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EFFECTS OF UNILATERAL AND BILATERAL CUTANEOUS ELECTRICAL STIMULATION ON UPPER LIMB FUNCTIONS IN PATIENTS WITH CHRONIC STROKE

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Effects of unilateral and bilateral cutaneous electrical stimulation on upper limb functions in patients with chronic stroke

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ABSTRACT

Stroke is recognized as a global disease which could lead to long-term disability. The upper limb impairment in motor control is one of the common sequelaes in people with chronic stroke. About one-third of the people with stroke suffered upper limb motor function deficit six months after stroke, which could be a great burden for them return to the normal daily lives. Therefore, one of the main goals of stroke rehabilitation is to enhance the motor recovery of the paretic upper limb among people with stroke.

Evidence showed that transcutaneous electrical nerve stimulation (TENS) was an effective intervention to enhance the motor recovery of upper limb in people with stroke when combined with task-oriented training (TOT). In addition, the bilateral upper limb exercise was found to induce significant greater improvement of upper limb motor control than the unilateral upper limb exercise in people with stroke. The bilateral exercise could recruit the pathway in both the intact and lesioned hemisphere to elicit a greater cortical activation so as to enhance the upper limb motor recovery in people with stroke.

Based on the evidence that the combination of TENS and TOT is an effective intervention in enhancing the upper limb motor recovery, and given the advantage of

bilateral exercise can recruit more neural pathway to elicit greater cortical activation**,** it is reasonable to hypothesize that bilateral TENS (Bi-TENS) could augment the effect of TOT of upper limb motor recovery in people with stroke. Hence, the aim of this study is to investigate whether Bi-TENS+TOT is superior to unilateral TENS (Uni-TENS)+TOT, Placebo-TENS+TOT and control without any active treatment in improving the motor function of upper limb in people with chronic stroke.

This thesis started with a systematic review and meta-analysis (Study 1) of comparing the effect of bilateral upper limb exercise with unilateral upper limb exercise on the recovery of upper limb motor control and functional performance in people with chronic stroke. The result of the current studies indicated that bilateral form of upper limb exercise was superior to unilateral upper limb exercise in enhancing the recovery of the upper limb motor control in people with stroke.

Study 2 investigated the impacts of self-perceived performance of the paretic upper limb on the recovery of the functional performance of paretic upper limb in people with stroke when controlled the influence from the upper limb motor control. The self-perceived performance, hand motor control and functional performance of paretic upper limb was measured by Motor Activity Log (MAL), hand subscale of Fugl-Meyer Assessment (FMA-hand) and Action Research Arm Test (ARAT), respectively. The finding of the study showed that the MAL score was a significant

predictor of ARAT score in people with stroke, when the impact of FMA-hand was controlled. In order to improve ARAT score after intervention, assessment and training protocol about self-perceived performance of upper limb functions should be included in the main study.

Study 3 is our main study which compared the effect of Bi-TENS+TOT with Uni-TENS+TOT, Placebo-TENS+TOT and control without active treatment in improving the upper limb motor control, muscle strength of upper limb, abnormal muscle activation, range of motion, functional performance of upper limb, performance of daily function of upper limb, self-perceived performance of upper limb and community integration level in people with chronic stroke. Total one hundred and twenty subjects were randomly assigned to Bi-TENS+TOT, Uni-TENS+TOT, Placebo-TENS+TOT and Control group. Among the four groups, the subjects in Bi-TENS+TOT, Uni-TENS+TOT and Placebo-TENS+TOT group received twenty sessions of intervention, while the Control group did not receive any active treatment. The primary outcome was FMA-UE score, while the secondary outcomes included peak torque and co-contraction ratio of wrist flexion/extension during maximum isometric voluntary contraction (MIVC), active range of motion of wrist flexion/extension, elbow flexion/extension, Jacket Test completion time, ARAT, MAL and Community Integration Measure score. These outcome measures were measured among the four groups in baseline, mid-intervention, immediately post-

intervention, one-month follow-up and three-month follow-up assessment. The result showed that the patients in Bi-TENS+TOT group got a significantly greater between-group improvement than Uni-TENS+TOT beginning from post-intervention assessment. While a significantly greater between-group improvement of FMA-UE score was shown in Bi-TENS+TOT group than Placebo-TENS+TOT and Control group beginning from mid-intervention assessment and maintained in one-month follow-up and three-month follow-up. Both the Bi-TENS+TOT and Uni-TENS+TOT group showed significant within-group improvement in FMA-UE at post-intervention assessment when compared with baseline. The Bi-TENS+TOT showed an earlier within-group improvement than Uni-TENS+TOT in the improvement of FMA-UE score. Only the patients in Bi-TENS+TOT group showed significant within-group improvement in peak torque during MIVC of wrist flexion and ARAT score in post-intervention assessment when compared with baseline. The significant improvement was maintained in one-month follow-up and three-month follow-up.

RESEARCH OUTPUT ARISING FROM THIS THESIS

PUBLICATIONS

Chen PM, Lai CK, Chung RC, Ng SS. (2016). The Jacket Test for assessing people with chronic stroke. *Disability and Rehabilitation*, 39(25), 2577-2583.

Chen PM, Kwong PW, Lai CK, Ng SS. (2019). Comparison of bilateral and unilateral upper limb training in people with stroke: *A systematic review and meta-analysis*. *PloS one*, 14(5), e0216357.

Chen PM, Liu TW, Kwong PW, Lai CK, Chung RC, Tsoh J, Ng SS. (2021) Bilateral TENS Improves Upper Limb Motor Recovery in Stroke: A Randomized Controlled Trial. *Stroke*, STROKEAHA-121.

Chen PM, Liu TW, Lai CK, Ng SS. (2021). Self-perceived performance in upper limb movement predicts the upper limb motor functions in people with stroke. *BMC Neurology*. (Submitted and under review).

CONFERENCE PRESENTATIONS

Chen PM, Lai CK and Ng SS, The Jacket Test: Its Reliability and Correlations with Upper Extremity Motor Functions in People with Chronic Stroke, *11th International Symposium on Healthy Aging*, 2016, P45.

Chen PM, Lai CK and Ng SS, The Jacket Test: Its Reliability and Correlations with Upper Extremity Motor Functions in People with Chronic Stroke. *10th Pan-Pacific Conference on Rehabilitation*, 2017.

Chen PM, Lai CK and Ng SS, Correlation of The Peak Torque and Agonist-Antagonist Cocontraction During Paretic Wrist Flexion and Extension with Upper Extremity Motor Functions in People with Chronic Stroke. *12th International Symposium on Healthy Aging*, 2017, P65.

Chen PM, Lai CK and Ng SS, The Correlation of Upper Limb Impairments and Function with Level of Community Integration in People with Stroke. *11th Pan-Pacific Conference on Rehabilitation*, 2018.

Chen PM, Lai CK and Ng SS, The Effect of Bilateral Movement Training and Conventional Upper Limb Exercise on Improving the Motor Impairment and Functional Ability after Stroke: A Systematic Review and Meta-Analysis. *11th Pan-Pacific Conference on Rehabilitation*, 2018.

Chen PM, Lai CK, Liu TW and Ng SS, Bilateral Transcutaneous Cutaneous Electrical Nerve Stimulation (TENS) is superior to Unilateral TENS in improving the upper limb muscle strength among people with chronic stroke: A pilot study. *11th WORLD CONGRESS FOR NEUROREHABILITATION*, 2020.

Chen PM, Lai CK, Liu TW and Ng SS, Effects of Bilateral Transcutaneous Electrical Nerve Stimulation Combined with Task-Oriented Training on the Recovery of Upper Limb Motor Impairment in People with Chronic Stroke. *International Stroke Conference 2021*. P218.

Chen PM, Liu TW, Lai CKY, Ng SSM, Prediction of Paretic Upper Limb Motor Function with Self-perceived Performance in Upper Limb Movement. *American Congress of Rehabilitation Medicine (ACRM) 98th Annual Conference*, e63.

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LIST OF ABBREVIATIONS

ADL activity of daily living

AOU amount of use

ARAT action research arm test

AROM active range of motion

AUC area under the curve

BBT block and box test

BI Barthel Index

Bi-TENS bilateral transcutaneous electrical nerve stimulation

BP blood pressure

BULT bilateral upper limb training

CI confidence interval

CIM community integration measure

CIMT constraint-induced movement training

EEG electroencephalogram

EMG electromyography

FES functional electrical stimulation

FIM Functional Independence Measure

FMA-hand hand subscale of Fugl-Meyer Assessment

FMA-UE Fugl-Meyer Assessment of Upper Extremity

fMRI functional magnetic resonance imaging

HR hazard ratio

ICC Intraclass Correlation Coefficient

ICF International Classification of Functioning, Disability, and Health

ICH intracerebral hemorrhage

iEMG integrated electromyography

IHI interhemispheric inhibition

LMM linear mixed model

M1 primary motor cortex

MAL motor activity log

MAS modified Ashworth Scale

MD mean difference

MEP motor evoked potential

MIVC maximum isometric voluntary contraction

NMES neuromuscular electrical stimulation

QOM quality of movement

RCT randomized controlled trial

ROC receiver operating characteristic

ROM range of motion

RR relative risk

SAH subarachnoid hemorrhage

SICI short-interval intra-cortical inhibition

SMD standard mean difference

TENS transcutaneous electrical nerve stimulation

TIA transient ischemic attack

TMS transcranial magnetic stimulation

TOT task-oriented training

Uni-TENS unilateral transcutaneous electrical nerve stimulation

UULT unilateral upper limb training

WMFT wolf motor function test

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Chapter 1

General introduction

1.1 An overview of stroke

1.1.1 The definition of stroke

According to the World Health Organization, stroke is, “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.” That has been a working definition created for assessing the prevalence and natural history of stroke (Kasner & Sacco, 2013).

1.1.2 Types of stroke and their prognoses

Etiologically, strokes can be classified into ischemic and hemorrhagic types. According to the American Heart Association, ischemic stroke is an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction (Kasner & Sacco, 2013). Hemorrhagic stroke is mainly due to arteriolar hypertensive disease, and more rarely due to coagulation disorders, vascular malformation within the brain, or diet (High alcohol consumption, low blood cholesterol concentration and high blood pressure are risk factors). Depending on the lesioned location, hemorrhage can be classified as intracerebral (ICH) (rapidly developing clinical signs of neurologic

dysfunction in response to focal collection of blood within the brain parenchyma or ventricular system which is not due to trauma) or subarachnoid hemorrhage (SAH) (bleeding into the subarachnoid space) (Kasner & Sacco, 2013).

In addition to the more common ischemic and hemorrhagic types, there is also transient ischemic attack (TIA), a special type of stroke which is "an episode of neurological dysfunction caused by focal cerebral ischemia with complete recovery within 24 hours" (Easton et al., 2009). TIA was found to be an indicator of future stroke in a study of 1137 people (Purroy et al., 2012). TIA survivors had a 2 to 4 times higher risk of stroke within 7 days (Hazard Ratio (HR), 3.97 (95%CI=1.91-8.26, p<0.001)) to 90 days (HR, 2.35 (95%CI=1.28-4.31, *p*=0.006)) after TIA when compared with non-TIA stroke survivors.

According to the global burden study database (Institute for Health Metrics and Evaluation, 2021), the total number of ischemia worldwide in 2019 was 77.19 million (72.65% of all strokes). ICHs were 20.66 million (19.44%) and SAHs were 8.40 million (7.91%). Giarola's cohort study (2018) found that about 4% of all strokes were reported in the preceding 90 days after TIA. A further cohort study (Lioutas et al., 2021) with 14,059 subjects between 1948 and 2017 found that the 90-day stroke risk after TIA was 16.7%, 11.1% and 5.9% in 1948-1985, 1986-1999 and 2000-2017, respectively. In Asia, the prevalence rates of ischemia, ICH and SAH were

approximately 46.83 million (71.45%), 13.89 million (21.19%) and 4.82 million (7.35%), respectively in 2019 (Institute for Health Metrics and Evaluation, 2021).

The data show that the one-year prognosis for an ischemic stroke is usually better than that of hemorrhage. Wei et al. (2010) compared the prognoses of 6354 subacute stroke cases in the first year post-stroke and found that the subjects with ischemia were superior to subjects with a hemorrhage to earn a good prognosis (modified rankin scale score<3) by the end of 12 months after their stroke (OR, 1.98 (95%CI=1.76-2.24, p<0.001). The mortality risk for subjects with a hemorrhage showed a gradually decreased trend (4-fold greater risk of mortality than for ischemia initially, 2.5 times after 1 week, 1.5 times after 3 weeks and same risk after 100 days) (Andersen et al., 2009). The poor prognosis for hemorrhage is mainly due to damaged brain cells, but also due to increased pressure in the brain or spasms in the blood vessels. These are more frequent compared to ischemia (Perna & Temple, 2015).

However, there is no significant difference in long-term prognosis between ischemic and hemorrhagic stroke (Li et al., 2015; Perna & Temple, 2015; Poon et al., 2014). Perna and Temple (2015) investigated the disability level of 172 subjects with ischemic stroke and 112 people with hemorrhagic stroke using the Mayo Portland Adaptability Inventory-4 from admission to discharge. They found that these was no significant difference in the improvements in the patients' disability level, on average, between ischemia and hemorrhage.

1.1.3 The epidemiology of stroke

Worldwide, there were about 7.63 million new ischemia, 3.41 million ICHs and 1.18 million new SAHs in 2019 (Institute for Health Metrics and Evaluation, 2021). In 119 high, middle and low income countries, the absolute incidence of ischemic stroke increased by 37%, and the absolute incidence of hemorrhagic stroke increased by 47% between 1990 and 2010 (Krishnamurthi et al., 2013). The total number of new strokes and of those who have survived, remained disabled or died almost doubled between 1990 and 2017 (Krishnamurthi et al., 2020). By 2030 there could be as many as 12 million deaths caused by stroke, 70 million people with stroke, and more than 200 million disability-adjusted life years lost from stroke annually all over the world (Feigin et al., 2014). A global burden of disease study has indicated that the age-standardized mortality rate of stroke has gradually decreased 22.5% between 1990 to 2013 as a result of better medical support (Feigin et al., 2016). A subsequent study (Amarenco et al., 2018) of 3,847 people with stroke in 21 countries showed that stroke's risk of recurrence averaged about 6.4% annually for first 5 years. Thus, a growing trend in the number of people with stroke must be expected, and more medical resources are needed for stroke rehabilitation worldwide.

In America about 79,500 suffer a new or recurrent stroke every year, of which 87% are ischemic, 10% are ICH, and 3% are SAH. From 2012 to 2030, an additional 3.4 million Americans over 18 (3.9% of the adult population) are projected to suffer a stroke, assuming a 20.5% increase in prevalence (Virani et al., 2021).

In more populous Asia, about 62.51 million people had been diagnosed with stroke by 2019 (Institute for Health Metrics and Evaluation, 2021). The number of stroke deaths is estimated to have been about 4.38 million, while the disability-adjusted life years due to stroke was approximately 143.23 million up to 2019.

In Hong Kong, nearly 55,000 people aged 65 or more suffered a stroke in Hong Kong in 2006 and over 60,000 in 2010 (Yu et al., 2012). The Hong Kong Census and Statistics Department estimated that there were about 57,500 people in Hong Kong in 2017 who had ever suffered a stroke (Census and Statistics Department HKSAR, 2019). There were 2,612 stroke inpatient discharges and 1,047 registered stroke deaths in 2018 (HKSAR, 2020). According to statistics from the Department of Health (Department of Health HKSAR, 2020), the number of deaths caused by cerebrovascular disease was 2,970 in Hong Kong in 2019. The deaths due to stroke increase dramatically with age (from 15 to 44 years old: 54 annually; from 45 to 64: 425; 65 years or older: 2,488). As Hong Kong's population ages, the number of cases of stroke is expected to increase to about 163,000 by 2036, with a corresponding 1.8-

times increase in the cost for their institutionalized care to HK$4.53 billion annually (Yu et al., 2012).

1.1.4 Stroke's direct and indirect costs

Stroke can be a heavy economic burden on society due to the enormous cost of treatment and subsequent daily care (Rajsic et al., 2019). That has a great impact on the utilization of post-stroke care services (Van Exel et al., 2003). The direct costs include hospital inpatient stays, outpatient or office-based provider visits, emergency department visits, home health care and prescribed medicines. The indirect costs arise mainly from the productivity lost (Virani et al., 2021) and informal caregiving (Joo et al., 2014).

Rajsic et al. (2019) reviewed 42 studies covering Australia, Britain, Canada, Cuba, Denmark, France, Germany, Italy, Malaysia, Netherlands, Norway, Sweden, Switzerland and the United States, and found that the overall cost of post-stroke care, including inpatient and outpatient costs, ranged from US$752 to $4,850 per patient per month. The main contributors to the overall cost of post-stroke care were general rehabilitation, home-based care, inpatient support, daily clinic services, outpatient rehabilitation, nursing home and aged care facilities and special accommodation.

In 32 European countries, the economic cost of stroke was estimated (Luengo-Fernandez et al., 2020) to be €60 billion in 2017. That included health care (45.0%), social care (8.3%), informal care (26.7%) and productivity losses (20.0%).

In the United States, the average annual direct and indirect cost of stroke in 2014 and 2015 was an estimated US$45.5 billion (Virani et al., 2021). The direct costs were estimated to be $28 billion with indirect costs, mostly from lost productivity, of about $17.5 billion. America's stroke-related medical costs are projected to more than double by 2035, from $36.7 billion to $94.3 billion (Nelson et al., 2016).

Turning to Hong Kong, the total direct medical cost in 2006 was estimated to be HK$1,332.1 million, including $1,108.3 million for public and private hospitalization, $67.0 million for outpatient care, $147.8 million for rehabilitation services and $8.9 million for community allied health services (Yu et al., 2012). The indirect cost due to premature death was estimated as $3,006.2 million (Yu et al., 2012).

1.2 Impairment of upper limb function in people with stroke

Upper limb motor impairment and loss of sensation are two of the most common deficits in people with stroke. About 30% to 66% of people with stroke have not regained full upper limb motor function 6 month after the stroke (Kwakkel et al., 2003). Fewer than 50% hemiplegic survivors regained functional arm use and fewer than 20% achieve good arm and hand recovery (Kong et al., 2011; Kwakkel et al., 2003). The 3 main types of motor impairment following a stroke are muscle weakness, spasticity and loss of dexterity.

1.2.1 Muscle weakness

Muscle weakness is reflected in an inability to generate normal levels of muscle strength or tension (Arene & Hidler, 2009). It is the most common upper extremity impairment in people with stroke and thus an important contributor to the survivor's reduced ability to use the arm and hand in daily activities (Ekstrand et al., 2016).

The strength of both the paretic and non-paretic upper limb often show some reduction in people with stroke. Andrews and Bohannon (2000) found that shoulder, elbow and wrist muscle strength dropped by 67.1% to 80.2% on the paretic side and 10.5% to 33.7% on the non-paretic side in a study of 48 subjects with 9.6±5.8 days post-stroke. Hunnicutt and Gregory (2017) reviewed 9 studies of knee extensor

strength on the non-paretic side and found it was about 63.2% to 105.1% of that of age-matched healthy adults.

Whether proximal muscles tend to be less impaired than distal muscles remains controversial, but flexor muscles are normally less impaired than extensor muscles. Two studies (Gowers, 1901; Twitchell, 1951) reported that shoulder muscle strength was tends to be less impaired than wrist and hand strength, and that elbow flexion strength tends to be less impaired than elbow extension strength (Moskowitz, 1969) in people with stroke. However, two other studies (Andrews & Bohannon, 2000; Thijs et al., 1998) did not find any significance in the impairment of the distal and proximal joint of paretic side in people with stroke.

Loss of motor units is known to be an important reason for muscle weakness in people with stroke. McComas et al. (1973) first documented the loss of motor units in people with lower limb hemiparesis in their study of 46 people with stroke. They found a more than 50% reduction in the number of functioning motor units in the paretic extensor digitorum brevis muscles (93.7±8.4) compared with the non-paretic limb (216.7±7.9) 6 months after the occurrence of stroke. The reduction in motor units mainly occurred from the 2nd to the 6th month after the stroke, and the surviving motor units remained dysfunctional until about the 19th month (McComas et al.,

1973). There was little axonal sprouting or collateral fiber innervation, which severely hampered neural reorganization (McComas et al., 1973).

A decreased rate of motor unit firing rate also causes muscle weakness in people with stroke. Rosenfalck and Andreason (1980) reported a decreased rate of motor unit firing rate in the tibialis anterior muscles of 10 subjects they studied 7 days to 16 years post-stroke. Others have attributed it to prolonged hyperpolarization of membrane potentials and preferential atrophy of fast switch muscle fibers (Chokroverty et al., 1976). Two studies (Hu et al., 2012; Suresh et al., 2011) investigated motor unit control in the paretic and non-paretic hand when performing isometric maximum voluntary finger abduction contractions found an approximately 25% reduction in the mean motor unit firing rate and 50–75% reduction of the threshold for recruiting motor units in the paretic first dorsal interosseous muscle as compared with the non-paretic side.

The altered neurophysiological properties of the motor unit affects recruitment, recruitment order, discharge rate and discharge pattern. It is known to be a main cause of muscle weakness (Shin et al., 2018). Previous studies have reported about 33.3% atrophy of fast-twitch, fatigable, high-force-producing fibers (Dietz et al., 1986; Edström et al., 1973) and about 16.7% hypertrophy of slow-contracting, fatigue-resistant, and low-force-producing fibers (Edström, 1970) 6 months post-stroke. That

can result in slower muscle contractions generating less force, and also poor endurance in repetitive tasks or movements. Lukács et al. (2008) used single-fiber macro-electromyography (EMG) to detect motor unit potentials in the abductor digiti minimi when people with stroke performed tasks requiring high (50% of the maximum load) and low (10%) force output. The results showed 70.7% higher motor unit potential on the non-paretic side than on the paretic side when the force output was high. The high and low force output in the paretic side showed similar motor unit potential amplitudes.

Previous cross-sectional studies have identified the relationship between upper limb muscle strength and upper limb motor function in people with stroke. Hand grip strength has been shown to be a useful predictor of upper limb motor function (Faria-Fortini et al., 2011; Mercierand & Bourbonnais, 2004). The paretic hand's grip strength was significantly correlated with functional mobility as measured by the block and box test (BBT) (r=0.69, $p<0.001$) or the nine-hole peg test (r=0.54, $p<0.001$) in 67 patients with chronic stroke (Faria-Fortini et al., 2011). Mercierand and Bourbonnais (2004) showed that hand grip strength and shoulder flexion strength were excellent predictors of upper limb functioning as measured by the BBT (r =0.787-0.813), the finger-to-nose test (r=0.622–0.704) or the Fugl-Meyer Assessment of Upper Extremity (FMA-UE) (r=0.691-0.729) in 13 subjects with chronic stroke.

Muscle weakness of course affects one's ability in the activities of daily living (ADL) and community integration in people with stroke. Harris and Eng (2007) have shown that paretic hand grip strength is significantly associated with ADL performance ($r=0.61$, $p<0.01$) and with Chedoke Arm and Hand Activity Inventory scale scores ($r=0.69$, $p<0.01$). Lieshout et al. (2020) reported that upper limb strength measured using the motricity index is a significant predictor ($\beta=0.696$, $p<0.001$) of health-related quality of life 3 months post-stroke. Kwong et al. (2017) developed a structural equation model and found the significant relationship between level of community integration and muscle strength ($\beta=0.18$, $p<0.05$), balance ($\beta=0.21$, $p<0.05$) and walking endurance ($\beta=0.41$, $p<0.001$).

1.2.2 Spasticity

Spasticity is a "motor disorder characterized by a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitability of stretch" (Lance, 1980). There is also a new definition from the Support Program for Assembly of a Database for Spasticity Measurement project which defines spasticity as "disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles" (Bhimani & Anderson, 2014).

A stroke impairs the upper motor neurons by disrupting corticospinal communication, resulting in a state of net disinhibition of the spinal reflexes (Bhimani & Anderson, 2014). In people with stroke, when muscles are stretched passively, sensory input is delivered from muscle spindles via primary group Ia afferent fibers to the spinal cord, activating alpha motor neurons. The excessive muscle activation occurs as a result of loss of supra-spinal inhibitory control in people with stroke (Nardone & Schieppati, 2005). Additionally, Ia and Ib interneurons and Renshaw cells in the spine lose descending inhibitory or facilitation influences from the central nervous system (Nielsen et al., 2007). The disruption of spinal interneuron-mediated influences reduced the inhibition of antagonist muscles and increase the action potentials in sensory neurons. That could also result in excessive muscle activation (Mukherjee & Chakravarty, 2010), which contributed to spasticity.

Previous clinical trials (Kuo & Hu, 2018; Lundström et al., 2008; Schinwelski et al., 2019; Sommerfeld et al., 2004; Watkins et al., 2002; Welmer et al., 2006; Wissel et al., 2010; Zorowitz et al., 2013) have reported that the prevalence of spasticity ranges from 20% to 80% among people with stroke. The incidence of upper limb spasticity has been reported as 4–27% at 1 month post-stroke, 19–26.7% from 1 to 3 months and 17–42.6% after 3 months (Opheim et al., 2014).

Functional deficits led by spasticity would be expected to reduce one's quality of life and lead to dependence in daily living. Watkins et al. (2002) demonstrated that the persons with upper or lower limb spasticity have significantly lower Barthel Index scores at 12 months post-stroke (p<0.001) compared with stroke subjects without spasticity. That can explain why stroke subjects with spasticity tend to be more seriously impaired functionally than those without it. Milinis et al. (2016) reviewed 17 studies covering 795 people with stroke and found that those with upper or lower limb spasticity showed significantly poorer quality of life than those without spasticity. The various studies used short form-36, the Life Situation questionnaire, a sickness impact scale and a life satisfaction questionnaire.

1.2.3 Dexterity

Poor dexterity is the inability to coordinate muscle activity in the performance of a motor task. It is a common sequela of loss of muscle strength and is most commonly found in the hands (Canning et al., 2000). On the neurophysiological level, loss of dexterity implies impairment of the distributed processing of the many parallel corticospinal channels which enable rapid transfer of sensorimotor information between the cerebral cortex and the spinal cord (Darian-Smith et al., 1996; Galea & Darian-Smith, 1997a, 1997b). Such impairment finally results in muscle activation abnormalities such as reduced velocity (Fagioli et al., 1988), excessive co-contraction

(Hammond et al., 1988) and abnormal spatial patterns of muscle use (Bourbonnais et al., 1989). Canning et al. (2000) has attributed loss of hand dexterity to the excessive biceps muscle activation (p=0.002) and reduced coupling of muscle activation (p=0.002) with the targeted movement.

A loss of hand dexterity is known to be correlated with participation in daily activities (Alon et al., 2007; Rand & Eng, 2015). Alon et al. (2007) has shown that grasping, holding and manipulating objects remain deficient in 55% to75% of patients 3 to 6 months post-stroke. Rand and Eng (2015) found that hand dexterity measured using the BBT can independently predicted 9.6% of the variance in daily use of an upper limb 12 months post-stroke, after controlling for age and upper limb daily use time measured by the wrist accelerometer.

1.2.4 Sensory impairment

Approximately 50 to 80% of people with stroke reported some loss of sensation (Carey et al., 2011; Doyle et al., 2010). The sensory impairment can be abnormal sense of touch, pain, temperature and/or proprioceptive input (Carey, 1995). Among them, tactile sensations (65%–94%), proprioception (17%–25%), vibration (44%), light touch (32%–89%) and pinprick sensation (35%–71%) are the most

frequently reported impairments following stroke (Acerra et al., 2005; Carey et al., 1993; Hunter & Crome, 2002; Tyson et al., 2008).

Sensory processing involves different pathways and areas of the brain, so lesioning anywhere from the brainstem to the cortex impairs sensation. Neuroimaging studies (Baier et al., 2014; Nudo et al., 2000; Preusser et al., 2015) have shown that lesions in the somatosensory cortex, insular cortex, thalamus, dorsal internal capsule, corona radiata, pons, and other cortical areas are all associated with sensory impairment.

Sensory impairment in people with stroke can give rise to secondary complications, such as pressure sores, abrasions and shoulder-hand syndrome which could severely influence quality of life (Rand et al., 2001; Suethanapornkul et al., 2008). Carey et al. (2018) assessed the motor and somatosensory impairment of 268 subjects 3 months post-stroke and found that 33.6% of them had experienced somatosensory impairment which significantly reduced their activity participation ($z=1.96$, $p=0.048$) as measured by the National Institutes of Health Stroke Scale. Sommerfeld and Von Arbin (2004) investigated 115 subjects in a stroke rehabilitation unit and found that those with normal somatosensory functioning (89%) had a significantly greater probability ($p<0.001$) of being discharged within 3 months compared with those impaired or not assessable (8%) somatosensory function, which indicated that better somatosensory function is associated with shorter length of

hospital stay. However, it should be noted that they could not determine to what extent the discharge outcome was influenced by poor compliance rather than the degree of impairment.

1.3 Recovery of upper limb motor function

The spontaneous recovery of motor function can usually be divided into 3 stages (see Figure 1.2) in people with stroke (Cassidy & Cramer, 2017). The first stage lasts from the initial hours for several days. It mainly involves salvaging threatened tissue through, for example, reperfusion or neuroprotection (Tan et al., 2003). The second stage begins after a few days and lasts for about 6 months. The main focus is initiating brain repair (Kwakkel & Kollen, 2013; Kwakkel et al., 2003). The third stage begins after about 6 months. In that stage, the brain's functioning is relatively stable with regard to endogenous repair-related events, but modifications in brain structure and function are still possible (Tombari et al., 2004).

1.4 Peripheral electrical stimulation and motor recovery in people with stroke

Electrical stimulation of peripheral nerves is a common therapeutic

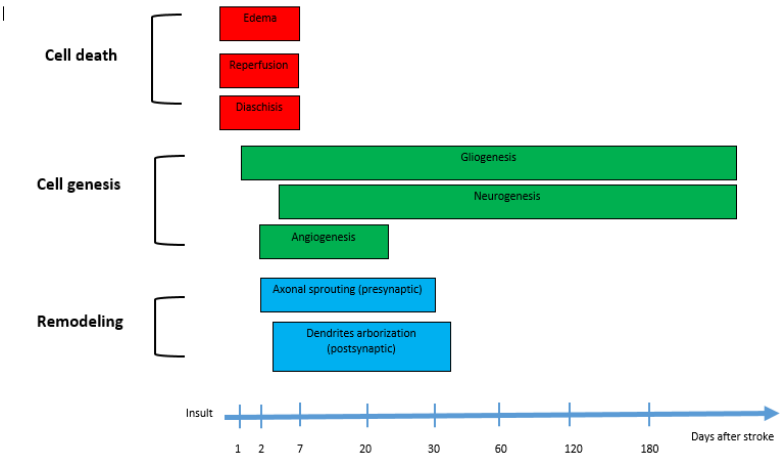


Figure 1.1 Time course of recovery (modified from (Dalise et al., 2014; Wieloch & Nikolich, 2006))

intervention to enhance motor recovery in people with stroke. Functional electrical stimulation (FES) and transcutaneous electrical nerve stimulation (TENS) are the most popular types of stimulation used. FES is widely used to facilitate voluntary muscle contraction of very weak muscles (Young, 2015), while TENS is more often applied to enhance limb function (Pan et al., 2018).

1.4.1 Functional electrical stimulation

FES is a technique that uses short bursts of electrical pulses to elicit action potential in the motor neurons enervating a target muscle to generate contraction and ideally functional movement (Raymond, 2006). It stimulates the intact peripheral motor nerves to promote functional activity. In order to generate tetanic contraction in

people with stroke, a pulse amplitude of 2–120mA and a pulse width of 100–350μs are typically used (Physiopedia, 2019). Monophasic or biphasic pulses can be used at a frequency between 20 and 40Hz (Marquez-Chin & Popovic, 2020).

Numerous reviews have shown that FES can improve upper limb and lower limb motor function in people with stroke, including reducing spasticity and the associated pain (Eraifej et al., 2017; Quandt & Hummel, 2014; Robbins et al., 2006; Roche et al., 2009; Vafadar et al., 2015), increasing joint range of movement (Roche et al., 2009), improving muscle strength (Eraifej et al., 2017; Robbins et al., 2006; Roche et al., 2009; Vafadar et al., 2015) and improving circulation (Quandt & Hummel, 2014). The two systematic reviews and meta-analyses led by Eraifej (2017) and Howlett (2015) both reported that FES can improve ability in the activities of daily living in people with stroke.

FES is effective in improving upper limb motor function in people with stroke (Hara et al., 2013; Mangold et al., 2009). Hara's et al. (2013) revealed that 40 sessions of EMG-triggered FES training for the hand, forearm, elbow and shoulder each 40 minutes long could generate significantly greater perfusion (lesioned side: 0.1403± 0.1039 mmol mm; intact side: 0.0691±0.0571 mmol mm, Scheffe test, $p<0.01$) in both the lesioned and the intact sensory-motor cortex as measured by functional near-infarct spectroscopy. That was more effective than the same dosage of voluntary muscle contraction training with simple transcutaneous electrical stimulation in 16

people with chronic stroke. Recent studies (Biasiucci et al., 2018; Jang et al., 2016) have suggested that FES involving a brain-computer interface is even more effective in enhancing the upper limb motor function in people with stroke. For example, Jang et al. (2016) showed that 30 sessions (5 times per week for 6 weeks) of FES controlled by a brain-computer interface could generate significantly greater improvement in the shoulder subluxation of a paretic upper limb than same dosage of pure FES group in 20 subjects with chronic stroke. They measured pain, hand function and vertical and horizontal range of the glenohumeral joint. Similar results had been reported in another randomized controlled trial (RCT) (Biasiucci et al., 2018).

FES is also an effective intervention in improving the lower limb motor function, which has been proved by the previous clinical trials. Shariat's systematic review and meta-analysis (2019) covered 14 clinical trials and found that FES combined with cycling exercise was superior to cycling exercise alone in improving the balance of people with stroke (SMD, 1.48; 95%CI, 0.99-1.97, I^2=91%). Bakhtiary and Fatemy (2008) also found that 20 sessions of FES combined with Bobath therapy was superior to the same dosage of Bobath therapy alone in reducing plantar flexor spasticity (mean difference=-0.5, p=0.001) and increasing plantar flexor strength (mean difference=0.3, p=0.04) in a study of 40 people with stroke.

1.4.2 Transcutaneous electrical nerve stimulation

1.4.2.1 Different modes and its parameters of TENS

TENS is a non-invasive peripheral stimulation technique which primarily aimed to relieve pain (Dowswell et al., 2009; Hansson & Ekblom, 1983; Kaplan et al., 1998; Pitangui et al., 2014). The gate control theory and the endogenous opioid system are the two primary theories to explain the pain relief mechanism of TENS. Melzack and Wall (1965) suggested that stimulation on the large diameter A-β afferents by TENS could inhibit nociceptive evoked responses in the fibers of the dorsal horn. Kalra et al. (2001) found that both high and low frequency TENS can activate μ-opioid and δ-opioid receptors on both the spinal and supraspinal level. The opioids released are effective within 5 minutes and 18 hours stimulation period (Woolf, 1994), and its effects persists even after cessation of the stimulation.

There are 3 typical modes of TENS applied in clinic: conventional mode, acupuncture mode and intense mode. Table 1.1 (Johnson, 2007) showed the details the different modes, their parameters and their clinical application.

All three modes of TENS activate A-β afferent fibers. Levin and Hui-Chan (1993) demonstrated that both conventional and acupuncture-like TENS could activate similar A-β afferent fibers on 17 healthy adults.

1.4.2.2 TENS in stroke rehabilitation

Many clinical studies over the past 3 decades have demonstrated the beneficial effects of TENS in upper limb stroke rehabilitation (Table 1.2). TENS was found to be effective in activating the somatosensory cortex (Peurala et al., 2002). It can improve spasticity (Kim, In, et al., 2013; Peurala et al., 2002; Tekeolu et al., 1998) and muscle strength (Conforto et al., 2002; Jung, Jung, et al., 2017; Klaiput & Kitisomprayoonkul, 2009), relieve pain (Peurala et al., 2002) and improve skin sensation (Peurala et al., 2002). Upper limb motor control can be improved in general (Conforto et al., 2007; Jung, Jung, et al., 2017; Kim, In, et al., 2013; Peurala et al., 2002; Sonde et al., 1998; Wu et al., 2006) or in terms of finger and hand tapping frequency (Koesler et al., 2009) in people with stroke. These studies reveal that both high intensity, low frequency TENS and TENS at low intensity and high frequency can improve upper limb motor function.

Table 1.1 Modes, parameters and clinical applications of TENS

	Conventional TENS	**Acupuncture-like TENS**	**Intense TENS**
Frequency	High (50-100Hz)	Low (2-4Hz)	High (up to 100Hz)
Intensity	Low (paraesthesia but not painful)	High (just tolerable)	High (just tolerable)
Targeted fibers being stimulated	Large diameter, low threshold A-β fibers	Small diameter, high threshold A-δ fibers; Large diameter, low threshold A-α and A-β fibers	Large diameter, low threshold A-β fibers; Small diameter, high threshold A-δ fibers
Clinical application	To inhibit the transmission of nociceptive signals from the spine to the central nervous system	(1) To activate extra segmental descending pain inhibition pathways. (2) To activate A-δ fibers by triggering non-painful muscle twitches	(1) To inhibit the transmission of nociceptive signals from the spine to the central nervous system. (2) To activate extra segmental descending pain inhibition pathways.

Table 1.2 Summary of studies investigating TENS in upper limb motor recovery in people with stroke

Study	Study Design	Sample Size (TENS/ Control)	Post-stroke Duration	Experimental Group Protocol				Control Group Protocol		Finding
				Stimulation Setting	Dosage	Exercise setting	Dosage	Treatment	Dosage	
Tekeoglu et al (Tekeolu et al., 1998)	RCT	30/30	42.6 months	100Hz active TENS on the musculus triceps brachii	30 minutes per session, 5 sessions per week for 8 weeks (40 sessions)	Todd–Davies exercise	30 minutes per session, 5 sessions per week for 8 weeks (40 sessions)	Placebo-TENS + Todd–Davies exercise	As in the experimental group	MAS: TENS↓, Control↓ BI: TENS↑>Control↑
Jung et al (Jung, Jung, et al., 2017)	RCT	23/23	13.9 months	100Hz TENS with intensity of two to three times the sensory threshold	30 minutes per session, 5 sessions per week for 4	TOT	30 minutes per session, 5 sessions per week for 4	Placebo-TENS+TOT	As in the experimental group	FMA-UE: TENS↑>Control↑ IEMG: TENS↑>Control↑

				on the triceps and wrist extensors	weeks (20 sessions)		weeks (20 sessions)			Muscle strength of the wrist and elbow extensors: TENS↑>Control↑ AROM: TENS↑>Control↑
Kim et al (Kim, In, et al., 2013)	RCT	17/17	13.0 months	100Hz TENS with intensity at two to three times the sensory threshold on the triceps and wrist extensors +TOT	30 minutes per session, 5 sessions per week for 4 weeks (20 sessions)	TOT	30 minutes per session, 5 sessions per week for 4 weeks (20 sessions)	Placebo-TENS+TOT	As in the experimental group	FMA-UE: TENS↑>Control↑ MFT: TENS↑>Control↑ BBT: TENS↑>Control↑ MAS: TENS↑, Control→

Peurala et al (Peurala et al., 2002)	RCT	32/8	3.3 years	50Hz glove-electrode cutaneous stimulation with intensity just below the sensory threshold on the whole hand	20 minutes per session, twice per day for 3 weeks (21.6±6 sessions)	N/A	N/A	Placebo stimulation without current	As in the experimental group	Skin sensation: TENS↑, Control→ SEPs: TENS↑, Control→ MMAS: TENS↑, Control→ Hand function: TENS↑, Control→ 10MWT: TENS↑, Control→
Wu et al (Wu et al., 2006)	Crossover design	9/9	6.5 years	10Hz somatosensory stimulation with intensity barely below the motor	2 hours (1 session)	N/A	N/A	No stimulation	- N/A	JTHFT: TENS↑>control→

				threshold of the median, ulnar and radial nerves						
Klaiput and Kitisompray oonkul (Klaiput & Kitisompray oonkul, 2009)	RCT	10/10	11.9 days	10Hz peripheral sensory stimulation with an intensity appreciating paresthesias on the ulnar and median nerves	2 hours (1 session)	N/A	N/A	Sham control stimulation with intensity at the minimal perception level	As in the experimental group	Lateral and tip pinch force: TENS↑>Control↑ ARAT: TENS→, Control→
Johansson et al (Johansson et al., 2001)	RCT	51/51	5 to 10 days after acute stroke	High intensity (elicit visible muscle contraction), 2Hz electrical stimulation at LI 11	30 minutes per session, twice per week for 10	PT, OT, ST	Not mentioned	Low intensity (below perception), High frequency (80Hz)	TENS dosage as in the TENS group;	RMI: TENS=Control Ability to walk 10m: TENS=Control

				and LI 4 on the paretic side upper limb	weeks (20 sessions)			electrostimulation + PT + OT + ST	PT, OT, ST: not mentioned	Walking speed: TENS=Control
Sonde et al (Sonde et al., 1998)	RCT	26/18	8.7 months	1.7Hz TENS with intensity to elicit distinct contraction of the elbow extensors or shoulder abductors	60 minutes per session, 5 sessions a week for 3 months (60 sessions)	PT	twice a week for 3 months (24 sessions)	PT	As in the experimental group	FMA-UE: TENS↑>Control→ Spasticity: TENS→, Control→ Sensitivity: TENS→, Control→ Pain: TENS→, Control→
Koesler et al (Koesler et al., 2009)	Crossover design	12/12	15.7 months	1Hz electrical stimulation of the median nerve with	2 hours (1 session)	N/A	N/A	idle time on a separate occasion	As in the experimental group	Finger and hand tapping frequency: TENS↑, Control→

				an intensity on average 60% above the individual somatosensory threshold						Wrist and finger velocity: TENS↑, Control→
Conforto et al (Conforto et al., 2002)	Crossover design	8/8	5.5 years	1Hz electrical stimulation causing strong paresthesias of the median nerve at the wrist	2 hours (1 session)	N/A	N/A	Stimulation below that required to elicit paresthesia	As for the experimental group	Pinch strength: TENS group↑ correlated with stimulation intensity↑
Conforto et al (Conforto et al., 2007)	Crossover design	11/11	4.3 years	1Hz suprathreshold electrical stimulation of the median nerve	2 hours (1 session)	N/A	N/A	1Hz subthreshold on the median nerve	As in the experimental group	JTHFT: TENS↑>Control↑

Celnik et al (Celnik et al., 2007)	Crossover design	9/9	3.2 years	1Hz synchronous nerve stimulation with intensity adjusted to elicit mild paresthesias on the ulnar and median nerves	2 hours (1 session)	N/A	N/A	No stimulation	N/A	Intracranial inhibition: TENS↓, Control→ JTHFT: TENS↑ at post and follow-up

Notes: ↑ indicates a significant improvement; → indicates no significant difference. ARAT: Action Research Arm Test; 10MWT: 10 metre walk test; BI: Barthel Index; FMA-UE: Fugl-Meyer Assessment for the Upper Extremities; IEMG: integrated electromyography; JTHFT: Jebsen-Taylor Hand Function test; LI: Large Intestine; MAS: Modified Ashworth scale; MFT: Manual function test; MMAS: Modified motor assessment scale; OT: Occupational therapy; PT: Physiotherapy; RCT, Randomized controlled trial; RMI: Rivermead Mobility Index; SEPs: somatosensory evoked potentials; ST: Speech therapy; TENS: Transcutaneous electrical nerve stimulation; TOT: Task-oriented training

Some other clinical trials (Hussain & Mohammad, 2013; Jung, In, et al., 2017; Kwong et al., 2018a; Ng & Hui-Chan, 2007, 2009; Tyson et al., 2013) have reported the effectiveness of TENS in promoting motor recovery of a lower limb. It was shown to reduce spasticity, improve muscle strength of the hip, knee and ankle, range of motion of the ankle, sitting balance, ankle proprioception and walking ability. Kwong et al.'s systematic review and meta-analysis (2018b) covering 11 RCTs and reported 60 minutes of TENS was superior to shorter stimulation times for increasing gait speed, improving timed up and go performance (Hedges's g=0.468, 95%CI=0.201—0.734) and reducing spasticity in paretic plantar flexors (Hedges's g=-0.884, 95%CI=-1.140—-0.625) in people with stroke. Mahmood et al. (2019) conducted a meta-analysis with 7 RCTs and found that active TENS combined with conventional physical therapy including task-oriented training (TOT), Bobath techniques, gait training and functional exercise can alleviate lower limb spasticity significantly better than placebo-TENS combined with conventional physical therapy (standard mean difference=-0.64, 95%CI=-0.98—-0.31, *p*=0.001) or conventional physical therapy alone (standard mean difference=-0.83, 95%CI=-1.51—-0.15, *p*=0.02) in people with stroke. For the purpose of this study, the detailed discussion of the literature will only focus on those pertaining to the TENS effect on upper limb.

1.4.3 Proposed TENS mechanisms for recovery of motor functions

1.4.3.1 Decreased hyperexcitability of alpha motor neurons

TENS has been found to alleviate the hyperexcitation of alpha motor neurons in people with stroke. After an upper motor neuron is lesioned, spinal reflex hyperactivity gradually

emerges. It is caused primarily by a loss of inhibition from the damaged cortical region to the dorsal reticulospinal tract in the brain stem or spinal cord (Sheean & McGuire, 2009). Bakheit et al. (2003) demonstrated this by recruiting 24 people with stroke (post-stroke duration 5 to 40 months) and assessed the excitability of alpha motor neurons by EMG and spasticity using the MAS. He showed that increased alpha motor neuron excitability of decreased presynaptic and reciprocal inhibition and reduced IA facilitation of the tibial nerve, and that is correlated with the spasticity.

Previous evidence (Joodaki et al., 2001; Levin & Hui-Chan, 1992, 1993) had shown that TENS can reduce the hyperactive stretch reflex, lengthen the H-reflex and lengthen the stretch reflex's latency by enhancing the presynaptic inhibition of group Ia terminals, so that the alpha motor neuron disinhibited. Joodaki et al. (2001) had shown that, in a study of 10 non-athletic but healthy men (mean age=25.6 ± 4.4 years), 30 minutes of high frequency (99Hz) TENS applied to the common peroneal nerve could significantly reduce the magnitude of the H-reflex and F-wave, H/M ratios and F/M ratios, and lengthen the latency of the H-reflex and F-wave of the soleus muscle. A small study led by Levin et al. (1992) with 10 subjects 7 to 56 months post-stroke showed that 15 daily 1-hour sessions of high frequency (99Hz) at low intensity (twice the sensory threshold) could reduce the stretch reflex in spastic ankle plantarflexors by 31.2%. They (Levin & Hui-Chan, 1993) later showed that even 1 45-minute session of high frequency (99Hz) TENS applied to the common peroneal nerve at twice the sensory threshold could produce a 50% lengthening of soleus H-reflex latency 60 minutes post-stimulation.

1.4.3.2 Reduction of short-interval intra-cortical inhibition

TENS can also improve motor function by reducing short-interval intra-cortical inhibition (SICI) in people with stroke. SICI is measured by transcranial magnetic stimulation (TMS) as the relative amplitude reduction of motor evoked potential (MEP) by subthreshold conditioning stimuli (Samusyte et al., 2018). Rossini et al. (2015) has demonstrated that SICI at an interstimulus interval of 2.5ms can serve as an indicator of gamma-aminobutyric acid receptor-mediated inhibition in the motor cortex. It has been suggested that neuroplasticity is probably suppressed by such mechanisms in healthy persons, and their release facilitated the reorganization of motor representation areas (Jacobs & Donoghue, 1991) and motor learning (Smyth et al., 2010).

Support of such a mechanism can be found in Murakami et al.'s study (2007) with 11 healthy subjects. The study showed that 30 minutes of high frequency somatosensory electrical stimulation on the right median nerve at the wrist (150Hz, produced a tingling sensation without muscle twitch) can significantly reduce SICI measured by TMS in 11 healthy subjects. Celink et al. (2007) reported that just one 120-minute TENS session at 1Hz applied to a paretic abductor digitiminimi and flexor pollicis brevis greatly reduced the Jebsen Taylor Hand Function Test completion time while also reducing (p<0.001) and GABA-mediated SICI (p<0.05) than 120-minute sham stimulation in his experiments with 9 people with stroke.

1.4.3.3 Enhancement of corticospinal excitability

Neuroimaging has demonstrated that TENS can improve motor functions following a stroke by enhancing corticospinal excitability. The corticospinal pathway includes the motor cortex, descending axons and spinal motor neurons (Brouwer & Ashby, 1990). It is considered the primary circuit for voluntary motor control (Weavil & Amann, 2018). Greater corticospinal excitability is considered as an important indicator of an activity-dependent change in the balance between inhibitive and facilitative circuits and their interactions, determining the final output from the primary motor cortex (M1) (Moscatelli et al., 2016).

Several studies have shown that transcutaneous electrical stimulation can enhance corticospinal excitability in healthy adults. Charlton et al. (2003) revealed that 2 hours of transcutaneous electrical stimulation (10Hz, intensity sufficient to elicit a weak contraction) applied on the radial and ulnar nerve or on the motor point of the first dorsal interosseous muscle induces a 50% increase in the MEP of the first dorsal interosseous point in the motor cortex for at least 2 hours in 12 healthy adults. Khaslavskaia et al. (2002) reported that 30 minutes of transcutaneous electrical stimulation (at 200Hz and 2 to 3 times the motor threshold) applied to the common peroneal nerve increased the MEP of the tibialis anterior muscle by up to 104% throughout the stimulation period, and that the effects lasted for 110 minutes after the stimulation. Similarly, Chipchase et al. (2011) showed that one 30–minute session of 100Hz transcutaneous electrical stimulation applied to the brachii elicited significant corticospinal activation (p=0.002). While 10Hz stimulation suppressed the responsiveness of the corticospinal pathway on the lesioned side (p<0.01) as measured by MEP induced by TMS. Kaelin-Lang et al.

(2002) found that one 2–hour transcutaneous electrical stimulation session with healthy adults (10Hz, intensity sufficient to elicit a small compound muscle action potential) applied to the ulnar nerve at the wrist produced an MEP of the abductor digiti minimi muscle by transcranial magnetic stimulation in healthy adults.

1.4.3.4 Enhancement of corticomuscular coherence

Neuroimaging studies (Lai et al., 2016; Pan et al., 2018) have also demonstrated TENS' effectiveness in improving the motor functioning in people with stroke by enhancing corticomuscular coherence. Corticomuscular coherence is a direct index of the connections and relationship between cortical and muscular neural activity as measured by electroencephalography (EEG) and electromyography (EMG), respectively. It is commonly reported as the extension of Pearson correlation coefficient in the specific spectrum frequency domain (Mima & Hallett, 1999), which quantifies the functional coupling level of the motor cortex and its associated muscles. Previous EEG and EMG findings (Fang et al., 2009; Gerloff et al., 2006; Mima et al., 2001; Strens et al., 2004) have shown that a lesion in the central nervous system (e.g. a stroke) can weaken corticomuscular coherence. During motor recovery (e.g. post-stroke), the level of corticomuscular coherence gradually recovers to a plateau where it may still be weaker than normal (Meng et al., 2008; von Carlowitz-Ghori et al., 2014).

Several studies (Lai et al., 2016; Pan et al., 2018) have demonstrated that transcutaneous electrical stimulation can improve corticomuscular coherence in people with stroke. Lai et al. (2016) showed that 1 session of 40-minute sensory electrical stimulation applied to the median

nerve could increase EEG-EMG coherence in the gamma band 22.1% in healthy adults and 48.6% in people with stroke. Pan et al. (2018) found that 16 TENS sessions of 40 minutes at 100Hz applied to the median nerve when combined with hand function training generated a significant increase in corticomuscular coherence (p=0.004) as measured by the EMG signal of the paretic thenar eminence and the EEG signal at the mid-intervention (forth week) in people with stroke, when compared with the group with similar setting of function task combining with sham electrical stimulation.

1.5 Task-oriented training in stroke rehabilitation

1.5.1 The definition of Task-oriented training

Task-oriented training (TOT) is developed based on the behavioral, experience-dependent, neural plasticity aspects (Kleim & Jones, 2008) and recent model of motor learning (Winstein et al., 2014). It is a goal-directed therapy designed to help people with neural diseases develop control of movements they need to deal with their real environments (Thielman et al., 2004). That rather than addressing the specific remediation of impairment or specific movement kinetics in isolation. An effective TOT design features challenges, is progressive and is adapted to the daily functional demands of interest (Harvey et al., 2008). TOT first breaks down the relevant activities into component tasks. It focuses on practice and repetition of the component tasks as well as of the functional task as a whole. TOT emphasizes the practice of meaningful functional activities rather than the remediation of impairment.

1.5.2 TOT in stroke recovery

Previous systematic reviews and meta-analyses (Bosch et al., 2014; French et al., 2010; Jeon et al., 2015; Langhorne et al., 2009; Rensink et al., 2009; Timmermans et al., 2010; Wevers et al., 2009) have demonstrated the beneficial effects of TOT in upper and lower limb motor recovery in people with stroke. Several clinical trials (da Silva et al., 2015; Winstein et al., 2016) have demonstrated the beneficial effects of TOT in motor recovery of hand and arm motor function in people with stroke. For example, Da Silva et al. (2015) compared the effectiveness of TOT without load with TOT against personalized resistance. The subjects were 20 people with chronic stroke. They performed not only elbow and wrist flexor stretching and shoulder abduction, but also hair brushing, putting on a scarf, feeding, handling a coffee pot, and putting a pot on a high shelf during 12 30-minute sessions over 6 weeks. With or without loading, all of the participants significantly improved their performance as measured by FMA-UE score (p=0.001-0.041), active shoulder range of movement (ROM) (p=0.001), hand grip strength (p=0.001) and shoulder flexion strength (p=0.001-0.004) in 20 subjects with chronic stroke. For another example, Winstein's 12 month RCT (2016) with 361 people with stroke (mean duration post-stroke=46 days) investigated the effect on upper limb motor function of 30 sessions (3 sessions per week for 10 weeks) of (1) TOT (n=119), (2) dose-matched occupational therapy (n=120) and (3) monitor-only occupational therapy without regulated dosage (n=122). All 3 therapies generated significant within-group progress but without significant between-group

difference. The within-group differences included significantly better Wolf Motor Function Test (WMFT) scores (mean change=0.75-0.84, $p<0.05$) and significantly reduced completion time (mean change=-8.8— -7.2, $p<0.05$). The authors suggested that higher intense training was needed to detect any superiority of TOT in improving the motor recovery of an upper limb in people with stroke.

