INVESTIGATION OF MULTI-JOINT COORDINATED UPPER LIMB REHABILITATION ASSISTED WITH ELECTROMYOGRAPHY (EMG)-DRIVEN NEUROMUSCULAR ELECTRICAL STIMULATION (NMES)-ROBOT AFTER STROKE

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Investigation of Multi-Joint Coordinated Upper Limb Rehabilitation assisted with Electromyography (EMG)-Driven Neuromuscular Electrical Stimulation (NMES)-Robot after Stroke

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CERTIFICATE OF ORIGINALITY

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ABSTRACT

More than 80% of stroke survivors worldwide suffer from permanent upper limb motor deficits. Restoration of upper limb motor functions in conventional rehabilitation remains challenging; the main difficulties are as follows: 1) lack of intensive, repetitive practice in manually delivered treatment; 2) lack of coordination management of upper limb motor tasks, particularly those involving the distal joints, e.g., the wrist and the hand; and 3) lack of understanding of the optimal joint supportive scheme in task-oriented upper limb training. More effective training strategies are necessary for upper limb rehabilitation following stroke. Robots have proved to be valuable assistants in labour-demanding post-stroke rehabilitation, with a controllable mechanical design and repeatable dynamic support in physical training. A series of rehabilitation robots for multi-joint practices were successfully designed in our previous works. In this work, we proposed a device-assisted multi-joint coordinated strategy for post-stroke upper limb training. The objectives of the study were as follows:

1) To evaluate the rehabilitation effectiveness of multi-joint coordinated upper limb practice assisted by an electromyography (EMG)-driven neuromuscular electric stimulation (NMES)-robot for stroke survivors in both the subacute and chronic stages.
2) To compare different joint supportive schemes using NMES-robots and identify the optimized scheme for upper limb rehabilitation.

The objectives were achieved through three independent clinical trials using

common clinical assessments, namely, the Fugl-Meyer Assessment (FMA), Modified Ashworth Scales (MAS), Action Research Arm Test (ARAT), and Functional Independence Measurement (FIM), and cross-session EMG evaluations to trace the recovery progress of individual muscle activities (i.e. EMG activation level) and muscular coordination (i.e. Co-contraction Index, CI) between a pair of muscles.

The first clinical randomized controlled trial (RCT) was conducted to investigate the clinical effects and rehabilitation effectiveness of the new training strategy in the subacute stroke period. Subjects were randomly assigned to two groups and received either 20 sessions of NMES-robot-assisted training (NMES-robot group, n=14) or time-matched conventional treatments (control group, n=10). Significant improvements were achieved in FMA (full score and shoulder/elbow), ARAT, and FIM for both groups [$P<0.001$, effect sizes (EFs)>0.279], whereas significant improvements in FMA (wrist/hand) and MAS (wrist) after treatment were only observed in the NMES-robot group ($P<0.05$, EFs>0.145), with the outcomes maintained for 3 months. In the NMES-robot group, CIs of the muscle pairs of biceps brachii and flexor carpi radialis (BIC&FCR) and biceps brachii and triceps brachii (BIC&TRI) were significantly reduced and the EMG activation level of the FCR decreased significantly. The result indicated comparable proximal motor improvements in both groups and better distal motor outcomes and more effective release of muscle spasticity across the whole upper limb in the NMES-robot group.

The second part of the work was a clinical trial with a single-group design. Recruited chronic stroke patients (n=17) received 20 sessions of NMES-robot-assisted

multi-joint coordinated upper limb training. Significant improvements were observed in FMA (full score and shoulder/elbow), ARAT, and FIM ($P<0.05$, $EFs>0.157$) and maintained for 3 months. CIs of the FCR&TRI and BIC&TRI muscle pairs and EMG activation levels of the FCR and BIC significantly decreased. The results indicated that the new training strategy was effective for upper limb recovery in the chronic stroke, with the long sustainability of the motor outcomes.

In the third trial, another clinical RCT was conducted to investigate the training effects of different joint supportive schemes. The recruited chronic subjects were randomly assigned to receive task-oriented multi-joint practices with NMES-robotic support either to the finger-palm (hand group, n=15) or to the wrist-elbow (sleeve group, n=15). Significant improvements in FMA (full score and shoulder/elbow) and ARAT ($P<0.05$, $EFs>0.147$) were observed in both groups, whereas significant improvements in FMA (wrist/hand) and MAS (finger, wrist, and elbow) ($P<0.05$, $EFs>0.149$) were only observed in the hand group. These results indicated that the distal supportive scheme was more effective in distal motor recovery and whole arm spasticity control than the proximal supportive one under the same training strategy.

In conclusion, NME-robot-assisted multi-joint coordinated training was able to achieve significant motor outcomes and effective muscle spasticity control in the entire upper limb, especially at the distal segments, i.e., the wrist and the fingers, in both subacute and chronic stroke patients. Moreover, the distal supportive scheme proved more effective than the proximal supportive scheme in multi-joint coordinated upper limb training.

PUBLICATIONS ARISING FROM THE THESIS

Journal papers

1. Q.Y. Qian, X.L. Hu, Q. Lai, S.C. Ng, Y.P. Zheng, W.S. Poon. (2017) Early stroke rehabilitation of the upper limb assisted with an electromyography-driven neuromuscular electrical stimulation-robotic arm. *Frontiers in Neuroscience*, 8(1):447.

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3. Q.Y. Qian, C.Y. Nam, Z.Q. Guo, Y.H. Huang, X.L. Hu, S.C. Ng, Y.P. Zheng, W.S. Poon. (2018) Distal or Proximal? An Investigation of Different Supportive Strategies by Robots for Upper Limb Rehabilitation after Stroke. Journal of NeuroEngineering and Rehabilitation. Submitted.

