腦部活動的影響。

研究方法:

所有合適的研究參加者將會接受下肢的經皮神經電刺激或模擬刺激，腦部活動評估，肌電訊號測試及數項身體檢查包括下肢肌力及功能性活動能力測試。研究會分三天進行，每次評估相隔一星期，而每次評估需時約九十分鐘。

潛在風險及得益:

參與此研究的好處是：參與此項研究的主要好處是參與研究者可以了解自己的下肢肌力及活動能力的表現，此外亦能提供重要數據幫助設計給中風病人改善活動能力的康復治療。整個檢查程序都已經過驗證，證明過程十分安全，不論在臨床上或實驗上，其副作用都可以忽略。參加者可按需要於測試期間作中段休息。

同意書:

本人 ____ 已瞭解此次研究的具體情況。本人願意參加此次研究。本人有權在任何時候、無任何原因的情況下放棄參與此次研究，而此舉不會導致本人受到任何懲罰或不公平的對待。本人明白參加此研究的潛在風險，以及本人的資料將不會泄露給與此研究無關的人員，我的名字或相片也不會出現在任何的出版物上。

本人可致電 2766-4889 與此研究的負責人伍尚美博士聯絡。若本人對研究人員有任何投訴，可聯絡鍾小姐 (部門科研委員會秘書)，電話：2766-4329。本人亦明白，參與此研究需要本人簽署一分同意書。

簽名 (參加者): ________________________ 日期:

簽署 (見證人): ________________________ 日期:

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