Some other RCTs have shown that TOT can induce great neural plastic changes which transfer to real-life activity (Jang et al., 2003; Timmermans et al., 2014). Jang et al. (2003) conducted a RCT involved 16 sessions (40 minutes per day, 4 days per week for 4 weeks) of TOT (including throwing two switches alternately, switching 5 different-colored switches horizontally, reaching-grasping-transfer-release of five plastic bottles, transferring 40 iron balls, switching four switches in 4 different locations and throwing a rubber ball at a target) to train the 4 people with chronic stroke. The subjects showed increased cortical activity in the lesioned primary sensorimotor cortex and decreased activation in the intact primary sensorimotor cortex measured by functional magnetic resonance imaging (fMRI) (mean change of laterality index=1.1) when performing timed finger flexion and extension exercises at a fixed rate. Timmermans et al. (2014) conducted a single-blind RCT with 22 people with chronic stroke who received either robot-assisted arm-hand training or TOT. All of the subjects received four 60-minute sessions per week for 8 weeks. Both groups showed significantly better performance and maintained for 6 months after the training in perceived performance as measured by Motor Activity Log (p=0.008-0.013). Moreover, there was a significant within-group improvement only in the TOT group in quality of life measured by the physical health section of Short form-36

(mean difference=12.0, p=0.01) and the EuroQol-5D (mean difference=8.0, p=0.012). The improvements were maintained for 6 months after the training ended (Timmermans et al., 2014).

TOT is also effective in promoting lower limb motor recovery in people with stroke. Body weight-supported treadmill training (Aaslund et al., 2013), circuit training (Dean, 2012) are found to improve lower limb motor function in people with stroke. Fernandes et al. (2015) randomly allocated 16 people with stroke (less than 1-month post-stroke) into either a TOT group which focused on balance and strength training of the paretic lower limb or a control group which received conventional rehabilitation. Both groups received 70 minutes of therapy per session, 4 sessions per week for 12 weeks. The TOT group generated a significantly greater improvement (mean change=15, p=0.008) in their average Berg Balance Scale score than the control group. Both groups showed significant within-group improvement but there was no significant between-group difference in the groups' average Barthel Index scores after 48 sessions.

Other clinical trials have found TOT to be effective in improving sitting balance and trunk control in people with stroke. Kim et al. (2012) compared the effect of supplementing conventional physiotherapy with TOT using 20 people with stroke. The exercises included sit-to-stand balance, walking and climbing. There were 3 sessions/week for 4 weeks. Adding TOT produced a significantly greater between-group improvement (mean difference=1.7, p<0.05) in trunk impairment, and a significant within-group improvement in dynamic sitting balance (mean difference=1.7, p<0.05) and coordination (mean difference=1.4, p<0.05) as measured using trunk impairment subscales after 4 weeks of intervention.

1.5.3 Bilateral TOT in stroke rehabilitation

1.5.3.1 Bilateral TOT in stroke recovery

In bilateral TOT, the subject performs motor tasks with both upper limbs. The involvement of the non-paretic limb helps to increase functional recovery by facilitating coupling between the two limbs (Cauraugh & Summers, 2005). According to the movement pattern, bilateral TOT can be classified as symmetrical or asymmetrical. In symmetrical movement training, both upper limbs carry mirror image movements such as picking up a ball from a table in phase and simultaneously (Wolf et al., 2014). In asymmetrical movement training, the movements are different and perhaps anti-phase, such as one upper limb opening a drawer and the other placing an item in the drawer (Wolf et al., 2014).

Symmetrical bilateral TOT can help to improve motor performance by training inter-limb coupling and inter-limb synergy. The coupling can be described as a similarity in performance between the left and right limbs. Kelso et al. (1979) further explained that inter-limb coupling involves organizing functional muscle groups to act as a single unit. Diedrichsen et al. (2004) suggested that when performing symmetrical bilateral exercise, the cognitive load of task organization can be alleviated by perceptual cues from the symmetrical movement. In addition, in the inter-limb synergy view of coordination, the central nervous system organizes sets of effectors, such as muscles, limb segments and limbs, which cooperate to stabilize task

performance.

Asymmetrical bilateral TOT is the movement that the two limbs performing alternating motions, either reciprocal or nonreciprocal. Performing the asymmetrical movement is known to elicit greater cortical activation than symmetrical movements in the primary motor cortex, the supplementary motor area, and the right dorsal premotor area than do symmetrical movements (Liuzzi et al., 2011; Takeuchi et al., 2012; Tazoe et al., 2013). Asymmetrical exercise could thus be more difficult to perform for people with stroke than symmetrical bilateral movement. However, asymmetric movement is more common in daily life: opening a can, riding a bike, eating, brushing the hair. Many clinical trials (Higgins et al., 2018; Lee et al., 2014; Lodha et al., 2012; Shen et al., 2018) have shown the effectiveness of asymmetric bilateral training in improving the motor function of people with stroke.

A number of studies have investigated the short-term and long-term effect of bilateral TOT in recovery of upper limb motor function in people with stroke. DeJong and Lang (2012) have documented that bilateral contractions can elicit about 11% greater grip force than contracting the paretic side only in 13 people with stroke. Draganski et al. (2004) has reported a 3% transient bilateral expansion in grey matter in the mid-temporal area and the left posterior intra-partietal sulcus by fMRI after 3 months of learning three-ball cascade juggling which involves bilateral upper limb use. Chang et al. (2007) found that 24 sessions of bilateral, symmetrical arm push and pull movements supplementing conventional rehabilitation within 8 weeks could generated 29.3% to 53.3% improvement in strength of grip, a 35.5% reduction in

completion time and a 31.2% reduction in the time to reach peak velocity compared with the baseline in 20 people with chr5onic stroke.

Several studies (Cauraugh & Kim, 2002; Lin et al., 2015; Lin et al., 2010) have shown that bilateral TOT is more effective than unilateral TOT in improving the motor functioning of both upper limbs in people with stroke. Cauraugh and Kim (2002) found that 12 30–minute sessions of bilateral, symmetrical wrist and finger extension with EMG-triggered stimulation of the extensor communis digitorum and extensor carpi ulnaris induced better performance in BBT, shorter reaction time and better sustained muscle contraction capability than the equivalent unilateral protocol in a study of 25 subjects with chronic stroke. The two studies (Lin et al., 2015; Lin et al., 2010) demonstrated that 12 to 15 sessions of bilateral functional task training (including lifting cups, stacking checkers, picking up dried beans and folding towels) and bilateral isometric handgrip force training generated significantly greater improvement than same dosage of traditional unilateral physiotherapy (neurodevelopmental technique, strengthening, stretching and functional task training) in improving the FMA-UE, WMFT, Functional Independence Measure (FIM), Modified Ashworth Scale and Barthel Index (BI) results of people who had suffered a stroke.

1.5.3.2 Proposed mechanism of bilateral intervention in motor recovery

Mechanims of bilateral exercise for recovery of motor functions are multifactorial. Compared with unilateral exercise, extra sensory input from the non-paretic limb brought by

bilateral exercise is delivered to the intact hemisphere. The activation of the intact hemisphere can augment stroke by (1) reducing interhemispheric inhibition (IHI) or (2) by directly activating the paretic limb via uncrossed contralesional corticospinal pathways.

1.5.3.2.1 Enhancement of the interhemispheric interaction via transcallosal pathway

One way bilateral exercise facilitates motor recovery is by reducing inter-hemispheric inhibition via the transcallosal pathway. The corpus callosum is the major tissue connecting to both hemispheres (Gilles et al., 2013). The corpus callosum may take an important role in reinforcing information transfer and integrating the interhemispheric connection in stroke recovery (van der Knaap & van der Ham, 2011).

Findings from an animal study (Liao et al., 2014) have shown that bilateral intervention can elicit greater cortical activation in the lesioned hemisphere via the corpus callosum than unilateral intervention. Further neurophysiological findings (Cunningham et al., 2019; Murase et al., 2004; Stinear et al., 2014) with human subjects also supported bilateral electrical stimulation or bilateral exercise as better able to enhance the excitability of the lesioned hemisphere via the corpus callosum. For example, Cunningham et al. (2019) found that 1 hour of bilateral FES of the extensor digitorum communis and extensor pollicis longus reduced lesioned M1 IHI as measured by the MEP of extensor of digitorum communis. No such IHI reduction was found in a unilateral stimulation control group (-15.3%±6.67% in bilateral vs 4.2%±5.62% in unilateral, p=0.018) in 15 people with chronic stroke.

1.5.3.2.2 Activation of the intact hemisphere uncrossed descending pathway

Another mechanism of bilateral intervention to improve the motor performance is activation of both the lesioned and intact hemispheres, and activation of the intact hemisphere, which increase the voluntary muscle contraction ability of a paretic upper limb using such uncrossed descending pathways (Cauraugh & Summers, 2005; Cohen, 1970; Debaere et al., 2004; Goldberg, 1985; Swinnen & Wenderoth, 2004; Wenderoth et al., 2004).

The limb muscles are innervated by projections from the intact and lesioned motor cortices (Lemon, 2008). Although in most mammals the majority of corticospinal axons cross to the contralateral side at the level of the medullary pyramids, about 10% of the descending fibers remain undecussated and project to the distal extremities in the ventral corticospinal tract (Lacroix et al., 2004). The pathway in the intact hemisphere plays a more important role in controlling the paretic upper limb after damage to the lesioned hemisphere.

Activation in the intact primary somatosensory cortex and premotor cortex is consistently found beginning immediately after stroke onset (Cao et al., 1998; Green et al., 1999; Marshall et al., 2000). Several neuroimaging studies (Cao et al., 1998; Cramer et al., 2000; Cramer et al., 1997; Nelles et al., 2001; Pariente et al., 2001; Seitz et al., 1998; Weiller et al., 1992; Weiller et al., 1993) revealed that both the lesioned and intact hemispheres contribute to any movement of a paretic upper limb.

Bilateral intervention could also help prevent secondary degeneration of the intact hemisphere. Crofts et al. (2011) used diffusion magnetic resonance imaging to measure the

structural connectivity between brain regions in 9 people with stroke without any active treatment. The result suggested that communicability in the intact hemisphere was significantly reduced, resulting in secondary degeneration of fiber pathways. That may be caused by direct or indirect disconnection from the remote lesioned cortical region. Bradnam et al. (2012) reported that suppression on the intact M1 by cathodal transcranial direct current stimulation worsened upper limb motor impairment and reduced motor function in 12 people who had survived a moderate to severe stroke (FMA-UE score=14–64). The afferent input generated in bilateral intervention plays an essential role in preventing secondary degeneration of fiber pathways in the intact hemisphere. The recruitment could be through an unmasking of the uncrossed corticospinal projections (Calautti & Baron, 2003) which are silent or latent in the healthy state. Caramia and Bernardi (1996) found that a single pulse stimulus of the intact hemisphere induced a short latency and low amplitude MEP in the paretic hand among people with stroke which was absent in their healthy subjects.

1.6 Summary

The literature review showed that stroke showed an increasing trend in the world. The upper limb motor impairment is one of the common sequelae post-stroke, which will take a long time for rehabilitation and lead to a great economic burden to individual and family concerned, as well as to the society.

TENS and TOT are found to be effective intervention for stroke rehabilitation of the upper limb motor impairment. In addition, bilateral TOT is found to generate greater improvement of motor function of the upper limb than unilateral intervention in people with stroke by recruiting different corticospinal pathways. These finding indicated that Bi-TENS may be superior to Uni-TENS in augmenting the effect of TOT in upper limb motor recovery in people with stroke.

Chapter 2

Thesis outline

2.1 Research Gaps

The literature review of Chapter 1 highlights several research gaps which need to be filled. It reports lots of evidence that bilateral is generally superior to unilateral intervention in facilitating upper limb motor recovery in people with stroke. In order to integrate those previous findings and draw a systematic and quantitative conclusion about the effect of bilateral treatment in upper limb motor recovery in people with stroke. A systematic review and meta-analysis was conducted, and its results will be reported here.

The International Classification of Functioning, Disability and Health (World Health Organization, 2001) indicated that physiological and psychological function ratings significantly contribute to people with stroke's level of activity. However, no study quantified the contribution of physiological and psychological function in activity of daily living. Hence, a cross-sectional study was used to quantify the contribution of self-perception to upper limb motor function among people with stroke. Those results too will be reported.

Several assessment tools, such as the Fugl-Meyer Assessment of Upper Extremity (Fugl-Meyer et al., 1975), Action Research Arm Test (Lyle, 1981) and Wolf Motor Function Test (Wolf et al., 2001), have been developed for evaluating upper limb motor control and functioning, and they are commonly used in assessing people with stroke. However, only a few assessment tools have been specifically designed for quantifying upper limb performance in the

activities of daily living in people with stroke. The Jacket Test is one item in the physical performance test (Reuben & Siu, 1990) which is used to assess the completion times donning a jacket, which involves shoulder abduction, arm flexion, elbow extension and hand gripping. It has shown great clinical utility in evaluating the physical functioning of healthy, community-dwelling older adults in daily tasks. However, the psychometric properties of the jacket test have not been quantified among in people with stroke. We will report the results of a study investigating the Jacket Test's psychometric properties: reliability, minimal detectable change in people with stroke and its ability to discriminate people with stroke from health older adults.

Chapter 1 reported the effectiveness of Uni-TENS over paretic limb in improving paretic upper limb functions (Jung, Jung, et al., 2017; Kim, In, et al., 2013) and the superiority of bilateral TOT over unilateral TOT in terms of generating greater improvement in upper limb motor function. Although a recent randomized controlled trial (RCT) (Kwong et al., 2018a) has suggested that Bi-TENS+TOT was superior to Uni-TENS+TOT in improving ankle dorsiflexion strength and reducing Timed Up and Go test times, neither placebo stimulation nor control group had been included in that study. Therefore, the results of our RCT, including placebo stimulation and control group, extending those findings to people with stroke will be reported in Chapter 6.

At last, we reported the limitation and summarize the research findings of the previous chapters. Then, we drew the clinical implication to the field of stroke rehabilitation, according to the research findings. Eventually, the overall conclusion of the thesis was reported in Chapter 7.

2.2 Null hypothesis

The null hypothesis of the main study was that Bi-TENS was not superior to Uni-TENS, Placebo-TENS or no active treatment in terms of augmenting the effectiveness of TOT in improving the upper limb motor control, upper limb motor function, self-perceived performance and level of community integration in people with stroke.

2.3 Aim and objectives

As shown in Chapter 1, the bilateral TOT is superior to unilateral TOT in enhancing the recovery of motor control and motor function of upper limb, the improved upper limb motor performance further induces better community integration in people with chronic stroke. Hence, we hypothesize that Bi-TENS will be superior to Uni-TENS to improve the upper limb motor function in people with stroke. The overall aim of this thesis is to investigate the effect of Bi-TENS in augmenting the TOT in improving the upper limb motor control, upper limb motor function and level of community integration in people with chronic stroke. In order to achieve this goal, the hypothesis was tested in 4 steps.

Step 1: To determine whether bilateral exercise was superior to unilateral exercise in improving upper limb motor function and documenting the optimal schedule and dosage of bilateral exercise for that purpose.

Step 2: To estimated and elucidate the relative contributions of hand motor control measured by hand subscale of Fugl-Meyer Assessment-UE (FMA-hand) and self-perceived performance measured by Motor Activity Log (MAL) in the recovery of upper limb motor function measured by Action Research Arm Test (ARAT) in people with stroke.

Step 3: To select a reliable and valid physical test for quantifying the performance of a paretic upper limb in daily tasks, and to assess its psychometric properties, reliability and validity with people with stroke. The aim was to ensure that the test is robust enough to detect daily activity-relevant changes in upper limb motor function.

Step 4: To answer the main research question, a RCT should be conducted to compare the effectiveness of Bi-TENS with that of Uni-TENS in promoting the effect of TOT in the treatment of upper limb paralysis, improving performance in the activities of daily living and promoting community integration in people with stroke.

Step 5: To summarize and conclude the research findings of the thesis, draw clinical implication from the research findings and indicate the further research direction.

2.4 Outline of the dissertation

2.4.1 Chapter 3: Comparison of bilateral and unilateral upper limb training in people with stroke: A systematic review and meta-analysis

Chapter 3 involved 21 RCTs to conduct the systematic review and meta-analysis, which comparing the effectiveness of bilateral with unilateral upper limb training in improving the upper limb control and the functional performance of upper limb in people with stroke.

2.4.2 Chapter 4: The predictive role of MAL and FMA-hand in ARAT in people with stroke

Chapter 4 estimated how the self-perceived performance of the upper limb measured by MAL and upper limb motor control measured by FMA-hand, influences functional performance of upper limb measured by ARAT. Its contribution will be quantified with respect to people with stroke.

2.4.3 Chapter 5: Methodology

Chapter 5 introduced main study, particularly its methodology, including the design, ethics, procedures and statistical analysis approach. Besides, it will report on a preliminary study investigating the psychometric property of the Jacket Test for use in the study's main RCT.

2.4.4 Chapter 6: Efficacy of Bilateral transcutaneous electrical nerve stimulation combined with task-oriented training in improving upper limb function in people with stroke: A randomized placebo-controlled clinical trial

This chapter reported the detailed result and discussion of our main study. It was a single-blinded RCT which compared the effect of Bi-TENS+TOT with those of Uni-TENS+TOT, Placebo-TENS+TOT and no active intervention. The indicators were upper limb motor control, upper limb motor function and the level of community integration in people with stroke.

2.4.5 Chapter 7: Summary, limitation and conclusion of the thesis

A final chapter will summarize all of the findings and suggest their implications for clinical stroke rehabilitation. The study's limitations will also be discussed with proposed directions for further research.

Chapter 3

Comparison of bilateral and unilateral upper limb training in people with stroke: A systematic review and meta-analysis

The study in this chapter has been published in a peer-reviewed journal.

Chen PM, Kwong PWH, Lai CKY., & Ng SSM. (2019). Comparison of bilateral and unilateral upper limb training in people with stroke: A systematic review and meta-analysis. *PloS one*, 14(5), e0216357. (Appendix 3.1)

The study in this chapter has been published in a conference.

Chen PM, Lai CKY and Ng SSM, The Effect of Bilateral Movement Training and Conventional Upper Limb Exercise on Improving the Motor Impairment and Functional Ability after Stroke: A Systematic Review and Meta-Analysis. *11th Pan-Pacific Conference on Rehabilitation*, 17-18 November 2018 Hong Kong. (Appendix 3.2)

3.1 Abstract

A number of clinical trials have determined the effect of bilateral and unilateral upper limb movement training in facilitating the recovery of upper limb motor function in people with stroke. Some other studies also compared different types of bilateral upper limb training (BULT) with same dosage of unilateral upper limb training (UULT) in augmenting the motor recovery of upper limb in people with stroke. However, the conclusions were controversial among these studies. In this chapter, we reported the conduction of a systematic review and meta-analysis to summarize and classify different clinical trials which included the comparison of the effects of BULT and UULT in terms of the improvement on motor control and functional performance in people with stroke.

This systematic review and meta-analysis begun by a systematic search in CINAHL, Medline, Embase, Cochrane Library and PubMed. Twenty-one RCTs met the inclusion criteria of this study, including total 842 subjects with subacute and chronic stroke. Compared with UULT, BULT yielded a significantly greater mean difference (MD) in the FMA-UE (MD=2.21, 95% Confidence Interval (CI), 0.12 to 4.30, p=0.04; I^2=86%, p<0.001). However, a comparison of BULT and UULT yielded insignificant mean difference (MD) in terms of the time required to complete the WMFT (MD=0.44; 95%CI, -2.22 to 3.10, p=0.75; I^2=55%, p=0.06) and standard mean difference (SMD) in terms of the functional ability scores on the WMFT, ARAT and BBT (SMD=0.25; 95%CI, -0.02 to 0.52, p=0.07; I^2=54%, p=0.02). According to our finding, BULT yielded superior improvements in the improving motor control as measured by the FMA-UE in

people with stroke. In order to increase the reliability of the conclusion, more comparative studies of the effects of BULT and UULT are warranted.

3.2 Introduction

Unilateral upper limb training (UULT) is a common rehabilitation technique. It often includes repetitive task-oriented training (Hubbard et al., 2015; Narayan Arya et al., 2012; Thielman et al., 2004) and constraint-induced movement training (CIMT) (Hammer & Lindmark, 2009; Kwakkel et al., 2016; Lin et al., 2007; Page et al., 2008; Wolf et al., 2006; Wu et al., 2007). CIMT requires people with stroke to use their paretic upper limb to compensate for the difficulties in their daily life early in people with stroke (Grotta et al., 2004). During CIMT the subject performs intensive training with the paretic side (at least 6 hours per day) and wears a mitten constraining use of the non-paretic upper limb. Lots of studies (Brunner et al., 2012; Taub et al., 2013; Wolf et al., 2010) have proved the effectiveness of CIMT in promoting the recovery of upper limb motor function form sub-acute to chronic phase of stroke. Wolf et al. (Wolf, et al., 2006) found that 14 sessions of CIMT had a significantly greater effect in increasing quality of movement scores in the Motor Activity Log (MAL) (p<0.001) and shortening the time consumed in completing the Wolf Motor Function Test (WMFT) (p<0.001) than the conventional treatment program, which included a daily treatment program, outpatient visits, physiotherapy and occupational therapy, in people with sub-acute stroke. CIMT studies, however, had at least moderate hand dexterity (wrist extension on the paretic side, thumb abduction on the paretic side and finger extension on the paretic side of at least 10 degrees in each case) (Brogårdh, 2006).

Thus, it limits the use of CIMT in a wider spectrum of people with stroke with different severity of motor impairment.

Task-oriented training (TOT) is one type of goal-directed training with less intensive load, which has a lower requirement for motor functioning. It helps subjects derive workable control strategies for solving problems related to motor abilities by different typical motor tasks. Narayan et al. (2012) showed that 20 sessions of task-oriented upper limb training, including reaching and lifting objects with different shapes using the paretic upper limb, is superior to dose-matched neurodevelopment-based therapy as measured by the score of FMA-UE, WMFT, MAL and Action Research Arm Test (ARAT).

In bilateral upper limb training (BULT), the non-paretic limb is used to increase functional recovery of the paretic limb by facilitating coupling between them (Cauraugh & Summers, 2005). BULT included several types of upper limb motor training, such as bilateral functional task training (Han & Kim, 2016; Lin et al., 2015; Lin et al., 2010; Morris et al., 2008; Wu et al., 2011), bilateral robotic-assisted training (Kim, Miller, et al., 2013; Liao et al., 2012; Meng et al., 2017) and bilateral arm training with rhythmic cueing (Luft et al., 2004; Whitall et al., 2011; Wu et al., 2013). A group of studies have shown the superiority of BULT over different types of conventional therapies including occupational therapy (Lee, Lee, et al., 2017; Lin et al., 2015; van Delden et al., 2013), physiotherapy (Meng et al., 2017; Morris et al., 2008; van Delden et al., 2013), neurodevelopmental therapy (Lin et al., 2010; Lum et al., 2006) and unilateral robotic-assisted training (Kim, Miller, et al., 2013) for improving the FMA-UE, the

ranges of motion (ROM) of the shoulder, elbow and wrist joints, ARAT, WMFT and MAL results among people with stroke.

Several clinical trials have also demonstrated the ability of BULT to improve hemiplegic arm functioning (Cauraugh et al., 2010; Coupar et al., 2010; Latimer et al., 2010; Stewart et al., 2006; Van Delden et al., 2012). Two systematic reviews led by Cauraugh and by Stewart (Cauraugh et al., 2010; Stewart et al., 2006) combined BULT to some therapies such as auditory rhythmic cueing and electrical stimulation, but those reviews (Cauraugh et al., 2010; Stewart et al., 2006) included single-group pre-post studies but not randomized controlled trial (RCT) (Cauraugh et al., 2008; Chang et al., 2007; Hesse et al., 2005; Richards et al., 2008; Stinear et al., 2008; Whitall et al., 2000). Besides, those studies (Cauraugh et al., 2010; Stewart et al., 2006) did not compare the difference between BULT and UULT directly among people with stroke. Hence, the optimal intervention could not be figured out for stroke rehabilitation of upper limb.

By contrast, two recently published meta-analyses (Lee, Kim, et al., 2017; Van Delden et al., 2012) compared BULT with UULT in terms of their ability to improve the FMA-UE, WMFT, ARAT and MAL results of people with stroke. Van Delden et al. (2012) categorized studies according to the upper limb motor control level as measured using the FMA-UE, Brunnstorm scale, the WMFT and the ARAT. The results showed that UULT and BULT yielded similar improvement with stroke subjects. Lee et al. (2017) compared the effects of BULT with those of unilateral task-oriented training and CIMT and found that CIMT was more effective than BULT in improving ARAT and WMFT scores. That finding should, however, be

interpreted cautiously because the analysis considered only 3 studies. CIMT is more beneficial for people with stroke with mild-to-moderate upper limb functional impairment. But not all people with stroke are suitable for CIMT. That introduces bias when comparing bilateral movement training with unilateral CIMT. Some previous studies have limited their subjects to those meeting the minimum standard for CIMT. The true effect of bilateral training may then not have been represented accurately.

It is fundamentally inappropriate to conduct the direct comparison of the effects of CIMT and BULT in upper limb motor function rehabilitation in people with stroke. First, the subjects in CIMT were required to wear a constraint mitten on the non-paretic hand and to train intensively for at least 6 hours every day (Taub et al., 1999). Page et al. (2002) found that about 68% of their stroke subjects could not complete the full schedule of CIMT due to the training requirement and the restrictive device. In accordance with Blanton and Wolf (1999), only 20–25% of stroke patients benefit from CIMT due to the tight training schedule and potential risk induced by the restricted training plan. BULT, by contrast, has a lower training intensity. Patients are expected to complete approximately 1 to 2 hours of training per session on 3 to 5 days per week (Hsieh et al., 2017; Wu et al., 2013), in contrast with the CIMT schedule of 6 hours of supervised task practice on each of 14 consecutive days (Hammer & Lindmark, 2009; Miltner et al., 1999; Taub et al., 1993). Some potential training dosage is estimated in CIMT. In addition, stringent inclusion criteria was applied by most CIMT studies, including the aforementioned 10 degrees of wrist, thumb and finger mobility (Brogårdh, 2006). Compared with CIMT, BULT only requires that the subject maintain volitional control of the non-paretic arm, to able to flex the paretic arm and shoulder and have some residual grip function in the paretic hand (Lin et al., 2010; Whitall

et al., 2011). CIMT is only suitable to people with stroke with mild to moderate levels of upper limb dysfunction. Thus, the excluding CIMT from a comparison of the effects of BULT and UULT would improve the validity of the quantitative results and draw a more unbiased conclusion.

Although several meta-analyses (Lee, Kim, et al., 2017; Van Delden et al., 2012) have compared the effects of BULT and UULT in people with stroke, CIMT was treated as a subtype of UULT and included it in the comparison with BULT in those review. As far as we know, no published study has excluded CIMT when comparing the effects of BULT and UULT with people with stroke. This systematic review and meta-analytical review was therefore designed to do so. It evaluated only RCTs that compared the effects of BULT and UULT while excluding CIMT.

3.3 Method

3.3.1 Study selection criteria

An exhaustive search of the literature on the effectiveness of BULT was conducted. Several databases were systematically searched through April 2018: CINAHL, Embase, Medline, PubMed and Cochrane Library. The headings and keywords used for searching are summarized in Table 3.1.

Table 3.1 Key words applied in the searches

	Key Words
AND	CVA OR cerebrovascular disease OR cerebrovascular accident OR stroke OR hemiparesis OR paresis OR hemiplegia
AND	bilateral arm training with rhythmic auditory cueing OR BATRAC OR bilateral robotic OR bilateral OR unilateral OR bimanual
AND	upper extremity OR upper limb OR hand OR finger OR wrist OR forearm OR arm
AND	randomized OR RCT OR randomized controlled trial

Note: This table was modified from the published paper (Chen et al., 2019)

All of the full-text English language journal articles identified were screened independently by two reviewers (PM and PK). The reference lists of the selected articles were then examined to identify additional potential articles. The inclusion criteria were applied to identify studies that (1) were RCTs; (2) included an intervention group with bilateral movement training; (3) had investigated the effects of interventions on upper limb function; (4) reported quantitative behavior outcome measures; (5) included people with stroke; and (6) had an intervention group which received unilateral movement training or conventional occupational therapy or physiotherapy. The exclusion criteria included: (1) the studies with a single session design; (2) failure to provide outcome measures data; (3) the use of BULT in both the experimental and control groups; (4) inclusion of CIMT as the UULT; and (5) systematic reviews or meta-analyses.

3.3.2 Risk of bias

The quality of the studies' methodologies was assessed using the Cochrane Collaboration bias assessment tool (Green & Higgins, 2005). Studies which provided clear information about, for example, randomization or subject blinding were marked as low risk for those items. If a report stated that the study was, for example, not randomized or not blinded, the study was marked as high risk for those items. If insufficient information was provided, the study was marked as unclear.

3.3.3 Data synthesis and analysis

The two reviewers extracted information about the participants' demographics for each study, the outcome measures used and the details of the intervention (duration, intensity and type). A third reviewer (SMN) adjudicated if the two reviewers disagreed. The categories of the International Classification of Functioning, Disability and Health (ICF) were used to assess motor control and functional performance. In the ICF framework, the outcome measures for such a meta-analysis should assess either motor control or functional performance.

The effect size for each outcome was quantified by calculating the mean difference (MD), standard mean difference (SMD) and 95% confidence interval (CI), as appropriate. If the standard deviation (SD) of the MD or SMD was not provided, it was estimated as:

$$SD=\sqrt{SDpre^2 + SDpost^2 - 2 \times Corr \times SDpre \times SDpost}$$

with the correlation coefficient (Corr) set to 0.8 (Green & Higgins, 2005).

The results of the meta-analysis were then demonstrated by forest plot (prepared using version 5.3 of the Review Manager software from The Nordic Cochrane Centre, Copenhagen). To compare the effects of BULT and UULT in different stages of stroke, the included studies were classified as acute (mean post-stroke duration <1 month), sub-acute (mean post-stroke duration 1 month to 1 year), chronic (mean post-stroke duration >1 year) or not reported.

To investigate the influence of treatment dosage on the effect size estimates, meta-regressions were evaluated using version 12.0 of the STATA software suite (Stata Corporation, College Station, TX, USA).

3.3.4 Publication bias

As more than 10 studies were included in the meta-analysis, Egger's test (Egger et al., 1997) was conducted to estimate the publication bias probability—the tendency to present only positive results, which is more frequently used than other tests to detect publication bias in a meta-analysis (Lin et al., 2018).

3.3.5 Heterogeneity test

The heterogeneity of the included studies was assessed by Higgins I^2 index. The boundary of I^2 was set at 50%. When I^2 >50% indicated heterogeneity, a random effect model was used. When I^2 <50% indicating homogeneity, a fixed effect model was used (Green & Higgins, 2005).

3.4 Results

3.4.1 Studies identified

The search (in April of 2018) yielded 828 citations. After excluding duplicates, there were 375 potentially relevant articles for further screening via a review of the abstracts. During this meta-analysis, the third reviewer was required to make a judgment about two of the articles

(Han & Kim, 2016; Kim, Miller, et al., 2013), both of which were finally included. Eventually, 21 full-text articles with a total of 842 subjects fulfilled the eligibility criteria. The details of those studies' identification, screening, eligibility and inclusion criteria are shown in Figure 3.1.

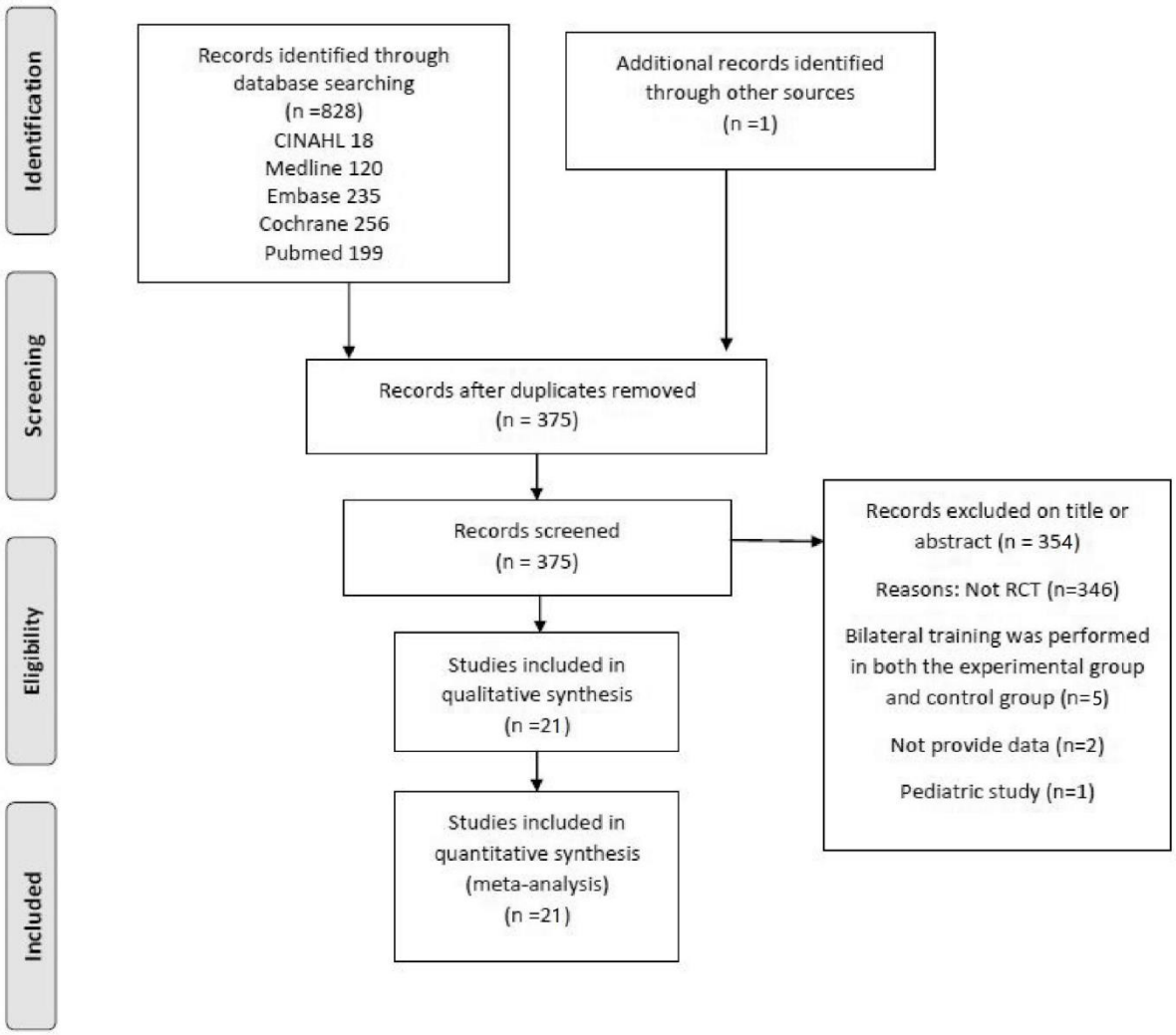


Figure 3.1 The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram for this study (Modified from the published paper (Chen et al., 2019))

3.4.2 Methodological quality

Figure 3.2 presents the assessments of the methodological quality of the included studies as evaluated using the Cochrane Collaboration's risk of bias assessment tool (Green & Higgins, 2005).

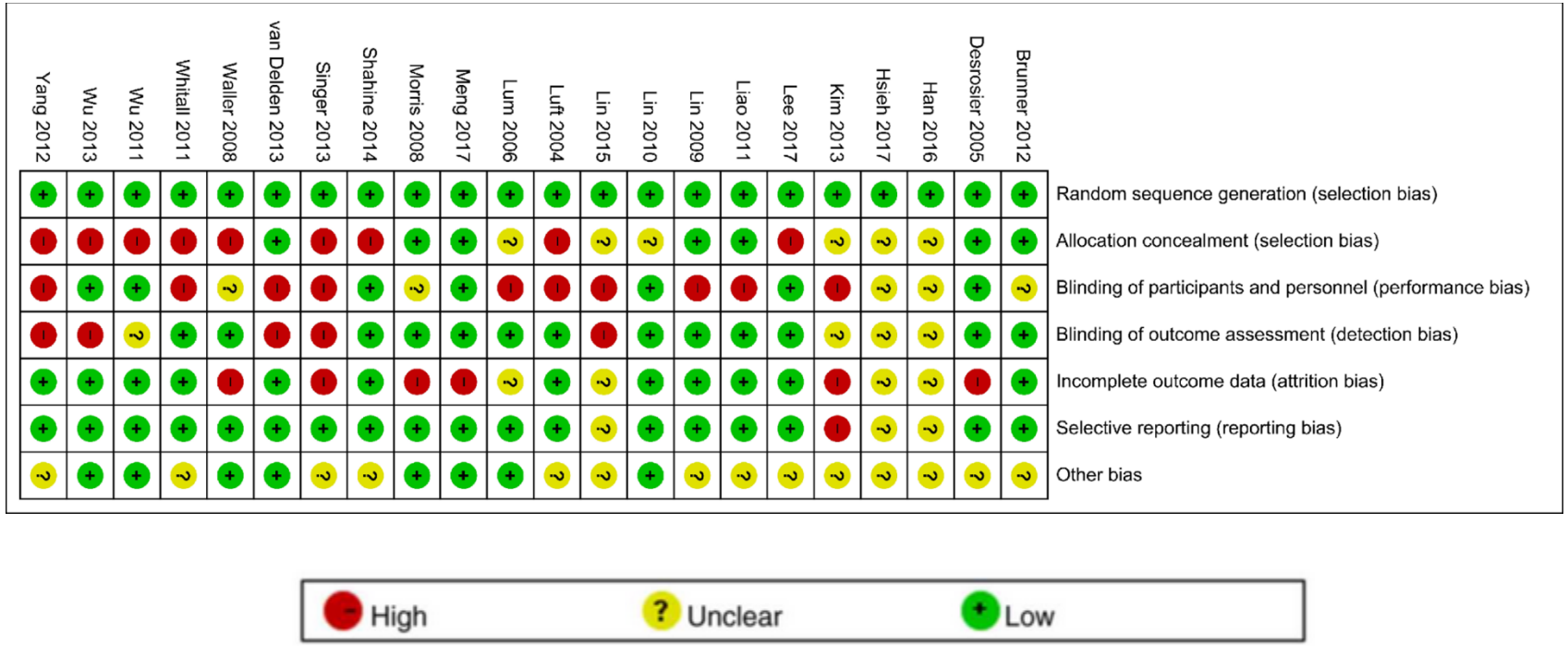


Figure 3.2 Risk of bias summary: The reviewers' consensus judgments about the risk of bias in each item in each included study (Modified from the published paper (Chen et al., 2019))

3.4.3 Characteristics of the subjects and the tests

Four studies (Brunner et al., 2012; Desrosiers et al., 2005; Meng et al., 2017; Morris et al., 2008) compared the effects of BULT and UULT on subjects with acute stroke. Two (Hsieh et al., 2017; Lum et al., 2006) compared the effects on people with sub-acute stroke. Two (Kim, Miller, et al., 2013; Lee, Lee, et al., 2017) only mentioned that their subjects were at least six months post-stroke without reporting more details. The other 13 studies (Han & Kim, 2016; Liao et al., 2012; Lin et al., 2015; Lin et al., 2010; Luft et al., 2004; Shahine & Shafshak, 2014; Singer et al., 2013; van Delden et al., 2013; Waller et al., 2008; Whitall et al., 2011; Wu et al., 2011; Wu et al., 2013; Yang et al., 2012) compared the effects in subjects with chronic stroke.

Only 8 of the studies (Brunner et al., 2012; Desrosiers et al., 2005; Hsieh et al., 2017; Lee, Lee, et al., 2017; Lin et al., 2015; Luft et al., 2004; Meng et al., 2017; Morris et al., 2008) reported their subjects' type of stroke in detail.

The subjects' demographic characteristics are summarized in Table 3.2. The characteristics of the studies are shown in Table 3.3.

Table 3.2 Cohort characteristics of the studies included in the meta-analysis

Author & year	**Gender (Male/Female)**	**Age**	**Mean stroke duration (year)**	**Lesion type (ischemia/ hemorrhage)**	**Side affected (left/ right)**	**Baseline average FMA-UE score**
Brunner 2012	BULT:8/8; UULT:11/3	BULT:64.8 ±12.8; UULT:61.0 ±10.0	BULT:0.1 ±0.1; UULT:0.1 ±0.1	BULT:4/12; UULT:1/13	BULT:4/12; UULT:1/13	Not Reported
Desrosier 2005	BULT:9/11; UULT:10/11	BULT:72.2±10.8; UULT:74.3±10.1	BULT:0.09±0.09; UULT:0.10±0.09	BULT:1/19; UULT:0/21	BULT:13/7; UULT:10/11	BULT: 42.90±20.00; UULT: 47.00±16.10
Han 2016	BULT:5/8; UULT:3/9	BULT:78.8; UULT:72.9	BULT:6.92; UULT:6.48	Not Reported	BULT:13/0; UULT:12/0	Not Reported
Hsieh 2017	BULT:11/5; UULT:7/8	BULT:49.28 ±10.90;	BULT:0.21 ±0.14; UULT:0.18 ±0.09	BULT:8/8; UULT:8/7	BULT:8/8; UULT:4/11	BULT: 26.81±12.13;

		UULT:52.87 ±10.40				UULT: 29.07±16.12
Kim 2013	Not Reported	Not Reported	Not Reported	Not Reported	BULT:1/4; UULT:2/3	BULT: 24.4±5.2; UULT: 23.8±7.7
Lee 2017	BULT:9/6; UULT:10/5	BULT:57.33 ± 9.88; UULT: 54.60 ± 16.03	Not Reported	BULT:7/8; UULT:9/6	BULT:5/10; UULT:6/9	BULT: 48.73±16.42; UULT: 46.60±12.03
Liao 2012	BULT:6/4; UULT:7/3	BULT:55.51±11.17; UULT:54.56±8.20	BULT:1.99±1.12; UULT:1.09±0.68	Not Reported	BULT:4/6; UULT:3/7	BULT: 44.90±9.02; UULT: 39.60±11.27
Lin 2010	BULT:10/6; UULT:9/8	BULT:52.08± 9.60; UULT:55.50±13.17	BULT:1.16±1.06; UULT:1.09±1.1	Not Reported	BULT:9/7, UULT:8/9	BULT: 45.50±10.35;

						UULT: 49.75±12.10
Lin 2015	BULT:12/4; UULT:16/1	BULT:52.63±10.49; UULT: 57.47±10.29	BULT:2.31±1.59; UULT:1.82±1.81	BULT:9/7; UULT:6/11	BULT:4/12; UULT:0/17	BULT: 35.69±15.56; UULT: 38.71±19.98
Luft 2004	BULT:7/2; UULT:5/7	BULT: 63.3±15.3; UULT:59.6±10.5	BULT:6.25; UULT:3.79	BULT:9/0; UULT:12/0	BULT:3/6; UULT:4/8	BULT: 29.60±12.25; UULT:28.30 ±4.41
Lum 2006	BULT:2/3; UULT:4/2	BULT:72.2±11.7; UULT:59.9±5.5	BULT:0.12±0.02; UULT:0.20±0.05	Not Reported	BULT:2/3; UULT:2/4	BULT: 39.20±4.30; UULT: 26.00±3.30
Meng 2017	BULT:34/30; UULT:31/33	BULT:55.38±6.97; UULT:55.19±7.82	BULT:8.87±2.69h; UULT:9.08±2.35h	BULT:14/50; UULT:19/45	BULT:29/35; UULT:31/33	BULT: 33.25±5.89; UULT: 32.86±5.11

Morris 2008	BULT:34/22; UULT:27/23	BULT:67.9±13.1; UULT:67.8±9.9	BULT:0.06±0.02; UULT:0.06±0.02	BULT:53/3; UULT: 44/6	BULT:27/29; UULT:27/23	Not Reported
Shahine 2014	BULT:21/19; UULT:19/17	BULT:61.4±5.5; UULT:62.7±3.1	BULT:2.6± 1.8; UULT:3.0±1.6	Not Reported	BULT:23/17; UULT:21/15	BULT: 40.50±6.20; UULT: 38.50±6.10
Singer 2013	BULT:6/4; UULT:8/2	BULT:68.6±9; UULT: 68±16.4	BULT:4.33±4.02; UULT:5.33±4.12	Not Reported	BULT:5/6; UULT:5/5	BULT: 38.00±9.60; UULT: 30.50±12.80
van Delden 2013	BULT:11/8; UULT:16/3	BULT:62.6±9.8; UULT:56.9±12.7	BULT:7.8±4.9; UULT:11.1±6.8	Not Reported	BULT:11/8; UULT:11/8	BULT: 42.70±12.40; UULT: 39.00±10.30
Waller 2008	BULT:5/4; UULT:2/7	BULT:58.0±12.4; UULT:54.1±8.6	BULT:6.1±5.8; UULT:2.6±1.8	Not Reported	BULT:5/4; UULT:5/4	BULT: 35.22±12.30;

						UULT: 34.00±13.20
Whitall 2011	BULT:26/16; UULT:24/26	BULT:59.8±9.9; UULT:57.7±12.5	BULT: 4.5±4.1; UULT:4.1±5.2	Not Reported	BULT:18/23; UULT:25/25	BULT: 32.30±2.20; UULT: 31.00±2.10
Wu 2011	BULT:18/4; UULT:16/6	BULT:52.22±10.72; UULT:55.19±2.50	BULT:1.33±1.15; UULT:1.48±1.04	Not Reported	BULT:10/12; UULT:12/10	Not Reported
Wu 2013	BULT:13/5; UULT:12/5	BULT:52.21±12.2; UULT:54.22±9.78	BULT:1.94±1.28; UULT:1.95±1.27	Not Reported	BULT:9/9; UULT:9/8	Not Reported
Yang 2012	BULT:4/3; UULT:5/2	BULT:51.4±10.9; UULT: 50.8±6.1	BULT:1.23±0.48; UULT: 1.03±0.37	Not Reported	BULT:4/3; UULT:4/3	BULT: 41.90±3.90; UULT: 40.90±6.40

Notes: BULT, bilateral upper limb training; UULT, unilateral upper limb training; FMA-UE, Fugl-Meyer Assessment for the Upper Extremities (cited from the published paper (Chen et al., 2019))

Table 3.3 Characteristics of the included studies

Author & year	The content of BULT and UULT interventions	Duration of therapy	Outcome measures
Brunner 2012	BULT: Press the buttons of a keyboard, Carry an object, Grip objects of different sizes and shapes, Fold a towel, Lift a glass, Point to a target, Catch a ball UULT: Similar to bilateral group but performed with the paretic hand	144–160 mins/session; 4 sessions/wk; 4 wks	ARAT, 9-hole peg test, MAL
Desrosier 2005	BULT: Roll out dough, Spoon out dry ingredients, Fold hand towels, Sort buttons quickly, Wipe the table, Open and close various types of locks UULT: Tearing up sheets of paper, Passive and assisted movements of the paretic arm, Unscrewing a light bulb, Shuffling playing cards, Putting a pillow in a pillow case, Putting blocks or cones in a pile	45 mins/session; 15–20 sessions 4 sessions/wk; 5 wks	FMA, Grip strength, BBT, Purdue Pegboard Test, Finger-to-nose test, TEMPA, MIF, FIM
Han 2016	BULT: Cleaning a desk with a towel bilaterally, Hanging a ring bilaterally, Drinking water bilaterally UULT: Similar to the bilateral group but performed with the paretic hand	Duration per session not given; 30 sessions,	BBT; Shoulder and elbow amplitude; Shoulder and elbow variability

		5 sessions/wk; 6wks	
Hsieh 2017	BULT: Approximately 1200 to 1600 repetitions of passive and active bilateral forearm pronation/supination and wrist flexion/extension, Folding towels and putting them in drawers, Filling a bottle from a fountain, Wipe the table with a cloth, Transferring it to the therapy room and drinking from it UULT: Similar to the bilateral group but performed with the paretic hand	90 min/session; 20 sessions, 5 sessions/wk; 4 wks	FMA; Grip strength; BBT; SIS; FIM; mRS; Actigraphy
Kim 2013	BULT: Flower game, Circular pong, Hand ball games, Paint game, Joint movement game, Reach game, Pinball game, Pong game UULT: Similar to the BULT, but only performed with the paretic hand	90 min/session; 12 sessions, 2 sessions/wk; 10wks	FMA; ROM of shoulder, elbow and wrist; Paint area; Travel distance; Area around straight line; Efficiency index
Lee 2017	BULT: 30min of general occupational therapy (neurodevelopmental treatment, stretching exercises, resistance movement), 30min of bilateral arm training (dishwashing, making coffee, typing, cutting fruit, and folding laundry) UULT: 60 min of general occupational therapy	60 min/session; 40 sessions 5 sessions/wk; 8wks	FMA; BBT; MBI

Liao 2012	BULT: 300 to 400 forearm cycles, totaling 600–800 repetitions of passive-passive mode and passive-active mode, 150–200 repetitions of resistance mode, 15 minutes of twisting a towel, Turning a door knob, Picking up coins, Turning a key in a lock, folding clothes, Opening a jar, Carrying heavy objects, Writing, Using chopsticks UULT: Paretic arm exercise or gross motor training, Muscle strengthening of the paretic arm, Fine motor or dexterity training, Picking up a telephone handset for listening, pulling out a drawer, Turning pages of a book, Writing, Using forks or safety knives for cooking, Opening a jar	90–105 min/session; 20 sessions, 5 sessions/wk; 4 wks	FMA; arm activity ratio; FIM; MAL; ABILHAND questionnaire
Lin 2010	BULT: use both hands to hold a sprinkler can to water plants, manipulate 2 coins, stack 2 checkers, pick up 2 small dried beans, turn 2 large screws, lift 2 cups, fold 2 towels UULT: weight bearing by the paretic arm, fine motor tasks practice, neurodevelopmental techniques, practice on compensatory strategies for daily activities, trunk–arm control	120 min/session; 15 sessions, 5 sessions/wk; 3wks	FMA; FIM; MAL
Lin 2015	BULT: Bilateral isometric handgrip force training, gradually increased or decreased grip strength with both hands to track the trajectory of the targeted force.	30 min/session; 12 sessions, 3	FMA; WMFT; MAS; BI; FIM

	UULT: Routine clinical rehabilitation: stretching, strengthening, practicing functional tasks, and coordination and weight bearing training of the paretic upper limb	sessions/wk; 4 wks	
Luft 2004	BULT: Eight times pushing and pulling 2 T-bar handles sliding in the transverse plane bilaterally with auditory cues, in synchrony or alternation	60 min/session; 18 sessions, 3 sessions/wk; 6wks	FMA; WMFT; Shoulder strength; Elbow strength; UMAQS; fMRI
	UULT: Scapular Mobilization, Thoracic spine mobilization, Opening a closed fist, Weight bearing with the paretic arm		
Lum 2006	BULT: 12 bilateral reaching movements, Rhythmic circular movement (bilateral), Tone normalization and limb positioning	60 min/session; 15 sessions; 4 wks	Ashworth scale; FMA; FIM; MSS; Motor power examination
	UULT: neurodevelopmental technique, Tone normalization and limb positioning		
Meng 2017	BULT: Bimanual coordination training, Haptic perception training, Functional training of the hands	120 min/session; 20 sessions	FMA; ARAT; AMP; RMT; CMCT
	UULT: Conventional rehabilitation training	10 sessions/wk; 2 wks	

Morris 2008	BULT: Wrist extension, Forearm pronation and supination, Reaching, Grasp UULT: Similar to the bilateral group but performed with the paretic hand	20 min/session; 30 sessions; 5 sessions/wk; 6 wks	ARAT; RMA; 9-hole peg test; MBI; Hospital Anxiety and Depression Scale; Nottingham Health Profile
Shahine 2014	BULT: 5min of pushing and pulling a handle symmetrically 3 times (in-phrase), 5min of pushing one handle away from the body with one hand and pulling the other handle toward the body with the other to an auditory cue for a total of 3 times (anti-phase), 10 min of rest for a total of three times UULT: Assisted range of motion exercises, Strengthening exercises, Fine motor tasks practice	60 min/session; 24 sessions 3 sessions/wk; 8wks	FMA; MEP
Singer 2013	BULT: Unscrewing a jar or bottle lid, Sorting cards, Pouring water into a cup, Opening an envelope, Grasp and release of a cup UULT: Similar to the BAT, but only performed with the paretic hand	30 min/session; 42 sessions 7 sessions/wk; 6 wks	FMA; Arm Motor Ability Test; Inter-hemispheric inhibition

Van Delden 2013	BULT: 3-minute movement periods interspersed with 5-minute rest periods for a total of 21 minutes of active movement: move both hands simultaneously in flexion and extension followed by extension and flexion following an auditory cue UULT: Exercise therapy recommended by the Royal Dutch Society of Physical Therapy and the Dutch Society of Occupational Therapy	60 min/session; 18 sessions, 3 sessions/wk; 6 wks	FMA; ARAT; Motricity Index; 9-hole peg test; Nottingham Sensory Assessment; MAL; SIS
Waller 2008	BULT: The arms moving simultaneously (in phase)/alternately (anti-phase) with auditory cuing at a preferred speed UULT: Opening the hand with finger extension, Weight bearing with the paretic arm, Thoracic spine mobilization with weight shifting, Scapular mobilization	60 min/session; 18 sessions 3 sessions/wk; 6wks	FMA; WMFT
Whitall 2011	BULT: The arms moving simultaneously (in phase)/alternately (anti-phase) with auditory cueing at a preferred speed UULT: Opening the hand with finger extension, Scapular mobilization, Thoracic spine mobilization with weight shifting, Weight bearing with the paretic arm	60 min/session; 18 sessions 3 sessions/wk; 6wks	FMA; WMFT; SIS; Isokinetic strength; Isometric strength; fMRI

Wu 2011	BULT: Wiping the table with 2 hands, Grasping and releasing 2 towels, Lifting 2 cups, Picking up 2 pegs UULT: 75% functional task practice for hand function, UE coordination, balance, stretching, and weight bearing of the paretic UE, 25% compensatory practice on functional tasks with the paretic UE or both UEs	120 min/session; 15 sessions, 5 sessions/wk; 3wks	Kinematic variables; WMFT; MAL
Wu 2013	BULT: The paretic arm moving a handle independently, The paretic arm moving the handle against a resistance determined by the therapist through the entire movement UULT: Strengthening of the paretic arm, Stretching, Weight bearing, Coordination tasks, Balance activities, Unilateral and bilateral fine motor tasks	90–105 min/session; 20 sessions, 5 sessions/wk; 4wks	Kinematic variables; WMFT; MAL; ABILHAND Questionnaire
Yang 2012	BULT: 5min of tone normalization for the arm, wiping a table with two hands, 75–80min of robotic-assisted training, 15–20min of functional task practice included reaching to move a cup, grasping and releasing blocks, picking up coins, picking up two pegs, opening a jar with one hand stabilizing while the other hand manipulates UULT: Similar to the BRT, but only perform with the paretic hand	90–105 min/ session; 20 sessions, 5 sessions/wk; 4wks	FMA; MRC muscle scale; Grip strength; MAS

Notes: AMP, Motor-evoked potentials amplitude; ARAT, Action Research Arm Test; BATRAC, Bilateral arm training with rhythmic auditory cueing; BAT, Bilateral arm training; BBT, Box and Block test; BULT: Bilateral upper limb training; CMCT, central motor conduction time; FIM, Functional Independence Measures; FMA-UE, Fugl-Meyer Assessment for the Upper Extremities; fMRI, functional magnetic resonance imaging; MAS: modified Ashworth Scale; MBI, modified Barthel Index; MIF, Mesure de l'independance fonctionnelle; MRC, Medical Research Council; mRS: modified Rankin Scale; MSS, motor status score; RAP, rehabilitation activities profile; RMA, Rivermead Motor Assessment upper-limb scale; RMT, rest motion threshold; ROM, range of motion; SIS, stroke impact scale; TEMPA: test d'évaluation des membres dupérieurs de personnes agées; TOT, task-oriented training; UE: upper extremity; UMAQS, University of Maryland Arm Questionnaire; UULT: unilateral upper limb training; wk, week; WMFT, Wolf Motor Function test (Modified from the published paper (Chen et al., 2019))

3.4.4 Quantitative analyses

Based on the ICF categorization of the measurement items used in previous studies (Salter et al., 2005; Santisteban et al., 2016), this review assessed the reported effects of bilateral training versus unilateral or conventional training on body function by pooling the FMA score. It assessed the effects of bilateral training versus unilateral or conventional training on functional performance in the activities of daily living by pooling out the WMFT, ARAT and Box and Block test (BBT) results. The details of these outcome measures are presented in Table 3.4.