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7. Y.H. Huang, Q.Y. Qian, X.L. Hu, Y.P. Zheng. (2017) Comparison of the rehabilitation effectiveness of EMG-driven robot hand assisted upper-limb training provided in practical clinical service and lab setting. Proceedings of the 8th World Association of Chinese Biomedical Engineering World Congress on Bioengineering. July-August 2017, Hong Kong: The Hong Kong Polytechnic University.

8. Q.Y. Qian, X.L. Hu, S. Ng, Y.P. Zheng, W.S. Poon. (2017) Multi-Joint Coordinated Upper Limb Training Assisted with a Neuromuscular Electrical Stimulation (NMES)-Robotic Arm in Early Stroke: A Pilot Study. *Wearable sensing, bio-robotics and molecular imaging for precision medicine*. Proceedings of the 11th IEEE-EMBS International Summer School and Symposium on Medical Devices and Biosensors (MDBS 2017) with the 10th International School and Symposium on Biomedical and

Health Engineering (BHE 2017). July 2017, Shenzhen: Southern University of Science and Technology.

9. Q.Y. Qian, X.L. Hu, Q. Lai, Y.P. Zheng, W.S. Poon. (2015) Post-stroke Upper Limb Rehabilitation Assisted with an Electromyography (EMG)-driven Functional Electrical Stimulation (FES)-robotic System. Proceedings of the 2015 IEEE-EMBS Hong Kong-Macau Joint Chapter Student Paper Competition. August 2015, Hong Kong: City University of Hong Kong.

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LIST OF ABBREVIATIONS

ARAT	Action Research Arm Test
CONSORT	Consolidated Standards of Reporting Trials
EMG	Electromyography
FIM	Functional independence measurement
FMA	Fugl-Meyer Assessment
FMA-SE	Fugl-Meyer Assessment for Shoulder-Elbow
FMA-UE	Fugl-Meyer Assessment for Upper Extremity
FMA-WH	Fugl-Meyer Assessment for Wrist-Hand
MAS	Modified Ashworth Scale
MMSE	Mini Mental State Exam
NMES	Neuromuscular Electrical Stimulation
UE	Upper Extremity

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CHAPTER 1

INTRODUCTION

1.1 Stroke

Stroke or cerebrovascular disorder is a public health issue associated with high rates of mortality and morbidity throughout the world [1]. A stroke episode occurs when the blood flow to part of the brain is interrupted or reduced, either due to an obstruction of blood supply or a rupture of the blood vessels or abnormal vascular structures [2]. Most strokes (80%) are classified as ischemic strokes, otherwise known as thrombotic or embolic strokes, which are caused by the narrowing or obstruction of the brain artery, significantly diminishing the flow of blood. Another type of stroke is the haemorrhagic stroke, which occurs when a blood vessel leaks or ruptures. There is also a milder form of stroke called transient ischemic attack (TIA), whereby the blood flow to the brain is disrupted transiently, without irreversible damage being inflicted. Regardless of type, stroke manifests as lack of oxygen and nutrients to the brain, as a result of which cells die in a matter of minutes (Figure 1-1). Furthermore, according to the brain area where the stroke lesion occurs, the condition manifests neurologically in different ways; for instance, hemiplegia (damage of the middle cerebral artery distribution area), cross sputum (damage of midbrain and pons), and quadriplegia (brain stem injury). Of these, the stroke manifestation with the greatest prevalence is hemiplegia with unilateral motor deficits that are the outcome of lesions in the middle cerebral region supplied by arterial blood.

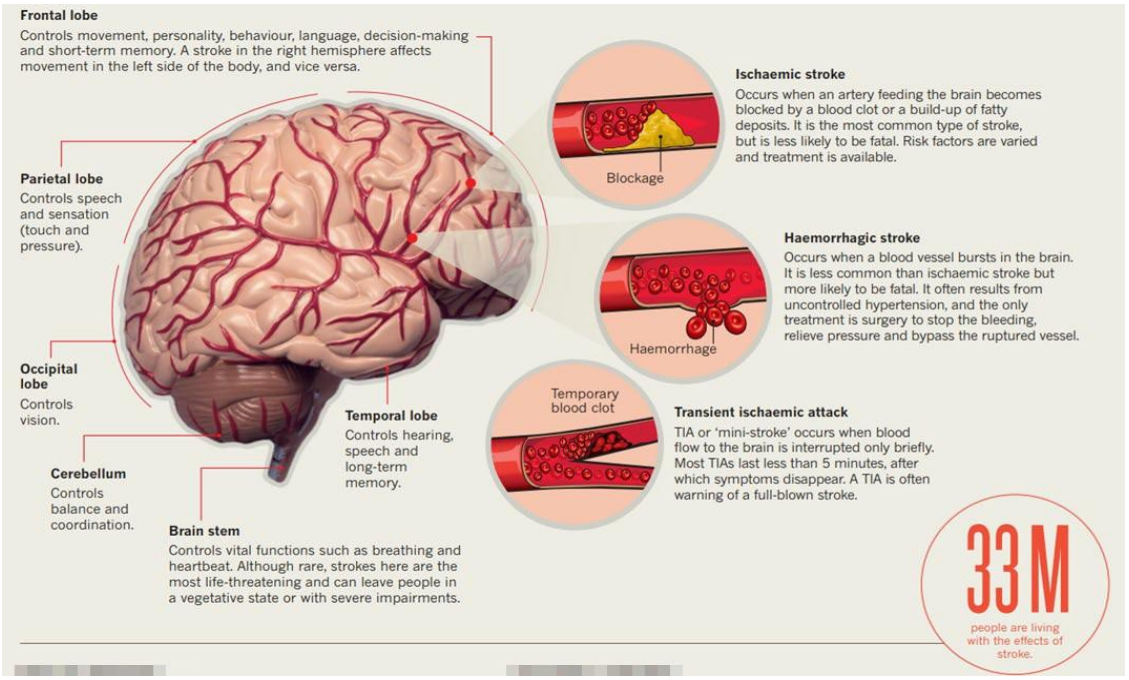


Figure 1-1. Overview of the various types of stroke according to onset pathogenesis and area of occurrence. Adapted from [3].

According to the World Health Report issued by the World Health Organization (WHO), stroke is the health condition with the second or third highest mortality rate in the majority of countries [4]. At the same time, the number of post-stroke patients has been increasing fast in the last ten years, as more and more stroke victims survive and as the general population ages [3, 5]. In Hong Kong, during the period 2008-2012, the number of stroke patients increased by over 24,000, as disclosed in the Hospital Authority Statistical Report (Table 1) [6]. The total number of stroke survivors in Hong Kong reached 300,000 by 2014 [7], while at the global level, this number exceeded 33 million [3], This massively increased the stroke-associated burden on the families of the patients or on society, with expenditure related to stroke care reaching around $73.7 billion in 2010 [8].

Disease 疾病類別	Detailed list number ICD 10th revision 《疾病和有關健康問題的國際統計分類》第十次修訂本的詳細序號	Number of in-patient discharges and deaths in Hospital Authority hospitals* 在醫院管理局轄下醫院住院病人出院人次及死亡人數*					Number of registered deaths in Hong Kong 全港登記死亡人數				
		2008	2009	2010	2011	2012	2008	2009	2010	2011	2012
1. Cancer 癌症	C00-C97	101,982	128,978	141,761	157,408	165,476	12,456	12,839	13,076	13,241	13,336
2. Cerebrovascular Disease 腦血管病	I60-I69	25,190	25,614	25,639	25,239	24,555	3,691	3,443	3,423	3,339	3,276
3. Ischaemic Heart Disease 缺血性心臟病	I20-I25	26,331	29,263	31,974	30,897	28,675	4,577	4,360	4,643	4,361	4,272
4. End Stage Renal Failure 末期腎衰竭	N18	88,293	103,615	108,951	115,940	122,731	1,021	1,037	991	1,103	1,132
5. Chronic Lung Disease 慢性肺病	J40-J47, J67	41,028	37,401	40,431	39,950	39,928	2,103	1,913	2,093	1,965	1,981
6. Diabetes Mellitus 糖尿病	E10-E14	18,495	24,502	23,274	22,138	19,587	548	492	522	457	398
	Total 合計	301,319	349,373	372,030	391,572	400,952	24,396	24,084	24,748	24,466	24,395

Notes: *Figures are on episode basis including day-patients.
Sources: Department of Health.
Hospital Authority.
註釋: * 數字包括日間病人，單位以人次計算。
資料來源: 衞生署。
醫院管理局。

Table 1-1. Statistical figures revealing the mortality rate associated with stroke in Hong Kong (Hospital Authority Statistical Report of Hong Kong 2012-2013) Adapted from [6]

1.1.1 Post-Stroke Upper Limb Impairment

A proportion of 75-90% of irreversible impairment is attributed to stroke, which is thus a major determinant of acquired adult disability [9]. Epidemiological studies reported that 80% of survivors of acute phase stroke started walking again on their own following rehabilitation therapy in the early post-stroke period [10, 11]; on the other hand, only 11.6% of stroke survivors demonstrated near-to-normal functional recovery when measured six months after the stroke episode, and 38% exhibited dexterity function to a certain extent [12, 13]. However, moderate to severe upper limb motor disabilities, primarily manifesting as irreversible motor impairment alongside

muscle weakness, spasticity or contraction and disrupted coordination of muscles, affect most stroke patients [14-16], having a significant impact on their functional independence and capability of undertaking activities of daily living (ADL) [17]. The dominant clinical perspective is that, compared to the lower limbs, the upper limbs recover motor function incompletely and less fast [18, 19]. Hence, stroke rehabilitation has always been geared towards the development of efficient clinical therapeutic strategies to achieve better neurological results for recovery of function in the upper limbs [20-22].

1.1.2 Post-Stroke Motor Recovery

Spontaneous and learning-dependent processes that occur at the same time are usually necessary to regain motor functions; these processes involve restoring the functionality of damaged neural tissue (restitution), restructuring of partly spared neural pathways to relearn lost functions (substitution), and attenuating the discrepancy between the capabilities possessed by patients and the environmental demands confronting them (compensation) [11, 23, 24]. Spontaneous recovery is defined as the self-generated neurological improvement with body functions, e.g. strength, attention and synergy, which is only determined by the passage of time. In large part, spontaneous recovery occurs in the initial days and weeks post-stroke, plateauing within six months [11]. Regarding the learning-based processes, one suggestion has been that severely impaired patients with poor prognosis following the initial weeks after stroke should be encouraged to make compensatory or substitutive

movements to make them more capable of undertaking activities. Meanwhile, repair of neurological functions by post-stroke interventions may be prioritized in patients with a more positive prognosis [25].