3.4.5 Characteristics of the intervention

Nine studies (Brunner et al., 2012; Desrosiers et al., 2005; Han & Kim, 2016; Lee, Lee, et al., 2017; Lin et al., 2010; Meng et al., 2017; Morris et al., 2008; Singer et al., 2013; Wu et al., 2011) compared the effects of bilateral functional task training with those of similar unilateral task-oriented training. Four studies (Brunner et al., 2012; Desrosiers et al., 2005; Meng et al., 2017; Morris et al., 2008) compared the effects with people with acute stroke. Two (Han & Kim, 2016; Singer et al., 2013) made similar comparisons using chronic stroke subjects. Two studies

Table 3.4 Pooled assessments used to conduct the meta-analysis

Assessment tool		Description
Motor Control	FMA-UE	The FMA-UE quantifies upper limb motor control using 33 items scored on an ordinal scale from 0 to 2. The total score's range is from 0 to 66.
Functional Performance	WMFT	The WMFT includes 2 strength-based tasks and 15 functional tasks. The 15 functional tasks are assessed by the time taken to complete each task and a quality rating of the use of the paretic hand in attempting each task. The functional tasks are graded from 0 to 5, giving a total score which ranges from 0 to 75.
	ARAT	The ARAT quantifies grasping, gripping, pinching and gross arm movement (Van der Lee et al., 2001) using 19 items. The quality of the performance on each item is rated from 0 to 3 points, giving a total score ranging from 0 to 57.
	BBT	The BBT tests gross manual dexterity (Mathiowetz et al., 1985). The number of wooden blocks that can be transported from one compartment of a box to another within 1 minute is counted, with a higher count indicating better functional performance.

Notes: ARAT, Action Research Arm Test; FMA-UE, Fugl-Meyer Assessment for the Upper Extremities; BBT, Box and Block Test; WMFT, Wolf Motor Function Test (Modified from the published paper (Chen et al., 2019))

(Lin et al., 2010; Wu et al., 2011) compared the effects of bilateral functional task training with those of dose-matched weight-bearing exercises, neurodevelopmental therapy and unilateral functional task training. Lee et al. (2017) investigated the combined effects of 30 minutes of

bilateral functional arm training and same dosage of standardized occupational therapy, which included resistance training, neurodevelopmental therapy, stretching exercises and fine movement training of the paretic upper limb. The outcomes of the combined therapy were then compared with those observed after 60 minutes of standardized occupational therapy.

Seven studies (Hsieh et al., 2017; Kim, Miller, et al., 2013; Liao et al., 2012; Lin et al., 2015; Lum et al., 2006; Wu et al., 2013; Yang et al., 2012) investigated the effects of bilateral robotic-assisted or resistance training. Three of them (Kim, Miller, et al., 2013; Wu et al., 2013; Yang et al., 2012) compared the effects of 1.5 hour of bilateral robotic-assisted training with those of same dosage of unilateral robotic-assisted training. Three of the others (Liao et al., 2012; Lin et al., 2015; Lum et al., 2006) compared the effects of bilateral robotic-assisted training with those of dose-matched unilateral functional task training in subjects with chronic stroke. Hsieh et al. (2017) compared robotic-assisted priming combined with TOT against TOT alone with people with sub-acute stroke. Only Liao's study (2012) reported the exact duration and dosage of each type of training in the bilateral group., including 300 to 400 forearm cycles, 150–200 repetitions of resistance mode, 600–800 repetitions of passive-passive mode and passive-active mode and 15 minutes of ADL task.

Five studies (Luft et al., 2004; Shahine & Shafshak, 2014; van Delden et al., 2013; Waller et al., 2008; Whitall et al., 2011) compared the effects of bilateral arm training with rhythmic auditory cueing against the effects of dose-matched unilateral upper limb training

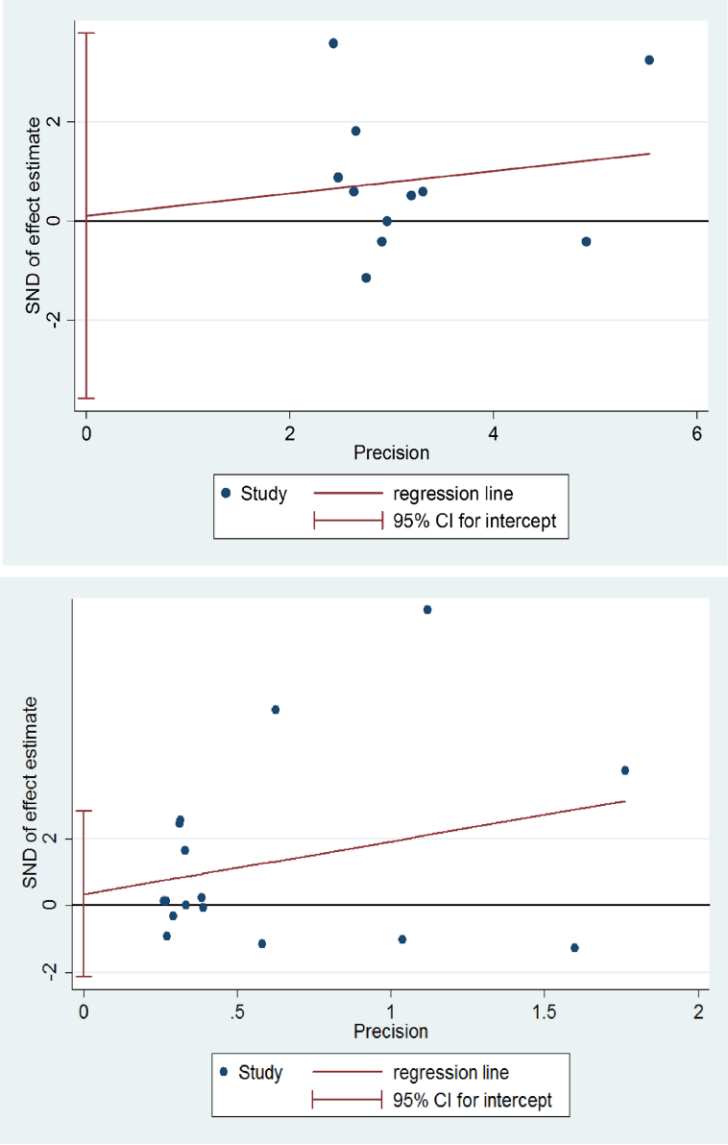
which included upper limb mobilization, neurodevelopmental therapy, fine movement training and strengthening exercises.

3.4.6 Meta-analysis

The training periods of per session ranged from 20 to 160 minutes. The total training time ranged from 640 to 2400 minutes. Meta-regression indicated that neither the number of training sessions (p=0.947), the total duration of training (p=0.217) nor the duration of training per session (p=0.316) was a significant predictor of FMA-UE results.

3.4.7 Publication bias

Egger's test showed no significant publication bias in any of the outcome measures in the meta-analysis (see Figure 3.3) of FMA-UE (p=0.774) or of WMFT, ARAT or BBT (p=0.950).

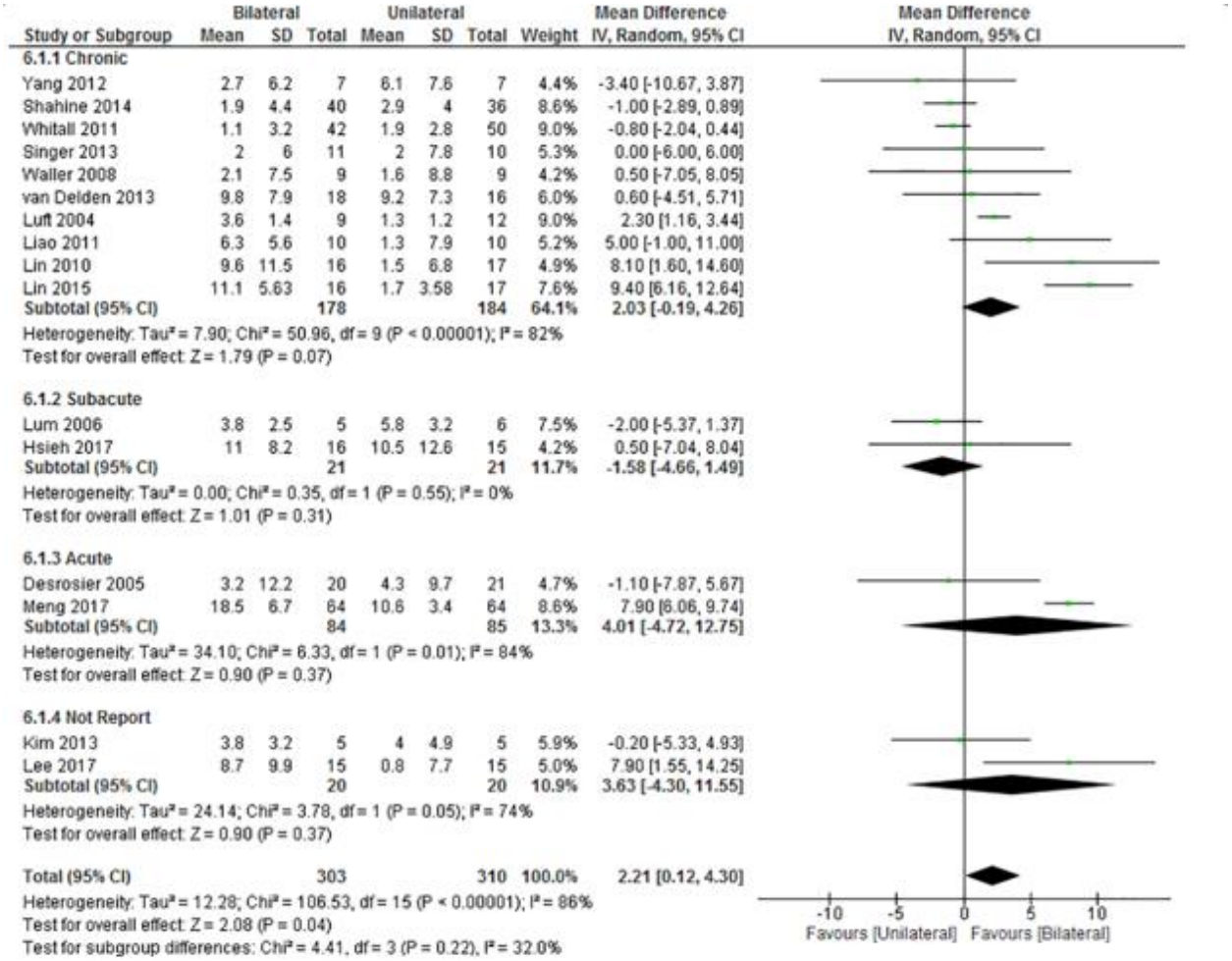


SND: standard normal deviation, CI: confidence interval

Figure 3.3 Results of Egger's test for publication bias in the motor control results (above) and functional performance results (below). (Cited from the published paper (Chen et al., 2019))

3.4.8 Motor control outcomes

The FMA-UE was used to measure improvements in upper limb motor control in 16 of the studies (Desrosiers et al., 2005; Hsieh et al., 2017; Kim, Miller, et al., 2013; Lee, Lee, et al., 2017; Liao et al., 2012; Lin et al., 2015; Lin et al., 2010; Luft et al., 2004; Lum et al., 2006; Meng et al., 2017; Shahine & Shafshak, 2014; Singer et al., 2013; van Delden et al., 2013; Waller et al., 2008; Whitall et al., 2011; Yang et al., 2012). The meta-analysis found a significantly greater improvement in motor control in the BULT group compared with the UULT group (MD=2.21, 95%CI: 0.12 to 4.30, p=0.04; I^2=86%, p<0.001). However, no significant improvement was shown with BULT when compared with UULT in the subgroups according to post-stroke duration (Figure 3.4) (acute: MD=4.01, 95%CI, -4.72 to 12.75, p=0.37; I^2=84%, p=0.01; subacute: MD=-1.58, 95%CI: -4.66 to 1.49, p=0.31; I^2=0%, p=0.55; chronic: MD=2.03, 95%CI: -0.19 to 4.26, p=0.07; I^2=82%, p<0.001; not report: MD=3.63, 95%CI: -4.30 to 11.55, p=0.37; I^2=74%, p=0.05).



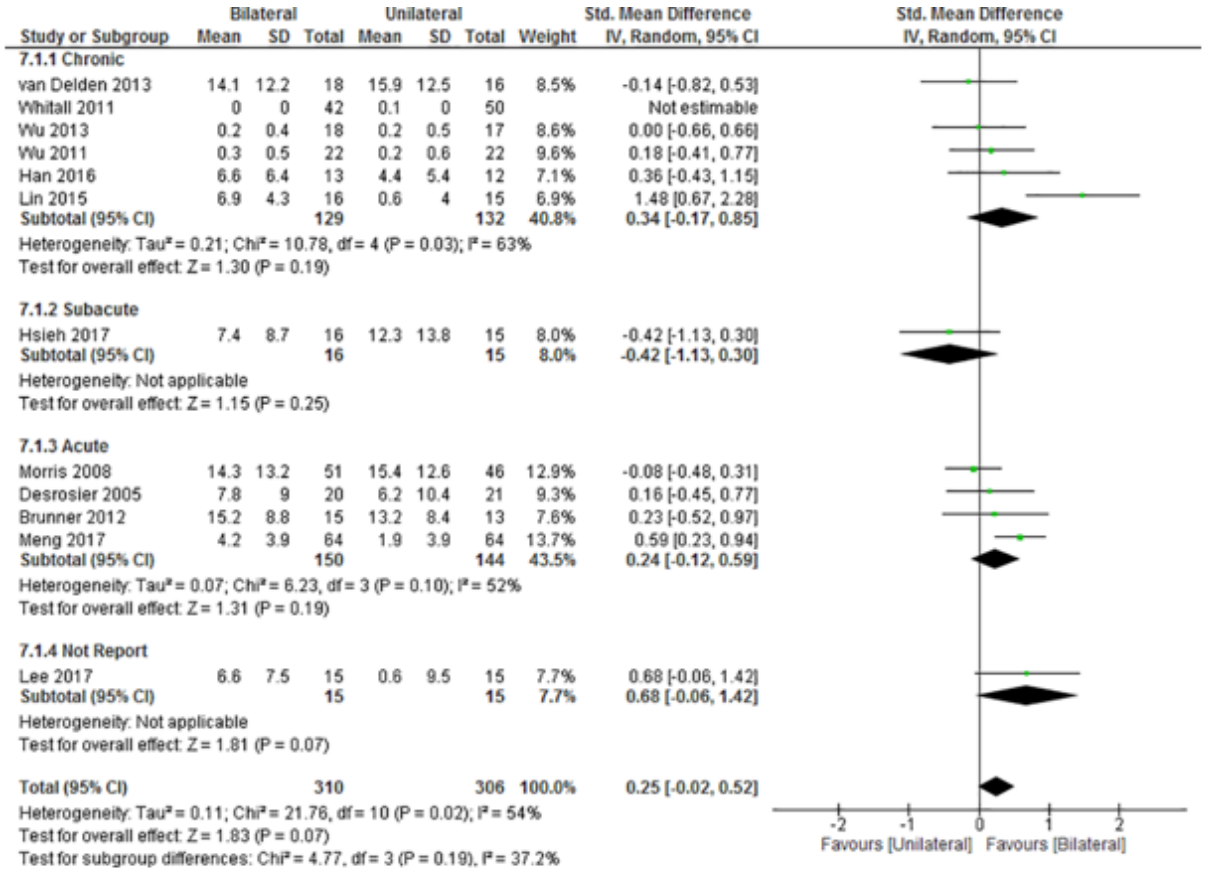
CI: confidence interval, IV: inverse variable, SD: standard deviation

Figure 3.4 Differences in the mean effect of BULT relative to UULT in terms of FMA-UE score (with 95%CIs) using pooled data from 16 studies (Cited from the published paper (Chen et al., 2019))

3.4.9 Functional performance outcomes

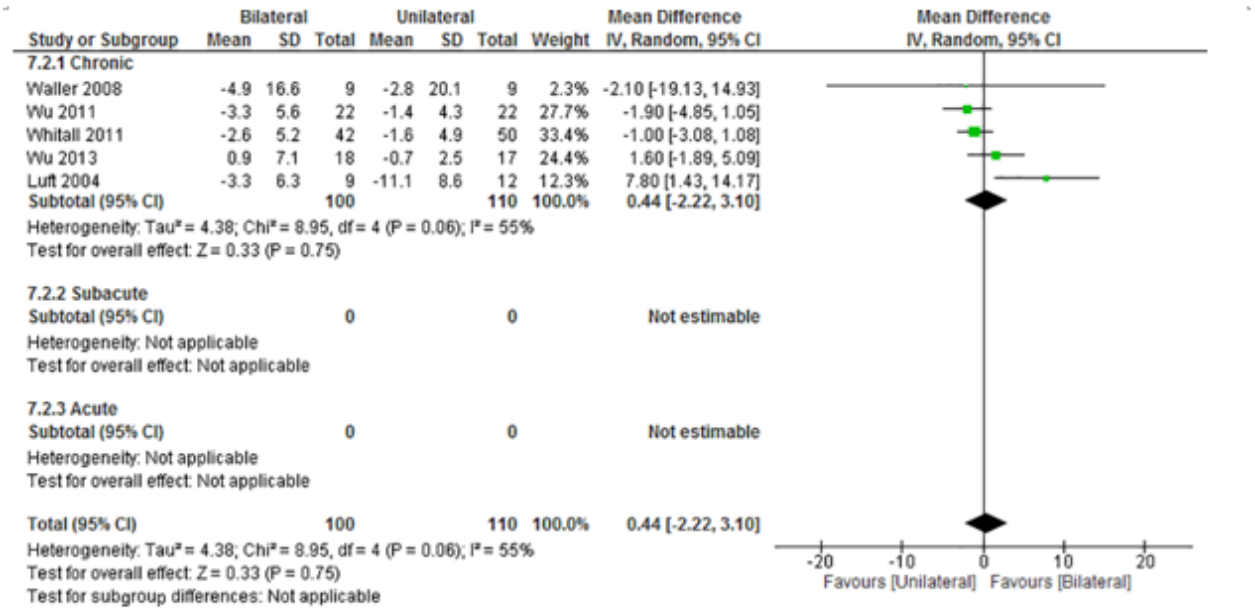
Functional performance was measured in terms of WMFT, ARAT scores and BBT counts in Figure 3.5. Among the 15 studies, four (Brunner et al., 2012; Meng et al., 2017; Morris et al., 2008; van Delden et al., 2013) used the ARAT, four (Lin et al., 2015; Whitall et al., 2011; Wu et al., 2011; Wu et al., 2013) used the WMFT and the other 4 used the BBT. The WMFT scores showed no significant difference between BULT and UULT in terms of improvements in the functional ability component of the WMFT (SMD=0.25, 95%CI: -0.02 to 0.52; p=0.07; I^2=54%, p=0.02). Similarly, BULT did not yield significant improvement when compared with UULT in any of the post-stroke duration subgroups (acute: SMD=0.24, 95%CI: -0.12 to 0.59, p=0.19; I^2=52%, p=0.10; subacute: SMD=-0.42, 95%CI: -1.13 to 0.30, p=0.25; chronic: SMD=0.34, 95%CI: -0.17 to 0.85, p=0.19; I^2=63%, p=0.03; not report: SMD=0.68, 95%CI: -0.06 to 1.42, p=0.07).

Five studies (Luft et al., 2004; Waller et al., 2008; Whitall et al., 2011; Wu et al., 2011; Wu et al., 2013) were used to evaluate the effect on improvement in the WMFT task completion time (Figure 3.6). A comparison of BULT and UULT revealed no significant difference in the time component of the WMFT (MD=0.44, 95%CI: -2.22 to 3.10; p=0.75; I^2=55%, p=0.06). Similarly, BULT did not yield a significant improvement over UULT in the subgroups (MD=0.44, 95%CI, -2.22 to 3.10, p=0.75; I^2=55%, p=0.06).



CI: confidence interval, IV: inverse variable, SD: standard deviation

Figure 3.5 Differences in the mean WMFT, ARAT and BBT results of BULT compared to UULT (with 95%CIs) using pooled data from 12 studies (Cited from the published paper (Chen et al., 2019))



CI: confidence interval, IV: inverse variable, SD: standard deviation

Figure 3.6 Difference in the mean effect of BULT relative to UULT using WMFT times pooled from 5 studies (Cited from the published paper (Chen et al., 2019))

3.5 Discussion

This has been the first published systematic review and meta-analysis comparing the effects of BULT and UULT on motor control and functional performance in people with stroke when excluded CIMT, which provides a more realistic overview of the actual rehabilitation effects. The meta-analysis examined the pooled results of 21 RCTs which included 842 people with stroke. According to meta-analysis, BULT yielded significantly greater improvement in FMA-UE scores than UULT. However, there was no significant difference in the improvement in functional performance between BULT and UULT.

3.5.1 Motor control

The finding of our study are partially consistent with the findings of a review by Coupar et al. (Coupar et al., 2010). In that review (Coupar et al., 2010) of two sets of 4 studies, the authors found that BULT was more effective than the usual care in terms of improving the FMA-UE scores, but they found no differential effects between BULT and UULT in terms of improving FMA-UE scores. This study's inclusion and exclusion criteria enabled it to include 4 studies (Desrosiers et al., 2005; Luft et al., 2004; Lum et al., 2006; Morris et al., 2008) reviewed by Coupar and 12 other RCTs in our meta-analysis. Thus, our review has elicited more robust estimations of the overall effects of BULT and UULT in improving FMA-UE scores.

There have been 2 reviews (Lee, Kim, et al., 2017; Van Delden et al., 2012) which found that BULT and UULT yielded similar alleviation of post-stroke motor impairment as indicated by FMA-UE scores. However, those results should be interpreted cautiously, as each of these reviews only included only 4 studies. In contrast, this meta-analysis treated 16 RCTs and had a much larger sample size. It therefore had stronger power to detect the difference between the effectiveness of BULT and UULT in terms of an improved FMA-UE score. In addition, the reviews conducted by Lee (2017) and by van Delden (2012) also included 2 studies (Stoykov et al., 2009; Van der Lee et al., 1999) that included CIMT. This study only compared BULT with task-oriented training. Those differences may explain the differences in the findings.

This review showed significantly greater improvement in FMA-UE scores after BULT compared with UULT. And it found no significant association of the training dosage with the FMA-UE score improvements. Hence, the difference in improvement was mainly attributable to the type of intervention (BULT versus UULT).

Excitability typically decreases in the lesioned hemisphere and increases in the intact hemisphere in people with stroke (Boddington & Reynolds, 2017; Grefkes & Ward, 2014; Murase et al., 2004). Studies (Calautti & Baron, 2003; Ferbert et al., 1992; Stinear & Byblow, 2004; Summers et al., 2007) using transcranial magnetic stimulation have indicated that motor recovery positively correlates with restoration of interhemispheric imbalance after stroke. Hence, the different levels of improvement in the FMA-UE scores after BULT and UULT may be related to the use of different mechanisms to facilitate the reorganization in the lesioned hemisphere. UULT is based on the principle of activation in the lesioned hemisphere via assisted or resisted unilateral training of the paretic limb (Bonita & Beaglehole, 1988; Grotta et al., 2004; Wolf et al., 2006). BULT instead activates similar neural networks in both hemispheres through simultaneous activation of homologous muscle groups (Carson, 2005; Cauraugh & Summers, 2005; Hallett, 2001; Swinnen & Duysens, 2012). Evidence has shown that BULT can activate the distributed corticospinal pathways bilaterally via ipsilateral and contralateral corticospinal fibers (Carson et al., 2004; Carson et al., 1999; Cattaert et al., 1999; Netz et al., 1997; Turton et al., 1996; Ziemann & Hallett, 2001) and the corpus callosum (Hanajima et al., 2001; Ugawa et al., 1993). Compared with UULT, BULT may evoke greater activation of the lesioned hemisphere by recruiting more neural pathways (Cauraugh & Summers, 2005). In the BULT

group, increased activation in the lesioned hemisphere made the contribution to greater improvements in motor control, as indicated by the FMA-UE scores.

3.5.2 Functional performance

Turning to functional performance, consistent with the findings of previous reviews (Lee, Kim, et al., 2017; Van Delden et al., 2012), BULT showed no signficant difference to UULT in aspects of improving performance of the WMFT, ARAT or BBT. Although there was significantly better improvement in the FMA-UE scores with BULT when compared to UULT, there was no significant difference in functional performance between the training techniques.

Buchner et al. (1996) has reported a non-linear relationship between leg strength and gait speed in people with stroke. The relationship's positive slope gradually decreases to zero and speed plateaus as leg strength increases. A certain threshold muscle strength is required to perform each type of activity. Beyond that, however, increased strength does not result to improved performance, at least in terms of gait speed (Bohannon, 2007). Similarly, improvement in FMA-UE score and functional performance also exhibited a non-linear relationship. Although previous studies (Edwards et al., 2012; Hodics et al., 2012; Platz et al., 2005; Wolf et al., 2001) have reported a moderate to good correlation between FMA-UE score and functional performance (or at least WMFT, ARAT and BBT results), the non-linear relationship shown

between these factors in this meta-analysis simply reflect an inability of the people with stroke to achieve the threshold level of motor control needed to perform the functional tasks tested. The FMA-UE improvement generated through BULT simply have been insufficient to yield a significant improvement in functional performance.

The meta-analysis revealed that bilateral training tended to yield a larger SMD in functional performance than BULT with robotic-assistance or auditory cueing. However, that result should be interpreted cautiously because although the meta-analysis included 9 studies (Brunner et al., 2012; Desrosiers et al., 2005; Han & Kim, 2016; Lee, Lee, et al., 2017; Lin et al., 2010; Meng et al., 2017; Morris et al., 2008; Singer et al., 2013; Wu et al., 2011) of bilateral functional task training (the largest proportion), it included only 7 studies (Hsieh et al., 2017; Kim, Miller, et al., 2013; Liao et al., 2012; Lin et al., 2015; Lum et al., 2006; Wu et al., 2013; Yang et al., 2012) of bilateral robotic-assistance and only 5 studies (Luft et al., 2004; Shahine & Shafshak, 2014; van Delden et al., 2013; Waller et al., 2008; Whitall et al., 2011) of bilateral arm training with auditory cueing. More included studies of auditory cueing and bilateral robotic-assisted training would help to generate more robust conclusions.

3.5.3 Limitation

This systematic review examined 21 studies with 842 subjects, but even that sample size may have been insufficient to detect significant differences in the functional performance outcomes. In addition, the results of this review may not be generalizable to all people with stroke. In addition to the 13 studies (Han & Kim, 2016; Liao et al., 2012; Lin et al., 2015; Lin et al., 2010; Luft et al., 2004; Shahine & Shafshak, 2014; Singer et al., 2013; van Delden et al., 2013; Waller et al., 2008; Whitall et al., 2011; Wu et al., 2011; Wu et al., 2013; Yang et al., 2012) of people with chronic stroke, only 4 studies (Brunner et al., 2012; Desrosiers et al., 2005; Meng et al., 2017; Morris et al., 2008) of people with acute stroke and 2 studies (Hsieh et al., 2017; Lum et al., 2006) of people with sub-acute stroke were included. The true effect of BULT may therefore be underestimated because of the small number of non-chronic stroke studies included. Including more studies with subjects in different phases of stroke would increase the generalizability of the conclusions.

Note that most of the studies of Asian populations reported significantly greater improvement after BULT compared with UULT. By contrast, most studies conducted with western subjects reported no significant difference. The reason underlying this discrepancy remains unclear. In future reviews, clear methodological information and a larger sample size help to explain this phenomenon.

In addition, only the immediate effects in terms of the outcome measures were evaluated. The meta-analysis did not deal with carryover effect, as only 29% of the studies (Brunner et al., 2012; Hsieh et al., 2017; Lum et al., 2006; Morris et al., 2008; Singer et al., 2013; van Delden et

al., 2013) included reported data from follow-up assessments. These findings therefore say nothing about the very important long-term effects of BULT and UULT for people with stroke. Carryover effect should be explored further.

At last, the studies included in this review did not consistently classify the severity of the motor impairment being treated. There was therefore insufficient information to compare the effects of BULT and UULT with respect to the severity of motor impairment.

3.6 Conclusions

Both BULT and UULT can help to improve motor control and functional performance in people with stroke. BULT is superior to UULT in terms of improving motor control as measured by the FMA-UE. BULT is not, however, significantly more effective in improving functional performance as measured by the WMFT, the ARAT or the BBT. All the finding can help to establish the theoretical basis of the effectiveness of bilateral transcutaneous electrical nerve stimulation in upper limb stroke rehabilitation in our main study.

Chapter 4

The predictive role of hand subscale of Fugl-Meyer Assessment and Motor Activity Log in Action Research Arm Test in people with stroke

Some of the information reported in this chapter has been submitted to a peer-reviewed journal.

Chen PM, Liu TW, Lai CKY, Ng SSM., Self-perceived performance in upper limb movement predicts the upper limb motor functions in people with stroke. *BMC neurology* 2021. (Submitted & under review) (Appendix 4.1)

Some of the information reported in this chapter has been presented at a conference.

Chen PM, Liu TW, Lai CKY, Ng SSM, Prediction of Paretic Upper Limb Motor Function with Self-perceived Performance in Upper Limb Movement. *American Congress of Rehabilitation Medicine (ACRM) 98th Annual Conference*, 26–29 September 2021, American (Online) (Accepted). (Appendix 4.2)

4.1 Abstract

Recent findings of clinical studies have demonstrated the significant positive relationship between the upper limb motor control and the functional performance of upper limb in people with stroke. Although self-perceived performance, the self-perception of the motor performance, could affect the performance of upper limb, the relationship between self-perceived performance and functional performance of upper limb is still remained unclear. Identifying the individual contribution of self-perceived performance to real performance of upper limb performance is important for designing and evaluating the effective intervention for improving the upper limb motor function in people with stroke. The objective of this study is to quantify the contribution of self-perceived performance of paretic upper limb assessed by Motor Activity Log (MAL) on the functional performance of upper limb assessed by Action Research Arm Test (ARAT) in people with stroke.

This cross-sectional study was conducted in a university-affiliated neurorehabilitation laboratory. There were total 87 subjects (50 males, 37 females; mean age=61.12±6.88 years old, post-stroke duration=6.31±2.84 years) included in this study. Self-perceived performance in using paretic limb was measured by MAL, including subscale of Amount of Usage (MAL-AOU) and Quality of Movement (MAL-QOM). Functional performance of upper limb was measured by ARAT. Upper limb motor control of hand was measured by hand subscale of Fugl-Meyer Assessment (FMA-hand).

The result showed that MAL-QOM (r=0.648, p<0.001), MAL-AOU (r=0.606, p<0.001), FMA-hand scores (r=0.663, p<0.001) and the use of a walking aid (r=-0.397, p<0.001) significantly correlated with the ARAT scores. A total 66.9% of the variance in the ARAT scores was predicted by the final regression model including MAL-QOM, MAL-AOU, FMA-hand scores and walking aid. The FMA-hand score was the best predictor of ARAT scores, which can predict 36.4% variance of ARAT scores in people with stroke, when controlled the effect of using a walking aid. After controlling for use of a walking aid and FMA-hand scores, the multiple linear regression modeling showed that MAL-QOM and MAL-AOU scores could also independently predict an additional 10.4% of the variance in ARAT scores.

4.2 Introduction

The Action Research Arm Test (ARAT) is a reliable and valid upper limb-specific instrument for evaluating the arm and hand functioning of people with neurological disorders, including stroke (Langhorne et al., 2009; Veerbeek et al., 2014), traumatic brain injury (Barden et al., 2014), multiple sclerosis (Carpinella et al., 2014; Platz et al., 2005) and Parkinson's disease (Hwang et al., 2009; Song, 2012). The ARAT quantifies the ability to grasp, grip and pinch, and to perform gross arm movements with objects of different sizes, weights and shapes.

Previous studies (De Weerdt & Harrison, 1985; Kwakkel & Kollen, 2007; Platz et al., 2005; Rabadi & Rabadi, 2006) have revealed that motor impairment limits the paretic upper limb's functioning in people with stroke. Muscle weakness, abnormal reflexes and motor coordination quantified using the Fugl-Meyer Assessment of Upper Extremities (FMA-UE) scores were all significantly correlated with ARAT scores in people with stroke ($r=0.770–0.925$) (De Weerdt & Harrison, 1985; Platz et al., 2005; Rabadi & Rabadi, 2006). Furthermore, Kwakkel and Kollen (2007) have shown that the hand subscale of the FMA (FMA-hand) is the best predictor of improvement in ARAT results in people with stroke (standardized $\beta=0.357$; $p<0.001$). The arm, leg and balance ability subscales show less predictive power ($\beta <0.007$; $p<0.001$). However, the independent contribution of FMA-hand to ARAT scores has not been systematically investigated and quantified when the demographic data was also considered.

Self-perceived performance is a personality trait as how well and satisfied the subjects think their performance is (Prentice, 2008) rather than objective performance in the real life. The low level of self-perceived performance are indeed associated with the objective performance in people with stroke (Brogårdh et al., 2012; Van der Lee et al., 2004). Van der Lee et al. (2004) has demonstrated a significant and moderate to good correlation ($r=0.63$, $p<0.001$) between self-perceived performance measured by Motor Activity Log (MAL) and ARAT scores in people with stroke. Poor self-perceived performance of upper limb discourages using it, which impedes recovery of the limb's motor skills, leading to even less self-perceived performance, and a downward spiral in upper limb functioning, objectively measured. That makes it important to identify the individual contribution of self-perceived performance to real performance of upper limb in developing rehabilitation programs for people with stroke. However, no proper evaluation of that contribution has yet been published.

This study was therefore designed to determine whether MAL scores can independently predict the ARAT scores in people with stroke, and if so, to quantify the relationship when FMA-hand scores and sociodemographic factors are also considered.

4.3 Methods

4.3.1 Subjects

A total of 87 subjects were self-selected through poster advertising among local self-help groups. Those included (1) were between 50 and 80 years of age, (2) had been diagnosed with stroke at least 1 year previously, (3) had volitional control of the non-paretic arm, (4) could induce at least minimal anti-gravity movement in the shoulder of the paretic arm, (5) had at least 5º of wrist extension in the anti-gravity position, and (6) scored ≥7 (out of 10) on the Cantonese version of the Abbreviated Mental Test.

People were excluded if they (1) had any additional medical, cardiovascular or orthopedic condition (e.g. angina pectoris), (2) had receptive dysphasia, (3) had visual impairment that could not be corrected by glasses (e.g. hemianopia), (4) had significant upper limb peripheral neuropathy, (5) had severe shoulder, elbow, wrist or finger contractures that would preclude testing the arm's passive range of motion, or (6) were involved in other clinical trials.

Ethical approval (Reference Number: HSEARS20131011003-01) was obtained from the Ethics Committee of the Hong Kong Polytechnic University. The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2001).

4.3.2 Data collection

The assessments were performed in the neurorehabilitation laboratory of the Hong Kong Polytechnic University. After obtaining the subjects' written informed consent, they completed a sociodemographic questionnaire and then were tested with all the tests administered in random order. All the tests were administered by a physiotherapist with 5 years of clinical experience. All of the instruments used had previously been validated in the local context.

4.3.3 Outcome measure

Action Research Arm Test (ARAT)

The ARAT was used to assess the functional performance of each subject's paretic upper limb (Lang et al., 2006). The ARAT scores functioning on an ordinal scale with 19 items each rated from 0 to 3 with "0=no movement, "1=movement task is partially performed", "2=movement task is completed but takes abnormally long", or "3=movement task is performed normally". The total score thus ranges from 0 to 57. According to the guidelines (Lyle, 1981), the subjects are asked to perform the most difficult task within a subscale first. If they complete it successfully and get a score of 3 on that task, then all the other items within that subscale are also scored as 3. A score between 0 to 2 on the first item indicates that the second item (easiest) should be evaluated. If the subject scores 0 on the second item, then the rest of the items within that subscale are also scored as 0. Otherwise, the rest of the tasks within the subscale are administered. A previous study (Van der Lee et al., 2001) has shown that the ARAT has

excellent intra-rater (r=0.996-0.997) and inter-rater (r=0.989) reliability in assessing people with chronic stroke.

Motor Activity Log (MAL)

The quality of movement (QOM) and amount of usage (AOU) subscales of MAL were used to quantify self-perceived performance in using a paretic upper limb. Each consist of 30 items quantifying the subject's self-perceived performance in using a paretic upper limb in life situations during the previous week, such as turning on a light and brushing the teeth (Winstein et al., 2003). Each of the 30 items is rated as 0 (never), 1 (very poor), 2 (poor), 3 (fair), 4 (almost normal) or 5 (normal) in QOM. For AOU, the ratings are 0 (not used), 1 (very rarely), 2 (rarely), 3 (half of the pre-stroke frequency), 4 (3/4 of the pre-stroke frequency) or 5 (the same as before the stroke). Higher scores indicate higher self-perceived performance in using the paretic upper limb. Both the MAL-QOM and MAL-AOU have demonstrated good test-retest reliability (QOM: Intraclass Correlation Coefficient (ICC)=0.82; AOU: ICC=0.79) (Uswatte et al., 2006) and excellent internal consistency (QOM: Chronbach's α=0.87; AOU: Chronbach's α>0.82) (Uswatte et al., 2005) in assessing people with stroke.

Fugl-Meyer Assessment-hand function (FMA-hand)

Motor control of the paretic hand was assessed using the FMA-hand instrument. It consists of 7 items (items 24 through 30 of the full upper limb assessment) with a total score of 14. It assesses motor control of finger flexion and extension, thumb adduction, finger opposition, cylindrical grip and spherical grip using ratings of 0, 1 or 2. Higher scores indicate better motor control of the paretic hand. The entire FMA-UE has shown excellent intra-rater (ICC=0.984–0.993) and inter-rater (ICC=0.995–0.996) reliability when used to assess people with stroke (Duncan et al., 1983).

4.3.4 Statistical analysis

The data were analyzed using version 22.0 of the Statistical Package for the Social Sciences software (SPSS Inc, Chicago, IL, USA). Descriptive statistics were compiled summarizing the demographic information and the FMA-UE, FMA-hand, MAL-QOM, MAL-AOU and ARAT scores. Kolomogorov-Smirnov test was used to evaluate the normality of the data distributions. Pearson or Spearman correlation coefficients was computed to evaluate the strength of the relationships between ARAT with FMA-hand, MAL-AOU, MAL-QOM and the demographic data, as appropriate. To control for sociodemographic differences, partial correlation coefficients were calculated for the FMA-hand, MAL-QOM and MAL-AOU scores. Their relative power in predicting the ARAT scores was determined by multiple linear regression model with the forced entry method. The significance level was set at 0.05 (two-tailed).

4.4 Results

4.4.1 Subject characteristics

Thirty-seven females (43%) and 50 males (57%) with a mean age of 61.12±6.88 years and a mean BMI of 24.07±3.79kg/m^2 were recruited. Their mean post-stroke duration was 6.31±2.84 years. Among them, forty-seven (54 %) had left hemiplegia and 40 (46%) had right hemiplegia. Forty-nine of the subjects had suffered an infarction while the other 38 had survived hemorrhagic strokes. Seven of the subjects lived alone; the others lived with family. Sixty-eight of the subjects used a walking aid; the others could walk without an aid. The group's mean FMA-UE score was 34.51±11.69. The mean FMA-hand score was7.55±2.84. The mean MAL-QOM score and MAL-AOU score were 39.35±37.77 and 29.61±30.84, respectively (Table 4.1).

Table 4.1 Demographic information describing the subjects

Baseline information	**mean±SD**
Age (years)	61.12±6.88
BMI (kg/m^2)	24.07±3.79
Post-stroke duration (years)	6.31±2.84
ARAT score	23.76±16.62
FMA-UE score	34.51±11.69
FMA-hand score	7.55±2.84
MAL-QOM score	39.35±37.77
MAL-AOU score	29.61±30.84
	Number of subjects
Gender (Female/Male)	37/50
Paretic side (Left/Right)	47/40
Type of stroke (Infarct/Hemorrhage)	49/38
Living situation (Live alone/Live with family)	7/80
Walking aid (Yes/No)	68/19

Notes: N=87; SD, standard deviation; BMI: body mass index; ARAT: Action Research Arm Test; FMA-UE: Fugl-Meyer Assessment for the Upper Extremities; FMA-hand: hand subscale of Fugl-Meyer Assessment; MAL-QOM: Motor Activity Log Quality of Movement subscale; MAL-AOU: Motor Activity Log Amount of Usage subscale

4.4.2 Relationships between ARAT scores and the other outcome measures

The mean ARAT score of 23.76±16.62 indicates that the subjects had a "moderate" level of functional performance of upper limb, on average. A published Rasch analysis has concluded that an ARAT score between 22 to 42 should be defined as moderate upper limb function (Hoonhorst et al., 2015). The ARAT scores were significantly correlated with the use of a walking aid (r=0.459, p<0.001), the FMA-hand (r=0.663, p<0.001), MAL-QOM (r=0.648, p<0.001) and MAL-AOU scores (r=0.606, p<0.001) (Table 4.2). After controlling for the use of a walking aid, strong and significant partial correlation coefficients were found between the ARAT scores and the FMA-hand (r=0.680, p<0.001), MAL-QOM (r=0.606, p<0.001) and MAL-AOU scores (r=0.551, p<0.001) (Table 4.3).

Table 4.2 The correlation between ARAT scores and the other variables

Demographic information	Correlation coefficients (r)
Age	0.121
Gender	-0.121
BMI	-0.189
Post-stroke duration	0.076
Paretic side	0.048
Type of stroke	-0.059
Living situation	0.048
Walking aid use	-0.459**
FMA-hand score	0.663**
MAL-QOM score	0.648**
MAL-AOU score	0.606**

Notes: N=87; ARAT: Action Research Arm Test; BMI: body mass index; FMA-hand: hand subscale of Fugl-Meyer Assessment; MAL-QOM: Motor Activity Log Quality of Movement subscale; MAL-AOU: Motor Activity Log Amount of Usage subscale

**indicates a correlation significant at the $p<0.001$ level of confidence, r indicated Pearson correlation

Table 4.3 Partial correlation coefficients (controlling for using a walking aid) between ARAT scores and other variables

Outcome measure	Partial correlation coefficient
FMA-hand score	0.680**
MAL-QOM score	0.606**
MAL-AOU score	0.551**

Notes: N=87; FMA-hand: hand subscale of Fugl-Meyer Assessment; MAL-QOM: Motor Activity Log Quality of Movement subscale; MAL-AOU: Motor Activity Log Amount of Usage subscale

** indicates a correlation significant at the $p<0.001$ level of confidence

4.4.3 Contributions of FMA-hand, MAL-QOM and MAL-AOU scores to ARAT score

Table 4.4 shows the predictive power of the different variables for ARAT scores as determined by multiple linear regression analysis with the forced entry method. The full model ($F_{3,83}=44.490$, $p<0.001$) was able to explain 66.9% of the variance in the ARAT scores. The FMA-hand score ($\beta=0.610$) was the best predictor of ARAT scores (model 3, table 4.4) with the highest Pearson correlation coefficient ($r=0.663$, $p<0.001$). After controlling for use of a walking aid and FMA-hand results, the multiple linear regression modeling (model 3) showed that MAL-QOM ($\beta=0.238$) combined with MAL-AOU ($\beta=0.174$) could independently predict an additional

10.4% of the variance in ARAT scores. The Pearson correlation coefficients were MAL-QOM: r=0.648, p<0.001; MAL-AOU: r=0.606, p<0.001.

Table 4.4 Relationships between ARAT scores and other variables

	Adjusted R^2	**R^2 change**	**Predictor**	**B**	**95% Confidence interval**	***β***	***p***
Model 1	0.201	0.201	Use of a Walking Aid	-18.355	-26.018–-10.693	-0.459	<0.001*
Model 2	0.565	0.364	Use of a Walking Aid	-14.864	-20.577–-9.151	-0.372	<0.001*
			FMA-hand score	3.571	2.735–4.407	0.610	<0.001*
Model 3	0.669	0.104	Use of a Walking Aid	-10.919	-16.124–-5.715	-0.273	<0.001*
			FMA-hand score	2.645	1.835–3.455	0.452	<0.001*
			MAL-QOM score	0.105	0.020–0.189	0.238	0.016*
			MAL-AOU score	0.094	-0.007–0.195	0.174	0.069

Notes: B, unstandardized regression coefficient; β, standardized regression coefficient; FMA-hand: hand subscale of Fugl-Meyer Assessment; MAL-QOM: Motor Activity Log-quality of movement subscale; MAL-AOU: Motor Activity Log Amount of Usage subscale

* indicated p<0.05

4.5 Discussion

4.5.1 Summary

To the best of our knowledge, this has been the first published study revealing that the MAL scores can independently predict their ARAT scores in people with stroke. That finding adds to the current knowledge about the roles of self-perceived performance in using paretic upper limb in people with stroke. The clinical implication is that enhancing self-perceived performance in using paretic upper limb could be helpful in promoting better actual upper limb functional performance among people with stroke.

4.5.2 ARAT and MAL scores

A previous study (Hoonhorst et al., 2015) used ARAT scores to classify performance as no capacity (ARAT score: 0–10), poor capacity (11–21), limited capacity (22–42), notable capacity (43–54) or full capacity (ARAT score 55–57). In this study, the mean ARAT score was 23.76, indicating only limited functional performance of the paretic upper limb in people with stroke. That is similar to the results reported by Van der Lee (2001) where the mean ARAT score

was 29.2 in people with chronic stroke. The similar demographics of the subjects of two studies could explain the similar results.

The mean MAL-QOM and MAL-AOU scores were 39.35±37.77 and 29.61±30.84, which means that the average score on each item was 1.31 and 0.99, respectively. According to the guidelines (Uswatte et al., 2006), those averages indicate quite a low level of self-perceived performance. Two other studies (Harris & Eng, 2006; Van der Lee et al., 2004) reported similar findings in people with stroke. The low self-perceived performance would be expected to influence a person's willingness to use the paretic upper limb. Using it less will tend to worsen its actual performance, feeding back to self-perceived performance in a potential downward spiral.

4.5.3 MAL score predicts performance of ARAT score

The full model predicted 66.9% of the variance in the ARAT scores. FMA-hand scores and MAL scores were significant independent predictors of the ARAT scores, accounting for 36.4 % and 10.4% of the variance, respectively. These findings are consistent with those of previous studies showing that FMA-hand scores are associated with the ARAT scores among people with stroke (Coupar et al., 2012; Kwakkel & Kollen, 2007). This study is the first

demonstrating that MAL-QOM and MAL-AOU scores are independent predictors of ARAT scores in people with stroke.

In Bandura's theory (1977), decisions about activity and behavior could be influenced by one's beliefs about the ability to engage in them successfully. Bandura and Adams (1977) suggest that the influence is partly cognitive—people predict specific behavioral consequences and their attitudes are based on those perceptions. In this study, those more satisfied with their performance in using their paretic upper limb were more likely to use it in their daily lives. That practice of the paretic upper limb would help them maintain or even improve their proficiency. Conversely, the people with stroke who have low self-perceived performance in using their paretic limb would probably avoid using it to some extent. It resulted in less motor control in the long term (Kunkel et al., 1999). That could explain why the MAL scores were significant predictors of ARAT scores in people with stroke.

Total 33.1% of the variance in the ARAT scores remained unexplained in the full model. Several psychological and physical factors which were not included could explain that. Some psychological factors like fatigue (Enoka & Duchateau, 2008; Yozbatıran et al., 2006) and depression (Gainotti et al., 2001) was not accounted for in this study's design. In addition, physical factors such as upper limb muscle weakness (Ekstrand et al., 2016), spasticity (Sommerfeld et al., 2004), limited range of motion (Beebe & Lang, 2009), impaired sensation (Meyer et al., 2014) and the hand dominance prior to the stroke (Harris & Eng, 2006) were also

not included in this study. Future studies investigating the contributions of all these psychological and physical factors on ARAT scores are certainly warranted.

4.5.4 Correlations of other parameters with ARAT scores

The analyses showed that using a walking aid was a significant predictor of ARAT scores, while age, gender, BMI, post-stroke duration, paretic side, type of stroke and living situation showed no significant predictive power. The explanation could be that using a walking aid indicates poor motor control of the upper limb reflected in a poor ARAT score.

In this study, type of stroke did not show significant correlation with ARAT scores. It could be explained by the subjects' post-stroke stages, which should influence the progress of neural recovery. Andersen et al. (2009) has reported that people with hemorrhagic stroke are more likely to have a poorer prognosis in acute phase than those have survived an ischemic one, because the lesioned area is generally more extensive. However, as spontaneous recovery after hemorrhage and ischemia progresses, people may regain comparable levels of upper limb function. That would tend to explain the lack of any significant association between ARAT scores and types of stroke in this study.

4.5.5 Clinical implications

These findings indicate that upper limb rehabilitation might usefully include techniques designed to enhance self-perceived performance in people with stroke. The goal should of course be to encourage greater, more frequent use. For example, physiotherapists could incorporate "graded" activity training into the customary physical training. The grades could boost commitment to using the paretic side by giving positive feedback. More frequent, more active use should eventually improve self-perceived performance (Kuss et al., 2016). All those strategies could be integrated into the treatment protocol of our main study.

4.5.6 Limitations

The study's full model (model 3, Table 4.4) accounted for only 66.9% of the total variance in the ARAT scores, leaving 33.1% of the variance unexplained. Future studies should investigate other factors such as depression and mental fatigue. The study had a cross-sectional design, so no causal relationships could be inferred. In addition, the subjects were all self-selected Chinese volunteers recruited from local self-help groups. That always raises the possibility that they were untypically active and relatively less impaired than typical stroke

population. The study's strict inclusion and exclusion criteria also limit the generalizability of the results.

4.6 Conclusions

These results demonstrate that the FMA-hand scores can usefully predict ARAT scores in people with chronic stroke. MAL-QOM and MAL-AOU scores are also significant independent ARAT score predictors. Thus, improving self-perceived performance should be one goal of rehabilitation in people with stroke. Further work developing and testing techniques to do so is clearly warranted. In order to identify how much self-perceived performance and ARAT score could be improved by the treatment in our main study, component of self-perceived performance of upper limb functions should be included in the assessment and training protocol.

Chapter 5

General methodology

This report has been published in part in a peer-reviewed journal.

Chen PM, Lai CKY, Chung RCK and Ng SSM (2017). The Jacket Test for assessing people with chronic stroke. *Disability and rehabilitation*, *39*(25), 2577–2583. (Appendix 5.1)

The study has also been presented at four international conferences.

Chen PM, Lai CKY and Ng SSM, The Jacket Test: Its Reliability and Correlations with Upper Extremity Motor Functions in People with Chronic Stroke, *11th International Symposium on Healthy Aging*, 12-13 March 2016 Hong Kong, p.45. (Appendix 5.2)

Chen PM, Lai CKY and Ng SSM, Correlation of The Peak Torque and Agonist-Antagonist Cocontraction During Paretic Wrist Flexion and Extension with Upper Extremity Motor Functions in People with Chronic Stroke, *12th International Symposium on Healthy Aging*, 11-12 March 2017 Hong Kong, p.65. (Appendix 5.3)

Chen PM, Lai CKY and Ng SSM, The Correlation of Upper Limb Impairments and Function with Level of Community Integration in People with Stroke. *11th Pan-Pacific Conference on Rehabilitation*, 17-18 November 2018 Hong Kong. (Appendix 5.4)

5.1 Abstract

The study's main objective was to investigate whether combining bilateral transcutaneous electrical nerve stimulation (Bi-TENS) with task-oriented training (TOT) was superior to unilateral transcutaneous electrical nerve stimulation (Uni-TENS) with TOT, Placebo transcutaneous electrical nerve stimulation (Placebo-TENS) with TOT or no active treatment control in generating earlier and greater improvements in upper limb motor function among people with stroke. In this chapter, we introduced the general methodology adopted in the main study. It mainly included the inclusion and exclusion criteria of the subjects, the study design, the rationale of the selected outcome measures, psychometric properties of the selected outcome measures. The primary outcome was Fugl-Meyer Assessment of Upper Extremity (FMA-UE), and the secondary outcome included peak torque and co-contraction ratio during maximum isometric voluntary contraction of wrist flexor and extensor, Active Range of Motion of elbow flexion/extension and wrist flexion/extension, Action Research Arm Test, Jacket Test, Motor Activity Log and Community Integration Measure (CIM).

In the section of outcome measures, one cross-sectional study was included, which has been demonstrated below:

The reliability and validity of Jacket Test for assessing the upper limb daily performance in people with chronic stroke: A cross-sectional study

The result demonstrated that Jacket Test had good to excellent intra-rater, inter-rater and test-retest reliability, and it also showed significant correlation with FMA-UE scores, paretic hand grip strength, Berg Balance Scale scores, Time "Up and Go" test completion times and CIM scores (r=-0.386 to -0.750).

5.2 Introduction

The literature review in Chapter 1 showed that transcutaneous electrical nerve stimulation (TENS) and task-oriented training (TOT) are both effective physical interventions in stroke rehabilitation when used individually. The Chapter 2 presented the outline of the PhD study. The systematic review and meta-analysis in Chapter 3 further revealed that bilateral upper limb exercise was superior to unilateral upper limb exercise in enhancing the improvement of Fugl-Meyer Assessment of Upper Extremity (FMA-UE) scores (mean difference=2.21, 95% confidence interval, 0.12 to 4.30, p=0.04; I^2=86%, p<0.001) in people with chronic stroke. The result of Chapter 4 demonstrated that, except FMA-hand scores, the Motor Activity Log (MAL) scores could predict an extra 10.4% variance of Action Research Arm Test (ARAT) score, when controlled the effect of hand subscale in Fugl-Meyer Assessment (FMA-hand). It indicated the potential benefit of adding self-perceived performance component in the treatment protocol of the main study.

Hence, the objective of this chapter is to describe the general methodology of our main study, which comparing the effect of Bi-TENS+TOT against Uni-TENS+TOT, Placebo Transcutaneous Electrical Nerve Stimulation (Placebo-TENS)+TOT and Control group without any active treatment in people with stroke. The primary outcome was FMA-UE. The secondary outcome included peak torque and co-contraction ratio of wrist flexion and extension, Active Range of Motion (AROM) of elbow flexion/extension and wrist flexion/extension, ARAT, Jacket Test, MAL and Community Integration Measure (CIM).

5.3 Participants

All of the subjects were recruited between May 2016 and June 2018 from a self-help group for community-dwelling stroke survivors in Hong Kong. The inclusion criteria included: (1) Aged between 50 to 80 years, as old age frailty is commonly seen in the people aged more than 80 years old, who are weak and required assistance in daily living (Torpy et al., 2006). (2) Had been diagnosed with ischemic or hemorrhagic stroke by magnetic resonance imaging or computer tomography within the previous 1 to 10 years, (3) Had volitional control of the non-paretic arm and at least minimal antigravity movement in the shoulder of the paretic arm, (4) Had at least 5 degrees in wrist extension in the antigravity position, (5) Had abbreviated Mental Test score$\geq$7 (Lam et al., 2010). (6) Were able to follow instructions and give informed consent.

The exclusion criteria included: (1) Had any additional medical, cardiovascular or orthopedic condition, (2) Had implant cardiac pacemaker which preclude the application of the TENS equipment, (3) Had skin allergy that would prevent the application of the TENS electrodes, (4) Had receptive dysphasia, (4) Had a significant upper limb peripheral neuropathy, (5) Involvement in drug studies or other clinical trials, (6) Had severe shoulder, elbow, wrist or finger contractures that would preclude testing the arm's passive range of motion.

5.4 Study design

This was a single-blinded, randomized, placebo-controlled experiment. The study was registered (Reference Number: NCT03112473) on clinicaltrials.gov and conducted in the Neurorehabilitation Laboratory at The Hong Kong Polytechnic University. A written informed consent (Appendix 5.5) was obtained from each subject before the study began. The study protocol was approved by the university's Ethics Committee (Reference Number: HSEARS20131011003-01) and conducted in accordance with the Declaration of Helsinki (World Medical Association, 2001).

5.5 Procedure

Figure 5.1 presents the flowchart of the experimental procedure. The training program included 20 sessions of treatment. All subjects were assessed at baseline, and then stratified and randomized into one of the 4 groups: Bi-TENS+TOT, Uni-TENS+TOT, Placebo-TENS+TOT and Control group. The subjects received 10 sessions of their group's intervention over 4 weeks before the mid-intervention assessment. Then they received 10 more sessions of treatment over another 4 weeks before the post-intervention assessment. The follow-up assessments were conducted at 1 month and 3 months after the completion of the intervention. All of the assessments were conducted by an experienced research assistant who was blind to the group allocation.

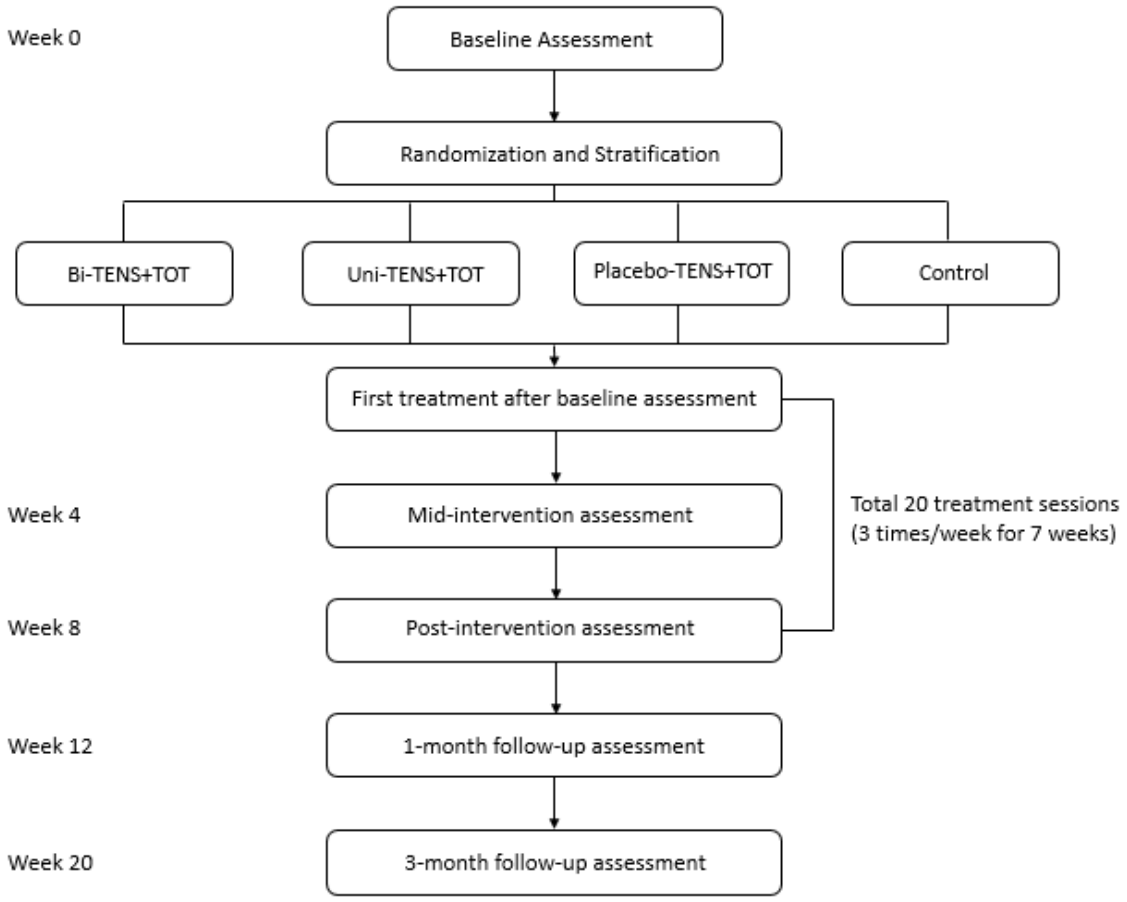


Figure 5.1 Flowchart of the procedure

5.6 Randomization and stratification

The randomization and stratification was planned using the online "QMinim Online Minimization" software based on "Minimize" software (Jensen, 1991). Previous studies have shown that age (Roy-O'Reilly & McCullough, 2018), gender (Gibson, 2013), type of stroke (Andersen et al., 2009), side of lesion (Rajashekaran et al., 2013) and initial motor impairment (Zarahn et al., 2011) all have significant impacts on upper limb motor function among people with stroke. In order to minimize any potential bias due to the imbalanced distribution of those factors, the stratification balanced the age (50–60, 60–70 and >70), gender (male, female), type of stroke (ischemia, hemorrhage), baseline FMA-UE score (0–22, 23–47, 48–56 and 57–66) and side of lesion (left, right) among the 4 groups (Jensen, 1991). In order to keep the assessor blind to the group assignments, the data entry and data analysis were performed by another full-time, trained research assistant.

To ensure effective concealed randomization (except for the Control group), the participants were informed of the results of the group allocation (only the group number but not the details of the treatment) and their resulting training schedule and venue by centralized telephone calls from an offsite volunteer.

5.7 Sample size calculation

As this was the first study designed to compare the effect of Bi-TENS+TOT against Uni-TENS+TOT, Placebo-TENS+TOT and no active treatment, the sample size was calculated based on a pilot study including 8 subjects with stroke in 4 groups (Bi-TENS+TOT, Uni-TENS+TOT, Placebo-TENS+TOT and Control groups, 2 patients each group) assessed at 3 time points (baseline, mid-intervention and post-intervention). The effect size (Cohen's d=0.314) was intended to detect a significantly greater improvement in the primary outcome—FMA-UE score—over 20 sessions of Bi-TENS+TOT than same dosage of Uni-TENS+TOT, Placebo-TENS+TOT and Control group without any active intervention. Version 3.1.0 of the G*power software suite (Faul et al., 2009) was used to calculate the minimum sample size assuming an α of 0.05, power of 0.80, correlation among the measures of 0.5 and a non-sphericity correlation of 1. The calculation recommended that at least 96 subjects (24 subjects in each group) would be necessary to reliably detect a significant between-group difference in the improvements of FMA-UE scores. A buffer was added to recommended minimum sample size based on the results of a previous clinical trial with a similar setting (Ng & Hui-Chan, 2007). The dropout rate in that trial was around 20%, thus a conservative sample size of 120 (30 per group) was used to help ensure the detection of any significant difference among the 4 groups.

5.8 Intervention

Table 5.1 summarizes the groups' intervention protocols.

Table 5.1 The arrangement of interventions by group

	Bi-TENS+TOT group	**Uni-TENS+TOT group**	**Placebo TENS+TOT group**	**Control group**
Paretic side	TENS	TENS	Placebo-stimulation	N/A
Non-paretic side	TENS	Placebo-stimulation	Placebo-stimulation	N/A
TOT	Yes	Yes	Yes	N/A

Notes: Bi-TENS, bilateral transcutaneous electrical nerve stimulation; Uni-TENS, unilateral transcutaneous electrical stimulation; TOT, task-oriented training; N/A, not applicable

The 3 intervention groups (Bi-TENS+TOT, Uni-TENS+TOT and Placebo-TENS+TOT groups) received twenty 60–minute treatment sessions, 3 sessions per week for 7 weeks. The dosage of the treatment was determined based on the findings of a previous study (Kwong et al., 2018a) with a similar treatment setting, where 20 sessions of Bi-TENS+TOT treatment for 60 minutes per session significantly improved the muscle strength of paretic ankle dorsiflexors and reduced their Timed Up and Go test times.

In the Bi-TENS+TOT group, the TENS was applied over both sides of the upper limbs. In the Uni-TENS group, TENS was applied only on the paretic side while placebo stimulation

was applied on the non-paretic side. In the Placebo-TENS+TOT group, placebo stimulation was applied on both upper limbs. The Control group subjects received no active treatment, but they took part in the assessment sessions.

5.8.1 TENS protocol

The stimulator was a 120z dual-channel machine from Ito Physiotherapy & Rehabilitation Ltd. (ITO PHYSITHERAPY&REHABILITION CO., LTD, Tokyo, Japan). The constant mode stimulation was at 100Hz applied in 0.2ms square pulses. The frequency and pulse width were calibrated using an oscilloscope (MSO6014A, Agilent Technologies, California, US). The stimulation intensity was set at twice the sensory threshold, defined as the minimum intensity at which the subject reported feeling a tingling sensation, and below the motor threshold as indicated by absence of muscle twitching (Ng & Hui-Chan, 2009). That intensity is considered to strengthen neuronal activity and excitability of the motor cortex via the corticocortical connection between S1 and M1 (Huang et al., 2004). The stimulation was set below the motor threshold because stimulation above that threshold could generate uncontrolled muscle twitching, which would produce conflicting afferent inputs during the performance of TOT.

To activate the cutaneous sensory fibers, TENS was applied over the superficial territory of the radial nerve (Cunningham et al., 2019; Tashiro et al., 2019) and the median nerve (Koesler

et al., 2009) during the TOT. That positioning was recommended by the stimulation protocol of previous studies (Koesler et al., 2009; Ng & Hui-Chan, 2009; Tashiro et al., 2019) involving people with stroke. Tashiro et al. (2019) showed that neuromuscular electrical stimulation applied over the muscle belly of a paretic extensor digitorum communis could induce significant improvement in proprioception and motor function in people with chronic stroke. Koesler et al. (2009) found that just one session 2h of somatosensory electrical stimulation applied over the wrist region of the median nerve could significantly enhance the frequency of index finger and hand tapping and the reach-to-grasp kinematics in people with stroke. Thus, disposable surface electrodes were applied to stimulate the median nerve from the carpal tunnel to the flexor digitorum superficialis (Figure 5.2) and the superficial radial nerve from the extensor pollicis longus to the extensor digitorum communis (Figure 5.3). The cathode was placed on the proximal location and the anode was placed on the distal location, in line with the protocols of a previous study with a similar treatment setting (Ng & Hui-Chan, 2009).

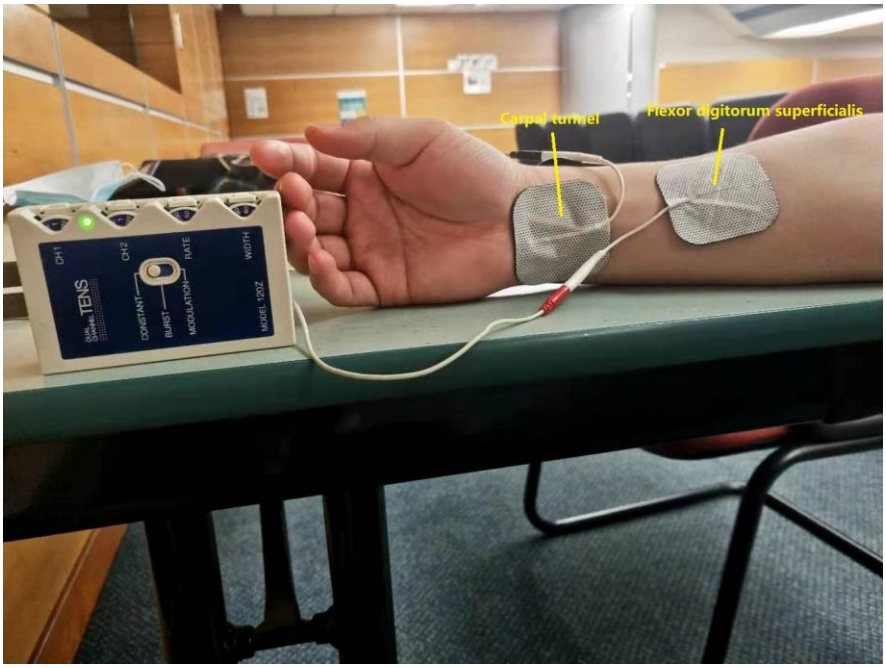


Figure 5.2 TENS applied over the median nerve

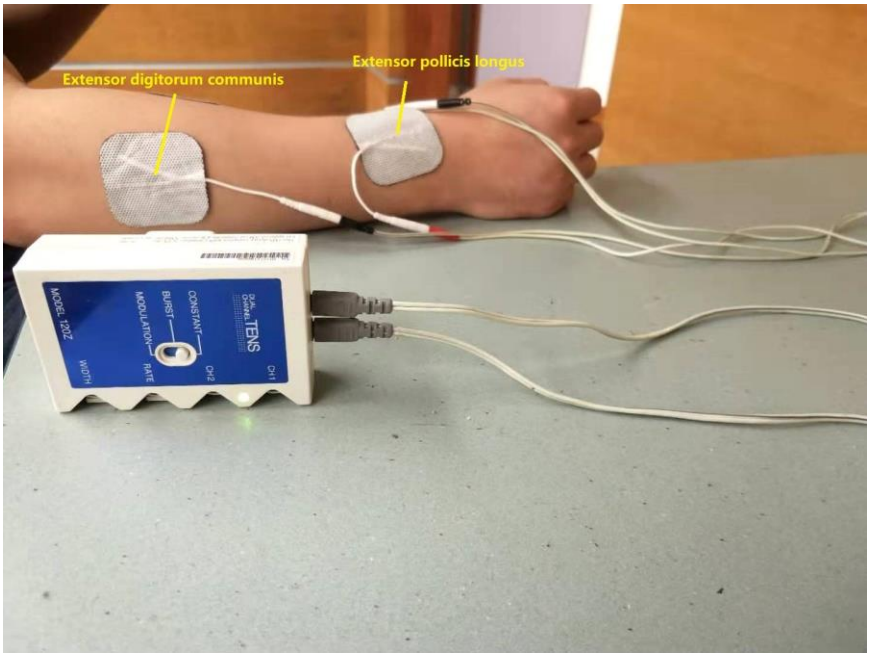


Figure 5.3 TENS applied over the radial nerve

5.8.2 Placebo-TENS protocol

The Placebo-TENS was applied by an apparently identical TENS unit. The unit's power indicator light was illuminated, but the unit's electrical circuit had been manually disconnected inside. In order to shape a common mindset, all subjects (except those in the Control group) were informed that they might or might not feel an electrical current, as different stimulation parameters were being applied.

5.8.3 TOT protocol

The aim of the TOT was to improve the passive and active range of motion, strengthen the upper limb muscles in a functional position, improve motor control of upper limb movement, increase hand dexterity and augment postural control in a seated position.

Concurrent with the electrical stimulation, the subjects were required to complete six 10-minute training sessions. The subjects began with the stretching exercise, then completed the other 5 exercises in random order. A 5-minute rest interval was provided between exercises.

The TOT included the exercises below:

1. Stretching exercises (10 minutes): To stretch the muscles of the shoulder girdle, elbow and wrist to prevent the development of muscle tightness and shortening.
2. Upper limb mobilizing exercises (10 minutes): To mobilize all joints of the paretic upper limb to their full range (with or without help from non-paretic upper limb), including shoulder, elbow, wrist and fingers.
3. Upper limb strengthening exercises (10 minutes): To strengthen the shoulder, elbow and wrist muscles required for reaching and grasping in daily activities.
4. Seated reaching tasks in different directions (10 minutes): To improve the reaching performance required in daily activities.
5. Manipulation and dexterity training (10 minutes): To improve fine control of hand movement in daily activities.
6. Bi-manual practice (10 minutes): To improve the coordination between the paretic and non-paretic upper limbs through the performance of daily activities.

Detailed guidelines of TOT protocol and the principle of progression for each exercise could be found in Appendix 5.6.

Safety consideration and precautions

Blood pressure (BP) and heart rate were measured before and after the training. According to the American Heart Association, a peak heart rate of 120 beats per minute or 70% of the age-predicted maximum heart rate should be the limit when doing such exercises in people with stroke (Fletcher et al., 2013). A systolic BP of 200mmHg or a diastolic BP of 110mmHg were set in advance as the absolute limits at which an exercise would be terminated. Therapists continuously monitored the subjects' BPs using an electronic sphygmomanometer from their arrival at a session to their departure. The exercise would be terminated and sufficient rest provided when a subject reported feeling uncomfortable or their BP exceeded the preset limits.

In order to reduce compensatory assistance, the subjects were encouraged to minimize the support from the non-paretic upper limb during the training. In addition, the finding in Chapter 4 showed that self-perceived performance of the paretic upper limb (MAL) was a significant predictor of its actual functional performance of paretic upper limb (ARAT). Thus, we intend to adding a component aimed at improving self-perceived performance of the paretic upper limb in the intervention. The subjects were encouraged to work as hard as they could, and positive verbal feedback and instructions were given.

5.9 Outcome measures

The outcome measures adapted in this study included:

Primary Outcome

1) Upper limb motor control was measured by the Fugl-Meyer Assessment of Upper Extremity (FMA-UE) (Appendix 5.7)

Secondary Outcome

2) Muscle strength was quantified using the peak torque generated during a maximum isometric voluntary contraction (MIVC) of the wrist flexor and extensor of the paretic side;
3) Activation of the agonist and antagonist muscles was quantified using the co-contraction ratio during MIVC of the wrist flexor and extensor;
4) Active range of motion (AROM) of elbow flexion/extension and wrist flexion/extension, was quantified using an electrogoniometer;
5) Functional performance of the paretic upper limb was quantified using the Action Research Arm Test (ARAT) (Appendix 5.8);
6) Performance of daily functions was quantified using the completion time of Jacket Test;
7) Self-perceived performance of the paretic upper limb was quantified using by Motor Activity Log (MAL) (Appendix 5.9);

8) Community integration level was quantified using the Community Integration Measure (CIM) (Appendix 5.10).

Those outcome measures were selected to align with the framework of International Classification of Functioning, Disability and Health (ICF) created by World Health Organization (World Health Organization, 2001), which classified the motor functioning into 3 domains: (1) body function and body structure; (2) activity; (3) participation. The outcome measure 1 to 4 belong to the body function and body structure domain. The outcome measure 5 to 7 belong to the activity domain. The outcome measure 8 belongs to the participation domain.

5.9.1 Primary Outcome

5.9.1.1 Fugl-Meyer Assessment of Upper Extremity (FMA-UE)

The FMA-UE (Fugl-Meyer et al., 1975), an instrument identified to have good predictive power, was used to quantify the subjects' upper limb motor control. It was originally developed for evaluating the motor control from the proximal to the distal part of the upper limb, and voluntary movement from synergistic to isolated, specifically in people with stroke. The assessment covers reflex activity, synergy in volitional movement, the wrist, the hand, grasp, coordination and speed. It rates 33 items on an ordinal scale (please refer to Appendix 5.7). The task performance scoring criteria are none=0, partial=1, and full=2. The total possible score is therefore 66. Higher scores indicate better recovery of upper limb motor control in people with

stroke. The FMA-UE is well known to have excellent inter-rater (Intraclass correlation coefficient (ICC)=0.997) and test-retest (ICC=0.965) reliability (Platz et al., 2005) in people with stroke.

5.9.2 Secondary Outcome

5.9.2.1 Peak torque of wrist flexor and extensor

Muscle strength was measured in terms of the peak torque during maximum isometric voluntary contraction (MIVC) of the wrist flexors and extensors. The wrist muscle strength was selected to quantify the upper limb muscle strength in this study, as previous study (Vergara et al., 2016) demonstrated that normal wrist functioning has great impacts on the activity of daily living in elderly people.

The wrist muscle strength was measured using a load cell mounted in a custom-built frame (Figure 5.4 and Figure 5.5). The subject was seated against the chair back with 0° of shoulder flexion, 0° of elbow flexion, forearm in the mid-prone position and the wrist on the paretic side in the neutral position (Figure 5.4). The paretic hand was fixed by Velcro straps and the forearm was fixed by two G-clamps. The 2 bar-shaped electrodes were placed on the flexor carpi ulnaris and the extensor carpi ulnaris. The subject was asked to perform a 5-second MIVC of the wrist flexors and extensors. Each was performed 3 times and the data were averaged. In

order to balance the learning effect, one practice trial was provided before data collection began. In order to minimize any fatigue, a one-minute rest was provided between trials.

The force of wrist flexor and extensor on the paretic upper limb was recorded by the load cell (model: RL 20000B-100, Output: 3.0mV/V at 100lb, capacity: 100, linearity 97%, Rice Lake Weighting System). The torque generated was the product of the force generated and the moment arm, which was taken as the length from the transverse crease of the wrist to the head of the 3rd metacarpal (Figure 5.5). The peak torque was recorded by extracting the peak value of torque being produced during MIVC of wrist flexor and extensor.

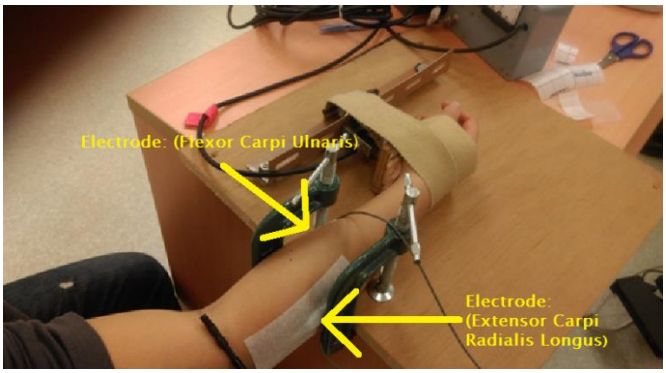


Figure 5.4 The placement of the upper limb in the custom-built torque measurement frame

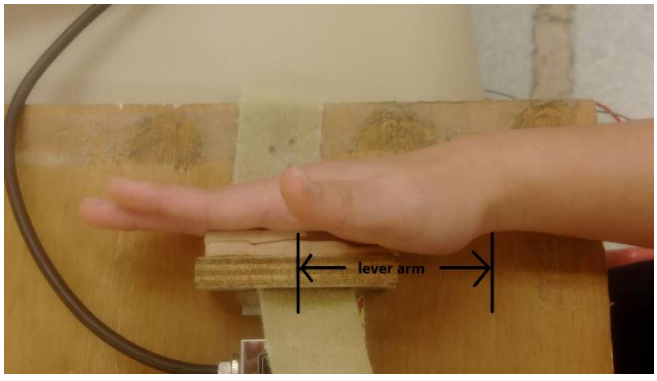


Figure 5.5 Hand placement on the load cell

In our pilot study, there was excellent intra-rater reliability of such peak torque measurements, with ICCs ranged from 0.970 to 0.980 were reported.

5.9.2.2 Co-contraction ratio

Muscle activation of agonist and antagonist was quantified by the co-contraction ratio during MIVC of wrist flexor and extensor. Muscle co-contraction refers to the simultaneous activation of agonist and antagonist muscle groups crossing the same joint to act in the same plane (Banks et al., 2017). Abnormal muscle activation patterns, especially excessive co-contraction, are commonly considered to be a major contributor to motor impairments in people with stroke (Banks et al., 2017).

To measure the muscle co-contraction, the skin on the extensor carpi radialis and flexor carpi ulnaris of the paretic upper limb were prepared by the vigorous rubbing with an alcohol pad. Then two bar-shaped, low noise EMG electrodes (preamplifier gain=388, impedance>100MΩ, rejection ratio=95dB) were placed over the extensor carpi radialis and flexor carpi ulnaris. The raw EMG signal of extensor carpi radialis and flexor carpi ulnaris for paretic upper limb during MIVC of the wrist flexors and extensors was recorded at 10kHz using an NI-USB 6210 data acquisition card (National Instruments, Texas, USA). The raw EMG from each 5-second trial was rectified and filtered through a 20–450Hz band pass filter and a 49–

51Hz notch filter via the Butterworth method by LabView 8.6 software (National Instruments, Texas, USA). The EMG signal was then integrated over the interval from 0.25 seconds before to 0.25 seconds after the peak torque. That integrated EMG (iEMG) was used to compute the co-contraction ratios using the following formula (Yan et al., 2005):

$$\text{Co-contraction Ratio}=\frac{iEMG\ antagonist}{iEMG\ agonist+iEMG\ antagonist}\times 100\%$$

In a pilot study, intra-rater reliability statistics of from 0.837 to 0.975 were demonstrated in co-contraction ratio measurements.

5.9.2.3 Active range of motion (AROM)

The full AROM from flexion to extension of the elbow and wrist joints was measured using an SG 110 electrogoniometer (Biometrics, Gwent, UK). A previous study (Beebe & Lang, 2008) showed that AROM can account for 82% of the variance in upper limb function as measured by the Jebsen Taylor Hand Function Test in people with stroke. The electrogoniometer has shown excellent intra-rater reliability in measuring ankle angles (r=0.979–0.998) in people with stroke (Bronner et al., 2010).

To quantify AROM at the wrist, the distal sensor was attached to the dorsal surface over the third metacarpal with the center axis of the hand and that of the sensor coincident. With the

wrist fully flexed, the proximal sensor was attached to the forearm so that when viewed from above the dorsal plane the axis of the forearm and that of sensor were coincident. In assessing AROM of elbow, the distal sensor was attached to the forearm with its center axis coincident with that of the forearm. With the elbow at a natural angle, the proximal sensor was attached to the upper arm so that the center of the sensor was in line with the surface projection of forearm center (KASAHARA et al., 2007).

Wrist flexion/extension: With 0° of shoulder flexion and 90° of elbow flexion, the subjects placed the forearm and wrist in a mid-prone position. When the task began, the subjects were asked to perform the full AROM from full wrist flexion to full wrist extension on the paretic side (Figure 5.6). The angles of 2 trials were averaged.

Elbow flexion/extension: With 90° of shoulder flexion and 0° of elbow flexion, the forearm was placed in a neutral position. When the task began, the subjects were asked to perform the full AROM from full elbow flexion to full elbow extension on the paretic side (Figure 5.6). The angles of 2 trials were averaged.

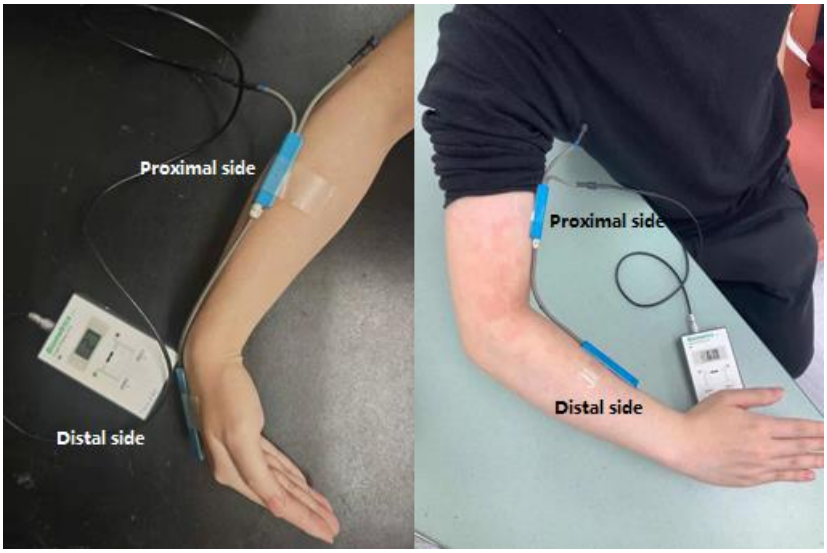


Figure 5.6 AROM from full wrist/elbow flexion to full wrist/elbow extension showing the electrogoniometer placement

5.9.2.4 Action Research Arm Test (ARAT)

Please refer to section 4.3.3 for details.

5.9.2.5 Jacket Test

The Jacket Test is one item in Physical Performance Test, which was originally developed to assess multiple domains of physical functioning in the elderly (Reuben & Siu, 1990). In this study, the time needed to don a jacket was used to quantify performance in daily activities. The Jacket Test evaluates gross motor functioning and the multi-joint coordination of the upper limbs, as the test involves abduction of the shoulder joint, flexion and extension of the

elbow joint and gripping with the hands. Jacket Test results have shown a close relationship with competence in the activities of daily living (Putri & Tjakrawiralaksana, 2017). The performance of Jacket Test may reflect the quality of performance in daily function of upper limb in people with stroke.

5.9.2.6 Cross-sectional study: The reliability and validity of Jacket Test in people with chronic stroke

Although the Jacket Test has great potential in assessing the proficiency of upper limb use in daily activities for people with chronic stroke, no published study has yet assessed the test's reliability and validity in people with stroke. So the test's intra-rater, inter-rater and test-retest reliability were quantified as part of this study. Jacket Test completion times were also correlated with the results of the Fugl-Meyer Assessment of Upper Extremities (FMA-UE), grip strength, the 5-times sit-to-stand (FTSTS) test, the Berg Balance Scale (BBS), the timed "up and go" (TUG) test and the Community Integration Measure (CIM). Another objective was to determine an optimal cut-off time for the Jacket Test that best discriminates people with stroke from healthy older adults. The minimal detectable change (MDC) in the test's completion times was also determined among people with stroke. This section is a slight modified version of the published paper on the Jacket Test. It is one part of the methodology.

5.9.2.6.1 Method

Subjects

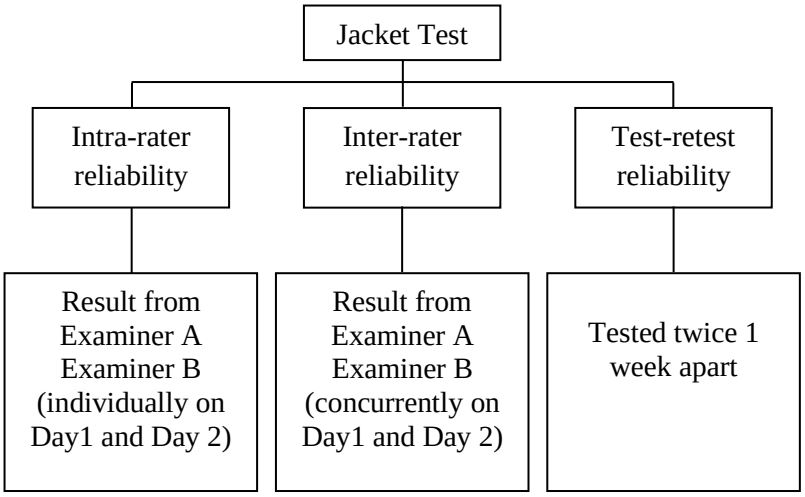


Figure 5.7 The structure of data collection and analysis for the Jacket Test

This study was cross-sectional design. Twenty-eight subjects with chronic stroke (18 males and 10 females; mean age=57.6±5.1; mean post-stroke duration=7.5±4.8) were recruited from a local self-help group for people with stroke in Hong Kong. Thirty healthy older adults (11 males and 19 females; mean age=61.8±5.7) were also recruited from local community centers.

Procedure

The structure of the data collection and analysis is shown in Figure 5.8. The subjects with stroke were assessed twice one week apart (Day 1 and Day 2). FMA-UE, FTSTS test, BBS, TUG test and CIM were administered and their maximum hand grip strength was assessed on Day 1. The order of the assessment was randomized by drawing lots. At least 2 minutes of rest was

allowed after each test in order to minimize any effect of fatigue. The healthy controls took only the Jacket Test but not FMA-UE, FTSTS test, BBS, TUG test and CIM on Day 1.

Statistical analysis

Statistics were calculated from all of these test data using version 17.0 of the Statistical Package for the Social Sciences software suite (SPSS Inc, Chicago, IL, USA). Descriptive statistics were compiled describing the subjects' demographic characteristics. $ICC_{3,1}$, $ICC_{3,2}$ and $ICC_{2,1}$ were computed to quantify the degree of intra-rater, inter-rater and test-retest reliabilities, respectively (Portney, 2020). An ICC<0.25 was considered as describing little or no correlation; ICC=0.25–0.50 was defined as fair; ICC=0.50–0.75 was termed moderate to good, and an ICC exceeding 0.75 was regarded as indicating good to excellent reliability (Portney, 2020).

The Kolmogorov-Smirnov test was used to determine whether or not the data were normally distributed. Pearson correlation coefficients were calculated relating the Jacket Test times with the other outcomes (FMA-UE, grip strength, BBS, FTSTS test, TUG and CIM) when the data were normally distributed. Otherwise, Spearman correlation coefficients were used.

The (MDC) in the Jacket Test completion time was calculated by using the standard error of measurement (SEM) of the Jacket Test time in the following formula (Portney, 2020):

$$\text{MDC}=1.96\times \text{SEM} \times \sqrt{2}$$

where

$$SEM = S_x \sqrt{1 - rxx}$$

and S_x is the standard deviation of the Jacket Test times and r_{xx} is the test-retest reliability coefficient. The 1.96 in the MDC equation defines the 95% confidence interval accounting for errors associated with repeated measurement.

Receiver operating characteristic (ROC) curves were constructed to quantify the performance of the Jacket Test's ability to discriminate between people with stroke and the healthy elderly. All the analyses were performed on the hypothesis that the area under the curve (AUC) was 0.5 (Kumar & Indrayan, 2011; Portney, 2020).

5.9.2.6.2. Result

Table 5.2 presents the test data and Table 5.3 presents the within-group and between-group comparisons. The mean values of all the other outcome measures are shown in Table 5.4.

The data presented in Table 5.5 show the Jacket Test's excellent intra-rater, inter-rater and test-rest reliability (ICCs between 0.781 and 1.00) in the subjects with chronic stroke. The MDCs were found to be 12.64s donning the jacket on the paretic side and 24.79s on the non-paretic side.

Table 5.6 shows the correlations between the Jacket Test completion times and the other outcome measures. Significant correlations were found between non-paretic side Jacket Test

completion times and FMA-UE scores, paretic side grip strength, BBS scores, CIM scores (r=-0.386 to -0.750), and TUG times (r=0.556). The paretic side Jacket Test completion times was also correlated with paretic side maximum hand grip strength (r=-0.615).

Table 5.2 Mean Jacket Test Completion Times

		Time, s, mean (SD)	
		Day1	**Day2**
Stroke group	Paretic		
	Rater 1	28.6 (9.4)	28.8 (10.6)
	Rater 2	28.5 (9.4)	28.7 (10.6)
	Non-paretic		
	Rater 1	124.8 (75.5)	125.4 (74.8)
	Rater 2	124.9 (75.4)	125.4 (74.9)
Healthy group	Dominant		
	Rater 1	14.3 (3.2)	
	Rater 2	14.1 (3.3)	
	Non-dominant		
	Rater 1	13.6 (2.6)	
	Rater 2	13.6 (2.5)	

Notes: Values are mean ± SD

Table 5.3 Mean Jacket Test Completion Times for the Healthy and the Stroke subjects

	Stroke (n=28)		**Healthy (n=30)**		***p* (Compared with Dominant)**		***p* (Compared with Non-dominant)**	
	Paretic	**Non-paretic**	**dominant**	**Non-dominant**	**Paretic**	**Non-paretic**	**Paretic**	**Non-paretic**
Time, s, mean (SD)	28.6 (9.9)	125.1 (74.1)	14.2 (3.2)	13.6 (2.6)	<0.001*	<0.001*	<0.001*	<0.001*
***p* (within group)**	<0.001*		0.187					

Notes: Values are mean ± SD

*indicates a between-group difference significant at the $p<0.05$ level of confidence

Table 5.4 Mean Values of Other Outcome

Assessment	Subjects with stroke
FMA-UE, score, mean (SD)	34.0 (16.5)
Maximum hand grip strength	
Paretic side strength, kg, mean (SD)	10.0 (9.8)
Non-paretic side strength, kg, mean (SD)	28.8 (8.3)
FTSTST, s, mean (SD)	15.2 (4.4)
BBS, score, mean (SD)	50.4 (4.0)
TUG, s, mean (SD)	14.7 (3.5)
CIM, score, mean (SD)	44.6 (5.5)

Notes: FMA-UE: Fugl-Meyer Assessment for Upper Extremity; FTSTST: 5-times sit-to-stand test; BBS: Berg Balance Scale; TUG: timed up and go test; CIM: Community Integration Measure

Table 5.5 Reproducibility of Jacket Test Completion Time in people with chronic stroke

	Examiner	Day	ICC (95%CI)	
			Paretic side	**Non-paretic side**
Intra-rater reliability $ICC_{3,1}$	A	1	0.845 (0.709–0.923)	1.000 (0.999–1.000)
		Y	0.879 (0.774–0.940)	0.999 (0.999–1.000)
	B	1	0.845 (0.711–0.923)	1.000 (0.999–1.000)
		Y	0.891 (0.795–0.946)	0.999 (0.999–1.000)
Inter-rater reliability $ICC_{3,2}$	A-B	1	1.000 (1.000–1.000)	1.000 (1.000–1.000)
		Y	1.000 (0.999–1.000)	1.000 (1.000–1.000)
Test-retest reliability $ICC_{2,1}$	A	1-Y	0.795 (0.558–0.905)	0.972 (0.940–0.987)
	B	1-Y	0.781 (0.528–0.899)	0.999 (0.999–1.000)

Notes: 95%CI: 95% confidence interval; ICC: intra-class correlation coefficient; Y, the second assessment date

Table 5.6 Correlations Relating Jacket Test Completion Time with Other Outcome Measures

	Paretic side		**Non-paretic side**	
	Time	***p***	**Time**	***p***
FMA-UE	-0.285	0.142	-0.750**	<0.001
Paretic handgrip (kg)	-0.615**	<0.001	-0.400**	0.035
Non-Paretic handgrip (kg)	0.208	0.289	0.060	0.761
FTSTST (s)	-0.086	0.664	0.177	0.368
BBS	-0.015	0.938	-0.424**	0.025
TUG (s)	0.115	0.559	0.556**	0.002
CIM	-0.061	0.757	-0.386**	0.042

Notes: FMA-UE: Fugl-Meyer Assessment for Upper Extremity; FTSTST: 5-times sit-to-stand test; BBS: Berg Balance Scale; TUG: timed up and go test; CIM: Community Integration Measure

** indicates a correlation significant at the $p<0.001$ level of confidence

The optimal cut-off time (Figure 5.8 and Figure 5.9) was determined to be 18.33s (sensitivity 96.7%; specificity 85.7%; AUC=0.965; $p<0.001$) when the paretic arm is inserted first and 18.38s (sensitivity 96.7%; specificity 94.4%; AUC=0.995; $p<0.001$) with the non-paretic arm inserted first.

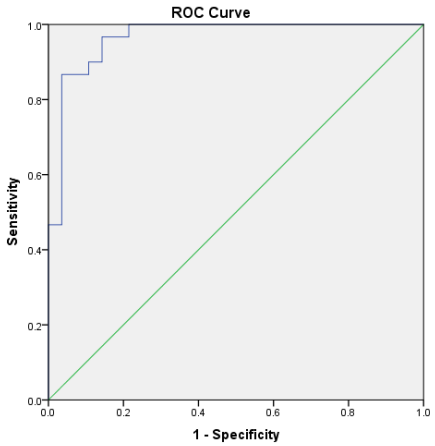


Figure 5.8 Receiver operating characteristic curve relating the paretic side Jacket Test times of subjects with chronic stroke and those of the healthy older adults. AUC=96.5%. The jagged line is the ROC curve. The straight line indicates non-discriminating characteristics of the test.

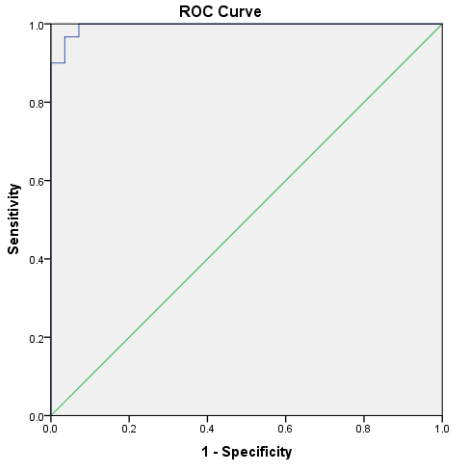


Figure 5.9 ROC curve relating the non-paretic side Jacket Test times of subjects with chronic stroke and healthy older adults. AUC=99.5%. The jagged line is the ROC curve. The straight line indicates non-discriminating characteristics of the test.

5.9.2.6.3 Discussion

The Jacket Test showed excellent discrimination power and reliability in this study. That is consistent with results of a previous study of the Physical Performance Test (King et al., 2000). Sufficient training provided to the assessors, clear instructions and standardized protocols presumably contributed to the excellent reliability results.

The FMA-UE is commonly used to assess volitional movement, reflex activity and coordination. The Jacket Test assessed proficiency in dressing, which involves combined movement of the shoulder, elbow, wrist and hand, so it was reasonable to expect good to excellent correlation between the two tests. Grip strength on the paretic side also showed significant correlation with the Jacket Test completion times. Al Snih et al. (Al Snih et al., 2004) has demonstrated that poor maximum hand grip strength is an independent predictor of poor ADL performance, including dressing skills, among older people. Hence, the significant correlation might be expected.

Non-paretic side Jacket Test completion times were significantly correlated with both BBS scores and TUG test times. The TUG test and the BBS are reliable measurement tools for assessing functional mobility and functional balance, respectively. The Jacket Test requires static balance in a standing position while putting on and removing the jacket. When the subjects performed the paretic side Jacket Test, some compensation such as using the non-paretic side to help insert on the paretic side may have masked some of the influence of balance. That might

explain the significant correlation with the non-paretic side Jacket Test completion times but not with those of the paretic side.

The CIM scores did, though, show a fair to moderate positive correlation with the non-paretic side Jacket Test completion times. A previous study has found that skill in dressing is one of the most important aspects of independent functioning for persons with profound disability (Reese et al., 1991). The moderate correlation could be explained by the fact that performance in the Jacket Test is closely related to ADL competence, as intended.

This has been the first published study which attempted to calculate the optimal cut-off Jacket Test completion time for distinguishing its performance of healthy older adults from people with chronic stroke. The optimal cut-off times of 18.33s on the paretic side and 18.38s on the non-paretic side were determined to discriminate best. The AUCs ranged from 0.965 to 0.995, which means that Jacket Test completion time can offer better than 95% accuracy in discriminating performance of the Jacket Test of stroke survivors from healthy older adults. The Jacket Test completion times showed both high sensitivity and specificity when assessing both upper limbs, which suggests that the Jacket Test has great potential as a clinical screening and diagnostic instrument for discriminating stroke survivors from the healthy older adults.

Limitations

The Jacket Test emphasizes speed in donning a jacket; it does not assess the quality of the movement. The compensatory strategies used in putting on a jacket should also be a focus in testing, but the test is not designed to do that. The sample size in this research was based on previous reliable findings, but it may have been insufficient to detect significant correlations between certain Jacket Test results and other outcome measures. Further investigation with larger sample size would be essential for prediction and multiple regression analysis, and establishing the cut-off times of Jacket Test in stroke survivors of different mobility levels.

There was also a significant difference ($p<0.05$) in the gender proportions between the stroke and healthy groups, the gender bias could be eliminated. Note too that the cut-off times provided here are only applicable to distinguishing performance of the Jacket Test of people with chronic stroke from healthy older adults who fulfil the study's inclusion criteria. The present study could not establish any causal relationship between the variables because of its cross-sectional design.

5.9.2.6.4 Conclusion

The Jacket Test has excellent intra-rater, inter-rater and test-rest reliability when used for measuring the upper limb daily performance in people with chronic stroke. The Jacket Test completion times were significantly correlated with FMA-UE scores, BBS scores, TUG test times and maximum hand grip strength on the paretic side. The Jacket Test is a reliable and valid measuring tool which can be applied in the clinic to evaluate the upper extremity function of people with chronic stroke.

5.9.2.7 Motor Activity Log (MAL)

As the finding in Chapter 4 showed that Motor Activity Log (MAL) score is an important and independent predictor of Action Research Arm Test score in people with stroke, accounting for 10.4 % of ARAT scores. Therefore, we intend to measure how much improvement of MAL score can be benefited from our intervention protocol. Details of MAL, including Quality of Movement (QOM) and Amount of Usage (AOU) subscales could be found in Chapter 4 (Section 4.3.3).

5.9.2.8 Community Integration Measure (CIM)

The level of community integration was assessed by Chinese version of Community Integration Measure (CIM). It is a self-report questionnaire that is easily administrated to assess the community integration level (Liu et al., 2014). The instrument consists of 10 items, each rated from 1 to 5, giving a total score ranging from 10 to 50. A higher score indicates greater community integration. Liu et al.(2014) reports that the Chinese version of the CIM showed good test-retest reliability (ICC=0.84) in people with stroke. A pilot study with 123 people with chronic stroke conducted as part of this research showed that CIM scores were significantly correlated with peak wrist flexion torque (r=0.203, $p<0.05$), WMFT scores (r=0.194, $p<0.05$) and Barthel Index scores (r=0.194, $p<0.05$) (Appendix 5.4).

5.10 Data analysis

The objective of the main study in Chapter 5 was to compare the change of each outcome in Bi-TENS+TOT group with those in Uni-TENS+TOT group, Placebo-TENS+TOT group and Control group. The Statistical Package for Social Science (Version 23.0 0, IBM, Armonk, NY) was used to analyze the result of the outcome measures. Descriptive analysis was used to summarize subjects' demographic information. Kolmogorov-Smirnov test was used to detect the normality of all the data. One-way analysis of variance, Chi-Squared test (χ^2 test) and Kruskal-Wallis test were used to compare the baseline characteristics of the 4 groups, as appropriate.

To implement the intention-to-treat principle, any missing data were filled in by last observation carry forward method. Linear mixed models (LMMs) were conducted to (1) compare the treatment effects of Bi-TENS+TOT group against Uni-TENS+TOT, Placebo-TENS+TOT and Control groups; (2) compare the baseline results with those at the mid-point and post-intervention time points, and to test for persistence of any treatment effect in 1 month and 3 months when compared with those in post-intervention in each group. In the LMM model, the group was set as the factor while the time was set as the covariate. The time, group and the time-by-group interaction effects were set as the fixed effects. The intercept was included in the fixed effect. The random slope and random intercept of the change in the outcome variables were set as the random effects. The repeated covariance type was diagonal. Maximum likelihood

estimation was used to determine the value of the model parameter. The variances of the random effects at each time point were assumed to be heterogeneous, while the correlation between repeated measurements was taken as strongest at adjacent time points (Field, 2013). A first-order autoregressive structure with heterogeneous variances (AR (1): heterogeneous) was used to estimate the parameters of the statistical models. The Bi-TENS+TOT group was the reference group, so that any effect in Bi-TENS+TOT group was compared with the effects in the other groups. In order to detect the within-group effect of each group, the 4 groups took turn to be chosen as the reference group and the LMM was re-conducted.

The intervention effect from baseline to post-intervention was first analyzed. Another LMM then quantified any carryover effect from post-intervention to the 3-month follow-up assessment. The significance level was set at 0.05. Post-hoc tests with the Bonferroni correction were conducted to adjust the *p*-value when there was an overall significant difference. In the post-hoc analysis of between-group effect differences, the data from one time point were removed to detect any between-group effect and within-group effect at another time point. For example, removing the mid-intervention data of the Bi-TENS+TOT group and the Uni-TENS+TOT from the LMM allowed estimating the difference in between-group effect between the baseline and post-intervention time points.

5.11 Summary

This chapter reported the general methodology, including the study design, inclusion and exclusion criteria, outcome measures, procedure, sample calculation, randomization and stratification method, intervention and data analysis of our main study. A cross-sectional study was conducted and reported that the Jacket Test is a reliable and valid measuring tool which can be applied in clinic to evaluate the functional performance of upper limb in people with chronic stroke.

Chapter 6

Bilateral Transcutaneous Electrical Nerve Stimulation Combined with Task-oriented Training Improves Upper Limb Motor Function in Stroke: a randomized controlled trial

Material reported in this chapter has been published in a peer-reviewed journal.

Chen PM, Liu TW, Kwong PWH, Lai CKY, Chung RCK, Tsoh J, Ng SSM. Bilateral TENS Improves Upper Limb Motor Recovery in Stroke: A Randomized Controlled Trial. *Stroke* 2021. (Accepted and in press). (Appendix 6.1 and Appendix 6.2)

Material reported in this chapter has been presented at 2 international conferences.