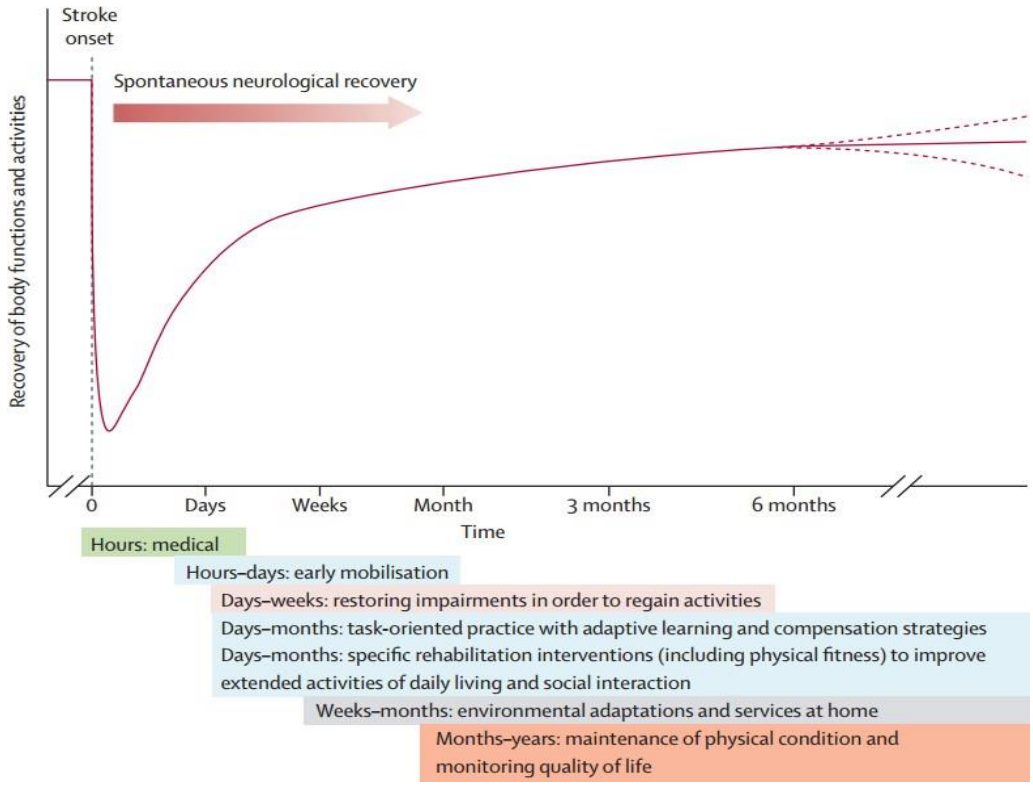


Figure 1-2. Presumptive recovery pattern post-stroke with intervention timing delineated by Langhorne et al. according to a systematic review of 178 clinical trial reports, reviews and associated protocols. Adapted from [11].

To maximize stroke survivors' functional independence through the use of various therapeutic strategies is the purpose of stroke rehabilitation. Both neurological recovery and functional or adaptive recovery are considered to be affected by rehabilitation and can take place at the same as they are interconnected [26]. The greatest proportion of recovery typically occurs in the initial six months after stroke, which is known as the subacute phase, while only 5% of stroke survivors showed

continued recovery at one year after stroke (Figure 1-2) [27]. According to some research, the affected upper extremity can improve functionally to a significant degree through physical activities of high intensity, even after six months from a stroke, which is known as the chronic phase [23, 28, 29]. The fast-paced development of neuro-biochemistry and molecular biology has recently led to a shift in motor recovery research towards modifications at synaptic/cellular level with molecular mechanisms. Nevertheless, there is a great deal of complexity attached to movement control after stroke and the characteristics and determinants of the movement recovery source have only partially been elucidated by the theories proposed [30-32]. The summary of clinical experience and past theoretical premises constitute the basis of widely applied manual-delivered rehabilitation strategies in a hospital or clinical context [11].

Stages	Characteristics
1	**Flaccid paralysis is present.** Phasic stretch reflexes are absent or hypoactive. Active movement cannot be elicited reflexively with a facilitatory stimulus or volitionally.
2	**Spasticity is present** and is felt as a resistance to passive movement. **No voluntary movement** is present but a **facilitatory stimulus will elicit the limb synergies reflexively**. These limb synergies consist of stereotypical flexor and extensor movements.
3	**Spasticity is marked**. The **synergistic movements can be elicited voluntarily** but are not obligatory.
4	**Spasticity decreases.** Synergy patterns can be reversed if movement takes place in the weaker synergy first. Movement combining antagonistic synergies can be performed when the prime movers are the strong components of the synergy.
5	**Spasticity wanes**, but is evident with rapid movement and at the extremes of range. Synergy patterns can be revised even if the movement takes place in the strongest synergy first. Movements that utilize the weak components of both synergies acting as prime movers can be performed.
6	**Coordination and patterns of movement can be near normal. Spasticity** as demonstrated by resistance to passive movement is **no longer present**. Abnormal patterns of movement with faulty timing emerge when rapid or complex actions are requested.
7	**Normal.** A "normal" variety of rapid, age appropriate complex movement patterns are possible with normal timing, coordination, strength and endurance. There is no evidence of functional impairment compared with the normal side. There is a "normal" sensory-perceptual motor system.

Table 1-2. Gowland's Brunnstrom stages of motor recovery after stroke. Adapted from [33].

In the aftermath of the Second World War, Signe Brunnstrom defined the post-stroke recovery process stages, which became known as the Brunnstrom staging approach and continues to be the main basis for the description of this process [34]. In 1993, Gowland and co-workers further refined this approach [33], identifying seven stages of the recovery process (Table 1-2). The overall purpose of this approach is to highlight the synergistic motion pattern post-stroke and how important early rehabilitation is for accomplishing movement autonomy. Another premise of this approach is that the process of recovery may stop at any stage but will never skip any one of them in the sequence. Among the standardized clinical evaluations of post-stroke functionality and recovery progress that have been significantly influenced by the Brunnstrom staging are the Fugl-Meyer Assessments (FMA) of voluntary physical performance [35] and the Action Research Arm Test (ARAT) of upper limb function and dexterity [36]. The present Stroke Rehabilitation Clinician Handbook and national physiotherapy guidelines for stroke level identification according to functional performance strongly advocate the associated clinical evaluation.

1.1.3 Assessments for Post-Stroke Recovery in the Upper Extremities

An essential condition for stroke rehabilitation is the stroke rehabilitation evaluation, which is intended to assess the aims of individual rehabilitation plans and estimate the likelihood of future recovery. Motor recovery in the upper extremities is usually assessed via the following clinical tests:

1) Mini-Mental State Examination (MMSE)

Prior to upper limb treatment, the Mini-Mental State Examination (MMSE), otherwise known as the Folstein test, is conducted to determine how severe and advanced cognitive impairment is, despite the fact that it does not undertake function evaluation or the task performance capability of the patient [37]. Consisting of a questionnaire with 30 items, the MMSE is an efficient approach for recording a patient's response following cerebrovascular system injury, a close correlation existing between that response and the therapist-patient interaction for the subsequent rehabilitation treatment [38].

2) Upper Extremity Fugl-Meyer Assessment (FMA-UE)

Proven to be highly consistent, responsive and accurate [39], the Fugl-Meyer Assessment (FMA) scale is a popular index for clinically evaluating motor function post-stroke [40]. The motor scale portion of FMA for upper limbs has the highest score of 66, which indicates that the paretic upper limb has attained complete moto-sensory recovery [41]. This scale consists of two sub-scales, namely, FMA-shoulder/elbow (42/66) and FMA-wrist/hand (24/66), which enable comparison of the functional recovery in the proximal and distal portions of the upper extremity. As previously mentioned, Brunnstrom staging approach was the basis for the development of the FMA-UE items, in keeping with a hierarchical scoring system determined by how challenging task performance was for patients.

3) Action Research Arm Test (ARAT)

Upper limb function and finger movement dexterity are measured based on the index called the Action Research Arm Test (ARAT), which comprises 19 items that evaluate four function aspects, namely, grasp, grip, pinch and gross movement. Every item is given a value of between 0, denoting lack of movement, to 3, denoting normal task performance, with impairment being more severe the lower the score is.

4) Modifies Ashworth Scale (MAS)

Spastic paralysis is engendered by a stroke over the process of recovery, as defined by Brunnstrom staging approach. A rapid and straightforward tool for evaluation of treatment efficiency, the Modified Ashworth Scale (MAS) undertakes measurement of resistance during passive soft-tissue stretching and creates a hierarchical scoring system, in which post-stroke spasticity increases the higher the score is [42].

5) Functional Independence Measurement (FIM)

In addition to assessing patients' post-stroke functional status, the Functional Independence Measure (FIM) also monitors alterations in patients' functional status from the start of stroke care until discharge and follow-up [43]. It is useful for gathering consistent data to compare training results over the rehabilitation continuum. It consists of 18 items, each of which is given a score of between 0 and 7. Patient autonomy in task performance related to a particular item is considered to be greater the higher the score achieved by that item is.

1.2 Upper Limb Rehabilitation After Stroke

1.2.1 Post-Stroke Neuroplasticity

Ample evidentiary support has been recently generated for the plasticity of the brain, even in adult individuals. Thus, numerous stroke rehabilitation treatments for motor recovery are based on post-stroke neuroplasticity.

Neuroplasticity refers to the capability of neurons and neuron aggregates to adapt their environment or use patterns, taking the form of either transient functional plasticity, such as alterations in synapse working efficiency and effectiveness [44], or durable structural modifications, such as restructuring and reactivation of nerve connections and neuronal structures [45]. Impulse conduction mediated by nerve fibres constitutes the basis of sensory input as well as the motor output of signals, and synapses are the major connections between nerve fibres. Owing to the possibility of removal (synaptic pruning) [46] or recreation (synaptogenesis) [47] of separate synaptic links according to the status and activities of the neurons bearing them, post-stroke neurological and structural recovery is crucially dependent on synaptic plasticity. The recovery process alongside behavioural experience post-stroke has a major impact on the reduction or increase in the number of synapses and on the increase or decline in the effectiveness of synaptic transmission. Several aspects frame the correlation between the theory of neuroplasticity and physical practice in the context of stroke rehabilitation:

1) The central nervous system of adult humans exhibits great capability for damage recovery and adaptation [48]. The research that has been conducted

in the past one hundred years has yielded ample proof for the contribution of neuroplasticity in the neural process during the early stroke, accomplished via spontaneous as well as rehabilitation process [49]. Early rehabilitation plans post-stroke are underpinned from a neural perspective by the mediation of alternative networks.

2) Damage to the neuron axon causes extension of its stump to the target issues or neuron cells for the creation of new synapses. Conversely, normal axons in the proximity of the injured region grow and extend to the target neurons. The structure and functions of neurons have been demonstrated to be changed by behavioural experience not only in damaged brains but also in healthy brains [50]. Earlier research has also highlighted that rehabilitation protocol and neuroplasticity were correlated in a 'dose-response' manner [51, 52], meaning that the growth of axons can be enhanced by high-intensity training, improving motor recovery after stroke.

3) Neuroplasticity is also associated with the activation of spared pathway residual arising during the human developmental process from cortex damage. Under normal conditions, the pathway is inactive, not being of great significance or even working for a particular function. This passive pathway is uncovered and takes on the primary function when the central nervous system sustains damage and the foremost neural pathway is obstructed. Recent research undertaken on human subjects revealed that passive pathway activation post-stroke depended significantly on task-based practices with

functional activities [53-55].

1.2.2 Efficient Training Standards for Upper Limb Motor Recovery

On the basis of the findings of systematic reviews of numerous clinical randomized controlled trials and neurological reports, a number of standards for efficient upper extremity rehabilitation training have been delineated to improve motor recovery and functional autonomy in everyday tasks as much as possible.