Chen PM, Lai CKY, Liu TW and Ng SSM. Bilateral Transcutaneous Cutaneous Electrical Nerve Stimulation (TENS) is superior to Unilateral TENS in improving the upper limb muscle strength among people with chronic stroke: A pilot study. *11th WORLD CONGRESS FOR NEUROREHABILITATION*, 7–11 October (Online) 2020. (Appendix 6.3)

Chen PM, Liu TW, Kwong PWH, Lai CKY, Chung RCK, Ng SSM. Effects of Bilateral Transcutaneous Electrical Nerve Stimulation Combined with Task-oriented Training

on the Recovery of Upper Limb Motor Impairment in People with Chronic Stroke. *International Stroke Conference*, 17–19 March Boston (Online) 2021. (Appendix 6.4)

6.1 Abstract

This study compared Bi-TENS+TOT against Uni-TENS+TOT, Placebo-TENS+TOT and control without treatment in motor functions of upper limb in subjects with chronic stroke.

Total 120 subjects with chronic stroke were randomly allocated into one of the 4 groups: Bi-TENS+TOT, Uni-TENS+TOT, Placebo-TENS+TOT or Control groups. Twenty 60-minute intervention sessions were administered at 3 sessions per week within 7 weeks in the Bi-TENS+TOT, Uni-TENS+TOT, Placebo-TENS+TOT groups, while the Control group did not receive any active treatment. The primary outcome was the Fugl-Meyer Assessment of Upper Extremity (FMA-UE) scores, and the secondary outcomes included peak torque and co-contraction ratio during maximum isometric voluntary contraction (MIVC) of wrist flexor and extensor, active range of motion (AROM) including elbow flexion/extension and wrist flexion/extension of the paretic side, Action Research Arm Test (ARAT) scores, Jacket Test completion time, Motor Activity Log (MAL) scores and Community Integration Measures (CIM) scores. All outcome measures were assessed at baseline, after 10 sessions (mid-intervention) and after 20 sessions of intervention (post-intervention), and 1-month follow-up, and 3-month follow-up.

The subjects who received Bi-TENS+TOT showed significantly greater improvement in FMA-UE scores than those in Uni-TENS+TOT (mean difference=2.02, p=0.005), Placebo-TENS+TOT (mean difference=2.49, p=0.001) and Control groups (mean difference=3.08, p<0.001) at post-intervention. The between-group improvement in Bi-TENS+TOT groups were maintained at 1-month follow-up and 3-month follow-up. Subjects in Bi-TENS+TOT (mean difference=3.25, p<0.001) group showed earlier within-group improvement in FMA-UE scores at mid-intervention than those in Uni-TENS+TOT group (mean difference=1.23, p=0.015) at post-intervention. The within-group improvement of FMA-UE score in Bi-TENS+TOT and Uni-TENS groups were maintained at 1-month follow-up and 3-month follow-up. In addition, subjects in the Bi-TENS+TOT group showed significantly greater within-group improvements in peak torque during MIVC of wrist flexor (mean difference=0.70, p<0.001) and ARAT scores (mean difference=2.37, p<0.001) at post-intervention when compared with baseline. The within-group improvements of peak torque during MIVC of wrist flexor and ARAT scores were maintained at 1-month and 3-month follow-up assessment. None of 4 groups demonstrated any significant difference in peak torque during MIVC of wrist extensor, co-contraction ratios during MIVC of wrist flexor and extensor, AROM of elbow flexion/extension and wrist flexion/extension), the Jacket Test completion time, MAL scores or CIM scores at the post-intervention, 1-month follow-up and 3-month follow-up. To conclude, Bi-TENS is a more effective complementary therapy to TOT in terms of improving FMA-UE scores than Uni-TENS with TOT.

6.2 Introduction

Recent evidence (Jung, Jung, et al., 2017; Kim, In, et al., 2013; Ng & Hui-Chan, 2007) has shown that when unilateral transcutaneous electrical nerve stimulation (Uni-TENS) applied on a paretic limb is combined with task-oriented training (TOT), they constitute an effective intervention for improving upper limb motor function in people with stroke. A recent study (Kwong et al., 2018a) has further indicated that bilateral transcutaneous electrical nerve stimulation (Bi-TENS) combined with TOT is superior to Uni-TENS+TOT in improving lower limb motor function following stroke.

Bilateral application of TENS (Bi-TENS) can provide extra sensory input from the non-paretic side (Chen et al., 2019; Kwong et al., 2018a), which tends to improve motor functioning on the paretic side by rebalancing inter-hemisphere inhibition (Stinear et al., 2014), activating the homologous neural networks in the intact and lesioned hemispheres (Grefkes et al., 2010; Renner et al., 2005) and recruiting the neural networks of the intact hemisphere (Calautti & Baron, 2003; Ferris et al., 2018; Luft et al., 2004). In a recent RCT, Kwong et al. (2018a) demonstrated that 20 sessions of Bi-TENS and TOT induced greater and earlier benefits than Uni-TENS and TOT in terms of enhancing the strength of paretic ankle dorsiflexors and reducing Timed Up and Go test completion times among 80 people

with chronic stroke, though neither placebo stimulation nor control groups were included in the study. Up till now, the potential clinical value of combining Bi-TENS with TOT for improving upper limb motor recovery following stroke has not yet been explored.

Since it has been established that combining Uni-TENS with TOT is effective in promoting upper limb recovery (Jung, Jung, et al., 2017; Kim, In, et al., 2013), and given the advantage of Bi-TENS in recruiting extra neural pathways in the intact hemisphere (Calautti & Baron, 2003; Ferris et al., 2018; Murase et al., 2004), it is reasonable to hypothesize that TENS applied to both the paretic and the non-paretic limbs concurrently could augment TOT's effect on upper limb motor function. This study was therefore designed to investigate whether Bi-TENS+TOT was superior to Uni-TENS+TOT, Placebo-TENS+TOT and control with no active treatment in improving the outcome measures on upper limb motor functions of people with stroke. The primary outcome included the FMA-UE score. The secondary outcomes included peak torque and co-contraction ratio during MIVCs of the wrist flexor and extensor, AROM including elbow flexion/extension and wrist flexion/extension, ARAT scores, the Jacket Test completion times, MAL scores and CIM scores.

6.3 Methods

Detailed methodology adopted in this study and its rationale has been reported in Chapter 5 (Section 5.3 to 5.10). It included participants, study design, procedure, randomization and stratification, sample size calculation, intervention, outcome measures and data analysis.

6.4 Results

6.4.1 Demographic information

One hundred and forty-one potential subjects were screened between May 2016 and June 2018, of whom 120 were recruited into the study. There was no significant difference among the 4 groups at baseline (see Table 6.1). Nine participants dropped out during the intervention phase for reasons not related to the study (e.g. forearm facture, knee osteoarthritis, not interested in the study). In total, 111 subjects completed the intervention and the post-intervention assessments, 107 (89%) completed the 1-month follow-up assessment and 99 (83%) completed the 3-month follow-up assessment (see Figure 6.1). Eleven of them (3 in the Uni-TENS+TOT group, 3 in the Placebo-TENS+TOT group and 5 in the Control group) were unable to complete the Jacket Test, primarily due to difficulty in maintaining a standing position unaided by a stick, frame or wheelchair. No adverse incident occurred during the study.

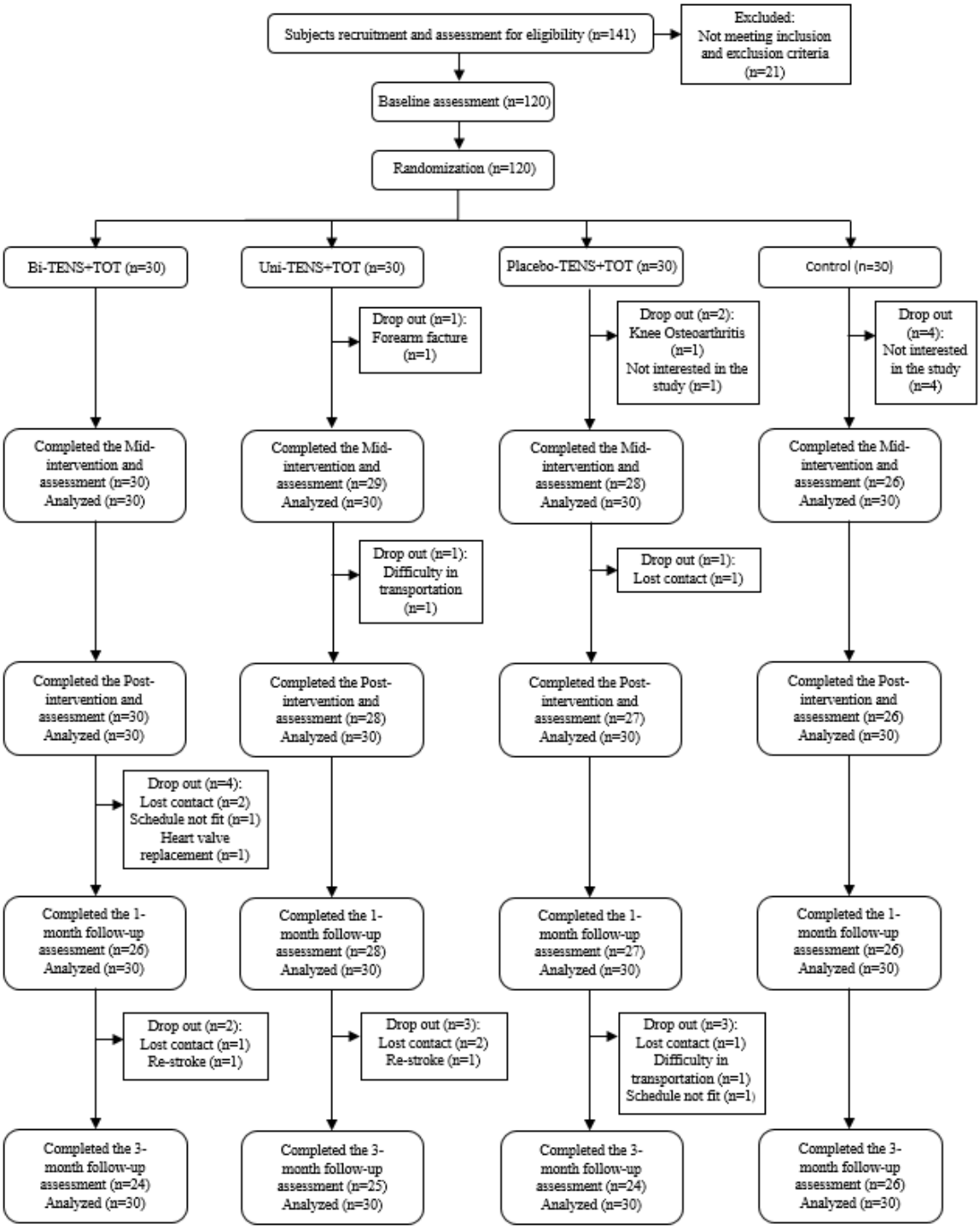


Figure 6.1 Flowchart of the subjects' recruitment

Table 6.1 Subject demographics

	Total Sample (n=120)	**Bi-TENS+TOT (n=30)**	**Uni-TENS+TOT (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**	***Between-groups Comparison***
Variables			Frequency (%)			χ^2 Test; *p*-Value
Gender (Male/Female)	76(63.3)/44(36.7)	18(60.0)/12(40.0)	17(56.7)/13(43.3)	21(70.0)/9(30.0)	20(66.7)/10(33.3)	1.44; 0.697
Side of Hemiplegia (Left/Right)	57(47.5)/63(52.5)	14(46.7)/16(53.3)	13(43.3)/17(56.7)	14(46.7)/16(53.3)	16(53.3)/14(46.7)	0.64; 0.888
Type of Stroke (ischemia/hemorrhage)	75(62.5)/45(37.5)	17(56.7)/13(43.3)	18(60.0)/12(40.0)	18(60.0)/12(40.0)	22(73.3)/8(26.7)	2.10; 0.552
Living arrangement (live alone/live with family)	10(8.3)/110(91.7)	0(0.0)/30(100.0)	3(10.0)/27(90.0)	4(13.3)/26(86.7)	3(10.0)/27(90.0)	3.93; 0.269

Education level (primary or below/secondary/college or above)	17(14.2)/87(72.5)/16(13.3)	3(10.0)/23(76.7)/4(13.3)	4(13.3)/17(56.7)/9(30.0)	4(13.3)/24(80.0)/2(6.7)	6(20.0)/23(76.7)/1(3.3)	12.03; 0.061

Variables	**Mean±SD**					**One-way ANOVA, *p-value***
Age, year	61.52±6.73	60.37±7.13	62.30±7.30	61.70±6.70	61.70±5.91	0.693
BMI, kg/m^2	23.91±3.61	23.96±3.14	23.84±4.04	23.87±2.67	23.98±4.48	0.998
Time since stroke, year	6.04±3.12	5.57±3.27	6.27±3.08	6.07±3.20	6.27±3.03	0.810
FMA-UE	40.39±16.13	37.03±12.02	41.83±17.12	38.77±15.78	43.93±18.74	0.329
Peak Torque of Wrist Flexor, Nm	4.55±2.44	3.69±1.79	4.51±2.63	4.86±2.82	5.14±2.29	0.147

Peak Torque of Wrist Extensor, Nm	3.39±2.27	3.38±1.95	3.12±2.36	3.40±2.17	3.39±2.27	0.852
Co-contraction Ratio of Wrist Flexion	0.25±0.13	0.28±0.14	0.24±0.11	0.25±0.15	0.24±0.13	0.619
Co-contraction Ratio of Wrist Extension	0.27±0.18	0.29±0.16	0.31±0.23	0.25±0.15	0.23±0.18	0.324
AROM-Elbow, degree	83.88±28.66	76.67±28.89	85.73±27.30	82.88±24.01	90.22±33.36	0.207
AROM-Wrist, degree	75.62±45.75	72.42±40.84	69.97±49.52	72.70±44.04	87.41±48.28	0.412
ARAT	30.93±20.89	28.70±20.09	31.73±20.09	28.30±21.69	34.97±21.97	0.539
Jacket Test, second	36.01±18.32	36.51±12.44	36.98±22.02	36.87±17.53	33.36±21.39	0.371
MAL-AOU	42.05±38.81	33.89±31.31	49.72±47.73	39.20±40.54	45.28±34.50	0.610
MAL-QOM	52.36±43.82	41.52±36.21	56.92±49.89	52.42±45.09	58.00±43.44	0.583
CIM	40.66±7.90	39.47±7.51	41.23±6.89	41.87±8.02	39.67±9.21	0.467

Variables			Median± 25th/75th Percentile (Ranges)			Mann-Whitney U test X; *p*-value
Abbreviated Mental Test	10±10/10(0)	10±10/10(0)	10±10/10(0)	10±10/10(0)	10±10/10(0)	1.000

Notes: ARAT, Action Research Arm Test; Bi-TENS, bilateral transcutaneous electrical nerve stimulation; BMI, body mass index; CIM, Community Integration Measure; FMA-UE, Fugl-Meyer Assessment of Upper Extremity; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; AROM, active range of motion; SD, standard deviation; Uni-TENS, unilateral transcutaneous electrical nerve stimulation.

6.4.2 Result of the Outcome measures

The results are summarized in Table 6.2. The Linear Mixed Model (LMM) analysis of all outcome measures from baseline to post-intervention demonstrated the time effect (Table 6.3), group effect (Table 6.4) and time-by-group effect (Table 6.5), respectively. The LMM

analysis of all outcome measures from post-intervention to the 3-month follow-up showed the time effect (Table 6.6), group effect (Table 6.7) and time-by-group effect (Table 6.8), respectively.

6.4.2.1 Primary Outcome

Referring first to Table 6.5, the LMM analysis revealed a significant between-group difference in the improvement in FMA-UE scores, with the Bi-TENS+TOT group showing greater improvement than the other 3 groups at post-intervention (Uni-TENS+TOT: mean difference=2.02, p=0.005; Placebo-TENS+TOT: mean difference=2.49, p=0.001; Control: mean difference=3.08, p<0.001). The post-hoc analysis indicated that the Bi-TENS+TOT group showed a significantly greater improvement of FMA-UE scores than the Uni-TENS+TOT group at post-intervention (mean difference=2.00, p=0.005), and greater improvement in FMA-UE scores than the Placebo-TENS+TOT group and Control group at mid-intervention (Placebo-TENS+TOT group: mean difference=2.47, p<0.001; Control group: mean difference=3.07, p<0.001). Subsequently, the LMM analysis (Table 6.8) revealed that the Bi-TENS+TOT group showed no significant between-group differences in FMA-UE scores to the other 3 groups between post-intervention, 1-month follow-up and 3-month follow-up assessment.

For the within-group improvement (Table 6.3), the Bi-TENS+TOT group (mean difference=3.25, $p<0.001$) and the Uni-TENS+TOT group (mean difference=1.23, $p=0.015$) both showed significant improvement in FMA-UE scores between the baseline and post-intervention assessment. The post-hoc analysis showed that the Bi-TENS+TOT group demonstrated earlier within-group improvement (mean difference=4.40, $p<0.001$) at the mid-intervention assessment, while the Uni-TENS+TOT group only showed significant within-group improvement (mean difference=1.77, $p=0.02$) at the post-intervention assessment. The LMM analysis (Table 6.6) revealed that the Bi-TENS+TOT and Uni-TENS+TOT groups showed no significant within-group change in FMA-UE scores between post-intervention, 1-month follow-up and 3-month follow-up, which indicated that the within-group improvement of FMA-UE score in Bi-TENS+TOT and Uni-TENS+TOT groups were maintained at 1-month follow-up and 3-month follow-up.

6.4.2.2 Secondary outcome

The LMM analysis (Table 6.3) indicated significant within-group improvement in the peak torque during MIVC of wrist flexor (mean difference=0.70, $p<0.001$) and the ARAT scores (mean difference=2.37, $p<0.001$) in the Bi-TENS+TOT group at the post-intervention assessment, but not in the other 3 groups. Post-hoc analysis indicated significant within-group improvements in peak torque

during MIVC of the wrist flexor (mean difference=0.70, $p<0.001$) and the ARAT scores (mean difference=2.35, $p<0.001$) in the Bi-TENS+TOT group at the post-intervention assessment. The LMM (Table 6.6) revealed that the Bi-TENS+TOT groups showed no significant within-group change in peak torque during MIVC of wrist flexor and ARAT scores between post-intervention, 1-month follow-up and 3-month follow-up, which indicated that the within-group improvement of these outcome measures in Bi-TENS+TOT group were maintained at 1-month follow-up and 3-month follow-up.

No significant between-group improvement or within-group improvement in all 4 groups was identified for the peak torque during MIVC of wrist extensor, co-contraction ratio during MIVC of wrist flexor/extensor, AROM of the elbow flexion/extension and wrist flexion/extension, the Jacket Test completion time, MAL or CIM scores from baseline to post-intervention (Table 6.3–Table 6.5). And it was also the case from post-intervention to the 3-month follow-up (Table 6.6–Table 6.8).

Table 6.2 Mean values of all outcome measures

Variables	Group	Baseline	Mid-intervention	Post-intervention	1-month follow-up	3-month follow-up
FMA-UE	Bi-TENS+TOT (n=30)	37.03±12.02	41.27±13.38	43.43±13.73	42.60±13.36	43.17±13.61
	Uni-TENS+TOT (n=30)	41.83±17.12	43.60±17.21	44.23±16.12	42.70±17.35	43.17±18.65
	Placebo-TENS+TOT (n=30)	38.77±15.78	40.13±15.41	40.23±14.97	40.90±14.43	40.60±14.67
	Control (n=30)	43.93±18.74	44.87±17.25	44.20±18.16	45.03±17.99	45.23±17.77
Peak Torque of Wrist Flexor, Nm	Bi-TENS+TOT (n=30)	3.69±1.79	4.40±1.90	5.10±2.17	4.86±2.30	5.08±2.12
	Uni-TENS+TOT (n=30)	4.51±2.63	4.77±2.74	4.74±2.43	4.85±2.60	4.89±2.50
	Placebo-TENS+TOT (n=30)	4.86±2.82	4.71±2.74	4.94±2.58	5.17±2.84	5.28±2.62
	Control (n=30)	5.13±2.29	5.35±2.68	5.39±2.64	5.57±2.72	5.70±2.78
	Bi-TENS+TOT (n=30)	3.38±1.95	3.62±1.70	3.77±1.70	3.87±1.89	3.91±1.98

Peak Torque of Wrist Extensor, Nm	Uni-TENS+TOT (n=30)	3.12±2.36	3.10±2.46	3.58±2.74	3.67±2.82	3.86±2.76
	Placebo-TENS+TOT (n=30)	3.40±2.17	3.41±2.48	3.81±2.62	3.61±2.35	3.66±2.86
	Control (n=30)	3.64±2.64	3.55±2.53	3.71±2.39	3.81±2.34	3.98±2.67
Co-contraction Ratio of Wrist Flexion	Bi-TENS+TOT (n=30)	0.28±0.14	0.26±0.13	0.26±0.14	0.26±0.16	0.27±0.16
	Uni-TENS+TOT (n=30)	0.24±0.11	0.27±0.13	0.28±0.12	0.26±0.11	0.25±0.11
	Placebo-TENS+TOT (n=30)	0.25±0.15	0.23±0.11	0.25±0.12	0.25±0.10	0.23±0.15
	Control (n=30)	0.24±0.13	0.24±0.13	0.24±0.12	0.25±0.13	0.23±0.11
Co-contraction Ratio of Wrist Extension	Bi-TENS+TOT (n=30)	0.29±0.16	0.25±0.12	0.27±0.14	0.29±0.17	0.28±0.18
	Uni-TENS+TOT (n=30)	0.31±0.23	0.28±0.20	0.28±0.21	0.28±0.23	0.27±0.18
	Placebo-TENS+TOT (n=30)	0.25±0.15	0.26±0.15	0.28±0.16	0.26±0.14	0.27±0.15
	Control (n=30)	0.23±0.18	0.22±0.18	0.27±0.20	0.23±0.15	0.22±0.14

AROM-Elbow, degree	Bi-TENS+TOT (n=30)	76.67±28.89	84.70±22.96	87.70±23.78	84.13±30.91	85.13±33.79
	Uni-TENS+TOT (n=30)	85.73±27.30	84.33±28.58	88.47±26.07	84.05±29.51	89.90±30.74
	Placebo-TENS+TOT (n=30)	82.88±24.01	86.75±22.64	83.60±18.82	81.85±23.81	81.95±20.10
	Control (n=30)	90.22±33.36	79.28±29.33	86.75±23.06	89.67±26.64	87.02±27.53
AROM-Wrist, degree	Bi-TENS+TOT (n=30)	72.42±40.84	71.43±36.45	73.83±35.51	72.92±37.84	70.67±39.57
	Uni-TENS+TOT (n=30)	69.97±49.52	74.77±47.35	75.42±47.96	78.30±48.23	78.32±54.34
	Placebo-TENS+TOT (n=30)	72.70±44.04	62.23±50.02	69.77±42.35	66.05±38.46	71.18±44.39
	Control (n=30)	87.41±48.28	87.72±40.34	90.07±42.02	87.97±46.11	90.78±45.25
ARAT	Bi-TENS+TOT (n=30)	28.70±20.09	31.27±20.86	33.40±19.77	31.33±19.24	32.20±20.12
	Uni-TENS+TOT(n=30)	31.73±20.09	33.93±20.27	33.13±20.80	34.90±19.74	33.33±21.17
	Placebo-TENS+TOT (n=30)	28.30±21.69	29.40±20.85	30.30±21.65	31.03±21.83	30.43±21.97

	Control (n=30)	34.97±21.97	35.30±21.61	36.07±22.85	36.77±21.79	36.27±22.29
Jacket Test, second	Bi-TENS+TOT (n=30)	36.51±12.44	33.02±13.66	32.55±11.70	33.35±12.46	32.00±12.51
	Uni-TENS+TOT (n=30)	36.98±22.02	35.78±20.92	30.67±15.66	32.83±20.32	32.54±18.11
	Placebo-TENS+TOT (n=30)	36.87±17.53	36.86±15.53	34.71±16.08	34.24±18.25	34.24±17.19
	Control (n=30)	33.36±21.39	32.58±23.41	34.08±23.55	31.47±21.79	31.77±22.19
MAL-AOU	Bi-TENS+TOT (n=30)	34.03±30.35	35.57±35.59	38.53±38.86	35.95±31.91	39.80±34.42
	Uni-TENS+TOT (n=30)	49.72±47.73	44.93±47.92	48.87±49.56	48.68±49.49	58.03±54.14
	Placebo-TENS+TOT (n=30)	39.20±40.54	53.27±50.99	54.70±50.15	48.58±50.04	50.53±48.84
	Control (n=30)	45.28±34.50	47.73±43.91	45.10±44.62	49.25±50.86	46.42±46.33
MAL-QOM	Bi-TENS+TOT (n=30)	42.10±36.15	41.83±37.57	40.93±35.97	43.05±35.85	43.28±39.07
	Uni-TENS+TOT (n=30)	56.92±49.89	53.20±47.32	61.38±53.73	54.00±51.32	59.08±54.20

	Placebo-TENS+TOT (n=30)	52.42±45.09	61.10±53.46	51.53±46.76	54.88±53.83	54.23±50.13
	Control (n=30)	58.00±43.44	51.53±46.79	52.77±44.83	57.13±53.52	57.18±50.78
CIM	Bi-TENS+TOT(n=30)	39.47±7.51	41.23±6.60	40.17±7.04	41.63±6.96	40.10±7.16
	Uni-TENS+TOT (n=30)	41.23±6.89	39.90±11.79	41.67±9.66	42.70±12.92	40.23±10.45
	Placebo-TENS+TOT (n=30)	41.87±8.02	42.20±7.40	42.17±8.33	43.17±7.00	41.03±7.93
	Control (n=30)	39.67±9.21	38.37±9.04	39.80±9.31	39.33±9.08	41.10±8.86

Notes: ARAT, Action Research Arm Test; Bi-TENS, bilateral transcutaneous electrical nerve stimulation; CIM, Community Integration Measure; FMA-UE, Fugl-Meyer Assessment of Upper Extremity; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; AROM, active range of motion; TOT, task-oriented training; Uni-TENS, unilateral transcutaneous electrical nerve stimulation

Table 6.3 The time effect of Linear Mixed Model of the outcome measures from baseline to post-intervention

	Time Effect (Mean Difference[a] (95%CI), *p*-value)			
Outcome measures	**Bi-TENS+TOT (n=30)**	**Uni-TENS+TOT (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**
FMA-UE	3.25 (2.27, 4.23), <0.001*	1.23 (0.25, 2.21), 0.015*	0.76 (-0.22, 1.75), 0.126	0.17 (-0.81, 1.15), 0.730
Peak Torque of Wrist Flexor, Nm	0.70 (0.43, 0.98), <0.001*	0.11 (-0.16, 0.38), 0.418	0.04 (-0.23, 0.32), 0.750	0.12 (-0.15, 0.40), 0.369
Peak Torque of Wrist Extensor, Nm	0.19 (-0.07, 0.45), 0.150	0.25 (-0.01, 0.51), 0.059	0.22 (-0.04, 0.48), 0.095	0.04 (-0.22, 0.30), 0.746
Co-contraction Ratio of Wrist Flexion	-0.01 (-0.03, 0.01), 0.334	0.02 (-0.00, 0.04), 0.059	0.00 (-0.02, 0.02), 0.787	0.00 (-0.02, 0.02), 0.808
Co-contraction Ratio of Wrist Extension	-0.01 (-0.03, 0.01), 0.423	-0.02 (-0.04, 0.01), 0.133	0.01 (-0.01, 0.04), 0.200	0.02 (-0.01, 0.04), 0.155
AROM-Elbow, degree	5.20 (1.53, 8.87), 0.006	1.71 (-1.96, 5.38), 0.358	-0.08 (-3.75, 3.59), 0.966	-0.59 (-4.26, 3.08), 0.752
AROM-Wrist, degree	0.93 (-3.97, 5.83), 0.708	2.45 (-2.45, 7.35), 0.324	-0.28 (-5.18, 4.62), 0.911	1.46 (-3.44, 6.36), 0.556

ARAT	2.37 (1.08, 3.65), <0.001*	0.82 (-0.46, 2.11), 0.207	1.01 (-0.28, 2.29), 0.123	0.53 (-0.75, 1.82), 0.414
Jacket Test, second	-2.15 (-4.24, 0.06), 0.044	-2.94 (-5.15, -0.74), 0.009	-0.96 (-3.09, 1.17), 0.373	0.23 (-2.06, 2.53), 0.840
MAL-AOU	2.29 (-4.90, 9.48), 0.530	-0.19 (-7.38, 7.00), 0.957	7.42 (0.23, 14.61), 0.043	0.23 (-7.42, 6.96), 0.950
MAL-QOM	-0.57 (-6.48, 5.33), 0.848	2.05 (-3.85, 7.96), 0.492	-0.17 (-6.07, 5.74), 0.955	-2.73 (-8.64, 3.17), 0.362
CIM	0.42 (-0.73, 1.57), 0.475	0.14 (-1.01, 1.30), 0.806	0.16 (-0.99, 1.31), 0.786	0.00 (-1.15, 1.15), 0.998

Notes: ARAT, Action Research Arm Test; Bi-TENS, bilateral transcutaneous electrical nerve stimulation; CI, confidence interval; CIM, Community Integration Measure; FMA-UE, Fugl-Meyer Assessment of Upper Extremity; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; AROM, active range of motion; TOT, task-oriented training; Uni-TENS, unilateral transcutaneous electrical nerve stimulation.

Mean difference [a]=The average gains for each subsequent time point of each group across the 3 endpoints: baseline, mid-intervention and post-intervention

*p<0.05

Table 6.4 The group effect of Linear Mixed Model of the outcome measures from baseline to post-intervention against the reference category of Bi-TENS +TOT

	Group Effect (Mean Difference[b] [95%CI], *p*-Value)		
Outcome measures	**Uni-TENS+TOT (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**
FMA-UE	-5.54 (-14.93, 3.86), 0.246	-10.89 (-20.28, -1.49), 0.023	-8.60 (-18.00, 0.79), 0.072
Peak Torque of Wrist Flexor, Nm	-2.08 (-4.00, -0.17), 0.033	-2.21 (-4.12, 0.30), 0.024	-1.42 (-3.33, 0.50), 0.146
Peak Torque of Wrist Extensor, Nm	-0.07 (-1.98, 1.85), 0.944	0.08 (-1.83, 2.00), 0.932	-0.54 (-2.45, 1.37), 0.578
Co-contraction Ratio of Wrist Flexion	0.11 (-0.01, 0.23), 0.080	0.00 (-0.12,0.13), 0.947	0.02 (-0.10, 0.14), 0.738
Co-contraction Ratio of Wrist Extension	-0.01 (-0.16, 0.14), 0.855	0.09 (-0.06, 0.24), 0.232	0.07 (-0.08,0.22), 0.349
AROM-Elbow, degree	-10.66 (-32.91, 11.59), 0.345	-19.77 (-42.01, 2.48), 0.081	-20.43 (-42.68, 1.82), 0.072
AROM-Wrist, degree	7.17 (-25.59, 39.93), 0.666	-9.69 (-42.45, 23.07), 0.559	18.01 (-14.75, 50.77), 0.279
ARAT	-4.26 (-17.19, 8.66), 0.515	-7.24 (-20.16, 5.69), 0.270	-3.06 (-15.98, 9.87), 0.641

Jacket Test, second	-2.73 (-16.42, 10.95), 0.693	6.87 (-6.56, 20.31), 0.313	8.84 (-5.13, 22.82), 0.213
MAL-AOU	1.49 (-38.04, 41.01), 0.941	34.25 (-5.27, 73.78), 0.089	0.28 (-39.25, 39.80), 0.989
MAL-QOM	26.61 (-13.02, 66.25), 0.187	14.24 (-25.40, 53.88), 0.479	4.21 (-35.43, 43.85), 0.867
CIM	-0.13 (-7.94, 7.68), 0.973	0.89 (-6.93, 8.70), 0.823	-2.37 (-10.19, 5.44), 0.549

Notes: ARAT, Action Research Arm Test; Bi-TENS, bilateral transcutaneous electrical nerve stimulation; CI, confidence interval; CIM, Community Integration Measure; FMA-UE, Fugl-Meyer Assessment of Upper Extremity; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; AROM, active range of motion; TOT, task-oriented training; Uni-TENS, unilateral transcutaneous electrical nerve stimulation.

Mean difference [b]=The group difference of each of 3 groups (Uni-TENS+TOT, Placebo and Control) against the reference category: Bi-TENS+TOT group.

Table 6.5 The time-by-group effect of Linear Mixed Model of the outcome measures from baseline to post-intervention against the reference category of (1) Bi-TENS +TOT; (2) Uni-TENS+TOT; (3) Placebo-TENS+TOT

	(1) Time-by-group Interaction Effect[c] (Mean Difference (95%CI), *p*-value)			**(2) Time-by-group Interaction Effect[d] (Mean Difference (95%CI), *p*-value)**		**(3) Time-by-group Interaction Effect[e] (Mean Difference (95%CI), *p*-value)**
Outcome measures	**Uni-TENS+TOT (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**	**Control (n=30)**
FMA-UE	2.02 (0.63, 3.41), 0.005*	2.49 (1.10, 3.87), 0.001*	3.08 (1.69, 4.47), <0.001*	0.46 (-0.93, 1.85), 0.510	1.06 (-0.33, 2.44), 0.135	0.59 (-0.80, 1.98), 0.400
Peak Torque of Wrist Flexor, Nm	0.59 (0.21, 98), 0.003	0.66 (0.28, 1.04), 0.002	0.58 (0.20, 0.96), 0.003	0.07 (-0.32, 0.45), 0.727	-0.01 (-0.40, 0.37), 0.950	-0.08 (-0.46, 0.30), 0.681
Peak Torque of Wrist Extensor, Nm	-0.06 (-0.43, 0.31), 0.744	-0.03 (-0.40, 0.34), 0.868	0.15 (-0.22, 0.51), 0.429	0.03 (-0.34, 0.40), 0.873	0.21 (-0.16, 0.57), 0.265	0.18 (-0.19, 0.54), 0.339
Co-contraction Ratio of Wrist Flexion	-0.03 (-0.06, -0.00), 0.044	-0.01 (-0.04, 0.02), 0.622	-0.01 (-0.04, 0.02), 0.393	0.02 (-0.01, 0.05), 0.126	0.02 (-0.01, 0.05), 0.242	-0.01 (-0.03, 0.02), 0.717
Co-contraction Ratio of Wrist Extension	0.01 (-0.02, 0.04), 0.617	-0.02 (-0.06, 0.01), 0.142	-0.03 (-0.06, 0.01), 0.117	-0.03 (-0.06, 0.00), 0.050	-0.03 (0.06, 0.00), 0.040	0.00 (-0.03,0.03), 0.920
AROM-Elbow, degree	3.49 (-1.70, 8.68), 0.186	5.28 (0.09, 10.47), 0.046	5.79 (0.60, 10.98), 0.029	1.79 (-3.40, 6.98), 0.496	2.30 (-2.89, 7.49), 0.383	0.51 (-4.68, 5.70), 0.847
AROM-Wrist, degree	-1.52 (-8.45, 5.41), 0.665	1.21 (-5.72, 8.14), 0.730	-0.53 (-7.46, 6.40), 0.879	2.73 (-4.20, 9.66), 0.437	0.99 (-5.94, 7.92), 0.779	-1.74, (-8.67, 5.19), 0.620

ARAT	1.54 (-0.27, 3.36), 0.095	1.36 (-0.46, 3.18), 0.141	1.84 (0.02, 3.65), 0.048	-0.19 (-2.00, 1.63), 0.840	0.29 (-1.53, 2.11), 0.752	0.48 (-1.34, 2.29), 0.605
Jacket Test, second	0.80 (-2.24, 3.84), 0.606	-1.19 (-4.17, 1.80), 0.432	-2.38 (-5.49, 0.72), 0.131	-1.98 (-5.05, 1.08), 0.203	-3.18 (-6.36, 0.00), 0.050	-1.20 (-4.32, 1.93), 0.451
MAL-AOU	2.48 (-7.69, 12.65), 0.630	-5.13 (-15.30, 5.04), 0.320	2.51 (-7.65, 12.68), 0.625	-7.61 (-17.78, 2.56), 0.141	0.03 (-10.14, 10.20), 0.995	7.64 (-2.53, 17.81), 0.139
MAL-QOM	-2.63 (-10.98, 5.72), 0.534	-0.41 (-8.76, 7.94), 0.923	2.16 (-6.19, 10.51), 0.610	2.22 (-6.13, 10.57), 0.599	4.79 (-3.56, 13.14), 0.259	2.56, (-5.79, 10.92), 0.544
CIM	0.27 (-1.36, 1.90), 0.740	0.26 (-1.37, 1.89), 0.754	0.42 (-1.21, 2.04), 0.615	-0.02 (-1.65, 1.61), 0.985	0.14 (-1.49, 1.77), 0.864	0.16, (-1.47, 1.79), 0.849

Notes: ARAT, Action Research Arm Test; Bi-TENS, bilateral transcutaneous electrical nerve stimulation; CI, confidence interval; CIM, Community Integration Measure; FMA-UE, Fugl-Meyer Assessment of Upper Extremity; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; AROM, active range of motion; TOT, task-oriented training; Uni-TENS, unilateral transcutaneous electrical nerve stimulation.

(1) Mean difference [c]=difference in the slope estimates for each of the 3 groups (Uni-TENS+TOT, Placebo-TENS+TOT and Control) against the reference category: Bi-TENS+TOT group across the 3 endpoints: baseline, mid-intervention and post-intervention.

(2) Mean difference [d]=difference in the slope estimates for each of the 2 groups (Placebo and Control) against the reference category: Uni-TENS+TOT group across the 3 endpoints: baseline, mid-intervention and post-intervention.

(3) Mean difference [e]=difference in the slope estimates for Control group against the reference category: Placebo-TENS+TOT group across the 3 endpoints: baseline, mid-intervention and post-intervention.

*$p<0.05$

Table 6.6 The time effect of Linear Mixed Model of the outcome measures from post-intervention to follow-up 3-month

	Time Effect (Mean Difference[a] (95%CI), *p*-value)			
Outcome measures	**Bi-TENS+TOT (n=30)**	**Uni-TENS+TOT (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**
FMA-UE	-0.30 (-1.22, 0.63), 0.523	-0.77 (-1.70, 0.15), 0.102	0.30 (-0.63, 1.22), 0.525	0.59 (-0.33, 1.52), 0.208
Peak Torque of Wrist Flexor, Nm	-0.02 (-0.25, 0.22), 0.889	0.08 (-0.15, 0.31), 0.504	0.17 (-0.06, 0.40), 0.137	0.16 (-0.08, 0.39), 0.184
Peak Torque of Wrist Extensor, Nm	0.07 (-0.14, 0.29), 0.504	0.13 (-0.08, 0.35), 0.220	-0.08 (-0.30, 0.13), 0.449	0.14 (-0.08, 0.35), 0.207
Co-contraction Ratio of Wrist Flexion	0.01 (-0.01, 0.03), 0.580	-0.01 (-0.03, 0.01), 0.321	-0.01 (-0.03, 0.01), 0.472	-0.01 (-0.03, 0.01), 0.542
Co-contraction Ratio of Wrist Extension	0.01 (-0.01, 0.02), 0.575	0.00 (-0.02, 0.02), 0.912	0.00 (-0.02,0.02), 0.678	-0.02 (-0.04, 0.00), 0.025
AROM-Elbow, degree	-1.73 (-5.89, 2.42), 0.411	-0.30 (-4.46, 3.86), 0.888	-1.01 (-5.17, 3.15), 0.633	0.68 (-3.48, 4.84), 0.746
AROM-Wrist, degree	-1.54 (-5.99, 2.90), 0.493	1.54 (-2.91, 5.98), 0.496	0.44 (-4.00, 4.89), 0.844	0.21 (-4.23, 4.66), 0.925

ARAT	-0.43 (-1.33, 0.48), 0.354	-0.10 (-1.00, 0.81), 0.833	-0.01 (-0.92, 0.90), 0.979	0.03 (-0.88, 0.94), 0.949
Jacket Test, second	-0.33 (-2.00, 1.33), 0.695	0.87 (-0.88, 2.63), 0.328	-0.23 (-1.92, 1.47), 0.791	-1.08 (-2.90, 0.75), 0.245
MAL-AOU	0.69 (-4.81, 6.19), 0.805	4.66 (-0.83, 10.16), 0.096	-2.01 (-7.51, 3.48), 0.470	0.60 (-4.90, 6.10), 0.830
MAL-QOM	1.19 (-3.45, 5.83), 0.612	-1.26 (-5.90, 3.38), 0.591	1.39 (-3.25, 6.03), 0.556	2.25 (-2.39, 6.89), 0.340
CIM	-0.03 (-1.18, 1.13), 0.965	-0.70 (-1.86, 0.45), 0.231	-0.56 (-1.71, 0.60), 0.340	0.61 (-0.54, 1.77), 0.297

Notes: ARAT, Action Research Arm Test; Bi-TENS, bilateral transcutaneous electrical nerve stimulation; CI, confidence interval; CIM, Community Integration Measure; FMA-UE, Fugl-Meyer Assessment of Upper Extremity; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; ROM, range of motion; TOT, task-oriented training; Uni-TENS, unilateral transcutaneous electrical nerve stimulation.

Mean difference [a]=The average gains for each subsequent time point of each group across the 3 endpoints: post-intervention, 1-month follow-up and 3-month follow-up.

Table 6.7 The group effect of Linear Mixed Model of the outcome measures from post-intervention to follow-up 3-month against the reference category of Bi-TENS +TOT

	Group Effect (Mean Difference[b] (95%CI), *p*-value)		
Outcome measures	**Uni-TENS+TOT (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**
FMA-UE	-0.67 (-9.14, 7.80), 0.876	-1.18 (-9.65, 7.29), 0.783	3.64 (-4.84, 12.11), 0.397
Peak Torque of Wrist Flexor, Nm	-0.07 (-1.47, 1.33), 0.918	0.42 (-0.98, 1.81), 0.557	0.81 (-0.59, 2.21), 0.252
Peak Torque of Wrist Extensor, Nm	-0.04 (-1.46, 1.37), 0.950	-0.49 (-1.90, 0.92), 0.493	0.10 (-1.31, 1.51), 0.890
Co-contraction Ratio of Wrist Flexion	-0.04 (-0.12, 0.05), 0.389	-0.05 (-0.13, 0.03), 0.242	-0.05 (-0.13, 0.03), 0.239
Co-contraction Ratio of Wrist Extension	-0.02 (-0.11, 0.08), 0.708	-0.03 (-0.12, 0.06), 0.524	-0.10 (-0.19, 0.00), 0.047
AROM-Elbow, degree	4.66 (--13.34, 22.65), 0.611	-1.72 (-19.72, 16.28), 0.851	7.05 (-10.94, 25.05), 0.441
AROM-Wrist, degree	11.08 (-13.41, 35.57), 0.373	0.17 (-24.32, 24.66), 0.989	20.44 (-4.05, 44.93), 0.101
ARAT	2.21 (-8.77, 13.19), 0.690	-0.84 (-11.82, 10.14), 0.880	5.02 (-5.96, 16.00), 0.367

Jacket Test, second	1.74 (-8.28, 11.77), 0.732	2.34 (-7.51, 12.18), 0.639	-0.98 (-11.22, 9.25), 0.850
MAL-AOU	21.77 (-4.40, 47.93), 0.102	7.80 (-18.36, 33.96), 0.557	8.43 (-17.73, 34.59), 0.526
MAL-QOM	11.40 (-14.85, 37.64), 0.393	11.43 (-14.82, 37.68), 0.391	15.29 (-10.96, 41.53), 0.252
CIM	-0.20 (-5.27, 4.86), 0.937	0.42 (-4.65, 5.48), 0.871	0.92 (-4.15, 5.99), 0.720

Notes: ARAT, Action Research Arm Test; Bi-TENS, bilateral transcutaneous electrical nerve stimulation; CI, confidence interval; CIM, Community Integration Measure; FMA-UE, Fugl-Meyer Assessment of Upper Extremity; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; ROM, range of motion; TOT, task-oriented training; Uni-TENS, unilateral transcutaneous electrical nerve stimulation.

Mean difference [b]=The group difference of each of 3 groups (Uni-TENS+TOT, Placebo-TENS and Control) against the reference category: Bi-TENS+TOT group.

Table 6.8 The time-by-group effect of Linear Mixed Model of the outcome measures from post-intervention to follow-up 3-month against the reference category of (1) Bi-TENS +TOT; (2) Uni-TENS+TOT; (3) Placebo-TENS+TOT

	(1) Time-by-group Interaction Effect[c] (Mean Difference (95%CI), *p*-value)			(2) Time-by-group Interaction Effect[d] (Mean Difference (95%CI), *p*-value)		(3) Time-by-group Interaction Effect (Mean Difference[e] (95%CI), *p*-value)
Outcome measures	**Uni-TENS+TOT (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**	**Placebo-TENS+TOT (n=30)**	**Control (n=30)**	**Control (n=30)**
FMA-UE	0.47 (-0.84, 1.78), 0.477	-0.60 (-1.91, 0.71), 0.368	-0.89 (-2.20, 0.42), 0.180	-1.07 (-2.38, 0.24), 0.108	-1.36 (-2.67, -0.05), 0.041	-0.29 (-1.60, 1.01), 0.657
Peak Torque of Wrist Flexor, Nm	-0.09 (-0.42, -0.23), 0.568	-0.19 (-0.52, 0.14), 0.249	-0.17 (-0.50, 0.15), 0.299	-0.10 (-0.42, 0.23), 0.560	-0.08 (-0.40, 0.25), 0.639	0.02 (-0.31, 0.35), 0.910
Peak Torque of Wrist Extensor, Nm	-0.06 (-0.37, 0.24), 0.691	0.16 (-0.15, 0.46), 0.314	-0.07 (-0.37, 0.24), 0.674	0.22 (-0.09, 0.52), 0.161	0.00 (-0.31, 0.30), 0.981	-0.22 (-0.53, 0.08), 0.154
Co-contraction Ratio of Wrist Flexion	0.02 (-0.01, 0.04), 0.275	0.01 (-0.02, 0.04), 0.369	0.01 (-0.02, 0.04), 0.412	0.00 (-0.03, 0.03), 0.846	0.00 (-0.03, 0.02), 0.786	0.00 (-0.03, 0.03), 0.938
Co-contraction Ratio of Wrist Extension	0.01 (-0.02, 0.03), 0.635	0.01 (-0.02, 0.04), 0.490	0.03 (0.00, 0.05), 0.047	0.00 (-0.02, 0.03), 0.830	0.02 (-0.01, 0.05), 0.129	0.02 (-0.01, 0.04), 0.192
AROM-Elbow, degree	-1.44 (-7.32, -4.44), 0.630	-0.73 (-6.61, 5.15), 0.808	-2.42 (-8.30, 3.46), 0.418	0.71 (-5.17, 6.59), 0.812	-0.98 (-6.86, 4.90), 0.742	-1.69 (-7.57, 4.19), 0.571
AROM-Wrist, degree	-3.08 (-9.37, 3.21), 0.334	-1.99 (-8.27, 4.30), 0.533	-1.75 (-8.04, 4.53), 0.582	1.09 (-5.20, 7.38), 0.732	1.32 (-4.96, 7.61), 0.677	0.23 (-6.06, 6.52), 0.942
ARAT	-0.33 (-1.61, 0.95), 0.612	-0.41 (-1.70, 0.87), 0.523	-0.46 (-1.74, 0.83), 0.483	-0.08 (-1.37, 1.20), 0.896	-0.13 (-1.41, 1.16), 0.846	-0.04 (-1.32, 1.24), 0.949

Jacket Test, second	-1.20 (-3.62, 1.22), 0.328	-0.10 (-2.48, 2.27), 0.931	0.75 (-1.72, 3.22), 0.551	1.10 (-1.34, 3.54), 0.375	1.95 (-0.58, 4.48), 0.130	0.85 (-1.64, 3.34), 0.501
MAL-AOU	-3.98 (-11.75, 3.80), 0.313	2.70 (-5.07, 10.48), 0.493	0.09 (-7.69, 7.86), 0.982	6.68 (-1.10, 14.45), 0.092	4.07 (-3.71, 11.84), 0.303	-2.61 (-10.39, 5.16), 0.507
MAL-QOM	2.45 (-4.11, 9.02), 0.461	0.19 (-6.76, 6.37), 0.953	-1.06 (-7.62, 5.51), 0.751	-2.65 (-9.21, 3.91), 0.426	-3.51 (-10.07, 3.05), 0.292	-0.86 (-.7.42, 5.70), 0.796
CIM	0.68 (-0.96, 2.31), 0.414	0.53 (-1.10, 2.17), 0.519	-0.64 (-2.27, 1.00), 0.441	-0.14 (-1.78, 1.49), 0.862	-1.31 (-2.95, 0.32), 0.114	-1.17 (-2.80, 0.46), 0.159

Notes: ARAT, Action Research Arm Test; Bi-TENS, bilateral transcutaneous electrical nerve stimulation; CI, confidence interval; CIM, Community Integration Measure; FMA-UE, Fugl-Meyer Assessment of Upper Extremity; MAL, Motor Activity Log; AOU, amount of use; QOM, quality of movement; ROM, range of motion; TOT, task-oriented training; Uni-TENS, unilateral transcutaneous electrical nerve stimulation.

Mean difference [c]=difference in the slope estimates for each of the 3 groups (Uni-TENS+TOT, Placebo-TENS and Control) against the reference category: Bi-TENS+TOT group across the 3 endpoints: post-intervention, 1-month follow-up and 3-month follow-up.

Mean difference [d]=difference in the slope estimates for each of the 2 groups (Placebo-TENS and Control) against the reference category: Uni-TENS+TOT group across the 3 endpoints: post-intervention, 1-month follow-up and 3-month follow-up.

Mean difference [e]=difference in the slope estimates for Control group against the reference category: Placebo-TENS+TOT group across the 3 endpoints: post-intervention, 1-month follow-up and 3-month follow-up.

6.5 Discussion

This has been the first study to compare the effects of Bi-TENS+TOT with that of Uni-TENS+TOT, Placebo-TENS+TOT and Control without active treatment on upper limbs motor functions in people with stroke. There were 4 major findings. First, the Bi-TENS+TOT group showed significantly greater improvement in terms of average FMA-UE score than the other 3 groups at post-intervention. Second, both Bi-TENS+TOT and Uni-TENS+TOT improved FMA-UE scores, and the effects persisted at least until the 3-month follow-up. Bi-TENS+TOT showed earlier improvement in FMA-UE scores at mid-intervention, while Uni-TENS+TOT showed significant improvement only at the end of the intervention. Third, only the subjects in the Bi-TENS+TOT group showed significant within-group improvement in the peak torque during MIVC of the paretic wrist flexor. That was also the only group to show a significant within-group improvement in ARAT score at the post-intervention assessment when compared with baseline. Fourth, the Bi-TENS+TOT group's improvement of FMA-UE scores, peak torque during MIVC of wrist flexor and ARAT score persisted through the 1-month and 3-month follow-ups. The Uni-TENS+TOT group's improvement in FMA-UE score also persisted through the 1-month and 3-month follow-ups.

6.5.1 Uni-TENS+TOT in motor recovery

Consistent with the results of previous studies (Jung, Jung, et al., 2017; Kim, In, et al., 2013), Uni-TENS+TOT group (mean difference=1.23) in the current study showed greater within-group improvement in FMA-UE scores at post-intervention when compared with Placebo-TENS+TOT group (mean difference=0.76). At the cortical level, the difference could be attributable to reduced short-interval intra-cortical inhibition (Celnik et al., 2007), enhanced corticospinal excitability (Charlton et al., 2003) and corticomuscular coherence (Lai et al., 2016) induced by the repetitive TENS over the paretic limb. These mechanisms have been discussed in better details in sections 1.4.3.1. Previous studies have revealed that peripheral sensory input from electrical stimulation over a paretic limb can enhance motor recovery by activating the lesioned motor cortex via two pathways: (1) via a thalamus-primary motor cortex (M1) pathway involving the ventro-posterior lateralis pars oralis and the ventro-posterior lateralis pars caudalis (Hirashima & Yokota, 1997); and (2) via a primary somatosensory cortex (S1) pathway which exploits the anatomical connection of the S1 and M1 areas (Zarzecki, 1991).

6.5.2 Bi-TENS+TOT in motor recovery

As expected, Bi-TENS+TOT group showed greater improvement in FMA-UE scores than Uni-TENS+TOT, Placebo-TENS+TOT and Control groups at post-intervention time point. Two possible underlying mechanisms of Bi-TENS can explain the facilitation of the paretic upper limb recovery. First, Bi-TENS could enhance interaction between the intact and lesioned hemispheres via the transcallosal pathway connecting the two cerebral hemispheres (Gilles et al.,

2013). Murase et al. **(2004)** has shown that greater inter-hemispheric inhibition (IHI) from the intact to the lesioned M1 leads to motor dysfunction in people with stroke. Cunningham et al. (2019) found that 60 minutes of bilateral electrical stimulation over paretic extensor digitorum communis and extensor pollicis longus muscles can reduce IHI, but that unilateral stimulation cannot. Reducing IHI with Bi-TENS therefore can likely help reinforce the inter-hemispheric interaction via the transcallosal pathway and enhance the motor recovery of the paretic upper limb in subjects with stroke.

Second, Bi-TENS could also enhance corticomuscular activation via uncrossed contralesional corticospinal pathway. The upper limb muscles are innervated by projections from the intact and lesioned motor cortex (Lemon, 2008). The nerves from the intact hemisphere plays a particularly important role in upper limb movement following stroke. Previous studies (Cao et al., 1998; Cramer et al., 2000; Cramer et al., 1997; Weiller et al., 1993) have consistently found that the intact hemisphere is activated during movement of a paretic upper limb. Cramer et al.'s fMRI study (1997) demonstrated that finger tapping with a paretic hand activated a larger area in the supplementary motor area, the sensorimotor cortex and the premotor cortex of the intact hemisphere than that was seen in normal subjects. Calautti and Baron (2003) have suggested that recruitment of motor areas from the intact hemisphere via the uncrossed corticospinal pathway to accomplish paretic side movement is a routine procedural adaptation following a stroke. That is supported by the findings of Ferris's study (2018) who demonstrated that 30 minutes of electrical stimulation over the bilateral sides of the radial nerves (at 0.25Hz and 150% of the motor threshold) increased the motor-evoked potential of the extensor carpi radialis on the paretic side for at least 30 minutes in people with stroke. Therefore, the sensory input from TENS being

applied to the non-paretic upper forearm could activate the intact hemisphere and help to mediate recovery of motor control via the uncrossed descending corticospinal pathway.