1) Early rehabilitation alongside voluntary effort:

There is ample evidentiary support for the widespread belief that rehabilitation should be commenced immediately following the stroke event [56]. A close correlation was found to exist between successful rehabilitation and self-motivation and engagement [11], while, by comparison to ongoing passive movement training, voluntary effort from the residual neuromuscular pathways has been proven to enhance performance [57, 58]. Furthermore, optimization of neural plasticity and motor responsiveness can be achieved through early physical rehabilitation alongside voluntary effort, maximizing motor results [59, 60].

2) Intensive training with precise repetition:

No ideal physical practice intensity has been specified by post-stroke rehabilitation standards, but a number of systematic reviews found that repeated practice of the impaired limbs at high-intensity level contributed significantly to successful motor rehabilitation post-stroke [29, 60]. Furthermore, cortical mapping studies based on functional MRI (fMRI) and PET [61, 62] and

neurological tests such as transcranial magnetic stimulation (TMS) [63, 64] revealed that training programs triggered modifications in cortical motor networks.

3) Coordinated motor control across multiple joints by task-oriented practice:

Coordinated movements in the context of particular training activities can help quicker achievement of motor autonomy in terms of functional daily tasks [65]. A number of systematic reviews provided evidence in support of this notion, highlighting that effective motor improvements could be transformed into relevant limb functions if movements from more than one joint were coordinated [16, 66] in task-oriented practice, particularly distal joints, such as the wrist and fingers [67]. Moreover, there is good compatibility between coordinated motor control and the recovery process based on Brunnstrom staging approach, focusing on transformations of muscle synergies in different parts of the upper extremities after stroke.

1.2.3 Conventional Therapeutic Treatments

Various rehabilitation therapies have been proposed for enhancing motor function in stroke survivors with impairment of the upper extremity, such as the Bobath approach [32] and constraint-induced movement therapy [68]. An overview of the main methods adopted in conventional stroke management was provided by Zorowitz and co-workers [69] (Table 1-3). The methods have been proven to be similar in their outcomes [70]. Furthermore, more than one method is usually employed in

conventional stroke rehabilitation of the upper extremity in clinical practice. It is rare for acute hospitalization for stroke to last long [19] and it excludes intensive rehabilitation due to the resource constraints, even in developed countries. Stroke patients survived the acute episode were either transferred to a rehabilitation hospital/unit or discharged back home.

Author/type	Theory
Bobath (NDT)	Suppress synergistic movement
	Facilitate normal movement
Taub (CIMT)	Suppress normal use of the unaffected limb
	Facilitate intensive use of the affected limb
Knott, Voss (PNF)	Suppress normal movement
	Facilitate defined mass movement
Rood	Modify movement with cutaneous sensory stimulation
Others	Range of motion/strengthening
	Compensatory strategies
	Mobility/activity of daily living training

Table 1-3. Overview of the main methods of conventional rehabilitation treatments

Two representative and widely used therapeutic methods are as follows:

Bobath approach, also known as the neuro-developmental treatments (NDT), is one of the major manual-delivered therapies in conventional stroke rehabilitation [32]. It aims to re-educate patient's affect limbs with normal movements and emphasizes on a hierarchical level of motor control. The concepts by Bobath describe the recovery of movement from a stroke as a predictable sequence that mimics the normal developmental sequence of maturing infants. According to the 'neuro-developmental' theoretical statements, the recovery of movement would initiate in the proximal (i.e.,

elbow, shoulder and shoulder girdles) and gradually generated to more distal segments (i.e., finger, palm and wrist) [71], and the training on the proximal segments would encourage the return of distal motor control [32, 72]. Besides, Bobath approach separates repetitive practices apart from task-oriented training, with a suggestion of 'facilitating the components of normal movement will automatically lead to improvement in functional tasks'. The concepts may either be due to the previous hierarchical model of motor control [73] or refer to the considerable pressure to provide rehabilitation in less resource cost [11]. Coordinated upper limb practices among different joints, especially the involvement of the distal joints (e.g., the wrist and fingers) was found more effective to translate the motor improvements into meaningful limb functions than single joint practice [67]. Nonetheless, David G. has pointed out that in the complex motor training, more than one single operator, either a therapist or nurse, should be involved to provide the complex treatment in manual-delivered practice [11]. The multi-joint training mode is in high-costly and not that feasible for the conventional rehabilitation treatments in current hospitals due to the resource constraints. The cooperative work among the trainer team as well as between trainers and the patient is also a great challenge with the requirement of high intensity and precise repetition in the training. That is why rare works have been done to investigate the training effects and effectiveness of the multi-joint coordinated physical training.

Classical constraint-induced movement therapy (CIMT) and its modified protocol (mCIMT) adopt representative intensive training strategy in conventional

rehabilitation and aim for post-stroke upper limb motor independence. The key feature is to restrict unaffected or less affected upper limbs and maximize the use of the affected side. The studies on its clinical effectiveness implied the training outcomes is strongly related to the intensity of CIMT, demanding a high cost of resource[74]. Besides, selection criteria for CIMT research have excluded patients with a moderate or more severe stroke[75].

1.2.4 Device-Assisted Therapeutic Interventions

1.2.4.1 Rehabilitation Robots

Robots could not merely provide consistent physical training with high-intensity and precise repetitions over a long duration [76], but also facilitate movement control on multiple UE joints through the application of electrical motors in different numbers and with varying sizes and mechanical structures [77]. Moreover, to determine improvement or degradation in functionality during training, patients' performance could be quantitatively measured with robotic devices through real-time monitoring or offline data processing.

According to types of movement, there are three categories of rehabilitation robots that have been created in the last ten years, namely, robots with continuous passive motion (CPM), robots with active-assisted movement, and robots with challenge-based movement.:

1) Robots with CPM take full control of the motions in patients' paretic upper extremities and the patients do not have to perform any voluntary effort of their own. Although these types of robots demonstrated efficiency in attenuating muscle spasticity after stroke, the effect was not maintained for long [78].