The significant within-group improvement in FMA-UE score was also shown in the Bi-TENS+TOT and Uni-TENS+TOT group at the post-intervention assessment with the mean change of 6.50 and 2.46, respectively. While no significant change was found in the Placebo-TENS+TOT or Control group. Only the change in the Bi-TENS+TOT group exceeded the minimal clinically important difference of 5.25 (Page et al., 2012), the patients should perceive it as beneficial (Mouelhi et al., 2020). That reveals the potential superiority of combining bilateral the Bi-TENS with TOT in clinical practice.

In our study, 38.2% and 16.4% within-group improvement in peak torque during MIVC of wrist flexor and ARAT scores was found in the Bi-TENS+TOT group, respectively. The improvement in peak torque during MIVC of wrist flexor found in the Bi-TENS+TOT group may have resulted from additional recruitment of neural pathways from the intact hemisphere compared with stimulating the paretic side only (Bradnam et al., 2012; Chen et al., 2019). Greater peak torque during MIVC of wrist flexor helps to stabilize hand movements, including grasping and gripping (Kornecki & Zschorlich, 1994). A previous study (Harris & Eng, 2007) has documented that upper limb muscle strength explained 78% to 81% of the variance in the performance of paretic upper limbs in ADL tasks.

However, there was no significant between-group difference in peak torque during MIVC of wrist flexor or ARAT scores was shown in this study between the Bi-TENS+TOT group and the other 3 groups. The ARAT involves multiple joints coordination of the paretic upper limb, but the training administered in this study aimed at improving motor control of individual joints. There was no specific intensive muscle strength training or training of high-level coordination in completing complex functional tasks. Also, the sample size was estimated based on detecting an improvement in FMA-UE scores. It may not have provided enough power to detect any differences in terms of peak torque generation or ARAT scores.

It is important that the Bi-TENS+TOT group's improvements in FMA-UE scores, peak torque during MIVC of wrist flexor and ARAT scores, and the Uni-TENS+TOT group's improved FMA-UE scores persisted through the 3-month follow-up assessment. Repetitive TENS, unilateral or bilateral, induced long-lasting improvement. Such improvement might encourage increased use of the paretic upper limb in daily life, which in turn could further improve the peak torque during MIVC of wrist flexor and ARAT scores in Bi-TENS+TOT group and the FMA-UE scores in both Bi-TENS+TOT and Uni-TENS+TOT group. Ideally, an upward spiral results.

In order to maximize the effectiveness of TENS in augmenting TOT, TENS was applied concurrently with the TOT in this study. Khaslavskaia et al. (2002) found that 30 minutes of electrical stimulation on the common peroneal nerve increased the motor-evoked potential of the tibialis anterior muscle by up to 104% as measured by transcranial magnetic stimulation

throughout the stimulation period, and that the effects lasted for 110 minutes after the stimulation ended.

6.5.3 Comparison of Placebo-TENS+TOT and Control in motor recovery

In this study, twenty 60-minute sessions of placebo-TENS combined with TOT could not induce significant within-group improvement in FMA-UE scores. The mean FMA-UE score of the Placebo-TENS+TOT group (mean difference=0.76) did, however, improve 4 times more than that of the Control group (mean difference=0.17) at the post-intervention time point when compared with the baseline. The more positive change in Placebo-TENS+TOT group provides some indication of the treatment effect of TOT. Placebo-TENS could influence the subjects' mindset, but any effect on motor recovery would have been minimal (Levin & Hui-Chan, 1992). TOT alone is known to improve muscle strength (Flansbjer et al., 2008), induce muscle hypertrophy (Ryan et al., 2011), improve neuromuscular efficiency (Marden-Lokken & Killough, 2006) and reinforce reorganization of the body parts being trained in the cerebral mapping (Jang et al., 2003; Yang et al., 2010) in people with stroke. In this study, it appears that higher TOT dosage would have been required to achieve significant improvement in motor recovery. Roos et al. (2012) found that in addition to the conventional rehabilitation training, the people with stroke often undertake 7–14 hours of inadvertent walking training every week, which contributes to rebuilding lower limb muscle strength and control. However, the subjects did not spend such

extra time training their upper limbs. In addition, TOT protocol adopted in this study might not provide the optimal dosage of TOT. That deserves further study to investigate.

6.5.4 Other outcomes

6.5.4.1 The effect on peak torque of wrist extension, co-contraction ratio during MIVC, AROM of elbow flexion/extension and wrist flexion/extension and completion time of Jacket test

None of the 4 groups showed any significant change in peak toque during MIVC of wrist extensor, co-contraction ratio during MIVC of wrist flexor/extensor or AROM of the paretic elbow flexion/extension and wrist flexion/extension had been found in all 4 groups. A possible factor contributed to the insignificant difference could be insufficient dosage of treatment to induce any physiological changes in motor units or muscle strength. As coordination of agonist and antagonist activation when performing muscle contraction remained unchanged, there was no significant change in AROM of elbow flexion/extension and wrist flexion/extension in the 4 groups of treatments (Nelson & Blauvelt, 2014).

No significant finding was shown in the Jacket Test completion time among the 4 groups in this study. The Jacket Test involves a complex motor task in which multiple joints in both paretic and non-paretic upper limbs must be coordinated. With no significant changes in muscle activation, muscle strength or AROM, the Jacket Test could not be expected to get effective improvement. Longer, more intensive treatment would be required, but it was beyond this study's scope to investigate the optimal dosage and scheme of the training protocol. Further

study should be conducted to explore the optimal dosage and protocol of Bi-TENS+TOT in people with stroke.

6.5.4.2 The effect on MAL scores

The lack of any significant difference in the MAL scores among the 4 groups, which indicates that the treatment did not influence self-perceived performance of the upper limb in our study. The ARAT scores confirm that those perceptions were not unrealistic. Inability to execute the ADL due to poor functional performance of upper limb would reduce a person's motivation to use the paretic upper limb (Morris et al., 2017), the self-perceived performance therefore got no improvement. Although the subjects in the Bi-TENS+TOT group showed statistically significant within-group improvement of ARAT scores at post-intervention, the improvement was not practically significant if the subjects failed to perceive it.

6.5.4.3 The effect on CIM scores

In this study, we did not identify any significant change in CIM scores among the 4 groups. The community integration is a complicated domain, but of great importance. The CIM tries to quantify it, but the scores can be dominated by multiple factors. Baseman et al. (2010) found that beyond physical functioning, psychological factors (especially depression) significantly predict social integration in people with stroke. No psychological factor was included as an explicit outcome measure in this study. The lack of any significant change of CIM

scores in the Bi-TENS+TOT group could be attributed to the study protocol's inability to improve psychological impairment in people with stroke.

6.5.5 Limitations

This study protocol had several limitations. First, the sample size was calculated for detecting the significant difference of our primary outcome on FMA-UE scores. It was apparently insufficient to detect any significant changes in the secondary outcomes. The effect of combining Bi-TENS with TOT on other outcomes would have to be investigated with a larger sample. Second, there could also have been a blinding problem. Those receiving TENS and placebo-TENS might have been able to discern their group allocation if they could sense different intensity of electrical current on their upper limbs. In order to maintain a common mindset, all of the subjects were informed that they might or might not feel a sensation during the stimulation period as they were to be given stimulation at different intensities and frequencies, but that deception may not have been enough. Third, due to limited manpower and research period, there were only 20 sessions 1-hour intervention for each subject in this study. That was enough to induce a significant improvement in FMA-UE scores in the Bi-TENS+TOT group but not enough to induce a significant changes in the other outcome measures. Forth, the study's duration was limited to only 3 months after the end of the intervention. A future study should use a longer assessment time window to better define the carryover effect. Fifth,

it is of course important to point out that these results may only be generalized to similar populations who fulfill the same inclusion and exclusion criteria. The fact that all of this study's subjects were urban Chinese may also be important.

6.6 Conclusions

Combining Bi-TENS with TOT produces significantly greater improvement in FMA-UE scores than Uni-TENS+TOT, Placebo-TENS+TOT and no treatment. Combining TOT with either Bi-TENS or Uni-TENS will improve FMA-UE scores, and the effects persisted for at least 3 months. Applying Bi-TENS produces earlier within-group improvement of FMA-UE score than Uni-TENS. Only the subjects who received Bi-TENS and TOT showed significant within-group improvement in peak torque during MIVC of wrist flexor and ARAT score at post-intervention. Those improvements in Bi-TENS+TOT and Uni-TENS+TOT groups persisted for at least 3 months. In conclusion, combining bilateral TENS with TOT shows great potential for clinical use. Further studies are warranted to investigate its neurophysiological mechanisms.

Chapter 7

Summary, limitations, and conclusions

7.1 Summary

Chapter 1 of this thesis began with a review of some of the vast corpus of prior research on stroke, which included the epidemiology and etiology of stroke, the cost due to stroke all over the world, the impairment caused by stroke and the effective treatment for stroke rehabilitation. Previous studies have shown that transcutaneous electrical nerve stimulation (TENS) (Jung, Jung, et al., 2017; Kim et al., 2016; Kim, In, et al., 2013) and task-oriented training (TOT) (da Silva et al., 2015; Kim et al., 2016; Kim, In, et al., 2013; Narayan Arya et al., 2012; Winstein et al., 2016) are effective treatments to improve the upper limb motor function among people with stroke. Additionally, bilateral upper limb TOT in particular has been found to be beneficial in people with stroke.

After the vast corpus of prior scholarship in Chapter 1, some research gaps remain and summarized in Chapter 2:

(1) The findings about whether bilateral upper limb training is superior to unilateral upper limb training in improving upper limb motor function in people with stroke remain inconclusive.
(2) No previous study has determined to what extent self-perceived performance of paretic upper limb is a significant predictor of functional performance of upper limb in people with stroke.
(3) Various assessment tools, such as the Fugl-Meyer Assessment of Upper Extremity (FMA-UE), Action Research Arm Test (ARAT) and Wolf Motor Function Test, have been

developed for evaluating upper limb motor control and functioning. They are commonly used in assessing the upper limb motor functions in people with stroke. However, only a few assessment tools (e.g. Jacket Test) have been specifically designed for quantifying upper limb performance in the activities of daily living. The study to investigate the psychometric properties of the Jacket Test among people with stroke remain insufficiently.

(4) To the best of our knowledge, there was no study investigated the effect of bilateral TENS to augment the TOT in improving the upper limb motor function in people with chronic stroke.

In Chapter 3, the systematic review and meta-analysis including 842 subjects of 21 randomized controlled trials (RCT) showed that bilateral upper limb training was superior to unilateral upper limb training in improving the FMA-UE score (mean difference=2.21, 95% Confidence Interval, 0.12 to 4.30, p=0.04; I^2=86%, p<0.001) in people with stroke. The finding indicated that bilateral exercise produced greater improvement in upper limb motor control than unilateral intervention over the paretic limb only.

Chapter 4 reported the results of a cross-sectional study which investigated the contribution of Motor Activity Log (MAL) score on the improvement of ARAT score when controlling the Hand subscale of Fugl-Meyer Assessment (FMA-hand) score in 87 subjects with chronic stroke. The multiple linear regression modeling showed that FMA-hand scores had the largest contribution to the ARAT score in people with stroke, which can predict 36.4% variance of ARAT scores in people with stroke. MAL scores can independently predict an additional

10.4% of variance in ARAT score in people with stroke. The MAL score is an independent and significant predictor of ARAT score in people with stroke. That finding suggests that enhancing self-perceived performance in using a paretic upper limb could be helpful. Self-perceived performance was quantified using MAL scores, which was adopted as one of the outcome measures to evaluate the effectiveness of the intervention.

Chapter 5 describes the general methodology adopted and its rationale in the main study of this thesis. It mainly included the inclusion and exclusion criteria of the subjects, the study design, the details of the selected outcome measures and its psychometric properties. The primary measures is (FMA-UE) and secondary outcomes included peak torque and co-contraction ratio during Maximum Isometric Voluntary Contraction (MIVC) of wrist flexor and extensor, Active Range of Motion (AROM) of elbow flexion/extension and wrist flexion/extension, ARAT, Jacket Test, MAL and Community Integration Measure (CIM). Reliability and validity of Jacket Test, which is a sub-item of physical performance test, was investigated in people with chronic stroke. The result showed that Jacket Test has excellent intra-rater, inter-rater and test-retest reliability (Intraclass Correlation Coefficient=0.781-1.000) in assessing the daily performance of upper limb.

Chapter 6 reported a placebo-controlled randomized controlled clinical trial which compared the effect of Bi-TENS+TOT with Uni-TENS+TOT, Placebo-TENS+TOT and control without active treatment in facilitating the motor recovery of upper limb motor functions in people with chronic stroke. One hundred and twenty subjects with chronic stroke were randomly

allocated into Bi-TENS+TOT group, Uni-TENS+TOT group, Placebo-TENS+TOT group and Control group. The Bi-TENS+TOT group, Uni-TENS+TOT group and Placebo-TENS+TOT group received 20 sessions 1-hour treatment over 7 weeks, while the Control group did not have any active treatment. The primary outcome was FMA-UE, and the secondary outcome included peak torque during MIVC of wrist flexor and extensor, AROM of elbow flexion/extension and wrist flexion/extension, ARAT, Jacket Test, MAL and CIM.

The result showed that: (1) Bi-TENS+TOT was superior to the other 3 groups in improving the FMA-UE scores at post-intervention (Uni-TENS+TOT: mean difference=2.02, p=0.005; Placebo-TENS+TOT: mean difference=2.49, p=0.001; Control: mean difference=3.08, p<0.001). (2) Both Bi-TENS+TOT (mean difference=3.25, p<0.001) and Uni-TENS+TOT (mean difference=1.23, p=0.015) group showed a significant within-group improvement in FMA-UE after 20 treatment sessions. (3) The Bi-TENS+TOT group showed an earlier and greater improvement in FMA-UE scores than Uni-TENS+TOT group. (4) Subjects in the Bi-TENS+TOT group got significant within-group improvement in ARAT scores (mean difference=2.37, p<0.001), peak torque during MIVC of wrist flexor (mean difference=0.70, p<0.001) at post-intervention, not in the other groups. (5) All significant improvement shown was maintained for at least 3 months after the intervention ended. In conclusion, Bi-TENS is an effective adjunct therapy to augment the effect of TOT in improving upper limb motor control than Uni-TENS.

7.2 Limitations and future directions

The systematic review in Chapter 3 indicated that bilateral exercise was more effective than unilateral intervention in improving the FMA-UE score in people with stroke, but no significantly greater improvement in the other outcome measures could be detected with this intervention volume. The study's protocol was not designed to define the optimum dosage and treatment schedule. That is an important gap which should be filled by future research. A larger sample size may be needed.

Strictly speaking, the findings of cross-sectional study in Chapter 4 can be only generalized to persons who fulfill study's inclusion criteria. It is well to keep in mind that all of the study's subjects were urban Chinese.

The psychometric property of Jacket Test among people with stroke was investigated in Chapter 5. However, the Jacket Test could only measure the speed of completing the dressing task, but not the quality of upper limb movement. The protocol does not account for the compensatory strategies adopted by the subjects. That is an aspect of the test worthy of improvement in future research. Thus, the Jacket Test should be assessed along with other upper limb function-related outcome measures, in order to get a comprehensive assessment of the upper limb function.

The RCT in Chapter 6 showed that Bi-TENS is a more effective adjunct intervention to augment the effect of TOT than Uni-TENS, Placebo-TENS to improve FMA-UE score in people with chronic stroke. However, all outcome measures in our studies were behavioral outcomes. Further physiological and neuroimaging studies investigating the neurophysiological mechanism of Bi-TENS in people with stroke is warranted. Due to the limitation of the manpower and time, this RCT can only detect the change of upper limb motor function from baseline assessment to 3-month after the intervention. Further study should be conducted to investigate the carryover effect of Bi-TENS.

7.3 Implication on Stroke Rehabilitation

Our RCT showed that Bi-TENS combined with TOT induced greater improvement in FMA-UE score than Uni-TENS+TOT, Placebo-TENS+TOT and no treatment control in people with chronic stroke. Thus, application of Bi-TENS to bilateral upper limb during TOT are recommended in clinical practice in order to improve upper limb functions in people with chronic stroke.

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Appendices

Appendix 3.1 Chapter 3 published on Plos One (Final manuscript)

Comparison of bilateral and unilateral upper limb training in people with stroke: a systematic review and meta-analysis

Introduction

Stroke often causes upper limb motor function deficits. Accordingly, people with stroke tend to be more reliant on others during their daily lives [1]. Severe motor impairments in the upper limbs were found to persist for 6 months after stroke in a third of people with stroke [2]. More than half of the activities of daily living (e.g. dressing, feeding and cooking) rely on upper limb functions [3]. Therefore, motor impairment in the upper limb presents a significant barrier to reintegration into society [4].

Unilateral upper limb training (UULT), a common rehabilitative strategy for people with stroke, includes repetitive task-related training [5-7] and constraint-induced movement training (CIMT) [8-13]. During CIMT, the subjects are required to wear a constraint mitten on the unaffected upper limb and to perform intensive training with affected side for at least 6 hours per day. Compared with CIMT, task-related training is a less intensive form of goal-directed training. This form uses various types of motor tasks to help subjects to derive optimal control strategies for solving problems related to motor abilities. Wolf et al. [8] compared the effects of a 14-session CIMT program with dose-matched conventional therapy (day treatment program, outpatient visits, physiotherapy and occupational therapy) on the motor outcomes of people with sub-acute stroke.

In that study, CIMT induced a significantly greater increase in the Quality of Movement in Motor Activity Log (MAL) score ($p<0.01$) and a significant reduction in the time needed to complete the Wolf Motor Function Test (WMFT) ($p<0.01$), compared to the conventional treatment program. Additionally, task-related training was also found to be superior to conventional therapy for rehabilitating upper limb function. Narayan et al. [7] found that 20 sessions of task-related upper limb training, including reaching and lifting objects with different shapes using the affected upper limb, were superior to dose-matched neurodevelopmental-based therapy as measured by the Fugl-Meyer Assessment of Upper Extremity (FMA-UE), WMFT, MAL and Action Research Arm Test (ARAT).

Bilateral upper limb training (BULT) is another stroke motor rehabilitation strategy in which the subjects are required to perform motor tasks with both upper limbs. Here, the unimpaired limb is used to increase the functional recovery of the impaired limb by facilitating coupling effects between the two limbs [14]. BULT includes bilateral functional task training [15-19], bilateral robotic-assisted training [20-22] and bilateral arm training with rhythmic cueing [23-25]. Several studies have indicated the superiority of BULT over various conventional therapies (including neurodevelopmental therapy [18, 26], occupational therapy [19, 27, 28], physiotherapy [17, 21, 28] and unilateral robotic-assisted training [20]) for improving the FMA-UE, WMFT, ARAT and MAL and the ranges of motion (ROM) of the shoulder, elbow and wrist joints in people with stroke.

Several clinical trials have also demonstrated the ability of BULT to improve hemiplegic arm functions [29-33]. In two systematic reviews [29, 32], combinations of BULT with other

therapies, such as electrical stimulation and auditory rhythmic cueing, effectively increased the functional WMFT scores of patients with acute to chronic stroke immediately after completion of the intervention. However, those reviews [29, 32] included single-group pre-post studies [34-39]. Moreover, the reviews [29, 32] did not directly compare the results of BULT and UULT in people with stroke and thus, were unable to demonstrate which approach more effectively improved the performance of the paretic upper limb, based on functional scales such as the FMA-UE, WMFT and ARAT.

By contrast, two recently published meta-analyses [33, 40] compare the abilities of BULT and UULT to improve the FMA-UE, WMFT, ARAT and MAL in people with stroke. Van Delden et al. [33] categorized studies according to the motor impairment level, as measured by the FMA-UE, Brunnstorm Stage, WMFT and ARAT. The results showed that UULT and BULT yielded similar improvement in the FMA-UE, WMFT, ARAT and MAL scores of people with stroke. Lee et al. [40] compared the effects of BULT with those of unilateral task-related training and CIMT during upper limb rehabilitation after stroke. Notably, CIMT was more effective than BULT in improving the WMFT and ARAT score. However, this finding should be interpreted cautiously because only three studies [16, 41, 42] were included in the meta-analysis.

Although CIMT can be used to train the paretic upper limb intensively, a direct comparison of the effects of CIMT and BULT on the rehabilitation of upper limb motor function in people with stroke may be inappropriate. First, CIMT requires the subjects to wear a constraint mitten on the unaffected upper limb and to perform intensive training for at least 6 hours per day [43]. Page

et al. [44] found that about 68% of subjects with stroke were unable to complete the full schedule of CIMT because of the training requirement and restrictive device. According to Blanton et al. [45], only 20-25% of patients with chronic stroke benefited from CIMT because of the tight training schedule and potential risk induced by the restricted training plan. By contrast, BULT has a lower training intensity. Patients are expected to complete approximately 1 to 2 hours of training per session on 3 to 5 days per week [24, 46], in contrast to the CIMT schedule of 6 hours of supervised task practice on each of 14 consecutive days [10, 47, 48]. Second, most CIMT studies applied stringent inclusion criteria, including at least 10 degrees of wrist extension, thumb abduction and finger extension on the affected side [49]. Compared with CIMT, BULT only requires people with stroke to maintain volitional control of the non-paretic arm, to be capable of flexing the paretic arm and shoulder and to have maintained the residual grip function of the paretic hand [18, 25]. CIMT is only applied to stroke survivors with mild to moderate levels of upper limb dysfunction. Thus, the exclusion of CIMT from a comparison of the effects of BULT and UULT in people with stroke would improve the validity of the quantitative results.

Although several meta-analyses [33, 40] have compared the effects of BULT and UULT in people with stroke according to the FMA-UE, WMFT and ARAT, these meta-analyses treated CIMT as a subtype of UULT and included it in comparison with BULT. To the best of our knowledge, no studies have excluded CIMT when comparing the effects of BULT and UULT in people with stroke. This systematic review and meta-analytical review aimed to evaluate the available randomized controlled trials (RCTs) that compared the effects of BULT and UULT, but excluding CIMT on improvements in the FMA-UE, WMFT and ARAT score of people after stroke.

Methodology

Study selection criteria

An exhaustive search of the literature was conducted to identify publications related to the effectiveness of BULT. The CINAHL, Medline, Embase, Cochrane Library and PubMed databases were searched systematically through April 2018 using the keywords listed in Table 1:

All identified full-text English language journal articles were screened independently by the two reviewers (PM and PK). The reference lists of the selected articles were then examined to identify additional potential articles. The inclusion criteria were applied to identify studies that (1) were randomized control trials; (2) reported quantitative behavior outcome measures; (3) had investigated the effects of interventions on upper limb function; (4) included an intervention group with bilateral movement training; (5) an intervention group with unilateral movement training or conventional occupational therapy or physiotherapy; and (6) included people with stroke. The following exclusion criteria were also applied: (1) the use of BULT in both the experimental and control groups; (2) failure to provide data on the outcome measures; (3) the studies with was a single session design; (4) systematic review or meta-analyses; and (5) inclusion of CIMT as the UULT.

Risk of bias

The methodological quality of the studies was assessed using the Cochrane Collaboration tool for assessing the risk of bias [50]. Studies that provided information clearly (i.e., randomized, subject-blinded) were rated as low risk for the corresponding items. If the study provided the information against the assessed items (i.e. non-randomized, not blinded), the study was rated as high risk for those items. If no information suitable for our judgment process was provided, the study was rated as unclear.

Data synthesis and analysis

Two reviewers (PM and PK) extracted the participants' demographic information (age, gender, post-stroke duration post stroke, type of lesion and side of hemiparesis), details of the intervention (type, intensity and duration) and outcome measures to identify the study characteristics. The third reviewer (SMN) made judgments if discrepancies occurred between the two reviewers. The International Classification of Functioning, Disability and Health (ICF), which is regarded as the international standard for evaluations of health and disability, was used to assess motor impairment and functional performance. The ICF can facilitate a more comprehensive understanding of the effectiveness of bilateral movement training during stroke rehabilitation and an optimal bilateral movement training scheme for improving upper limb function.

According to the ICF framework, the outcome measure for the meta-analysis was divided into two domains: (1) motor impairment and (2) functional performance. The effect size of each outcome was computed by calculating the mean difference (MD), standard mean difference

(SMD) and 95% confidence interval (CI), as appropriate. If a study did not provide the standard deviation (SD) of the MD or SMD, this value was estimated using the following formula, with the correlation coefficient (Corr) set to 0.8 [50]:

$$SD=\sqrt{SDpre^2 + SD\ post^2 - 2 \times Corr \times SDpre \times SDpost}$$

The results of the meta-analysis were then visualized using a forest plot (Review Manager 5.3; The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). To compare the effects of BULT and UULT during different phases of stroke, the included studies were classified as acute (mean post-stroke duration<1 month), sub-acute (mean post-stroke duration>1month to <1 year), chronic (mean post-stroke duration>1 year) or not reported.

To investigate the influence of treatment dosage on the effect size estimates, meta-regression analyses were performed using STATA 12.0 (Stata Corporation, College Station, TX, USA).

Publication Bias

Egger's test is more frequently used than other tests to detect publication bias in a meta-analysis [51]. Accordingly, Egger's test [52] was used to detect the probability of publication bias in this study.

Heterogeneity Test

The Higgins I^2 index was used to evaluate the heterogeneity of the studies. The I^2 boundary was set at 50%. A random effect model was used when I^2 >50%, indicating heterogeneity. A fixed effect model was used when I^2 <50%, indicating homogeneity [51].

Results

Study identification

The search strategy yielded 828 citations on April 10, 2018. After excluding duplicated articles, 375 potentially relevant articles were subjected to further screening via a review of the abstracts. During this meta-analysis, the third reviewer made judgments on two of the screened articles [15, 20] that were ultimately included. Finally, 21 full-text articles with 842 subjects fulfilled the eligibility criteria of the review. Details of the studies' identification, screening, eligibility and inclusion criteria are shown in Fig 1.

Fig 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart of study identification

Methodological quality

Fig 2 presents the methodological quality of the included studies as evaluated using the Cochrane Collaboration risk of bias assessment tool [50].

Fig 2 Risk of bias summary: A review of the authors' judgments about the risk of bias of each item in each included study

Characteristics of the subjects

Four studies [17, 21, 53, 54] compared the effects of BULT and UULT in subjects with acute stroke. Two studies [26, 46] compared the effects of BULT and UULT in people with sub-acute stroke. Thirteen studies [15, 16, 18, 19, 22-25, 28, 55-58] compared the effects of these rehabilitation strategies in subjects with chronic stroke. Two studies [20, 27] did not report details of the post-stroke duration. The demographic characteristics of the subjects and the characteristics of the studies are shown in Table 2 and 3, respectively.

Characteristics of the Intervention

Nine studies [15-18, 21, 27, 53, 54, 57] compared the effects of bilateral functional task training (e.g., folding a towel, lifting two cups and picking up two pegs bilaterally) and unilateral task-related training. Four studies [17, 21, 53, 54] compared these effects in people with acute stroke. Two studies [16,18] compared the effects of bilateral functional task training and dose-matched neurodevelopmental therapy, weight-bearing exercises and unilateral functional task training. Two studies [15, 57] compared the effects of bilateral functional task training and unilateral functional task training in people with chronic stroke. Lee et al. [27] investigated the combined effects of 30 minutes of bilateral functional arm training and 30 minutes of standardized occupational therapy, which included neurodevelopmental therapy, stretching exercises, resistance training and fine movement training of the affected upper limb. The outcomes of combined therapy were then compared with those after 60 minutes of standardized occupational therapy.

Seven studies [19, 20, 22, 24, 26, 46, 55] explored the effects of bilateral robotic-assisted or resistance training on upper limb motor function after stroke. Three studies [20, 24, 55] compared the effects of 90 minutes of bilateral robotic-assisted training and of 90 minutes of unilateral robotic-assisted training. Three studies [19, 22, 26] compared the effects of bilateral robotic-assisted training and of dose-matched unilateral functional task training in subjects with chronic stroke. Hsieh et al. [46] compared a combination of robotic-assisted priming and task-oriented training with task-oriented training alone on the affected upper limbs of patients with sub-acute stroke.

Five studies [23, 25, 28, 56, 58] compared the effects of bilateral arm training involving rhythmic auditory cueing with the effects of dose-matched unilateral upper limb training, which included neurodevelopmental therapy, upper limb mobilization, strengthening exercises and fine movement training.

Meta-analysis

Based on the measurement items categorized by the previous studies [59, 60], this review compared the overall effects of BULT and UULT on (1) improved motor impairment by pooling the results of the FMA-UE and on (2) functional performance by pooling the results of the WMFT, ARAT and the box and block test (BBT). The details of these outcome measures are presented in Table 4.

The meta regression indicated that the number of training sessions (p=0.947), total duration of training (p=0.217) and duration of training per session (p=0.316) had no significant impact on the effect size of FMA-UE.

Publication Bias

According to the results of Egger's test (Fig 3), no significant publication bias was shown in the meta-analysis of FMA-UE (p=0.774) or of WMFT, ARAT or BBT (p=0.950).

Fig 3 Results of Egger's test for the publication bias in motor impairment (above) and functional performance (below). SND: standard normal deviation, CI: confidence interval

Outcomes on Motor Impairment

In 16 studies [18-23, 25-28, 46, 54-58], the FMA-UE was used to measure improvements in stroke-induced motor impairment (Fig 4). The meta-analysis revealed a significantly greater improvement in motor impairment in the BULT group, compared with the UULT group (MD=2.21, 95%CI: 0.12 to 4.30, p=0.04; I^2=86%, p<0.001). However, no significant improvements were demonstrated with BULT when compared with UULT in the subgroups according to post-stroke duration (chronic: MD=2.03, 95%CI: -0.19 to 4.26, p=0.07; I^2=82%, p<0.001; subacute: MD=-1.58, 95%CI: -4.66 to 1.49, p=0.31; I^2=0%, p=0.55; acute: MD=4.01, 95%CI, -4.72 to 12.75, p=0.37; I^2=84%, p=0.01; not report: MD=3.63, 95%CI: -4.30 to 11.55, p=0.37; I^2=74%, p=0.05).

Figure 4 Differences in the mean (95%CI) effect of BULT relative to UULT in terms of FMA-UE, using pooled by pooling data from 16 studies. CI: confidence interval, IV: inverse variable, SD: standard deviation.

Functional Performance Outcomes

In this study, improvements in functional performance were assessed using the time component of WMFT and the WMFT, ARAT and BBT scores.

The improvement in functional performance was measured by the functional ability scores of the WMFT, ARAT and BBT in 12 studies (15-17, 19, 21, 24, 25, 27, 28, 46, 53, 54) (Fig 5). Among them, four studies [17, 21, 28, 53] investigated the improvement in functional ability by ARAT, four studies [16, 19, 24, 25] measured the functional ability score of the WMFT and four studies (15, 27, 46, 54) measured BBT. No significant difference was found between BULT and UULT in terms of improvements in the score component of the WMFT (SMD=0.25, 95%CI: -0.02 to 0.52; p=0.07; I^2=54%, p=0.02). Similarly, BULT did not yield significant improvement when compared with UULT in any of the post-stroke duration subgroups (chronic: SMD=0.34, 95%CI: -0.17 to 0.85, p=0.19; I^2=63%, p=0.03; subacute: SMD=-0.42, 95%CI: -1.13 to 0.30, p=0.25; acute: SMD=0.24, 95%CI: -0.12 to 0.59, p=0.19; I^2=52%, p=0.10; not report: SMD=0.68, 95%CI: -0.06 to 1.42, p=0.07).

Fig 5 Difference in the mean (95%CI) effect of BULT related to UULT on the measures of WMFT, ARAT and BBT in data pooled from 12 studies. CI: confidence interval, IV: inverse variable, SD: standard deviation.

Five studies [16, 23-25, 56] were used to evaluate the effect on improvement in the time required for the WMFT (Fig 6). A comparison of BULT and UULT revealed no significant difference in the time component of the WMFT (MD=0.44, 95%CI: -2.22 to 3.10; p=0.75; I^2=55%, p=0.06). Similarly, BULT did not yield a no significant improvement over UULT in the subgroups (chronic: MD=0.44, 95%CI, -2.22 to 3.10, p=0.75; I^2=55%, p=0.06).

Fig 6 Difference in the mean (95%CI) effect of BULT relative to UULT on the time component of WMFT in data pooled from 5 studies. CI: confidence interval, IV: inverse variable, SD: standard deviation.

Discussion

This is the first systematic review and meta-analysis to compare the effects of BULT and UULT on motor impairment and functional performance in people with stroke after excluding CIMT. The exclusion of CIMT may provide a more realistic overview of the effects of actual rehabilitation efforts. The meta-analysis examined the pooled results of 21 RCTs including 842 subjects with stroke. According to this analysis, BULT yielded significantly greater improvement in the FMA-UE, compared to UULT. However, no significant differences in the

change of functional performance as indicated by the WMFT, ARAT and BBT were found between BULT and UULT.

Motor Impairment

Our results are partially consistent with the findings of a review by Coupar et al. [30]. In that review [30] of two sets of four studies, the authors found that BULT was more effective than the usual care in terms of improving the FMA-UE scores in people with stroke. However, Coupar and colleagues [30] found no differential effects between BULT and UULT in terms of improving the FMA-UE score [17, 26, 65, 66]. Our inclusion and exclusion criteria enabled us to include 4 studies [17, 23, 26, 54]from the review by Coupar and 12 other RCTs in our meta-analysis. Thus, our review may have elicited more robust estimations of the overall effects of BULT and UULT on improvements in the FMA-UE.

Two reviews [33, 40] found that BULT and UULT yielded similar reductions in motor impairment in people with stroke, as indicated by the FMA-UE score. However, these results should be interpreted cautiously because van Delden [25, 42, 65, 66] and Lee [25, 42, 65, 67] each reviewed four studies to estimate the effects of BULT and UULT on the FMA-UE. In contrast, our meta-analysis on FMA-UE was based on 16 RCTs, and included a larger sample size. Our review would therefore have a stronger power to detect a difference between BULT and UULT in terms of an improved FMA-UE score. The reviews by Lee [40] and van Delden [33] also included two studies [42, 66] that compared the effects of BULT and CIMT on improved FMA-UE scores. In

our study, we only compared BULT with task-related training. This heterogeneity in the study samples explains the different conclusions of our review and the other two reviews.

Our review demonstrated a significantly greater improvement in the FMA-UE scores of people with stroke after BULT, compared with UULT. Moreover, we found no significant association of the training dosage with the improvements in FMA-UE. Therefore, the different levels of improvement between BULT and UULT was mainly attributable to the types of intervention (BULT/UULT). The excitability typically decreases in the lesional cerebral hemisphere and increases in the contralesional hemisphere [68-70]. TMS studies [67, 71-73] have indicated that this restoration of interhemispheric imbalance positively correlates with motor recovery after stroke. Accordingly, the different levels of improvement in the FMA-UE scores after BULT and UULT may be related to the use of different mechanisms to facilitate the reorganization in the lesional hemisphere. UULT is based on the principle of activation in the lesional hemisphere via assisted or resisted unilateral training of the paretic limb [8, 74, 75]. Compared with UULT, BULT activates similar neural networks in the bilateral hemispheres during the simultaneous activation of homologous muscle groups [14, 76-78]. Studies have shown that BULT can activate the distributed corticospinal pathway bilaterally via ipsilateral corticospinal fibers [79-81], contralateral corticospinal fibers [82-84] and the corpus callosum[85, 86]. Compared with UULT, BULT may evoke greater activation of the lesional hemisphere by recruiting more neural pathways [14]. In the BULT group, increased activation in the lesional hemisphere might have led to greater improvements in motor impairment, as indicated by the FMA-UE scores.

Functional Performance

Consistent with the findings of previous reviews [33, 40], our meta-analysis indicated that BULT was not superior to UULT in terms of improving the functional performance of people with stroke, as measured by the WMFT, ARAT and BBT. Although we found a significantly greater improvement in the FMA-UE with BULT than with UULT, we found no significant differences in functional performance between the training strategies. Buchner [87] reported a non-linear relationship between leg strength and gait speed in people with stroke. This curve revealed a positive slope that gradually decreased to zero; in other words, the curve eventually reached a plateau, as the leg strength increased. A muscle strength threshold is required to perform each type of activity. However, increased strength does not result in an improved gait speed until a certain threshold is reached [88]. Similarly, the improvement in the FMA-UE score and the functional performance may also exhibit a non-linear relationship. Although previous studies [62, 89-91] reported a moderate to good correlation between the FMA-UE and functional performance-related scales (e.g., WMFT, ARAT and BBT), the non-linear relationship found between these factors in our meta-analysis may reflect an inability of the stroke survivors to achieve the motor control threshold needed to perform the functional tasks. Although the FMA-UE improved to a significantly greater level in the BULT group when compared with the UULT group, this significant improvement may have been insufficient to yield a significant improvement in functional performance.

Our meta-analysis revealed that bilateral functional task training tended to yield a larger SMD for improving functional performance, compared to bilateral robotic-assisted training and bilateral arm training with auditory cueing. However, this result should be interpreted cautiously because although our meta-analysis included 9 of studies [15-18, 21, 27, 53, 54, 57] on bilateral functional task training (the largest proportion), it also included only 7 studies [19, 20, 22, 24, 26, 46, 55] of bilateral robotic-assisted training and 5 studies [23, 25, 28, 56, 58] of bilateral arm training with auditory cueing. Therefore, the inclusion of more studies of bilateral robotic-assisted training and bilateral arm training with auditory cueing would support more robust conclusions regarding the effects of the different types of BULT. Moreover, we used WMFT, ARAT and BBT to estimate improvements in functional performance. The items included in these evaluation tools, such as gripping objects, folding a towel and lifting objects, are similar to the components of bilateral functional task training. Accordingly, there may be a stronger learning effect in the studies that investigated bilateral functional task training, compared to those that investigated bilateral robotic-assisted training and bilateral arm training with auditory cueing.

This systematic review had several limitations. First, we only examined 21 studies with 842 subjects. This sample size may not have been sufficiently large to detect significant differences in the functional performance outcomes. Second, the results of this review may not be generalizable to all stroke survivors. In addition to the 13 studies [15, 16, 18, 19, 22-25, 28, 55-58] of people with chronic stroke included in this study, only 4 studies [17, 21, 53, 54] of people with acute stroke and 2 studies [26, 46] of people with sub-acute stroke investigated the effects of BULT. Therefore, the true effect of BULT may be underestimated because of the small number of included non-chronic stroke studies. The inclusion of more studies with subjects in different phases of stroke

would increase the generalizability of our conclusions. Third, most studies of Asian populations reported a significant improvement after BULT, compared with UULT. By contrast, most studies conducted in western countries reported insignificant differences between BULT and UULT. However, the reason underlying this discrepancy remains unclear. In future reviews, clear methodological information and a larger sample size may help to explain this phenomenon. Fourth, we only evaluated the immediate effects of the outcome measures. Our meta-analysis did not calculate the carry-over effects of BULT and UULT in terms of improving the FMA-UE, WMFT, ARAT and BBT score, as only 29% of the studies [17, 26, 28, 46, 53, 57] included in our review provided data from the follow-up assessments. Thus, our findings may not provide sufficient power to estimate the carry-over effects of BULT and UULT in people with stroke. These carry-over effects should be explored further. Fifth, the studies included in this review did not classify the severity of the motor impairment experienced by people with stroke. Therefore, we did not have sufficient information to analyze the effects of BULT and UULT with respect to the severity of the motor impairment.

Conclusions

Both BULT and UULT can help to improve motor impairment and functional performance after stroke. Notably, BULT was superior to UULT in terms of improving motor impairment after stroke, as measured by the FMA-UE. However, BULT and UULT yielded similar effects on functional performance in people with stroke, as measured by the WMFT, ARAT and BBT.

Author Contributions

Conceptualization: PC, SMN. Formal Analysis: PC, PWHK. Funding Acquisition: SMN. Methodology Writing – Review & Editing: PC, SMN, PWHK, CKYL. Writing – Original Draft Preparation: PC.

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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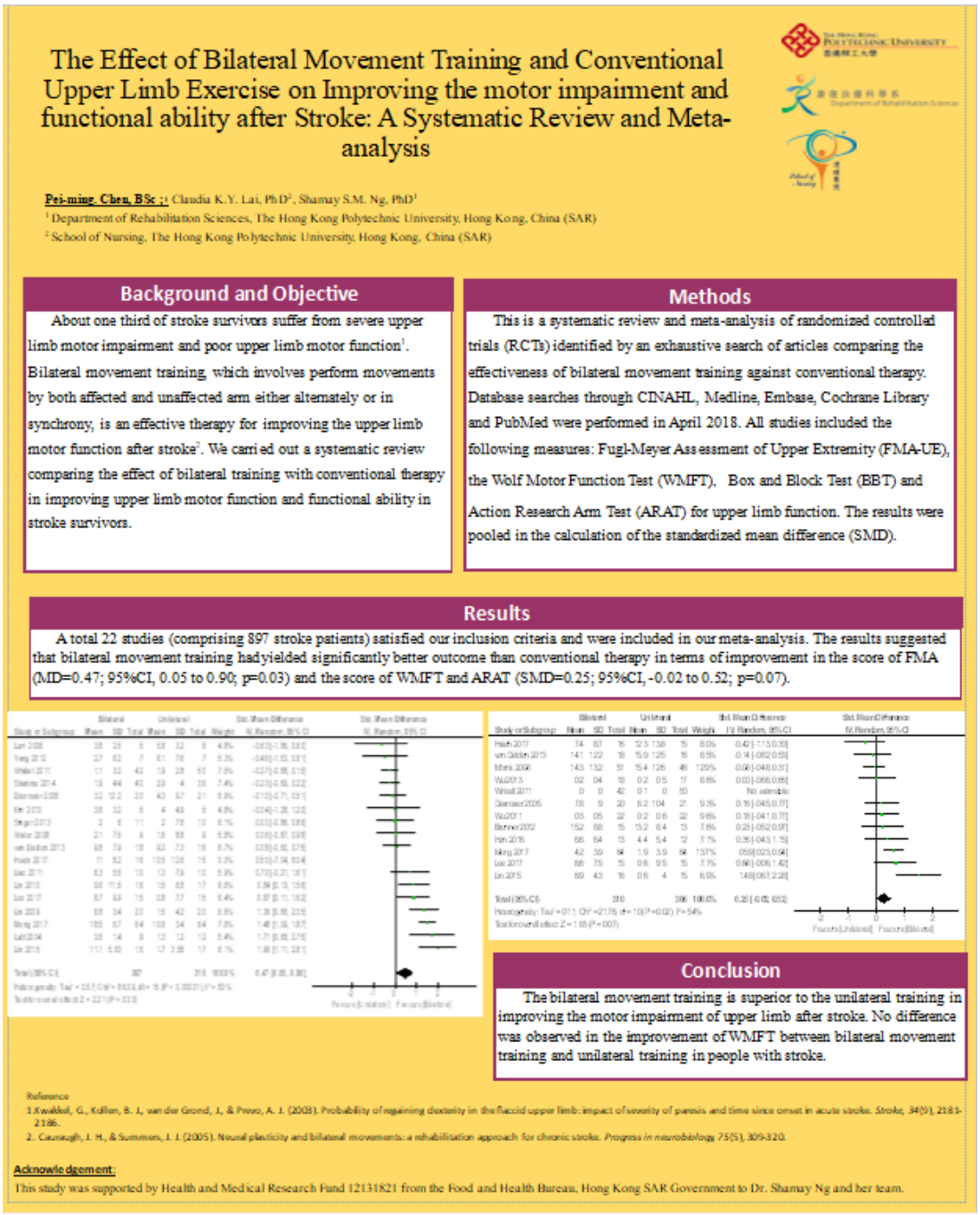
Appendix 3.2 The poster of "The Effect of Bilateral Movement Training and Conventional Upper Limb Exercise on Improving the Motor Impairment and Functional Ability after Stroke: A Systematic Review and Meta-analysis" demonstrated in *11th Pan-Pacific Conference on Rehabilitation.*



The Effect of Bilateral Movement Training and Conventional Upper Limb Exercise on Improving the motor impairment and functional ability after Stroke: A Systematic Review and Meta-analysis

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Background and Objective

About one third of stroke survivors suffer from severe upper limb motor impairment and poor upper limb motor function[1]. Bilateral movement training, which involves perform movements by both affected and unaffected arm either alternately or in synchrony, is an effective therapy for improving the upper limb motor function after stroke[2]. We carried out a systematic review comparing the effect of bilateral training with conventional therapy in improving upper limb motor function and functional ability in stroke survivors.

Methods

This is a systematic review and meta-analysis of randomized controlled trials (RCTs) identified by an exhaustive search of articles comparing the effectiveness of bilateral movement training against conventional therapy. Database searches through CINAHL, Medline, Embase, Cochrane Library and PubMed were performed in April 2018. All studies included the following measures: Fugl-Meyer Assessment of Upper Extremity (FMA-UE), the Wolf Motor Function Test (WMFT), Box and Block Test (BBT) and Action Research Arm Test (ARAT) for upper limb function. The results were pooled in the calculation of the standardized mean difference (SMD).

Results

A total 22 studies (comprising 897 stroke patients) satisfied our inclusion criteria and were included in our meta-analysis. The results suggested that bilateral movement training had yielded significantly better outcome than conventional therapy in terms of improvement in the score of FMA (MD=0.47; 95%CI, 0.05 to 0.90; p=0.03) and the score of WMFT and ARAT (SMD=0.25; 95%CI, -0.02 to 0.52; p=0.07).

Conclusion

The bilateral movement training is superior to the unilateral training in improving the motor impairment of upper limb after stroke. No difference was observed in the improvement of WMFT between bilateral movement training and unilateral training in people with stroke.

Reference
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Appendix 4.1 Chapter 4 manuscript to *BMC Neurology* (Final manuscript)

Self-perceived performance in upper limb movement predicts the upper limb motor functions in people with stroke

INTRODUCTION

Upper limb function refers to the performance of the upper limbs in the activities or tasks of daily life [1]. At least one-third of people with stroke experience impaired upper limb motor function 6 months after their stroke [2-4] due to muscle weakness, abnormal muscle tone or poor upper limb coordination [5]. Improving upper limb function and reducing the associated negative impacts in daily life are often the main goals of stroke rehabilitation [6, 7].

The Action Research Arm Test (ARAT) is a reliable and valid upper limb-specific instrument for evaluating upper limb motor function in patients having neurological disorders [8-10]. In the ARAT, upper limb function is operationalized as the ability to grip, grasp, pinch and perform gross arm movements with objects of different sizes, weights and shapes. The ARAT has been used with people after traumatic brain injury [11] and stroke [12, 13] and with those suffering from multiple sclerosis [14, 15].

Previous studies [16, 17] have revealed that motor impairment limits the paretic upper limb's functioning after a stroke. Muscle weakness, abnormal reflexes and motor coordination

quantified using the Fugl-Meyer Assessment for the upper extremities (FMA-UE) were all significantly correlated with upper limb motor function after a stroke (r=0.770–0.925)[14, 18, 19]. Furthermore, Kwakkel and Kollen et al. have shown [20] that motor control of hand as measured using the FMA is the best predictor of improvement in ARAT results after a stroke (β=0.357; p<0.001), while motor control of arm , leg and balance ability shows minimal predictive power (β < 0.007; p<0.001). However, the relative contribution of motor control in hand has not been quantified, and the role of self-perceived performance has not been addressed.

Self-perceived performance is a personality trait as how well and satisfied the subject thinks their performance is [21] rather than objective performance in the real life. The low level of self-perceived performance was significant associated with the objective performance in people with stroke [22, 23]. Low level of self-perceived performance discourages using a paretic upper limb, which impedes recovery of the limb's motor skills, leading to even less self-perceived performance, and a downward spiral in upper limb functioning. Eventually, the objective performance would be demoted gradually by low self-perceived performance. A study has demonstrated a significant and moderate to good correlation (r=0.63, p<0.001) between self-perceived performance measured by Motor Activity Log (MAL) about upper limb movement and the functioning of a paretic upper limb measured by ARAT after a stroke [24]. In addition, Brogardh et al. [22] found self-perceive limitations in their walking ability is significantly associated with their objective walking ability quantitated by the Walk-12 and the 4 gait performance tests in people with chronic stroke.

According to the World Health Organization's International Classification of Functioning, Disability and Health [25], body function is an interplay of physiological and psychological functions of body systems. Although the relationship between upper limb motor control and upper limb function has been well investigated, the predictive ability of psychological factor—self-perceived performance in using the upper limbs—has not been investigated among people with stroke. This study was therefore designed to determine whether self-perceived performance about upper limb movement makes an independent contribution to the paretic upper limb motor functions after a stroke, and if so to quantify its relative contribution when motor control of hand and sociodemographic factors are also considered.

METHODS

Subjects

A total of 87 subjects were self-selected through poster advertising among local self-help groups. Those included were between 50 and 80 years of age, had been diagnosed with stroke for at least 1 year, had volitional control of the non-paretic arm, at least minimal anti-gravity movement in the shoulder of the paretic arm and were able to understand Cantonese. They had at least 5º of wrist extension in the anti-gravity position and scored ≥7 (out of 10) on the Cantonese version of Abbreviated Mental Test [26].

People were excluded if they had any additional medical, cardiovascular or orthopedic condition (e.g. angina pectoris), had receptive dysphasia, had visual impairment that could not be

corrected by glasses (e.g. hemianopia), had a significant upper limb peripheral neuropathy, had severe shoulder, elbow, wrist or finger contractures that would preclude a passive range of motion of the arm, or were involved in drug studies or other clinical trials.

Ethical approval was obtained from the Ethics Committee of the Hong Kong Polytechnic University. The study was conducted in accordance with the Declaration of Helsinki [27].

Data collection

The assessments were performed in a university-affiliated neurorehabilitation laboratory. After obtaining the subjects' informed written consent, they completed a sociodemographics questionnaire and then were tested with all the outcome measures in random order. All of the tests were administered by a physiotherapist with 5 years of clinical experience. All instruments used have been validated in the local context

Measures

Quality of Movement (QOM) subscale of MAL (MAL-QOM)

Self- perceived performance in using a paretic upper limb was evaluated using MAL-QOM. The QOM consists of 30 items quantifying the subject's self-perceived performance in using a paretic upper limb in life situations in the past week by semi-interview, such as turning on a light and brushing the teeth [28]. Each item of the 30 items was rated as 0 (never), 1 (very

poor), 2 (poor), 3 (fair), 4 (almost normal) or 5 (normal). Higher scores indicate higher self-perceived performance in using the paretic upper limb. The QOM has demonstrated good test-retest reliability (ICC=0.82) [29] and excellent internal consistency (Chronbach's α=0.87) [30] in testing people with stroke.

Action Research Arm Test (ARAT)

The ARAT [31] was used to assess each subject's paretic upper limb motor function. It is a 19-item measure with ratings on a 3-point ordinal scale (0–3) with a total score 57. Higher scores indicate higher motor function of the paretic upper limb. It can objectively quantify a subject's ability to grasp, grip, pinch and perform gross arm movements. The ARAT has demonstrated excellent intra-rater (r=0.996–0.997) and inter-rater (r=0.989) reliability when administered to people with stroke [32].

Hand section of Fugl-Meyer Assessment (FMA-hand)

Motor control of hand was assessed using the hand subscale of the Fugl-Meyer assessment. It consists of 7 items (items 24 through 30 of the full upper limb assessment) with a total score of 14. It assesses motor control of finger flexion and extension, thumb adduction, finger opposition, cylinder grip and spherical grip using ratings of 0, 1 or 2. Higher scores indicate better motor control of the paretic hand. The entire FMA-UE has shown excellent intra-rater (Intraclass Correlation Coefficient **(**ICC)=0.984–0.993) and inter-rater (ICC=0.995–0.996) reliability when used to assess people with stroke [33].

Statistical analysis

The data analysis was conducted using version 22.0 of the Statistical Package for the Social Sciences software (SPSS Inc, Chicago, IL, USA). Descriptive statistics were compiled summarizing the demographic information. The Kolomogorov-Smirnov test was used to evaluate the normality of the data's distribution. Pearson and Spearman correlation coefficients were computed to evaluate the strength of any relationships among the variables as appropriate. To control for the sociodemographic differences, partial correlation coefficients were calculated for the scores from the FMA-hand and QOM tests. The relative contributions of the FMA-hand and QOM scores in predicting the ARAT scores was determined by evaluating multiple linear regressions with the forced entry method. The significance level was set at 0.05 (two-tailed).

RESULTS

Characteristics of the participants

Thirty-seven men (43%) and fifty women (57%) with a mean age of 61.12±6.88 years and a mean BMI of 24.07±3.79kg/m^2 were recruited. Their mean post-stroke duration was 6.31±2.84 years. Among them, forty-seven (54 %) had left hemiplegia and forty (46%) had right hemiplegia. Forty-nine of the subjects had suffered an infarct stroke while the other thirty-eight had strokes which were hemorrhagic. Seven of the subjects lived alone; the others lived with family. Sixty-eight of the subjects used a walking aid; the others could walk without an aid. The

subjects' mean FMA-UE score was 34.51±11.69. The mean FMA-hand score was 7.55±2.84 and the mean QOM score was 39.35±37.77 (Table 1).

Relationships between ARAT scores and the other independent variables

The mean ARAT score of 23.76±16.62 indicates a moderate level of upper limb motor function [34]. The ARAT scores were significantly correlated with the use of a walking aid (r=0.397, $p<0.001$), the FMA-hand (r=0.663, $p<0.001$) and QOM scores (r=0.648, $p<0.001$) (Table 2). Partial correlation coefficients relating the ARAT scores with the FMA-hand and MAL-QOM results were also computed controlling for the use of a walking aid. The correlations remained strong and significant: r=0.689, $p<0.001$ for the FMA-hand data and r=0.610, $p<0.001$ for the QOM scores (Table 3).

Contributions of FMA-hand and MAL-QOM scores to ARAT scores

Table 4 shows the abilities of different variables to predict ARAT scores as determined by multiple linear regression analysis with the forced entry method. After controlling for use of a walking aid and FMA-hand results, the multiple linear regression modeling showed that MAL-QOM results could independently predict an additional 10.8% of the variance in ARAT scores. The addition of MAL-QOM scores significantly improved the models' predictive power, as indicated by the magnitude of the standardized regression coefficient (β=0.362) and Pearson correlation coefficient (r=0.648, $p<0.001$). A total of 65.5% of the variance in the ARAT scores was predicted by the final regression model ($F_{3,83}=52.466$, $p<0.001$). The FMA-hand score was

the best predictor of ARAT scores as indicated by the magnitude of the standardized regression coefficient (β=0.480) (model 3, table 4) and the highest Pearson correlation coefficient (r=0.663, p<0.001).

DISCUSSIONS

Summary

To the best of our knowledge, this has been the first study revealing that MAL-QOM independently contributes to ARAT performance in a paretic upper limb after a stroke. The study's findings add to the current knowledge about the roles of MAL-QOM in determining ARAT after a stroke. The clinical implication is that enhancing self-perceived performance could be helpful in promoting better upper limb function among people with stroke.

Performance of ARAT and MAL-QOM after a stroke

A previous study [34] classified upper limb function into no capacity (ARAT score: 0–10), poor capacity (11–21), limited capacity (22–42), notable capacity (43–54) or full capacity (ARAT score 55–57). In this study the people with stroke's mean score was 23.76, indicating only limited upper limb function. Compared with the subjects in this study, that in Van der Lee et al's study [32] which showed comparable level of motor function with mean ARAT scores of 29.2. The consensus today is that most of the observed spontaneous recovery occurs within the first few months after a stroke [35]. Spontaneous recovery [36, 37] during the acute phase has been

completed and the similar subjects' demographic data of two studies could explained why they had comparable ARAT scores.

The mean total MAL-QOM score was 39.35±37.77 in this study, which means that the average score on each item was 1.31. According to the guideline [29], the mean MAL-QOM score represents quite a low level of self-perceived performance among this study's subjects. This study's findings are comparable with those of two other studies [24, 38] of people with stroke. One study [38] showed a comparable MAL-QOM mean score of 1.5 on each item in their severely-impaired group (FMA<44). The mean MAL-QOM score in the study [24] led by Van der Lee was 1.37 on each item and the median ARAT score was 30.0. The low MAL-QOM score could possibly influence the willingness to use the paretic upper limb, which may lead to decreased usage of the upper limb. In the long term, the motor control of upper limb would be worsening due to lacking of practice of the paretic upper limb which could impede recovery of the upper limb motor function. Finally, the poor motor function would result in downward spiral in MAL-QOM score.

MAL-QOM score predicts ARAT performance

This study's final model (Table 4) predicted two-thirds of the variance in the ARAT scores. FMA-hand and MAL-QOM were useful independent predictors of the ARAT scores, accounting for 39.0 % and 10.8% of the variance in the scores, respectively. These findings are consistent with those of previous studies showing that motor control of hand quantified using the FMA-hand score is associated with upper limb motor function measured using the ARAT among

people with stroke [20, 39]. But these findings demonstrate that, in addition to the level of paretic upper limb motor control measured using the FMA-hand instrument, MAL-QOM score serves as an independent predictor of people with stroke's ARAT scores. Our finding consisted with previous study [40] that physical motor function has a positive correlation with the self-perceive quality in daily life in health older adults.

In Bandura's theory [41] decisions about activity and behavior could be influenced by beliefs about the ability to engage in them successfully. Bandura and Adams suggest that the influence is partly cognitive where people predict specific behavioral consequences and their attitudes are based on those cognitions [41]. The people with stroke who highly satisfied with their self-perceived performance were more likely to use their paretic upper limb in their daily lives. The more amount of practice of the paretic upper limb would help them maintain or even improve the level of upper limb motor control which eventually result in better upper limb motor function. Conversely, the people with stroke who have low level of self-perceived performance would be more probably to avoid using their paretic upper limb. The low usage of the paretic side would deteriorate the upper limb motor control in the long term [42] and finally decrease the upper limb motor function.

Note, however, that about a third of the variance in the ARAT scores remained unexplained. A possible reason is that several psychological and physical factors were not included in the model. Fatigue is an obvious one [43, 44]. Depression is another [45]. Subjects with upper limb dysfunction may well find many daily activities exhausting, which would have a

negative impact on their self-perceived performance in attempting them. How fatigue, depression and other psychological factors impact self-perceived performance and upper limb function should be explored in a future study.

Then there are physical factors such as upper limb muscle weakness [46], spasticity [47], limited range of motion [48], impaired sensation [16] and the hand dominance prior to the stroke [38]. All have been shown to influence ARAT performance after a stroke. Harris and Eng [38] have shown that hand dominance can be particularly influential. People with stroke whose dominant hand was affected demonstrated less disability in activities of daily living such as zipping, buttoning and eating than those whose non-dominant hand was affected.

Correlations of ARAT scores

The analyses showed that whether using a walking aid was a significant predictor of ARAT scores, while age, gender, BMI, post-stroke duration, paretic side, type of stroke and living situation showed no significant predictive power, despite the fact that the ARAT focuses entirely on upper limb motor function. The explanation could be that not using a walking aid indicates good leg motor control. It has been reported that better motor control of leg is positively associated with better upper limb recovery [39]. That would tend to explain the seemingly-strange correlation observed here.

In terms of the type of stroke, to the best of our knowledge, there was no study investigating the association between type of stroke and upper limb function in people with chronic stroke. A previous study [20] has shown that the type of stroke is significantly associated with changes in ARAT scores in the acute stage. The inconsistent result in this study could be explained by the different post-stroke stages of the subjects, which should influence the progress of neural recovery. A group led by Andersen has reported [49] that a hemorrhagic stroke is more likely to have a poorer prognosis in acute phase than an ischemic one, because the lesion is generally more extensive. However, as spontaneous recovery progresses, the two types of people with stroke may regain comparable levels of upper limb function. That would tend to explain the significant association between ARAT score and type of stroke found in this study.

Clinical implications

These findings indicate that at a given level of upper limb motor control, self-perceived performance in upper limb movement makes an important contribution to the quality of paretic upper limb motor function. The physiotherapist may therefore usefully add a component to the rehabilitation program aimed at enhancing self-perceived performance in upper limb movement. The objective of the training is to retain the daily usage of the paretic upper limb in the daily living and unlearn habits of nonuse molded by poor self-perceived performance so that improve motor control and motor function. For example, physiotherapists could incorporate “graded” activity training into customary physical training in which people with stroke would boost their activation in using the paretic side by getting positive feedback on functionally relevant improvements and, in turn, leading to improvement in self-perceived performance [50].

Limitations

The study's final model could account for only 65.5% of the total variance in the ARAT scores, leaving one-third unexplained. Future studies should look into other factors such as depression and mental fatigue. Also, this was a cross-sectional study, so that no causal relationships could be verified. Further longitudinal study should be conducted to determine the strength of any causal relationship between ARAT performance and MAL-QOM score. Then, the study's subjects were all Chinese. They were recruited from a self-help group and self-selected. That always raises the possibility that they were untypically active, relatively unimpaired and thus not really typical even of Hong Kong's people with stroke. Some strict inclusion criteria were also applied, which tends to further limit the generalizability of the results. At last, this was a pilot study to investigate the contribution of MAL-QOM on ARAT. In order to draw a more reliable conclusion, repeated measured should be proposed in the future.

CONCLUSION

Consistent with the results of previous studies, the level of hand motor control was found to contribute the most to the quality of the upper limb functioning. The data show, however, that self-perceived performance is also a significant predictor of paretic upper limb functioning. Therefore, improving self-perceived performance in using a paretic upper limb could be an important way to further enhance upper limb motor function after a stroke. Further studies aimed at enhancing self-perceived performance are warranted.

Funding

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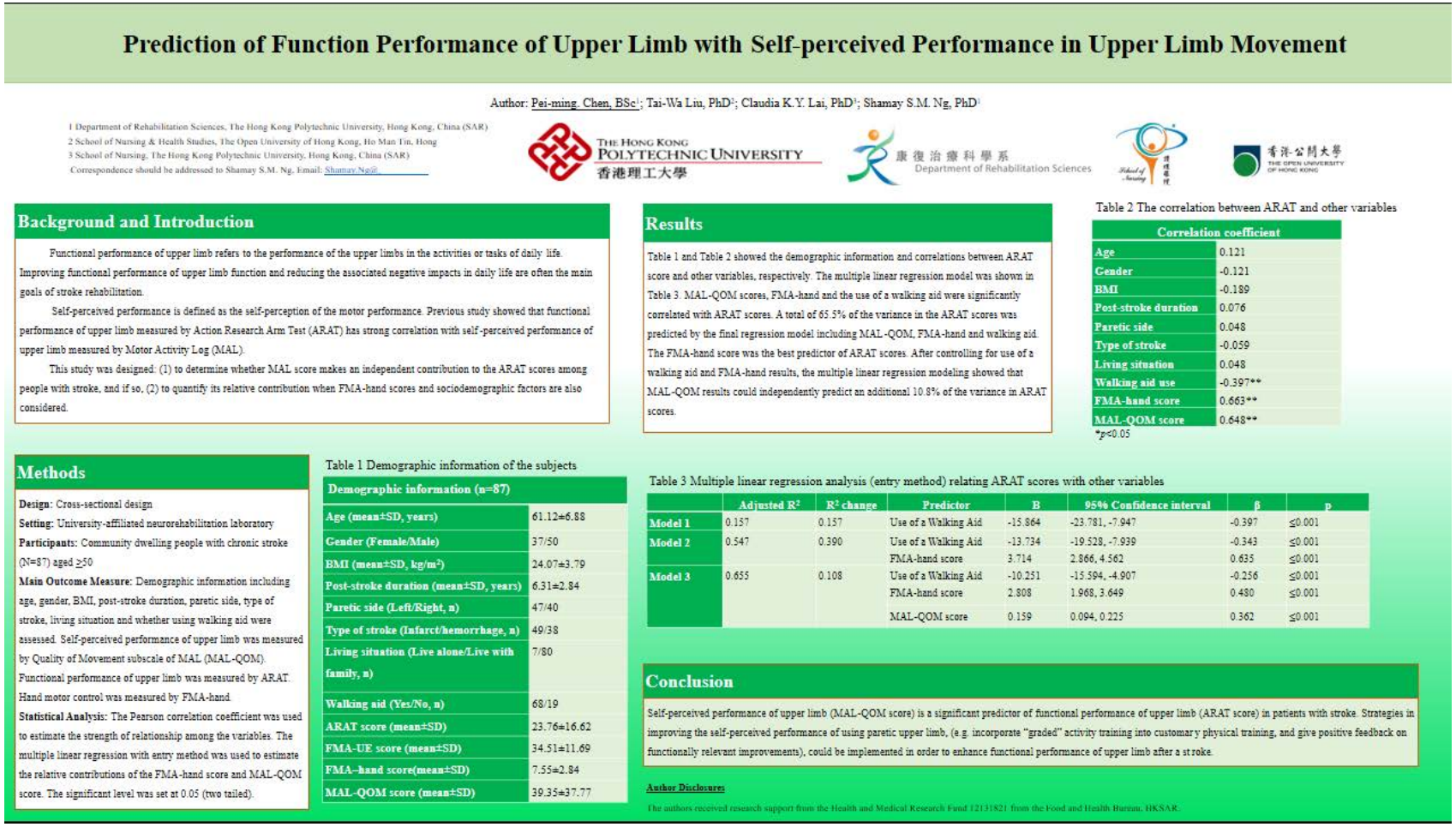
Appendix 4.2 The poster of "Prediction of Paretic Upper Limb Motor Function with Self-perceived Performance in Upper Limb Movement." submitted to *98th Annual Conference American Congress of Rehabilitation Medicine*.



Prediction of Function Performance of Upper Limb with Self-perceived Performance in Upper Limb Movement

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Background and Introduction

Functional performance of upper limb refers to the performance of the upper limbs in the activities or tasks of daily life. Improving functional performance of upper limb function and reducing the associated negative impacts in daily life are often the main goals of stroke rehabilitation.

Self-perceived performance is defined as the self-perception of the motor performance. Previous study showed that functional performance of upper limb measured by Action Research Arm Test (ARAT) has strong correlation with self-perceived performance of upper limb measured by Motor Activity Log (MAL).

This study was designed: (1) to determine whether MAL score makes an independent contribution to the ARAT scores among people with stroke, and if so, (2) to quantify its relative contribution when FMA-hand scores and sociodemographic factors are also considered.

Methods

Design: Cross-sectional design
Setting: University-affiliated neurorehabilitation laboratory
Participants: Community dwelling people with chronic stroke (N=87) aged ≥50
Main Outcome Measure: Demographic information including age, gender, BMI, post-stroke duration, paretic side, type of stroke, living situation and whether using walking aid were assessed. Self-perceived performance of upper limb was measured by Quality of Movement subscale of MAL (MAL-QOM). Functional performance of upper limb was measured by ARAT. Hand motor control was measured by FMA-hand.
Statistical Analysis: The Pearson correlation coefficient was used to estimate the strength of relationship among the variables. The multiple linear regression with entry method was used to estimate the relative contributions of the FMA-hand score and MAL-QOM score. The significant level was set at 0.05 (two tailed).

Table 1 Demographic information of the subjects

Demographic information (n=87)	
Age (mean±SD, years)	61.12±6.88
Gender (Female/Male)	37/50
BMI (mean±SD, kg/m²)	24.07±3.79
Post-stroke duration (mean±SD, years)	6.31±2.84
Paretic side (Left/Right, n)	47/40
Type of stroke (Infarct/hemorrhage, n)	49/38
Living situation (Live alone/Live with family, n)	7/80
Walking aid (Yes/No, n)	68/19
ARAT score (mean±SD)	23.76±16.62
FMA-UE score (mean±SD)	34.51±11.69
FMA--hand score(mean±SD)	7.55±2.84
MAL-QOM score (mean±SD)	39.35±37.77

Results

Table 1 and Table 2 showed the demographic information and correlations between ARAT score and other variables, respectively. The multiple linear regression model was shown in Table 3. MAL-QOM scores, FMA-hand and the use of a walking aid were significantly correlated with ARAT scores. A total of 65.5% of the variance in the ARAT scores was predicted by the final regression model including MAL-QOM, FMA-hand and walking aid. The FMA-hand score was the best predictor of ARAT scores. After controlling for use of a walking aid and FMA-hand results, the multiple linear regression modeling showed that MAL-QOM results could independently predict an additional 10.8% of the variance in ARAT scores.

Table 2 The correlation between ARAT and other variables

	Correlation coefficient
Age	0.121
Gender	-0.121
BMI	-0.189
Post-stroke duration	0.076
Paretic side	0.048
Type of stroke	-0.059
Living situation	0.048
Walking aid use	-0.397**
FMA-hand score	0.663**
MAL-QOM score	0.648**

*p<0.05

Table 3 Multiple linear regression analysis (entry method) relating ARAT scores with other variables

	Adjusted R^2	R^2 change	Predictor	B	95% Confidence interval	β	p
Model 1	0.157	0.157	Use of a Walking Aid	-15.864	-23.781, -7.947	-0.397	≤0.001
Model 2	0.547	0.390	Use of a Walking Aid	-13.734	-19.528, -7.939	-0.343	≤0.001
			FMA-hand score	3.714	2.866, 4.562	0.635	≤0.001
Model 3	0.655	0.108	Use of a Walking Aid	-10.251	-15.594, -4.907	-0.256	≤0.001
			FMA-hand score	2.808	1.968, 3.649	0.480	≤0.001
			MAL-QOM score	0.159	0.094, 0.225	0.362	≤0.001

Conclusion

Self-perceived performance of upper limb (MAL-QOM score) is a significant predictor of functional performance of upper limb (ARAT score) in patients with stroke. Strategies in improving the self-perceived performance of using paretic upper limb, (e.g. incorporate "graded" activity training into customary physical training, and give positive feedback on functionally relevant improvements), could be implemented in order to enhance functional performance of upper limb after a stroke.

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Appendix 5.1 Chapter 5 Manuscript published in *Disability & Rehabilitation* (Final Manuscript)

The Jacket Test for Assessing People with Chronic Stroke

Introduction

Stroke is the second most frequent cause of death and the leading cause of disability worldwide after cardiovascular disease [1]. A World Health Report (2004) reveals that stroke causes approximately 5.5 million deaths annually with the loss of 44 million disability-adjusted life-years [2]. The incidence of stroke doubles with each decade of life after the age of 55 [3].

Up to 70% of people with chronic stroke need physical or occupational therapy in the initial phrase of rehabilitation due to paresis in their upper and/or lower limbs [4]. More than 60% of people with stroke fail to regain full upper limb function within 6 months post-stroke [5]. Upper extremity dysfunction is of course a major barrier to return to normal daily activity [6]. Efficient use of the upper limbs for reaching and grasping is required in more than half of the activities of daily living (ADL) [7], including dressing, cooking and eating. Compared with the lower limbs, upper extremity function is more essential for resuming independent living and regaining self-esteem [8, 9].

The Physical Performance Test (PPT) was originally developed to assess multiple domains of physical function in the elderly [10]. The scale has 9 items which cover many daily living activities: writing a sentence, simulated eating, lifting a book and putting it on a shelf, putting on and removing a jacket, picking up a coin from the floor, turning 360 degrees, a 50-

foot walk test, climbing one flight of stairs and climbing four flights of stairs. Rozzini and colleagues suggested that PPT results are independently associated with some chronic diseases in elderly people (with regression coefficients ranging from -2.34 to -9.00) [11], including stroke, cardiac disease and Parkinsonism. Brown and colleagues suggested defining scores of 32–36 as not frail, 25–31as mild frailty and 17–24 as moderate frailty. A score less than 17 is taken to indicate that an individual is unlikely to function well in the community [12].

Putting on and removing a long-sleeved jacket is one of the items in the PPT. The subject is required to don jacket or a cardigan sweater such that it is straight on his or her shoulders, and then remove it completely [10]. The time for completing the task is recorded. This Jacket Test can be used to evaluate the functional mobility of the upper limbs, as the test involves abduction of the shoulder joint, flexion and extension of the elbow joint and gripping with the hands.

The Jacket Test has great potential in assessing the proficiency of upper limb use in daily activities for people with chronic stroke. Compared with other existing upper extremity measurement scales, the Jacket Test consists of functional movement of daily living which only takes less than a minute to complete. However, no published study has yet assessed the test's reliability and validity with stroke survivors. The objectives of this study were to examine the test's intra-rater, inter-rater and test-retest reliability and any correlation of Jacket Test times with the results of other stroke-specific impairment assessments including the Fugl-Meyer upper extremities assessment (FMA-UE), grip strength, the 5-times sit-to-stand (FTSTS) test, the Berg Balance Scale (BBS), the timed "up and go" (TUG) test and the Community Integration Measure (CIM). Another objective was to determine an optimal cut-off time for the Jacket Test that best

discriminates people with stroke from healthy older adults and to quantify the minimal detectable change (MDC) for the completion time among stroke survivors.

Methods

Subjects

A previous study has demonstrated an Intra-class Correlation Coefficient (ICC) value of 0.90 for the PPT performance in assessing the elderly people with mobility impairment [13]. A sample of 27 subjects with 2 observations per subject can therefore achieve 80% power to detect an ICC value of 0.9 under alternative hypothesis for test-retest reliability at a significance level of 0.05.

This study was cross-sectional in design. Twenty-eight subjects with chronic stroke were recruited from a local self-help group for stroke survivors. Subjects with stroke were included if they (1) were aged between 50 and 85 years, (2) had suffered a stroke at least 1 year previously; (3) had an Abbreviated Mental Test score ≥7; (4) had volitional control of the non-paretic arm, and at least minimal anti-gravity movement in the shoulder of the paretic arm and wrist; and (5) were in a stable medical condition that allowed them to complete the test protocol successfully.

Candidate subjects were excluded if they (1) were unable to use an upper limb because of musculoskeletal problems (usually arthritis or frozen shoulder); (2) had an acute or terminal illness; (3) had a cognitive disorder caused by severe disorders of the central nervous system (usually Parkinson's disease or Alzheimer's disease); or (4) had any additional medical, cardiovascular or orthopedic condition, which would hinder proper assessment.

Thirty healthy older adults who met the criteria were recruited from local community centers. Healthy controls were included if they (1) were aged 50 or older; (2) were able to complete the Jacket Test; (3) were able to understand and comply with verbal commands; (4) were not concurrently involved in any drug study or other clinical trial; and (5) did not have any additional medical, cardiovascular or orthopedic condition, which would hinder proper assessment.

The ethics committee of the Hong Kong Polytechnic University approved the study protocols as meeting all of the guidelines set by the Declaration of Helsinki. The objectives of the study were clearly explained to all of the subjects, and all gave written informed consent prior to the testing.

Procedure

The structure of data collection and analysis are shown in fig 1. The subjects with stroke were assessed twice one week apart (Day 1 and Day 2). The Jacket Test would be assessed on Day1 and Day 2. The FMA-UE, FTSTS test, BBS, TUG test and CIM were administered and their maximum hand grip strength was assessed on Day 1. The order of the test was randomized by drawing lots. At least 2 minutes of rest was allowed after each test in order to minimize any effect of fatigue. The healthy controls took only the Jacket Test on Day 1.

Outcome measurements

The Jacket Test

On the command “Go”, the subject was required to put on completely a long-sleeved lab coat so that it was straight on his or her shoulders and then to remove it completely [11]. In our study, the time from the command to when the garment had been completely removed in the standing stance was recorded using a stopwatch. Buttoning or zipping up the jacket is not required in our study.

The test was completed thrice in each session. The time of affected-side Jacket Test time was from inserting the affected arm first to finishing the rest part. The time of unaffected-side and affected-side Jacket Test time was from inserting the unaffected arm and affected arm first to finishing the rest part, respectively. The time of dominant-side and non-dominant Jacket Test time was from inserting the dominant arm and non-dominant arm first to finishing the rest part, respectively.

Fugl-Meyer Upper Extremity Assessment

The FMA-UE is a comprehensive, quantitative measure of motor function in terms of isolated movement and synergy. It tests volitional movement, reflex activity and coordination. It has excellent test-retest reliability (ICC≥0.98) in subjects with chronic stroke [14]. The FMA-UE consists of 33 items, and each item is scored on a 0–2 scale, giving a maximum possible score of 66. Higher scores indicate less motor impairment.

Hand grip strength

Griping movement is required in completing the Jacket Test as it helps to grip the jacket tightly and insert the arm straight into the long sleeve of the jacket. Grip strength [15] was measured using a Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA) with the standardized positioning and instructions recommended by the American Society of Hand Therapists. Excellent test-retest reliability (ICC=0.80–0.89) has been reported in people with chronic stroke [16]. The subjects were seated with their shoulders adducted and neutrally rotated, the elbow flexed at 90°, the forearm in a neutral position and the wrist in 0 to 30° of flexion and between 0 and 15° of ulnar deviation. In that position the testees were instructed to squeeze the dynamometer as hard as possible for 5 seconds with the standardized verbal reinforcement of 'Harder! ... Harder! ... Relax'. The subjects were asked to firstly complete three trails with the unaffected hand and then completed three trails with affected hand. Between each trial, 2 minutes' rest interval was provided. The means of the three trials of unaffected and affected hand were used in the data analysis.

Five-times sit-to-stand test

The standing balance ability is one of the essential conditions for the Jacket Test performed successfully, as subject needs to put on and off the jacket in standing position. The FTSTS test measures lower extremity muscle strength and standing balance in the transition from sitting to standing and back [17]. Excellent reliability (ICC≥0.97) has been reported among subjects with chronic stroke [17]. At the beginning the subject sat with his/her back against the back of a chair with a seat height 45cm. The subject was then asked to stand up and sit down 5 times as quickly as possible. The time from the command "Go" to the subject's reaching the standing position on the 5th repetition was recorded using a stopwatch.

Berg's Balance Scale

The BBS [18] is designed to quantify functional balance, as balance is an essential condition for performing upper limb function in standing position. Excellent reliability [ICC=0.95] had been demonstrated in subjects with chronic stroke [19]. The BBS consists of 14 items, and each item scored on a 0–4 scale, giving a maximum possible score of 56. Higher scores indicate less motor impairment.

Timed "up and go" test

The TUG test [20] assesses functional mobility. It has demonstrated excellent test-retest reliability (ICC=0.95) in assessing stroke survivors [21]. Initially, the subject sat on the chair with a seat height of 46cm. The subject was then required to stand up, walk 3 meters, turn back, walk to the chair, turn again and sit down. The time from "Go" command to the subject's sitting down again was recorded using a stopwatch.

Community Integration Measure

The Jacket Test is an ADL task in itself. The Chinese version of the Community Integration Measures (CIM) was used to assess each subject's level of community integration, including general assimilation, support, occupation and independent living. The Chinese version of CIM has 10 items with each item rating on a five-point scale, giving a maximum score of 50. Higher score indicates better community integration [22]. The performance of ADL is expected

to affect the degree of CIM. The CIM has shown good internal consistency (Cronbach's α=0.84) and test-retest reliability (ICC=0.84) among people with chronic stroke [22].

Statistical analysis

All the statistics were calculated using version 17 of the SPSS software suite (SPSS Inc, Chicago, IL, USA). Descriptive statistics were compiled describing the subjects' demographic characteristics. Model 3 ICCs (ICC3,1 and ICC3,2) were used to quantify the degree of intra-rater and inter-rater consistency, respectively. The subjects are considered as a random effect and rater is considered as a fixed effect. The test-retest reliability of the observations was estimated using ICC model 2 (ICC2,1), where both the raters and subjects were considered as random effects with a single rating [23]. An ICC<0.250 was considered as describing little or no correlation, ICC=0.250–0.500 was defined as fair, ICC=0.500–0.750 was termed moderate to good, and ICC=0.750–1.000 was regarded as good to excellent [23].

The Kolmogorov-Smirnov test was used to determine whether or not the data were normally distributed. Pearson correlation coefficients were calculated relating the Jacket Test times with the outcomes of the other tests (FMA-UE, grip strength, BBS, FTSTS, TUG, and CIM) when the data were normally distributed. Otherwise, Spearman correlation coefficients were used.

The significance of the differences in mean Jacket Test times of the healthy control and chronic stroke groups were assessed using independent t-tests. The differences within the stroke and healthy control groups were compared using paired t-tests.

The minimal detectable change in the Jacket Test completion time was calculated by using the test-retest reliability and standard deviation of the Jacket Test time in the following formula [23]:

$$MDC=1.96\times SEM \times \sqrt{2}$$

where

$$SEM=S_x \sqrt{1 - rxx}$$

and S_x is the standard deviation of the Jacket Test times and r_{xx} is the reliability coefficient. The 1.96 in the MDC equation is used to determine the 95% confidence interval(95%CI). The product of SEM multiplied by 1.96 is multiplied by the square root of 2 to account for errors associated with repeated measurement.

To discriminate the Jacket Test performance of subjects with stroke from that of the healthy controls, receiver operating characteristics (ROC) curves were constructed. The curve is a plot of "sensitivity" versus "specificity" for all the possible cut-off points which might distinguish the performance of the two groups [24]. The optimum cut-off times were sought using the Youden Index for the trade-off between sensitivity and specificity [25]. The area under an ROC curve (AUC) quantifies the accuracy of the Jacket Test in discriminating the healthy controls from subjects with chronic stroke based on their times. All the analyses were performed on the hypothesis that the AUC was 0.5 [23,26].

Results

Demographic data describing 28 subjects with chronic stroke (18 male and 10 female; mean age ± SD=57.6 ± 5.1; mean post-stroke duration± SD=7.5 ± 4.8 years) and the 30 healthy controls (11 male and 19 female; mean age ± SD=61.8 ± 5.7 years) are shown in Table 1. Significant gender difference(p=0.036) can be found between the two groups. Table 2 presents the outcome of Jacket Test. Table 3 presents the within group comparisons and between group comparisons of Jacket Test. The mean values of all of the outcome measures are shown in Table 4.

The data in Table 5 show good to excellent intra-rater, inter-rater and test-rest reliability (ICC=0.781–1.000) of the Jacket Test times in the subjects with chronic stroke. The MDC (95% CI) in the Jacket Test times for affected and unaffected side were 12.64s and 24.79s, respectively.

Table 6 shows the correlations between the Jacket Test times and the other outcome measures. Significant correlations were found between unaffected-side JT times and FMA-UE results, affected-side grip strength, BBS, CIM scores (r=-0.386 to -0.750), and TUG times (r=0.556). The affected-side JT times also correlated with affected-side maximum hand grip strength (r=-0.615).

The optimal cut-off time (Fig. 2 and 3) was determined to be 18.33s (sensitivity 96.7%; specificity 85.7%; AUC=0.965; p<0.001) when the affected arm is inserted first and 18.38s(sensitivity 96.7%; specificity 94.4%; AUC=0.995; p<0.001) with the unaffected arm inserted first.

Discussion

This study has been the first to investigate the intra-rater, inter-rater and test-retest reliability of the Jacket Test among people with chronic stroke and to determine the cut-off time which best distinguishes the performance of those with stroke from the healthy older adults.

Reliability of the Jacket Test in stroke evaluation

Consistent with results of a previous study of the Physical Performance Test [13], the Jacket Test showed excellent reliability in this study. A previous study led by King [13] revealed the PPT's excellent inter-rater (ICC=0.96) and test-retest (ICC=0.88) reliability with the healthy elderly. Sufficient training provided to the assessors, clear instructions and standardized protocols might contribute to the high reliability observed here with stroke survivors. Between two adjacent trials, 2 minutes' rest was provided to minimize any fatigue effects. In stroke group, the interval of 1 week between sessions was apparently sufficient to minimize any learning effect [27,28].

Performance of the Jacket Test in stroke evaluation

There is no previous study investigating the performance of the Jacket Test among stroke survivors. In this study, the mean completion times of the stroke group (affected: 28.6s; unaffected 125.1s) were significantly longer than those of the healthy controls (dominant:14.2s; non-dominant:13.6s). The MDC in Jacket Test times was 12.64s on the affected side and 24.79s on the unaffected side. The difference in mean Jacket Test times between the two groups was far

greater than the MDC on both affected and unaffected sides. The different means apparently reflected real differences, not measuring error. This could be explained by the muscle weakness, poor coordination [29] and disorganized motor unit pool activation [30] after stroke, which seriously impair motor function in the upper limbs.

The Jacket Test completion times of the healthy controls observed in this study (mean: 13.6–14.2s) were slightly longer than those observed in Donnell's study [31] (mean: 12.90–13.43s). This might due to the differences in the gender proportions between the two studies. All of Donnell's subjects were males, while most of the subjects here (63.3%) were women. The performance of functional tasks and the muscle strength of older males has been demonstrated to be better than that of older females in previous studies [32,33]. The Jacket Test includes the coordinated movement of shoulder, elbow, wrist and even the lower limb muscle in order to accomplish the whole task. The known gender effect on muscle strength might influence the performance of the Jacket Test completion time.

Correlation between the Jacket Test times and other outcome measures

The FMA-UE is commonly used to assess volitional movement, reflex activity and coordination. The Jacket Test assessed proficiency in dressing, which involves combined movement of shoulder, elbow, wrist and hand, so it was reasonable to expect good to excellent correlation between the two tests. Grip strength on the affected side showed significant correlation with the Jacket Test times. A study led by has Soham demonstrated that, among older people, poorer maximum hand grip strength is an independent predictor of poorer ADL performance, such as dressing skill [28]. So the significant correlation is not unexpected.

No significant correlation could be found between FTSTS times and the Jacket Test times. The FTSTS test mainly measures functional lower extremity muscle strength and dynamic balance [17]. Although the Jacket Test required the subjects to complete the task while standing, it mainly focused on the coordination of upper limb movement.

Unaffected-side Jacket Test times were both significantly correlated with both BBS scores and TUG test times. The TUG test and the BBS are reliable measurement tools for assessing functional mobility and functional balance respectively. The Jacket Test requires static balance in a standing position while putting on and removing the jacket. When the subjects performed the affected-side Jacket Test, some compensatory strategies might be conducted, such as using the unaffected side to help complete the major part of inserting the affected side into the sleeve, which might mask some of the balance performances. That might explain the significant correlations observed with the unaffected-side Jacket Test times but not with that of affected-side.

The CIM scores did, though, show a fair to moderate positive correlation with the unaffected-side Jacket Test times. A previous study has found that skill in dressing is one of the most important aspects of independent functioning for persons with profound disability [34]. The moderate correlation could be explained by the fact that the Jacket Test is closely related to ADL competence.

Cut-off time for the Jacket Test

This study also attempted to calculate the optimal cut-off Jacket Test time for distinguishing the performance of healthy older adults from people with chronic stroke. There was no significant difference between dominant and non-dominant Jacket Test times in the healthy control. Thus, the Jacket Test time of affected and unaffected side in the stroke group were compared with the mean of dominant and non-dominant Jacket Test time in the healthy control respectively. The optimal cut-off times of 18.33s on the affected side and 18.38s on the unaffected side were determined to discriminate best.

The AUCs of the Jacket Test times ranged from 0.965 to 0.995, which means that the Jacket Test time can give better than 95% accuracy in discriminating people with stroke from healthy older adults. The Jacket Test times showed both high sensitivity and specificity when assessing both upper limbs, which suggests that the Jacket Test has great potential as a clinical screening and diagnostic instrument for discriminating people with stroke from the healthy older adults.

Clinical Implication of the Jacket Test

Dressing, as an important independent functional task of daily living, has been an indispensable skill to help the people with stroke to return to a normal daily life [35]. Although the ability to dress is included in some assessment tools about activities of daily living [36,37], those assessment tools take a longer duration to complete in clinical situations [36, 37]. In addition, those measurement tools only focus on whether the participants could perform dressing, but overlook the detail of dressing skill. The Jacket Test, thus, could provide a quantitate result to assess the upper limb motor functions while performing daily functional task. Furthermore, the Jacket Test is easy to administrate and has low time

cost. These could increase the values in using the Jacket Test in clinical situations to assess upper limb functions in people with stroke.

Limitations

The Jacket Test emphasizes speed in donning a jacket; it does not assess the quality of the movement. The compensatory strategies used in putting on a jacket should also be a focus in testing, but the test is not designed to do that. A standardised lab coat had been used in this study, the size and style of the lab coat might affect the strategy selected of completing the task. The sample size in this research was based on previous reliable findings, but in retrospect it may have been insufficient to detect significant correlations between certain Jacket Test results and other outcome measures. Further investigation with larger sample size would be essential for prediction and multiple regression analysis, and establishing the Jacket Test times in stroke survivors of different mobility levels.

Each subject performed the test 3 times, introducing the possibility of learning and fatigue effects which might have had some impacts on the results. There was also a significant difference ($p<0.05$) in the gender proportions between the stroke and healthy groups. Gender-related differences in muscle strength [38] and functional task skill [31,32] have been reported in previous studies. With more data added in the future, the gender bias could be eliminated. Note too that our findings and the cut-off times provided here are only applicable to people with chronic stroke and healthy older adults who fulfil the study's inclusion criteria. The present study could not establish any causal relationship between the variables because of its cross-sectional design.

Conclusion

The Jacket Test has good to excellent intra-rater, inter-rater and test-rest reliability when used for measuring the upper limb function of people with chronic stroke. The Jacket Test times significantly correlate with FMA-UE scores, BBS scores, TUG test times and maximum hand grip strength on the affected side. Completion times of 18.33s on the affected side and 18.38s on the unaffected side effectively discriminate people with chronic stroke for the healthy older adults.

The Jacket Test is a reliable and valid measuring tool which can be applied in the clinic to evaluate the upper extremity function of people with chronic stroke.

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Appendix 5.2 The abstract of "The Jacket Test: Its Reliability and Correlations with Upper Extremity Motor Functions in People with Chronic Stroke" published in the *11th International Symposium on Healthy Aging*

P45 **The Jacket Test: Its Reliability and Correlations with Upper Extremity Motor Functions in People with Chronic Stroke**

PM Chen[1], *CKY Lai* [2] *and SSM Ng*[1]

[1]*Department of Rehabilitation Sciences,* [2]*School of Nursing, The Hong Kong Polytechnic University, Hong Kong*

Background: The Jacket Test (JT) is an outcome measure to assess the use of upper limbs in putting on and off a jacket. The JT is one of the seven items in the Physical Performance Test, which is used to evaluate the overall physical function in older adults. The JT completion time records the time taken in putting on the long-sleeve jacket straight on their arms, and to undress it completely. The affected and unaffected JT completion times are the mean completion time of firstly putting on and off the jacket via affected arm and unaffected arm, respectively.

Objective: To examine: (1) the intra-rater, inter-rater and test–retest reliabilities of JT completion times; (2) the Minimal Detectable Change (MDC) for the JT completion times; (3) the correlation of JT completion times with stroke-specific impairments and functional mobility; and (4) the cut-off JT times which best discriminates people with stroke from healthy elderly.

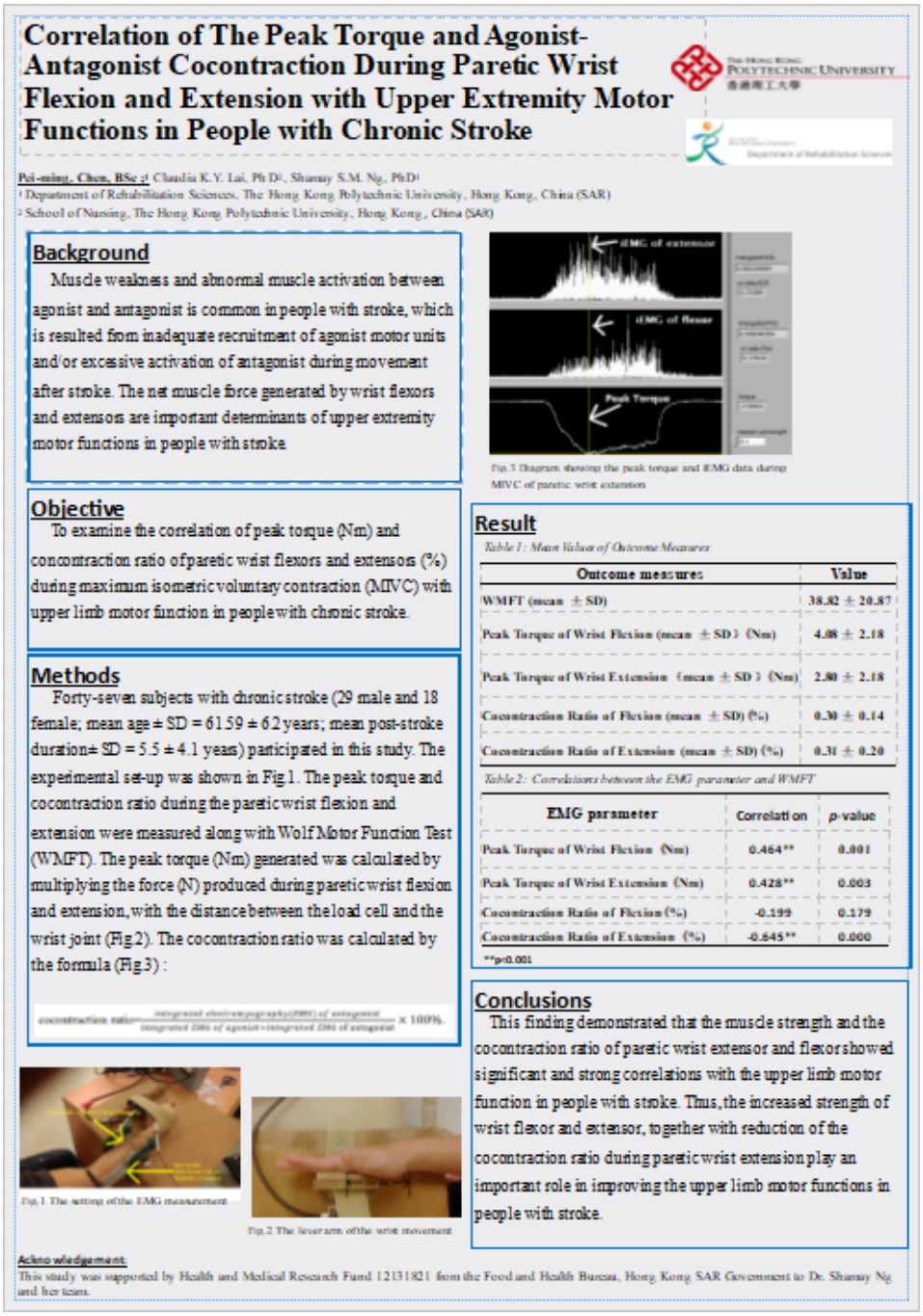
Methods: Twenty-eight subjects with chronic stroke (18 male and 10 female; mean age ± SD = 57.6 ± 5.1; mean post-stroke duration± SD = 7.5 ± 4.8 years) and thirty healthy older subjects (11 male and 19 female; mean age ± SD = 61.8 ± 5.7 years) participated in this study. The JT completion time were measured along with Fugl-Meyer Upper Extremity Assessment (FMA-UE), hand grip strength, 5- times Sit-to-stand (FTSTS), Berg Balance Scale (BBS) and timed up and go (TUG) time, Short Form-36(SF-36).

Results: The JT completion time showed excellent intra-rater, inter-rater and test-retest reliability (ICC = 0.781-1.000). The MDC (affected: 12.64s; unaffected: 24.79s) were obtained for JT completion times. The unaffected JT completion times significantly correlated with FMA-UE score (r=-0.750), affected hand grip strength, BBS score (r=-0.424), TUG times (r=0.556). The affected JT completion times significantly correlated with affected hand grip strength (r=-0.400). Both affected and unaffected JT completion times showed no correlation with SF-36 scores. The cut-off time of 18.33s in affected side and 18.38s for unaffected side (sensitivity 96.7%; specificity 85.7%-96.4%) to best discriminate the subjects with stroke and healthy older adults.

Conclusions: JT completion times showed excellent intra-rater, inter-rater and test-rest reliabilities. The unaffected JT completion time showed significant correlation with FMA-UE, affected hand grip strength, BBS and TUG scores, while the affected JT completion time showed significant correlation with affected hand grip strength. In conclusion, JT is a reliable, easy-to-administer clinical tool to evaluate the upper extremity function in people with chronic stroke.

Acknowledgement:
This study was supported by Health and Medical Research Fund 12131821 from the Food and Health Bureau, Hong Kong SAR Government to Dr. Shamay Ng and her team.

Appendix 5.3 The poster of "Correlation of The Peak Torque and Agonist-Antagonist Cocontraction During Paretic Wrist Flexion and Extension with Upper Extremity Motor Functions in People with Chronic Stroke" submit to *12th International Symposium Healthy Aging*



Correlation of The Peak Torque and Agonist-Antagonist Cocontraction During Paretic Wrist Flexion and Extension with Upper Extremity Motor Functions in People with Chronic Stroke

Pei-ming, Chen, BSc [1] Claudia K.Y. Lai, Ph D[1], Shamay S.M. Ng, PhD[1]

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Background

Muscle weakness and abnormal muscle activation between agonist and antagonist is common in people with stroke, which is resulted from inadequate recruitment of agonist motor units and/or excessive activation of antagonist during movement after stroke. The net muscle force generated by wrist flexors and extensors are important determinants of upper extremity motor functions in people with stroke.

Fig.3 Diagram showing the peak torque and iEMG data during MIVC of paretic wrist extension

Objective

To examine the correlation of peak torque (Nm) and concontraction ratio of paretic wrist flexors and extensors (%) during maximum isometric voluntary contraction (MIVC) with upper limb motor function in people with chronic stroke.

Methods

Forty-seven subjects with chronic stroke (29 male and 18 female; mean age ± SD = 61.59 ± 6.2 years; mean post-stroke duration± SD = 5.5 ± 4.1 years) participated in this study. The experimental set-up was shown in Fig.1. The peak torque and cocontraction ratio during the paretic wrist flexion and extension were measured along with Wolf Motor Function Test (WMFT). The peak torque (Nm) generated was calculated by multiplying the force (N) produced during paretic wrist flexion and extension, with the distance between the load cell and the wrist joint (Fig.2). The cocontraction ratio was calculated by the formula (Fig.3) :

$$\text{cocontraction ratio} = \frac{\text{integrated electromyography (iEMG) of antagonist}}{\text{integrated iEMG of agonist + integrated iEMG of antagonist}} \times 100\%$$

Result

Table 1: Mean Values of Outcome Measures

Outcome measures	Value
WMFT (mean ± SD)	38.82 ± 20.87
Peak Torque of Wrist Flexion (mean ± SD) (Nm)	4.08 ± 2.18
Peak Torque of Wrist Extension (mean ± SD) (Nm)	2.80 ± 2.18
Cocontraction Ratio of Flexion (mean ± SD) (%)	0.30 ± 0.14
Cocontraction Ratio of Extension (mean ± SD) (%)	0.31 ± 0.20

Table 2: Correlations between the EMG parameter and WMFT

EMG parameter	Correlation	p-value
Peak Torque of Wrist Flexion (Nm)	0.464**	0.001
Peak Torque of Wrist Extension (Nm)	0.428**	0.003
Cocontraction Ratio of Flexion (%)	-0.199	0.179
Cocontraction Ratio of Extension (%)	-0.645**	0.000

**p<0.001

Conclusions

This finding demonstrated that the muscle strength and the cocontraction ratio of paretic wrist extensor and flexor showed significant and strong correlations with the upper limb motor function in people with stroke. Thus, the increased strength of wrist flexor and extensor, together with reduction of the cocontraction ratio during paretic wrist extension play an important role in improving the upper limb motor functions in people with stroke.

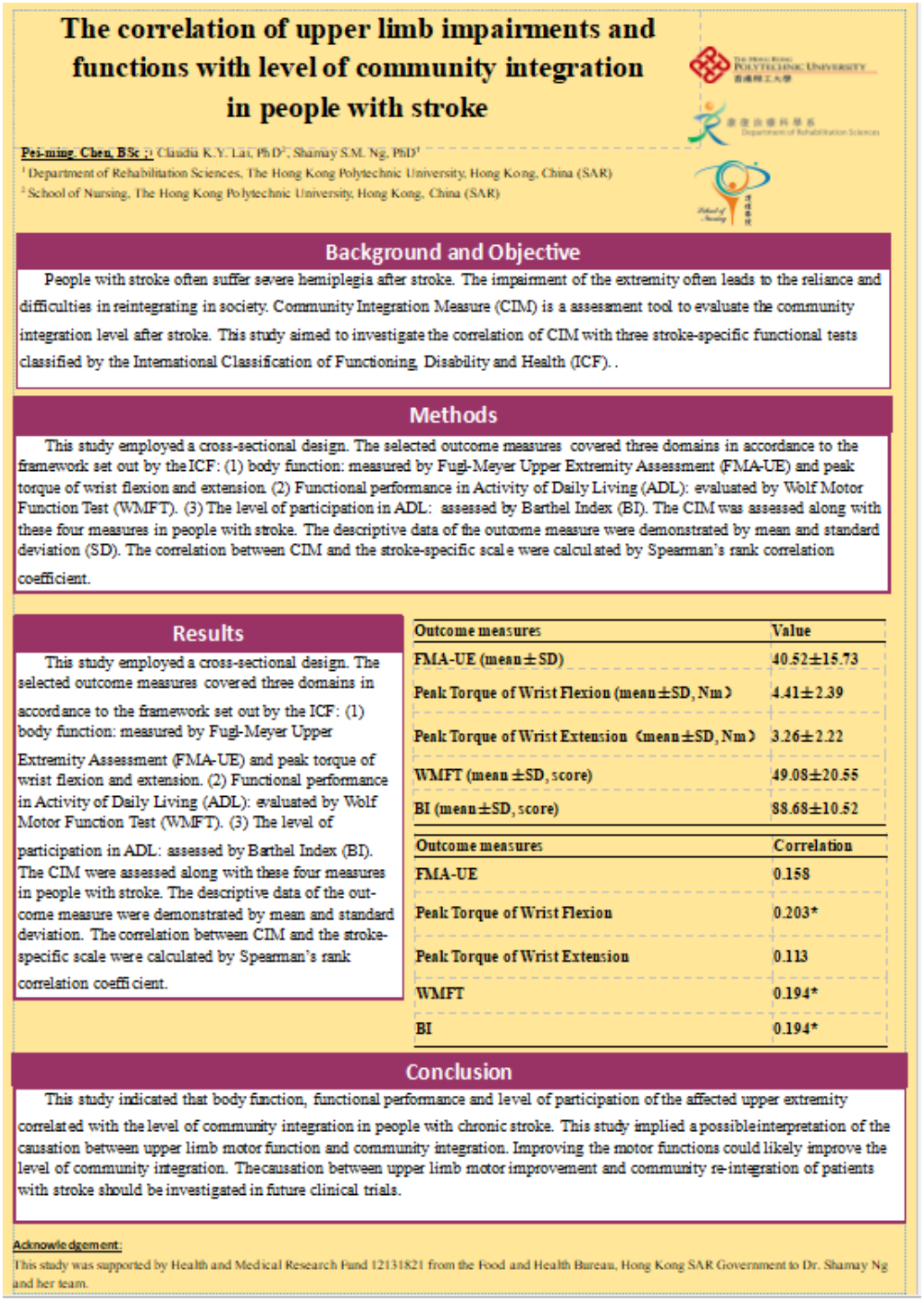
Fig.1 The setting of the EMG measurement

Fig.2 The lever arm of the wrist movement

Acknowledgement:

This study was supported by Health and Medical Research Fund 12131821 from the Food and Health Bureau, Hong Kong SAR Government to Dr. Shamay Ng and her team.

Appendix 5.4 The abstract of "The Correlation of Upper Limb Impairments and Function with Level of Community Integration in People with Stroke" submit to *11th Pan-Pacific Conference on Rehabilitation*



The correlation of upper limb impairments and functions with level of community integration in people with stroke

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[1] Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, China (SAR)

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Background and Objective

People with stroke often suffer severe hemiplegia after stroke. The impairment of the extremity often leads to the reliance and difficulties in reintegrating in society. Community Integration Measure (CIM) is a assessment tool to evaluate the community integration level after stroke. This study aimed to investigate the correlation of CIM with three stroke-specific functional tests classified by the International Classification of Functioning, Disability and Health (ICF). .

Methods

This study employed a cross-sectional design. The selected outcome measures covered three domains in accordance to the framework set out by the ICF: (1) body function: measured by Fugl-Meyer Upper Extremity Assessment (FMA-UE) and peak torque of wrist flexion and extension. (2) Functional performance in Activity of Daily Living (ADL): evaluated by Wolf Motor Function Test (WMFT). (3) The level of participation in ADL: assessed by Barthel Index (BI). The CIM was assessed along with these four measures in people with stroke. The descriptive data of the outcome measure were demonstrated by mean and standard deviation (SD). The correlation between CIM and the stroke-specific scale were calculated by Spearman's rank correlation coefficient.

Results

This study employed a cross-sectional design. The selected outcome measures covered three domains in accordance to the framework set out by the ICF: (1) body function: measured by Fugl-Meyer Upper Extremity Assessment (FMA-UE) and peak torque of wrist flexion and extension. (2) Functional performance in Activity of Daily Living (ADL): evaluated by Wolf Motor Function Test (WMFT). (3) The level of participation in ADL: assessed by Barthel Index (BI). The CIM were assessed along with these four measures in people with stroke. The descriptive data of the outcome measure were demonstrated by mean and standard deviation. The correlation between CIM and the stroke-specific scale were calculated by Spearman's rank correlation coefficient.

Outcome measures	Value
FMA-UE (mean±SD)	40.52±15.73
Peak Torque of Wrist Flexion (mean±SD, Nm)	4.41±2.39
Peak Torque of Wrist Extension (mean±SD, Nm)	3.26±2.22
WMFT (mean±SD, score)	49.08±20.55
BI (mean±SD, score)	88.68±10.52

Outcome measures	Correlation
FMA-UE	0.158
Peak Torque of Wrist Flexion	0.203*
Peak Torque of Wrist Extension	0.113
WMFT	0.194*
BI	0.194*

Conclusion

This study indicated that body function, functional performance and level of participation of the affected upper extremity correlated with the level of community integration in people with chronic stroke. This study implied a possible interpretation of the causation between upper limb motor function and community integration. Improving the motor functions could likely improve the level of community integration. The causation between upper limb motor improvement and community re-integration of patients with stroke should be investigated in future clinical trials.

Acknowledgement:

This study was supported by Health and Medical Research Fund 12131821 from the Food and Health Bureau, Hong Kong SAR Government to Dr. Shamay Ng and her team.