2) Volpe [79] and Tong [80], who were in two separate research groups, reported the involvement of voluntary motor efforts of the paretic limbs in stroke patients receiving active-assisted robotic training. External mechanical assistance from the robotic devices was provided only in cases where patients could not carry out a particular movement on their own and compensate for the muscle weakness in the affected upper extremity. The study outcomes revealed that, compared to the results of CPM intervention, voluntary involvement with robot assistance led to improved motor rehabilitation.

3) A robotic rehabilitation system based on robot resistance as the challenging control in challenge-focused movement mode was created by Fasoli et al. [81] who argued that, compared to neuro-developmental approaches, enhanced motor recovery could be achieved through repetitive practice of hand and finger motion against resistive loads, as reflected in the clinical scores obtained. This was confirmed by other studies as well [82, 83]

In recent years, various rehabilitation robotic systems have been developed for specific training purposes and applied to different upper limb segments [35, 79, 84-

87]. The three types of movements discussed before can be achieved with the majority of these systems. Furthermore, one or multiple randomized controlled trials were conducted to assess systems like the MIT-MANUS (designed and built at the Massachusetts Institute of Technology; Interactive Motion Technologies, Inc, Cambridge, MA), the ARM Guide (Assisted Rehabilitation and Measurement guide), the MIME (Mirror-Image Motion Enabler), the InMotion Shoulder-Elbow Robot, and the BiManu-Track. The MIT-MANUS permits reaching motions in the horizontal plane in case of upper extremity impairment caused by stroke, while its impedance control property allows free shoulder and elbow joint movements with two degrees of freedom (DoF) in perturbed circumstances [83, 88]. Taking the shape of a trombone, the ARM Guide helps the training as well as the assessment of the reaching ability of the upper extremity in a linear direction [89]. Meanwhile, bilateral movement of the shoulder and elbow with three degrees of movement is allowed by the MIME robot, with the paretic limb being guided by the non-paretic one [90, 91]. The InMotion Shoulder-Elbow Robot, which is the commercial version of MIT-MANUS, enables training of the shoulder and elbow in a horizontal plane with two degrees of freedom and support for the forearm [92]. The Bi-Manu-Track permits practice not only of bilateral elbow pronation and supination but also of wrist flexion and extension in a mirror or parallel manner for the purposes of training the motions of the distal part of the upper limb [93]. Such robots were proven in clinical research to enhance functionality in the proximal part of the upper limb following post-stroke

rehabilitation training, but they failed to improve the functionality of the distal part of the upper limb.

A number of robotic systems initially intended for the hand can be used for training after stroke as well. One such system is the Hand Wrist Assistive Rehabilitation Device (HWARD) system [94] and the HapticKnob system [95], which can respectively enable the hand grasping/opening and wrist extension/flexion movement and the hand grasping and forearm pronation/supination movement. Furthermore, hand motor functions were improved after rehabilitation training with hand/wrist robotic assistance. According to Takahashi and Lambercy, who designed the robots, the restricted improvement of functionality in the proximal joints could be explained in terms of the fact that the robotic systems are used primarily in hand/wrist practices, rather than the entire upper extremity.

The use of robots permits the sharing of a considerable proportion of repetitive manual work between therapists, while customization of upper extremity movements in keeping with the requirements of each patient is possible. As regards the training results of robot-assisted treatment, however, the outcomes obtained by previous studies have lacked consistency. Nevertheless, the majority of studies indicated that by comparison to standard therapy delivered manually, training with robotic systems led to either similar or better improvements [96-99]. Meanwhile, CPM robots with support provided to large and proximal joints did not achieve the favourable outcomes achieved by standard manual treatment on the entire upper extremity [79, 100].

With regard to the long-term outcomes of the use of robotic devices in rehabilitation training, the findings obtained by earlier studies are inconsistent as well. For example, Bovolenta et al. reported that the marked improvements in the motor function of the upper limb observed in their study immediately after training with robotic assistance largely disappeared within three months after therapy [98]. On the other hand, a different study by Housman and colleagues reported that training with robotic assistance led to a major motor recovery in the upper limb and its effects were maintained for six months or more after therapy [81]. The various rehabilitation effects induced by robots are not only due to discrepancies in the control design of these devices but also to the different ways in which upper limb joints are mechanically supported during training. As reported by Krebs and colleagues, robotic assistance was applied on a single wrist joint but the treatment achieved additional motor improvements in the elbow-shoulder segments, while the elbow-shoulder parts were restricted to move in the training [101]. Similar motor improvements in the proximal joints relative to the target distal joints were also reported by Hu and colleagues when using electromyography (EMG)-driven robots to assist respective physical practices at the fingers and the wrist, with the effects achieved in both the proximal and the distal joints lasting for three months following therapy completion [102, 103]. The competitive proximal-distal joint interaction in post-stroke physical rehabilitation and the compensatory muscular activities in the proximal joints in response to the distal joint movement were the reasons for proximal joint improvement when training was focused on the distal joints [104]. It must be noted that, during physical training,

muscular synergies in the upper limb could be disrupted by mechanical strategies of support. Additionally, previous research has not paid sufficient attention to the different rehabilitation effects of various strategies for joint support.

1.2.4.2 Neuromuscular Electrical Stimulation (NMES)

Neuromuscular electrical stimulation (NMES) is a technique that can generate limb movements by applying safe levels of electrical current to activate the damaged or disabled neuromuscular system [105], typically by using surface electrodes. When a sufficiently strong external electric field is applied to a nerve via a pair of electrodes, depolarization of the axon will occur. And if the depolarization with sufficient intensity reaches the threshold, an action potential will fire on the axon membrane and propagate bidirectionally. The number of nerve fibres activated during applied stimulation will be related to the amount of phase charge delivered with each pulse [106]. Depolarization of motor axons or terminal motor nerve branches leads to the electrical activation of motor units. Direct muscle stimulation could retard muscle atrophy and it has been reported that denervated motor neurons in the lower extremity muscles could be restored through surface electrode-based NMES therapy [107].