Appendix 5.5 The consent form of the randomized control trial

香港理工大學康復治療科學系參加研究同意書

科研題目: 隨機對照試驗: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上肢功能之功效。

科研人員: 伍尚美博士, 鍾志强博士

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，兩邊電刺激配合任務導向訓練或空白對照更有效於改善慢性中風病人上肢功能之功效。

研究方法: 所有合資格參加者會被隨機分為四組，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，第三組：兩邊安慰電刺激配合任務導向訓練， 第四組：空白對照。 前三組每星期接受三次治療，接受為期七星期（共二十次治療）。 第四組不接受任何治療。參加者將會接受患邊上肢的肌肉及功能測試、日常生活運用手部功能的問卷以評估進展。

潛在危險性及得益: 若參與此研究，參加者可以了解自己的上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上肢功能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，可以聯繫文女士（部門科研委員會秘書），電話：2766 4394。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：** _____

Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project entitled: A randomized controlled clinical trial of task-oriented upper limb training (TOT) with bilateral transcutaneous electrical nerve stimulation (Bi-TENS) to improve upper limb functions in patients with chronic stroke

Investigator: Dr. Shamay S. M. Ng (RS), Dr. Raymond C.K. Chung

Purpose:

To investigate whether bilateral transcutaneous electrical nerve stimulation (Bi-TENS) over both paretic and non-paretic upper limb will be more superior to transcutaneous electrical stimulation (Uni-TENS) over paretic upper limb when combined with task-orientated upper limb training (TOT), placebo transcutaneous electrical stimulation (Placebo-TENS) over both paretic and non-paretic upper limb when combined with TOT, and no active treatment control in improving the upper limb motor function, respectively.

Methods:

All eligible subjects will be randomly assigned into 4 groups: Group A: Bi-TENS over both paretic and non-paretic upper limbs combined with TOT; Group B: Uni-TENS over paretic upper limb combined with TOT; Group C: Placebo-TENS over both paretic and non-paretic upper limbs combined with TOT; Group D: No active treatment control. The Group A, B and C receive 3 session of intervention per week in total 7 weeks (total 20 treatment sessions). Group D don't receive any active treatment. Subjects will be assessed on improvement of the Fugl-Meyer

Assessment of Upper Extremity, peak torque during maximum isometric voluntary contraction of wrist flexor and extensor, Active range of motion in elbow flexion/extension and wrist flexion/extension, Action Research Arm Test, Jacket Test, Motor Activity Log and Community Integration Measure questionnaire.

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 motor functions of their upper limbs. The results may also be beneficial for planning an intensive rehabilitation program for improving upper limb motor functions in patients 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.

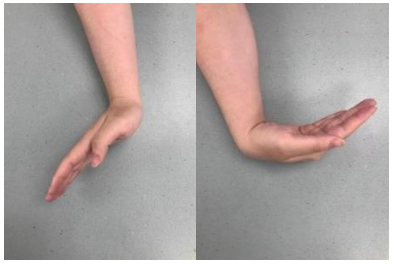
I can contact the chief investigator, Dr. Shamay Ng at telephone 2766-4889 for any questions about this study. If I have complaints related to the investigators, I can contact Ms. Gloria Man secretary of Departmental Research Committee, at 2766-4394. I know I will be given a signed copy of this consent form.

Signature (participant): _____ Date: _____

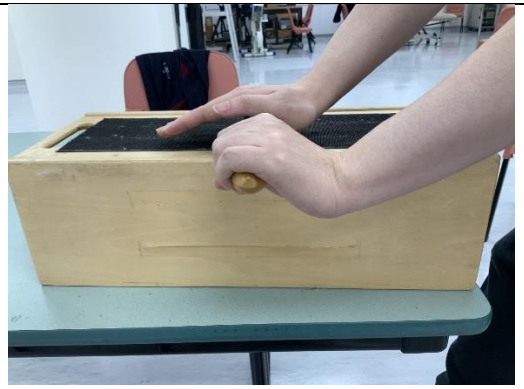
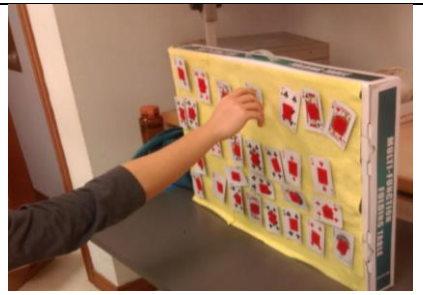
Signature (Witness): _____ Date: _____

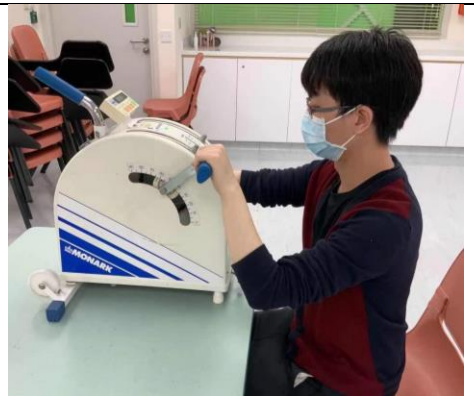
Appendix 5.6 Component of TOT and the principle of progression

Item	Exercise component	Demonstration
Upper limb stretching exercises	**Aim:** To increase the passive ROM of shoulder, elbow, wrist and finger. **Types of exercise:** (1) The subjects held the paretic upper limb on the wall with the non-paretic upper limb. With the whole body moved close to the wall, both sides of the upper limbs gradually lifted up and increased the passive ROM of shoulder flexion. In order to hold the stretching position for sufficient time, 3 minutes of stretching was conducted. (2) The subjects grasped the parallel bar with both sides of the upper limbs were grasping the parallel bar. Strap could be used to fix the paretic hand on the bar if the paretic hand was too weak to hold the bar. Then the subjects were instructed to perform lunge and gradually lower the body's center of mass so that the elbows were gradually reach the 180° extension position and shoulder extension. In order to hold the stretching position for sufficient time, 3 minutes of stretching was conducted. (3) The subjects used the non-paretic hand to stabilize the paretic hand on the table. With the body move closer to the table, the passive ROM of wrist flexion/extension gradually increase until reach 90° wrist flexion/extension. In order to hold the stretching position for sufficient time, 3 minutes of stretching was conducted. **Standardized progression of exercises:** To gradually increase the passive ROM until achieve the normal ROM	

	(180˚ shoulder flexion, 180˚ elbow extension, 75˚ wrist flexion and extension)	
Upper limb mobilizing exercise	**Aim:** To increase the active ROM of shoulder, elbow and wrist. **Types of exercise:** (1) The subject was asked to perform shoulder flexion as much as they could until reach the end of active ROM. The subjects were required to repeat this exercise for 100 time per treatment session or as much as they could. (2) The subject was asked to perform elbow flexion as much as they could until reach the end of active ROM. The subjects were required to repeat this exercise for 100 time per treatment session or as much as they could. (3) The subject was asked to perform wrist flexion/extension as much as they could until reach the end of active ROM. The subjects were required to repeat this exercise for 100 time per treatment session or as much as they could. **Standardized progression of exercises:** Gradually increase repetition of the active ROM by 10 times	  

Upper limb strengthening exercises	**Aim:** To improve the muscle strength of shoulder flexion, shoulder horizontal abduction, shoulder abduction, wrist flexion and extension. **Types of exercise:** (1) The subject was asked to perform the shoulder flexion with elbow extension against the strong resistance from the rubber band as far as they can. The subject was then required to hold this position and count 15 times loudly each trial so that they can breathe normally while performing the strengthening exercise. The subject was required to repeat it for 5 time each treatment session. (2) The subject was asked to perform the shoulder horizontal abduction with elbow extension against the strong resistance from the rubber band as far as they can. The subject was then required to hold this position and count 15 times loudly each trial so that they can breathe normally while performing the strengthening exercise. The subject was required to repeat it for 5 time each treatment session. (3) The subject was asked to perform the shoulder abduction with elbow extension against the strong resistance from the rubber band as far as they can. The subject was then required to hold this position and count 15 times loudly each trial so that they can breathe normally while performing the strengthening exercise. The subject was required to repeat it for 5 time each treatment session. (4) The subject was asked to place the wooden stick on the velcro surface of the wooden box, while the non-paretic hand help to stabilize the wooden stick. Then the subject was required to roll the stick on the wooden box with the paretic hand against the resistance generated by Velcro as far as it could. The exercise will last for 3 minutes each treatment session. **Standardized progression of exercises:**	  

	Shoulder and elbow: Increase the resistance by changing to a therapy band with greater resistance (green<blue<black) Wrist: Increase the repletion as many as possible	
Seated reaching tasks in different directions	**Aim:** To strengthen the shoulder girdle muscle of the paretic side and trunk control for daily activities. **Types of exercise:** When the exercise began, the subject was required to pick the card in different position on the board as much as it could. The whole exercise last for 10 minutes each treatment session. The subject was required to perform as much as it could. **Standardized progression of exercises:** To pick up all the cards without the gloves and increase the distance to reach the cards, as well as the number of repetitions completed.	 

Manipulation and dexterity training	**Aim:** To improve the fine motor control of hand in daily activity. **Types of exercise:** The subject was required to pick up the objects with different size and shape as much as they could for 10 minutes each treatment session, such as the plastic block, cylinder, marble and metal ball. **Standardized progression of exercises:** To pick up the objects with a smaller size (cylinder, marble and iron ball) than the plastic blocks with different fingers and gradually increase the repetition.	
Bimanual practice	**Aim:** To improve the bilateral coordination of the upper limb. **Types of exercise:** The subject was sitting in front of the Monark 881E Rehab Trainer ergometer and putting both sides of upper limb on the handles of the upper limb bicycle. The paretic upper limb could be attached on the handle with the strap if needed. Then the subjects performed bilateral upper limb cycling exercise with the ergometer for 10 minutes each treatment session. The subject was required to perform as much as it could. **Standardized progression of exercises:** To gradually increase the resistance.	

Appendix 5.7 Primary Outcome Measure: Fugl-Meyer Assessment (Upper Extremity)

A. UPPER EXTREMITY, sitting position			
I. Reflex activity		**none**	**can be elicited**
Flexors: biceps and finger flexors		0	2
Extensors: triceps		0	2
	Subtotal I (max 4)		
II. Volitional movement within synergies, without gravitational help		**none**	**partial**
Flexor synergy: Hand from contralateral knee to ipsilateral ear. From extensor synergy (shoulder adduction/internal rotation, elbow extension, forearm pronation) to flexor syngery (shoulder abduction/external rotation, elbow flexion, forearm supination)	Shoulder: retraction	0	1
	Shoulder: elevation	0	1
	Shoulder: abduction (90^0)	0	1
	Shoulder: external rotation	0	1
	Elbow: flexion	0	1
	Forearm: supination	0	1

Extensor synergy: Hand from ipsilateral ear to the contralateral knee.	Shoulder: adduction/internal rotation Elbow: extension Forearm: pronation	0 0 0	1 1 1
	Subtotal II (max 18)		
III. Volitional movement mixing synergies, without compensation		**none**	**partial**
Hand to lumbar spine	-Cannot be performed, hand in front of SIAS -Hand behind SIAS (without compensation -Hand to lumbar spine (without compensation)	0	1
Shoulder flexion 0^0 - 90^0 Elbow at 0^0 Pronation–supination 0^0	-immediate abduction or elbow flexion -abduction or elbow flexion during movement -complete flexion at 90^0, and maintains 0^0 in elbow	0	1
Pronation- supination Elbow at 90^0 Shoulder at 0^0	-no pronation / supination, starting position impossible -limited pronation / supination, maintains position -complete pronation / supination, maintains position	0	1
	Subtotal III (max 6)		
IV. Volitional movement with little or no synergy		**none**	**partial**

Shoulder abduction 0^0 - 90^0 Elbow at 0^0 Forearm pronated	-immediate supination or elbow flexion - supination or elbow flexion during movement -abduction 90^0, maintains extension and pronation	0	1
Shoulder flexion 90^0 - 180^0 Elbow at 0^0 Pronation–supination 0^0	-immediate abduction or elbow flexion - abduction or elbow flexion during movement -complete flexion, maintains 0^0 in elbow	0	1
Pronation- supination Elbow at 0^0 Shoulder at 30^0-90^0 flexion	-no pronation / supination, starting position impossible -limited pronation / supination, maintains extension -full pronation / supination, maintains elbow extension	0	1
	Subtotal IV (max 6)		
V. Normal reflex activity evaluated only if full score of 6 points achieved on part IV			
Biceps, triceps, finger flexors	-0 points on part IV or 2 of 3 reflexes markedly hyperactive -1 reflexor markedly hyperactive or at least 2 reflexes lively -Maximum of 1 reflex lively, none hyperactive	0	1

Subtotal V (max 2)	
TOTAL A (MAX 36)	

B. WRIST support may be provided at the elbow to take or hold the position, no support at wrist, check the passive range of motion prior testing		**none**	**partial**
Stability at 15^0 dorsiflexion Elbow at 90^0, Forearm pronated, shoulder at 0^0	-less than 15^0 active dorsiflexion - dorsiflexion 15^0, no resistance is taken -maintain s position against resistance	0	1
Repeated dorsiflexion/volar flexion Elbow at 90^0, Forearm pronated, shoulder at 0^0, slight finger flexion	-cannot perform volitionally -limited active range of motion -full active range of motion, smoothly	0	1
Stability at 15^0 dorsiflexion Elbow at 0^0, Forearm pronated, slight shoulder flexion/abduction	--less than 15^0 active dorsiflexion - dorsiflexion 15^0, no resistance is taken -maintain s position against resistance	0	1
Repeated dorsiflexion/volar flexion Elbow at 0^0, Forearm pronated, slight shoulder flexion/abduction	-cannot perform volitionally -limited active range of motion -full active range of motion, smoothly	0	1
Circumduction	-Cannot perform volitionally -jerky movement or incomplete -complete and smooth circumduction	0	1
	TOTAL B (MAX 10)		

C. HAND support may be provided at the elbow to keep 90^0 flexion, no support at wrist, compare with unaffected hand, the objects are interposed, active grasp		**none**	**partial**
Mass flexion From full active or passive extension		0	1
Mass extension From full active or passive flexion		0	1
GRASP			
A. flexion in PIP and DIP (digits II-V) **Extension in MCP II-V**	-cannot be performed -can hold position but weak -maintains position against resistance	0	1
B. thumb adduction 1-st CMC, MCP, IP at 0^0, scrap of paper between thumb and 2-nd MCP joint	-cannot be performed -can hold paper but not against tug - can hold paper against a tug	0	1
C. opposition pulpa of the thumb against the pulpa of 2-nd finger, pencil, tug upward	-cannot be performed -can hold pencil but not against tug - can hold pencil against a tug	0	1
D. cylinder grip Cylinder shaped object (small can), tug upward, opposite in digits I and II	-cannot be performed -can hold cylinder but not against tug - can hold cylinder against a tug	0	1
E. spherical grip Fingers in abduction/flexion, thumb opposed, tennis ball	-cannot be performed -can hold ball but not against tug - can hold ball against a tug	0	1

TOTAL C (MAX 14)	

D. COORDINATION / SPEED after one trial with both arms, blind-folded, tip of the index finger from knee to nose, 5 times as fast as possible		marked	slight
Tremor		0	1
Dysmetria	-Pronounced or unsystematic -slight and systematic -no dysmetria	0	1
		>5s	2-5s
Time	-more than 5 seconds slower than unaffected side -2-5 seconds slower than unaffected side -maximum differences of 1 second between sides	0	1
TOTAL D (MAX 6)			

TOTAL A-D (MAX 66)	

Reference: Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post stroke hemiplegic patient. A method for evaluation of physical performance. Scandinavian Journal of Rehabilitation Medicine 1975;7:12-31.

Appendix 5.8 Secondary Outcome Measure: Action Research Arm Test

ACTION Patient Name: _____

RESEARCH Rater Name: _____

ARM TEST Date: _____

Instructions

There are four subtests: Grasp, Grip, Pinch, Gross Movement. Items in each are ordered so that:

- if the subject passes the first, no more need to be administered and he scores top marks for that subtest;
- if the subject fails the first *and* fails the second, he scores zero, and again no more tests need to be performed in that subtest;
- otherwise he needs to complete all tasks within the subtest

Activity Score

Grasp

1. Block, wood, 10 cm cube (If score = 3, total = 18 and to Grip) _____

Pick up a 10 cm block

2. Block, wood, 2.5 cm cube (If score = 0, total = 0 and go to Grip) _____

Pick up 2.5 cm block

3. Block, wood, 5 cm cube _____

4. Block, wood, 7.5 cm cube _____

5. Ball (Cricket), 7.5 cm diameter _____

6. Stone 10 x 2.5 x 1 cm _____

Coefficient of reproducibility = 0.98

Coefficient of scalability = 0.94

Grip

1. Pour water from glass to glass (If score = 3, total = 12, and go to Pinch) _____

2. Tube 2.25 cm (If score = 0, total = 0 and go to Pinch) _____

3. Tube 1 x 16 cm _____

4. Washer (3.5 cm diameter) over bolt _____

Coefficient of reproducibility = 0.99

Coefficient of scalability = 0.98

Pinch

1. Ball bearing, 6 mm, 3rd finger and thumb (If score = 3, total = 18 and go to Grossmt) _____

2. Marble, 1.5 cm, index finger and thumb (If score = 0, total = 0 and go to Grossmt) _____

3. Ball bearing 2nd finger and thumb _____

4. Ball bearing 1st finger and thumb _____

5. Marble 3rd finger and thumb _____

6. Marble 2nd finger and thumb _____

Coefficient of reproducibility = 0.99

Coefficient of scalability = 0.98

_____ _____

Grossmt (Gross Movement)

1. Place hand behind head (If score = 3, total = 9 and finish) _____

2. (If score = 0, total = 0 and finish _____

3. Place hand on top of head _____

4. Hand to mouth _____

Coefficient of reproducibility = 0.98

Coefficient of scalability = 0.97

References

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De Weerdt WJG, Harrison MA. “Measuring recovery of arm-hand function in stroke patients: a comparison of the Brunnstrom-Fugl-Meyer test and the Action Research Arm test.

Physiotherapy Canada. 1985;37:65-70.

Lyle RC. “A performance test for assessment of upper limb function in physical rehabilitation treatment and research.”*Int J Rehabil Res*. 1981;4:483-492.

Appendix 5.9 Secondary Outcome Measure: Motor Activity Log (MAL)(Chinese Prototype)

家居活動紀錄表	使用程度 (甲) (AOU)	動作質素 (乙) (QOM)	如沒有進行此活動，請說明 (填代號)
1. 開關輕觸式的燈掣			
2. 開抽屜			
3. 從抽屜取出一件衣物			
4. 拿起電話聽筒			
5. 抹枱或廚櫃面			
6. 落車(只包括當車門打開後，從坐到站之動作)			
7. 打開雪櫃			
8. 扭開門鎖並推開門			
9. 使用電視遙控器			
10. 洗手 (包括使用皂液及冲洗，但不包括開關水龍頭)			
11. 開關水龍頭			
12. 抹手			
13. 穿襪子			
14. 脫下襪子			
15. 穿鞋子 (包括綁鞋帶或貼魔術貼)			
16. 脫下鞋子 (包括解開鞋帶或解開魔術			

貼)			
17. 從有扶手的椅子站起來			
18. 坐下前把椅子從桌下拉開			
19. 坐下後把椅子拉近桌子			
20. 拿起杯子、水杯、水樽或罐頭 (不包括飲用)			
21. 刷牙 (不包括預備牙刷或洗刷除下來的假牙)			
22. 搽潤膚露 / 剃鬚膏 / 美容用品到臉上			
23. 用鎖匙開門			
24. 在紙上寫字 (如中風前使用健側手寫字，則可忽略此題)			
25. 手拿著物件 (不包括用手臂掛起物件)			
26. 使用义子或湯匙進食			
27. 梳頭			
28. 拿著杯柄拿杯			
29. 扣鈕			
30. 進食三文治或用手指拿小食			

Reference: Ng AKY, Leung DPK, Fong KNK. Clinical utility of action research arm test, the Wolf motor function test and the motor activity log for hemiparetic upper extremity functions after stroke: a pilot study. Hong Kong Journal of Occupational Therapy 2008;18:20-27.

Amount Scale (AS)

0- Did not use my weaker arm (**not used**).

0.5

1- Occasionally used my weaker arm, but only very rarely **(very rarely).**

1 .5

2 - Sometimes used my weaker arm but did the activity **most of the time** with my stronger arm **(rarely).**

2.5

3 - Used my weaker arm about half as much as before the stroke **(half pre-stroke).**

3.5

4 - Used my weaker arm almost as much as before the stroke **(3/4 pre-stroke).**

4.5

5 - Used my weaker arm as often as before the stroke **(same as pre-stroke)**

How Well Scale (HW)

0 - The weaker arm was not used at all for that activity

(never).

0.5

1 - The weaker arm was moved during that activity but was not helpful **(very poor).**

1.5

2 - The weaker arm was of some use during that activity but needed some help from the stronger arm or moved very slowly or with difficulty **(poor).**

2.5

3 - The weaker arm was used for the purpose indicated but movements were slow or were made with only some effort **(fair).**

3.5

4 - The movements made by the weaker arm were almost normal, but were not quite as fast or accurate as normal **(almost normal).**

4.5

5 - The ability to use the weaker arm for that activity was as good as before the stroke **(normal).**

Possible Reasons for Not Using the Weaker Arm for the Activity:

Reason A. "I used the unaffected arm entirely."

Reason B. "Someone else did it for me.".

Reason C. "I never do that activity, with or without help from someone else because it is impossible." For example, combing hair for people who are bald.

Reason D. "I sometimes do that activity, but did not have the opportunity since the last time I answered these questions."

Reason E. "That is an activity that I normally did only with my dominant hand before the stroke, and continue to do with my dominant hand now."

Appendix 5.10 Secondary Outcome Measure: Guidelines for Community Integration Measure

社區整合量法

For each of the following statements, please indicate whether you agree or disagree:

在下列的問題裡，請選擇同意或不同意

1. I feel like part of this community, like I belong here.

我覺得我是這個社會的一部分，我屬於這個社會

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

2. I know my way around this community.

我清楚我在這個社會的方向

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

3. I know the rules in this community and I can fit in with them.

我知道在這個社會的規則，我可以適應它

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

4. I feel that I am accepted in this community.

我覺得我被這個社會所接納的

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

5. I can be independent in this community.

我可以在這個社區獨立

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

6. I like where I'm living now.

我喜愛我現在居住的地方

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

7. There are people I feel close to in this community.

在這個社會裡有我相熟的人

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

8. I know a number of people in *this* community well enough to say hello and have them say hello back.

在*這個*社會裡我認識一了些朋友會跟我打招呼的

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

9. There are things that I can do in this community for fun in my free time.

在這個社會裡我可以在空餘時間做自己喜歡的事

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

10. I have something to do in this community during the main part of my day that is useful and productive.

在這個社會裡，我每天都可以做到一些有用和有生產力的事

[ ] 經常同意 Always agree

[ ] 有時同意 Sometimes agree

[ ] 中立 Neutral

[ ] 有時不同意 Sometimes disagree

[ ] 經常不同意 Always disagree

Appendix 6.1 Chapter 6 published on *Stroke* (Final manuscript)

Bilateral TENS Improves Upper Limb Motor Recovery in Stroke: A Randomized Controlled Trial

Introduction

Upper limb impairment is a common but serious sequela of stroke. About one-third of stroke survivors continue to suffer upper limb motor function deficits 6 months later[1]. Interventions for enhancing the recovery of upper limb motor recovery following stroke are crucial.

Transcutaneous electrical nerve stimulation (TENS) has been used in stroke rehabilitation for decades. At the peripheral level, repetitive TENS over paretic limb (Uni-TENS) can reduce the magnitude of the stretch reflex as well as lengthen the latency of the H-reflex and the stretch reflex[2]. At the cortical level, Uni-TENS over paretic limb excites the areas of the cortex corresponding to the body parts being stimulated[3] and evokes greater activation of the lesioned hemisphere[4]. The bilateral application of TENS (Bi-TENS) on both paretic and non-paretic upper limbs can provide extra sensory input from the non-paretic side [5, 6] which can reduce paresis by rebalancing inter-hemisphere inhibition[7], activating the homologous neural networks in the intact and lesioned hemispheres[8] and recruiting the neural networks of the intact hemisphere[9].

Task-oriented training (TOT) is goal-directed exercise therapy designed to help people derive optimal control strategies for specific motor tasks in real environments[10]. Rensink[11],

Timmermans and their colleagues[12] have published systematic reviews showing that TOT on a paretic upper limb can improve arm-hand performance and health-related quality of life in stroke.

TENS could be used concurrently with TOT, and it yields greater treatment benefits than using TOT alone. For Uni-TENS over paretic limbs with TOT, results of a randomized clinical trial have shown that Uni-TENS and TOT are more effective than Placebo-TENS and TOT in increasing flexor muscle strength of paretic wrist, reducing upper limb muscle spasticity and improving motor control in paretic upper limb in people with stroke[13]. For Bi-TENS over both paretic and non-paretic limbs with TOT, a recent randomized clinical trial[14] reported that 20 sessions of Bi-TENS and TOT induced greater and earlier benefits than Uni-TENS and TOT in terms of improving the strength of paretic ankle dorsiflexors and functional mobility among people with stroke. However, the clinical value of Bi-TENS and TOT for improving upper limb motor recovery in people with stroke has not yet been explored.

On the basis that combining Uni-TENS with TOT is an effective intervention in promoting upper limb recovery[13], and given the advantage of Bi-TENS in recruiting extra neural pathways [9, 15] in the intact hemisphere, it is reasonable to hypothesize that TENS applied to both the paretic and the non-paretic limb concurrently could augment TOT's effect on upper limb motor control following stroke. This study was designed to investigate whether Bi-TENS+TOT is superior to Uni-TENS+TOT, Placebo-TENS+TOT, or no active treatment, in improving the Fugl-Meyer Upper Extremity Assessment (FMA-UE) score.

Methods

The complete dataset supporting these findings is available from the corresponding author on request.

Design

This is a 4-group parallel design. To compare the effect of Bi-TENS+TOT with Uni-TENS+TOT, Placebo-TENS+TOT and control with no active treatment, we conducted a single-blinded, randomized and placebo-controlled trial. The protocol followed the Consolidated Standards of Reporting Trials statement[16]. The study was conducted in the Neurorehabilitation Laboratory at the Hong Kong Polytechnic University. The protocol was approved by the University's Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Randomization

After obtaining the written consent from the subjects and completing the baseline assessment, an offsite research assistant randomized the subjects to one of the 4 groups by Minimize software[17]: Bi-TENS+TOT, Uni-TENS+TOT, Placebo-TENS+TOT or Control group without treatment. In order to minimize any potential bias, the stratification balanced the age (50–60, 60–70 and >70), gender (male, female), type of stroke (ischemia, hemorrhage), baseline FMA-UE score (0–22, 23–47, 48–56 and 57–66) and side of lesion (left, right) among the 4 groups before the randomization. To ensure effective concealed randomization (except for the

Control group), the participants were informed of the results of the group allocation (only the group number but not the details of the treatment), training schedule and venue by the centralized telephone calls from the offsite research assistant.

Subjects

One hundred and twenty subjects (mean age=61.5±6.7 years, post-stroke duration=6.0±3.1 years) were recruited from local self-help groups for people with stroke. The inclusion criteria were (1) between 50 and 80 years of age; (2) had been diagnosed with stroke within the previous 1 to 10 years; (3) had volitional control of the non-paretic arm and at least minimal antigravity movement in the paretic shoulder; (4) had at least 5 degrees of wrist extension in the antigravity position; and (5) had an Abbreviated Mental Test score ≥ 7[18]. Candidates were excluded if they (1) had any active uncontrolled medical, cardiovascular or orthopedic condition; (2) had contraindications to TENS such as an implanted cardiac pacemaker or skin allergy; (3) had receptive dysphasia; (4) had a significant upper limb peripheral neuropathy; (5) were involved in a drug study or another clinical trial; or (6) had severe shoulder, elbow, wrist or finger contractures.

Sample calculation

As no study has previously investigated the effect of Bi-TENS+TOT on upper limb motor control among people with stroke, the effect size (Cohen's d=0.314) used to calculate the minimum sample size for detecting the significant between-group difference was obtained from a

pilot trial with 4 groups (Bi-TENS+TOT, Uni-TENS+TOT, Placebo-TENS+TOT and Control, 2 subjects per group). It was then calculated by using version 3.1.0 of the G*power software with an α of 0.05, power of 0.80, correlation among measures of 0.5 and a non-sphericity correlation of 1. Ninety-six subjects would be necessary to detect a significant between-group difference in upper limb motor control measured by the FMA-UE. A dropout rate of 20% was assumed, and therefore the target sample size was 120 (30 per group).

Interventions Protocols

The 3 intervention groups (Bi-TENS+TOT, Uni-TENS+TOT and Placebo-TENS+TOT groups) received twenty 60–minute treatment sessions (corresponding TENS setting and TOT), 3 sessions per week for 7 weeks, as the findings of previous study suggested that 20 TENS sessions of 60 minutes each can provide sufficient stimulus to elicit detectable recovery of motor function in people with stroke[14, 19]. The Control group did not get any active treatment.

TENS protocol

The stimulator was a 120z Dual-Channel TENS Unit (ITO PHYSITHERAPY & REHABILITION CO., LTD, Tokyo, Japan). The stimulation was at 100Hz, applied in 0.2ms square pulses at an intensity of twice the sensory threshold (defined as the minimum intensity at which the subject reported feeling a tingling sensation) and below the motor threshold as indicated by absence of muscle twitching[14]. Disposable surface electrodes were applied to stimulate the median nerve from the carpal tunnel to the flexor digitorum superficialis and the superficial radial nerve from the extensor pollicis longus to the extensor digitorum communis.

The placebo stimulation was apparently identical TENS unit. The unit's power indicator light was illuminated but the electrical circuit had been disconnected.

In the Bi-TENS group, the subjects received TENS on both upper limbs. In the Uni-TENS group, TENS was applied only on the paretic side and placebo stimulation was applied on the non-paretic side. In the Placebo-TENS+TOT group, placebo stimulation was applied on both upper limbs. The Control group subjects received no active treatment.

TOT protocol

All subjects were required to complete 60 minutes' TOT of upper limbs which includes six 10-minute TOT items concurrently with TENS treatment, under the supervision of a well-trained research personnel with stroke rehabilitation training. The TOT training items included: (1) stretching exercises for increasing flexibility of tight muscles; (2) mobilizing exercises for increasing range of movement of upper limb joints; (3) strengthening exercises for increasing shoulder, elbow and wrist muscle strength; (4) seated reaching tasks for improving strength of shoulder girdle muscles; (5) dexterity training for improving fine motor control of paretic hand; and (6) bimanual practice for improving coordination of both paretic and non-paretic limbs in daily tasks. More detailed could be found in the Supplement.

Procedure

An experienced rehabilitation therapist who was blinded to the group allocation assessed the FMA-UE for each subject at 5 assessment time-points.: before the intervention, after the 4th

week of intervention, at the end of the 8th week of intervention, and 1-month and 3-months after completion of the intervention.

Outcome Measures

The Fugl-Meyer Assessment of Upper Extremity (FMA-UE)

The FMA-UE was used for evaluating the upper limb motor control[20]. It is a measure of proximal-to-distal, synergistic-to-isolated movement behavior in people with stroke[20]. FMA-UE has 4 subsections: (1) shoulder-arm; (2) wrist; (3) hand; (4) coordination and speed. The maximum total score is 66, with 33 items and ordinal scoring from 0 to 2. It had excellent intra-rater (r=0.997) and inter-rater (r=0.993) reliability[21] in assessing people with stroke.

Statistical Analyses

Statistical analyses were performed using version 23.0 of the SPSS software (IBM, Armonk, NY). Descriptive analysis was used to summarize the subjects' demographic information. Intention-to-treat analysis was conducted. The linear mixed-effect model (LMM) was used to compare the changes over time in FMA-UE score between those in the 4 groups. Maximum likelihood estimation was used to select the best-fitting model. The first-order autoregressive structure with heterogeneous variances (AR (1): heterogeneous) was used to estimate the parameters of the statistical models. The intervention effect across baseline, mid-intervention and post-intervention was analyzed by the LMMs, and any carryover effect across baseline, 1-month follow-up and 3-month follow-up assessment was analyzed using the same

LMM method. The significance level was set at 0.05. The post-hoc analysis was conducted by Bonferroni correction when there was an overall significant difference.

Results

One hundred and forty-one potential subjects were screened between May 2016 and June 2018, and 120 were recruited into the study. The demographic information of the subjects was shown in Table 1. The result of FMA-UE from baseline to 3-month follow-up assessment was shown in Table 2. There was no significant difference among the 4 groups at baseline. Nine participants dropped out for reasons not related to the study during the intervention (e.g. lost contact, schedule not fit). One hundred and eleven subjects completed the experiments and the post-intervention assessments, 107 (89%) completed the 1-month follow-up and 99 (83%) completed the 3-month follow-up. No adverse incident occurred in this study. The result of LMM from baseline to 3-month follow-up was shown in Table 3 and Table 4.

The LMM revealed a significant group-by-time interaction effect in FMA-UE scores, indicating that the Bi-TENS+TOT group showed greater improvement in FMA-UE scores than the other three groups at post-intervention (Uni-TENS+TOT: mean difference=2.13, p=0.004; Placebo-TENS+TOT: mean difference=2.63, p<0.001; Control: mean difference=3.11, p<0.001). The post-hoc analysis indicated that the Bi-TENS+TOT group showed significantly greater improvement in FMA-UE scores than the Uni-TENS+TOT group at post-intervention (mean difference=2.13, p=0.005). The Bi-TENS+TOT group also showed greater improvement in FMA-UE scores than the Placebo-TENS+TOT and Control groups at the mid-intervention point

(Placebo-TENS+TOT group: mean difference=2.96, p=0.012; Control group: mean difference=3.18, p=0.009).

The LMM revealed that the Bi-TENS+TOT group showed significant carryover effect in between-group difference (Uni-TENS+TOT: mean difference=1.34, p<0.001; Placebo-TENS+TOT: mean difference=1.49, p<0.001; Control: mean difference=1.58, p<0.001) of FMA-UE scores with the other 3 groups between baseline, 1-month follow-up and 3-month follow-up. The post-hoc analysis indicated that the Bi-TENS+TOT group demonstrated between-group improvement than the other 3 groups in FMA-UE scores from baseline to both 1-month follow-up (Uni-TENS+TOT: mean difference=1.62, p<0.001; Placebo-TENS+TOT: mean difference=1.38, p=0.002; Control: mean difference=1.59, p=0.001) and 3-month follow-up (Uni-TENS+TOT: mean difference=1.19, p=0.003; Placebo-TENS+TOT: mean difference=1.49, p<0.001; Control: mean difference=1.56, p<0.001), which indicated that the between-group improvement in Bi-TENS+TOT group could be maintained at 1-month follow-up and 3-month follow-up.

For the time effects, the Bi-TENS+TOT group (mean difference=3.39, p<0.001) and the Uni-TENS+TOT group (mean difference=1.26, p=0.015) showed significant improvement in FMA-UE scores between baseline and post-intervention assessment. The post-hoc analysis showed that the Bi-TENS+TOT group demonstrated within-group improvement (mean difference=4.35, p<0.001) in FMA-UE scores from baseline to the mid-intervention assessment, while the Uni-TENS+TOT group showed significant within-group improvement (mean difference=1.21, p=0.024) from the mid-intervention to the post-intervention assessment.

The LMM revealed that the Bi-TENS+TOT (mean difference=1.94, $p<0.001$) and Uni-TENS+TOT (mean difference=0.61, $p=0.020$) groups showed significant carryover effect in the within-group change of FMA-UE scores between baseline, 1-month follow-up and 3-month follow-up. The post-hoc analysis indicated that the Bi-TENS+TOT group demonstrated within-group improvement in FMA-UE scores from baseline to both 1-month follow-up (mean difference=2.05, $p<0.001$) and 3-month follow-up (mean difference=1.92, $p<0.001$), while the Uni-TENS+TOT group showed significant within-group improvement from the baseline to 3-month follow-up (mean difference=0.71, $p=0.013$). It indicated that the within-group improvement in Bi-TENS+TOT group could be maintained at 1-month follow-up and 3-month follow-up, while the within-group improvement in Uni-TENS+TOT group could be only maintained at 3-month follow-up.

Discussion

This is the first published study to compare the effects of Bi-TENS+TOT with that of the Uni-TENS+TOT, Placebo-TENS+TOT, and no active treatment (Control) on upper limb motor control in people with stroke. There were 2 major findings. First, the Bi-TENS+TOT group showed greater improvement in FMA-UE scores than the other 3 groups at post-intervention. Second, the Bi-TENS+TOT and Uni-TENS+TOT groups showed within-group improvement in FMA-UE scores at post-intervention, and the effects persisted until 3-month follow-up. Bi-TENS+TOT showed earlier within-group improvement in FMA-UE scores at mid-intervention assessment, while Uni-TENS+TOT showed the improvement at post-intervention assessment.

Uni-TENS+TOT in motor recovery

The Uni-TENS+TOT (mean difference=1.26) group showed greater within-group improvement in FMA-UE scores at post-intervention assessment when compared with Placebo-TENS+TOT group (mean difference=0.76). Previous studies showed that Uni-TENS could reduce short-interval intra-cortical inhibition[22], enhance corticospinal excitability[23] and corticomuscular coherence[24]. Huang et al.[25] suggested that peripheral sensory input from electrical stimulation over a paretic limb enhances motor recovery by activating the lesioned motor cortex via two pathways: (1) between thalamus and primary motor cortex (M1); and (2) between primary somatosensory cortex and M1.

Bi-TENS+TOT in motor recovery

As hypothesized, the Bi-TENS+TOT group showed greater improvement in FMA-UE scores than the Uni-TENS+TOT, Placebo-TENS+TOT and Control groups at post-intervention. There could be two possible mechanisms. First, Bi-TENS could enhance interactions between the intact and lesioned hemispheres via the transcallosal pathway that connects the two cerebral hemispheres[26]. Cunningham et al.[15] found that 60 minutes of bilateral functional electrical stimulation over paretic extensor digitorum communis and extensor pollicis longus muscles could reduce interhemispheric inhibition, but that unilateral stimulation did not. Reducing interhemispheric inhibition with Bi-TENS help reinforce the interhemispheric interaction via the transcallosal pathway and enhance the motor recovery of paretic upper limb[15].

Second, Bi-TENS could enhance corticomuscular activation via uncrossed contralesional corticospinal pathway. The nerves from the intact hemisphere plays an important role in upper limb movement following stroke. Calautti et al.[9] suggested that recruitment of motor areas from the intact hemisphere via the uncrossed corticospinal pathway to accomplish paretic side movement is a routine adaptation following stroke.

There was a significant within-group improvement in FMA-UE scores in the Bi-TENS+TOT and Uni-TENS+TOT groups at post-intervention, with a mean change of 6.78 and 2.52 respectively. No significant change was found in the Placebo-TENS+TOT and Control groups. As only the Bi-TENS+TOT group exceeded the minimal clinically important improvement of 5.25[27], patients should perceive it as beneficial.

The within-group improvements in FMA-UE scores persisted for at least 3 months in the Bi-TENS+TOT and Uni-TENS+TOT groups. Repetitive TENS, applied unilaterally or bilaterally, could induce long-lasting improvement of impaired neurons in the lesioned hemisphere[28]. Such improvement might encourage more use of the paretic upper limb in activities of daily living. If so, that would help to explain the persistence of the improvements in the 2 groups with TOT.

In order to maximize the effectiveness of TENS in augmenting TOT, TENS was applied concurrently with the TOT in this study. Khaslavskaia et al.[29] found that 30 minutes of electrical stimulation on the common peroneal nerve increased the motor-evoked potential of the tibialis

anterior muscle by up to 104% as measured by transcranial magnetic stimulation throughout the stimulation period, and that the effects lasted for 110 minutes after the stimulation. To activate the cutaneous sensory fiber, TENS was applied over the superficial territory of radial nerve and the median nerve concurrently with the TOT in this study, as suggested by the stimulation protocol of previous studies[15, 30, 31] involving people with stroke.

Limitations

This study had several limitations. First, all subjects were informed that they might or might not feel a sensation during the stimulation period as they were to be given stimulation at different parameters in order to maintain a common mindset, but this deception may not have been enough to blind the subjects in the Placebo-TENS+TOT group. Second, the study's final assessment time point was limited to only 3-month follow-up due to limited manpower and research period. A longer period of follow-up assessment could be set up to further investigate the carryover effect in the future. Third, the generalization of these treatment results may only be limited to a similar population who fulfilling our inclusion/exclusion criteria.

Conclusions

Bi-TENS is a more effective adjunct therapy for enhancing the effect of TOT in improving upper limb motor recovery than Uni-TENS, Placebo-TENS or no treatment in people with stroke. Further studies investigating the neurophysiological mechanism are warranted.

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Appendix 6.2 The letter from *Stroke* of accepting the manuscript: Bilateral TENS improves Upper Limb Motor Recovery in Stroke: A Randomized Controlled Trial

American Stroke Association. A division of the American Heart Association.

Stroke

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Date: 09-15-2021 17:33
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Subject: STROKE/2021/036895DR1 Decision Letter
Message: September 15, 2021

Prof. Shamay S.M. Ng
The Hong Kong Polytechnic University
Department of Rehabilitation Sciences
Hung Hom, Kowloon
HONG KONG

MS ID#: STROKE/2021/036895DR1
MS TITLE: Bilateral TENS Improves Upper Limb Motor Recovery in Stroke: A Randomized Controlled Trial

Dear Prof. Ng:

We are pleased to inform you that your manuscript has been accepted for publication in Stroke.

Prior to sending the manuscript to the publisher, we ask that all material required for publication is submitted. Timely publication depends upon your compliance with these requirements. We cannot process your manuscript until all final documents have been received. Please review your submission for the following:

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During the copy-editing phase, there may be some changes in phraseology, but there will be no alteration to scientific content. When you receive your galley proofs, please read, correct, and return them immediately so that publication will not be delayed.

Congratulations on this outstanding work and thank you for contributing to Stroke.

With kind regards,

Argye E. Hillis, MD
Deputy Editor

Appendix 6.3 The poster of "Bilateral Transcutaneous Electrical Nerve Stimulation (TENS) is superior to Unilateral TENS in improving the upper limb muscle strength among people with chronic stroke: A pilot study" submit to *11th WORLD CONGRESS FOR NEUROREHABILITATION*, 2020.

Bilateral Transcutaneous Electrical Nerve Stimulation (TENS) is superior to Unilateral TENS in improving the upper limb muscle strength among people with chronic stroke: A pilot study

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Background and Objective

Transcutaneous electrical nerve stimulation (TENS) is the application of low intensity and high frequency electrical stimulation on the peripheral nerves. It could help to reduce the muscle spasticity, improve the muscle strength, and improve motor control and functions in patients with stroke.

Results of neurophysiological studies demonstrated that activation of the both ipsilesional and contralesional hemispheres could recruit more neural pathways and cortical neurons through bilateral interventions. Previous clinical studies demonstrated that Unilateral TENS (Uni-TENS) and task oriented training (TOT) are effective in promoting upper limb recovery instroke rehabilitation. Thus, we hypothesized that bilateral TENS(Bi-TENS) is superior to Uni-TENS in improving the muscle strength of the paretic upper limb of people with chronic stroke.

The objectives of this pilot study aimed to compare the effects of the combined use of Bi-TENS and TOT (Bi-TENS+TOT) with Uni-TENS and TOT (Uni-TENS+TOT) in improving the upper limb muscle strength in people with chronic stroke.

Method

Study Design: Randomized controlled clinical pilot trial

Subject: Eighteen subjects with chronic stroke

Intervention:

(1)Bi-TENS+TOT group: TENS was applied on the median nerve and radial nerves of the bilateral upper limbs.

(2) Uni-TENS+TOT group: TENS was only applied on the affected upper limb, while placebo-TENS was applied on the unaffected side.

Dosage: 20 treatment sessions (1 hour per session, 3 sessions per week within 7 weeks,)

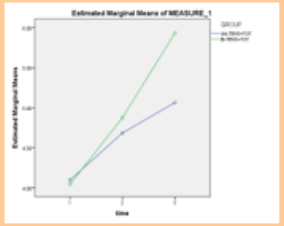
Assessment: The muscle strength of paretic wirst flexor was measured by custom-built load-cell at 3 time points at: (1) baseline; (2) mid-treatment, and (3) post-treatment.

Outcome measures	Treatment group	
	Uni-TENS+TOT	Bi-TENS+TOT
Age (mean±SD, year)	59.44±3.47	62.78±6.22
Gender (Female/Male)	3/6	3/6
Post stroke duration (mean±SD, year	6.11±3.69	9.67±6.36
Type of Stroke (Hemorrhagic/Ischemic)	1/8	2/7
Side of hemiplegia (Left/Right)	3/6	4/5

Results

For between-group comparison, two-way Mann-Whitney U-test indicated that the Bi-TENS+TOT group showed marginally, but significantly, greater improvement in paretic wrist flexion strength than Uni-TENS+TOT after 20 treatment sessions (p=0.034).

For within-group comparison, Friedman's one way ANOVA indicated only Bi-TENS+TOT showed significant improvement (p=0.002) in paretic wrist flexion strength after 20 treatment sessions, but not the Uni-TENS+TOT group.



Conclusion

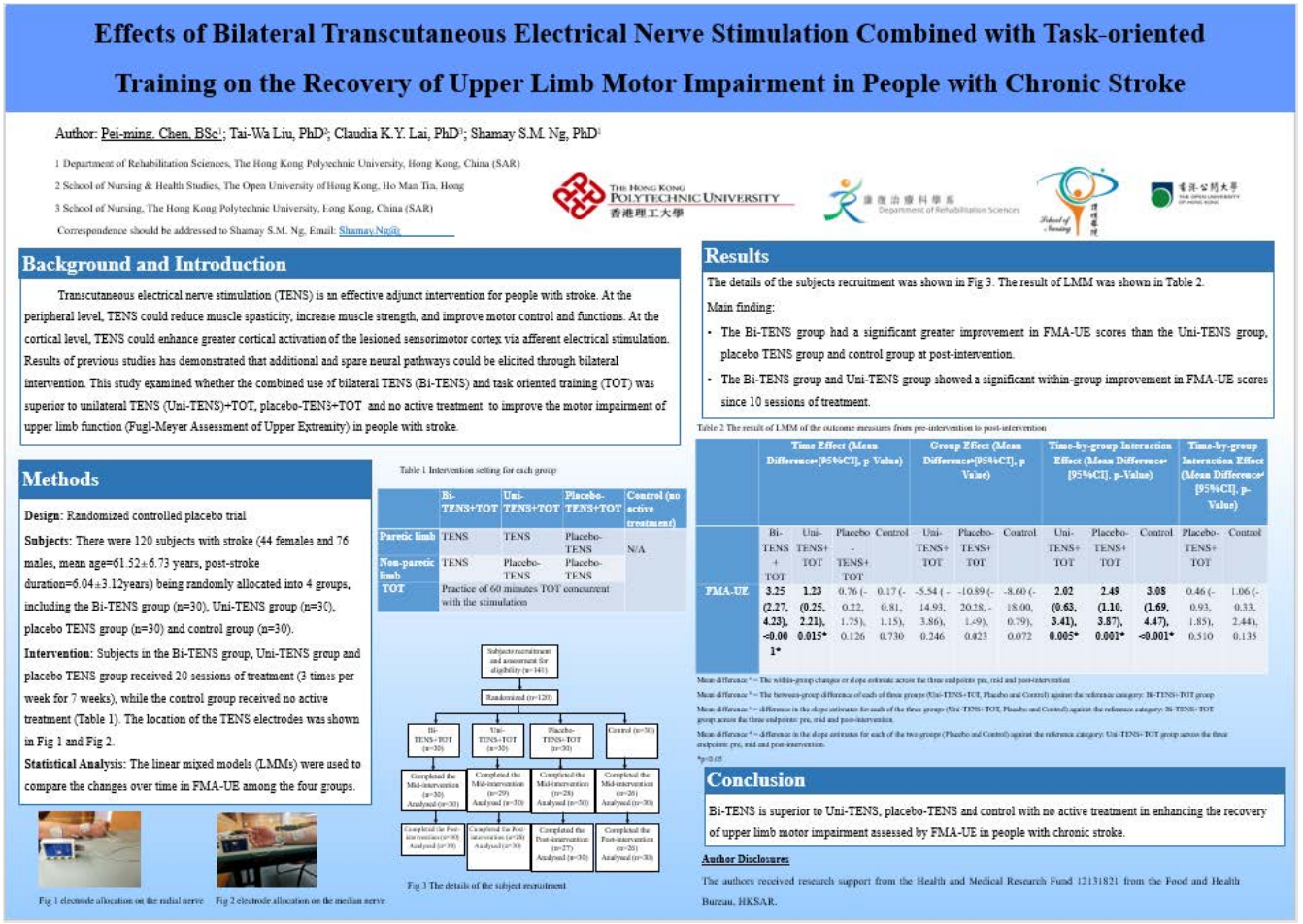
This pilot study revealed that Bi-TENS+TOT was superior to Uni-TENS+TOT in improving the paretic muscle strength of wrist flexion in people with chronic stroke.

Clinical Implication

These findings of this pilot study indicated the potential value of Bi-TENS in augmenting the effect of TOT in recovery of upper limb muscle strength in people with chronic stroke. Larger sample size with different type and severity of stroke in the future study are warranted to investigate the efficacy of using Bi-TENS in stroke rehabilitation.

Acknowledgement
This study was supported by the Health and Medical Research Fund 12131821 awarded to Prof. Shamay S.M. Ng and her team from the Food and Health Bureau, HKSAR Government.

Appendix 6.4 The poster of "Effects of Bilateral Transcutaneous Electrical Nerve Stimulation Combined With Task-Oriented Training on the Recovery of Upper Limb Motor Impairment in People With Chronic Stroke" submit to *11th WORLD CONGRESS FOR International Stroke Conference 2021*.



Effects of Bilateral Transcutaneous Electrical Nerve Stimulation Combined with Task-oriented Training on the Recovery of Upper Limb Motor Impairment in People with Chronic Stroke

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Background and Introduction

Transcutaneous electrical nerve stimulation (TENS) is an effective adjunct intervention for people with stroke. At the peripheral level, TENS could reduce muscle spasticity, increase muscle strength, and improve motor control and functions. At the cortical level, TENS could enhance greater cortical activation of the lesioned sensorimotor cortex via afferent electrical stimulation. Results of previous studies has demonstrated that additional and spare neural pathways could be elicited through bilateral intervention. This study examined whether the combined use of bilateral TENS (Bi-TENS) and task oriented training (TOT) was superior to unilateral TENS (Uni-TENS)+TOT, placebo-TENS+TOT and no active treatment to improve the motor impairment of upper limb function (Fugl-Meyer Assessment of Upper Extremity) in people with stroke.

Methods

Design: Randomized controlled placebo trial

Subjects: There were 120 subjects with stroke (44 females and 76 males, mean age=61.52±6.73 years, post-stroke duration=6.04±3.12years) being randomly allocated into 4 groups, including the Bi-TENS group (n=30), Uni-TENS group (n=30), placebo TENS group (n=30) and control group (n=30).

Intervention: Subjects in the Bi-TENS group, Uni-TENS group and placebo TENS group received 20 sessions of treatment (3 times per week for 7 weeks), while the control group received no active treatment (Table 1). The location of the TENS electrodes was shown in Fig 1 and Fig 2.

Statistical Analysis: The linear mixed models (LMMs) were used to compare the changes over time in FMA-UE among the four groups.

Table 1 Intervention setting for each group

	Bi-TENS+TOT	Uni-TENS+TOT	Placebo-TENS+TOT	Control (no active treatment)
Paretic limb	TENS	TENS	Placebo-TENS	N/A
Non-paretic limb	TENS	Placebo-TENS	Placebo-TENS	
TOT	Practice of 60 minutes TOT concurrent with the stimulation			

Fig 1 electrode allocation on the radial nerve

Fig 2 electrode allocation on the median nerve

Fig 3 The details of the subject recruitment

Results

The details of the subjects recruitment was shown in Fig 3. The result of LMM was shown in Table 2.

Main finding:

- The Bi-TENS group had a significant greater improvement in FMA-UE scores than the Uni-TENS group, placebo TENS group and control group at post-intervention.
- The Bi-TENS group and Uni-TENS group showed a significant within-group improvement in FMA-UE scores since 10 sessions of treatment.

Table 2 The result of LMM of the outcome measures from pre-intervention to post-intervention

	Time Effect (Mean Difference+[95%CI], p Value)				Group Effect (Mean Difference+[95%CI], p Value)			Time-by-group Interaction Effect (Mean Difference+[95%CI], p-Value)			Time-by-group Interaction Effect (Mean Difference+[95%CI], p-Value)	
	Bi-TENS + TOT	Uni-TENS+ TOT	Placebo - TENS+ TOT	Control	Uni-TENS+ TOT	Placebo-TENS+ TOT	Control	Uni-TENS+ TOT	Placebo-TENS+ TOT	Control	Placebo-TENS+ TOT	Control
FMA-UE	3.25 (2.27, 4.23), <0.001*	1.23 (0.25, 2.21), 0.015*	0.76 (-0.22, 1.75), 0.126	0.17 (-0.81, 1.15), 0.730	-5.54 (-14.93, 3.86), 0.246	-10.89 (-20.28, -1.49), 0.023	-8.60 (-18.00, 0.79), 0.072	2.02 (0.63, 3.41), 0.005*	2.49 (1.10, 3.87), 0.001*	3.08 (1.69, 4.47), <0.001*	0.46 (-0.93, 1.85), 0.510	1.06 (-0.33, 2.44), 0.135

Mean difference * = The within-group changes or slope estimate across the three endpoints pre, mid and post-intervention

Mean difference ^ = The between-group difference of each of three groups (Uni-TENS+TOT, Placebo and Control) against the reference category: Bi-TENS+TOT group

Mean difference * = difference in the slope estimates for each of the three groups (Uni-TENS+TOT, Placebo and Control) against the reference category: Bi-TENS+ TOT group across the three endpoints: pre, mid and post-intervention.

Mean difference * = difference in the slope estimates for each of the two groups (Placebo and Control) against the reference category: Uni-TENS+ TOT group across the three endpoints: pre, mid and post-intervention.

*p<0.05

Conclusion

Bi-TENS is superior to Uni-TENS, placebo-TENS and control with no active treatment in enhancing the recovery of upper limb motor impairment assessed by FMA-UE in people with chronic stroke.

Author Disclosures

The authors received research support from the Health and Medical Research Fund 12131821 from the Food and Health Bureau, HKSAR.