The training effects triggered by NMES have been elucidated in terms of two mechanisms [108, 109]. One mechanism is that NMES enhances muscle strength in a comparable way to the voluntary physical activity. Therefore, NMES strengthening strategies must comply with standard strengthening protocols, which require few repetitions with high external loads and highly intense muscle contraction. The other

mechanism purports that reversal of voluntary recruitment sequence with the selective strengthening of type II muscle fibres is the reason why muscles strengthen after NMES training. Muscles can be made stronger on the whole through selective enhancement of type II muscle fibres, as the specific force of these fibres is greater than that of type I fibres. In the context of stroke rehabilitation training, muscles are strengthened and prevented from atrophying based primarily on the second mechanism [105, 110]. This is because that the type II glycolytic fibres will convert to type I oxidative fibres over weeks to months, depending on the intensity and frequency of stimulation.

The principle underpinning the mechanism of NMES-based therapeutic effects of rehabilitation after stroke is that recurrent sensorimotor experiences are triggered by a cyclic electrical stimulation on the muscles, modulating the plasticity of the central nervous system when the paralyzed or paretic muscle contracts [111]. NMES induces transmission of afferent inputs along sensory pathways originating from both muscular and noncontractile structures. Functional MRI studies have demonstrated that NMES in the periphery can activate both sensory and motor areas of the brain with facilitated motor relearning [112].

Evidence-based review of stroke rehabilitation concurs that NMES can serve as effective auxiliary therapy. This review encompassed 49 RCTs published up to 2015 and focusing on NMES-based upper extremity training after stroke [70]. There is strong evidence that NMES treatment improves upper extremity function in acute

stroke (<6months post onset) and chronic stroke (>6 months post onset), either on its own or alongside conventional therapeutic treatment. Improvement of functionality is achieved by NMES through limiting the “learned disuse”, which is deemed a major obstacle to successful recovery as it causes patients to progressively get used in their daily activities post-stroke, relinquishing the use of particular muscles [113].

1.2.4.3 Electromyography(EMG)-driven NMES-Robotic System

The neuroplasticity theory of sensorimotor integration argues that brain restructuring draws on both voluntary motor efferent and afferent sensor experiences [114]. It is advisable for post-stroke physical training to include voluntary effort [70] which should be induced immediately in the movements of the paretic upper extremity [115]. Among the wide range of signals employed to highlight voluntary effort in rehabilitation training are limb torque, trajectory and electromyography (EMG) [79, 116, 117]. In our previous studies, a series of voluntary intention-driven rehabilitation robotic systems [118-121], e.g. the PolyJbot (Figure 1-3) and the Robotic Hand Training system (Figure 1-4), have been designed for different joints motor functions by using residual EMG as a bio-indicator from the paretic muscles.

EMG is the electricity generated in muscles under the control of the nervous system. Its detection can be done at the surface of the skin in a manner that is not invasive, with the amplitude in millivolt. Numerous orthotic and prosthetic devices for aiding paralysis incorporate EMG signals as markers of voluntary effort [122-125]. The EMG-driven control strategy has been one of the rapidly expanding techniques

for maximizing the involvement of voluntary efforts during the training process [57, 79]. Earlier studies reported that, compared to CPM robots, EMG-based robots not only helped stroke patients to undertake a voluntary effort task but also led to improved motor results [126].

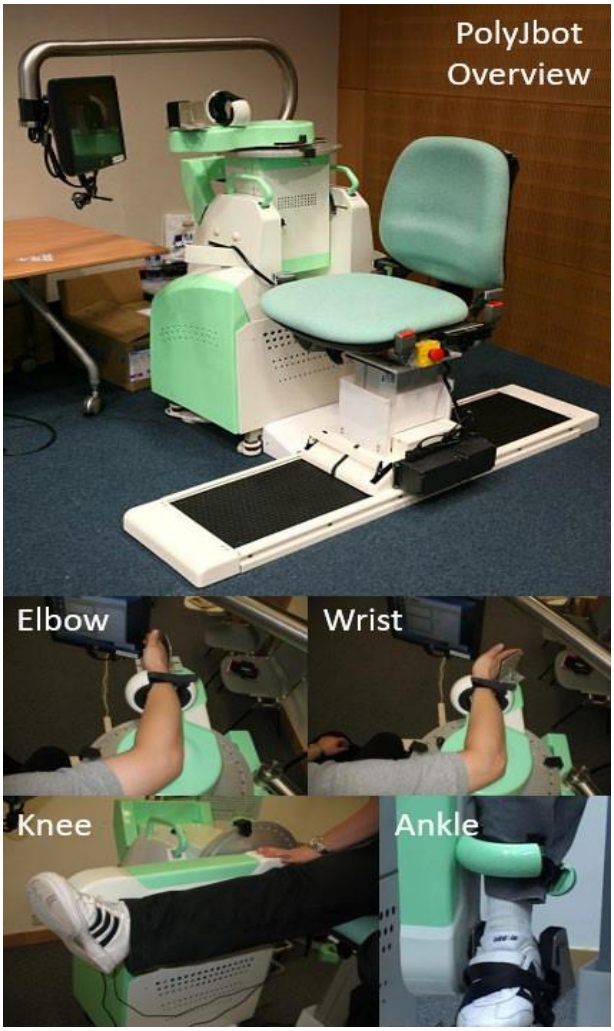


Figure 1-3. The PolyJbot rehabilitation training system. Adapted from [127].

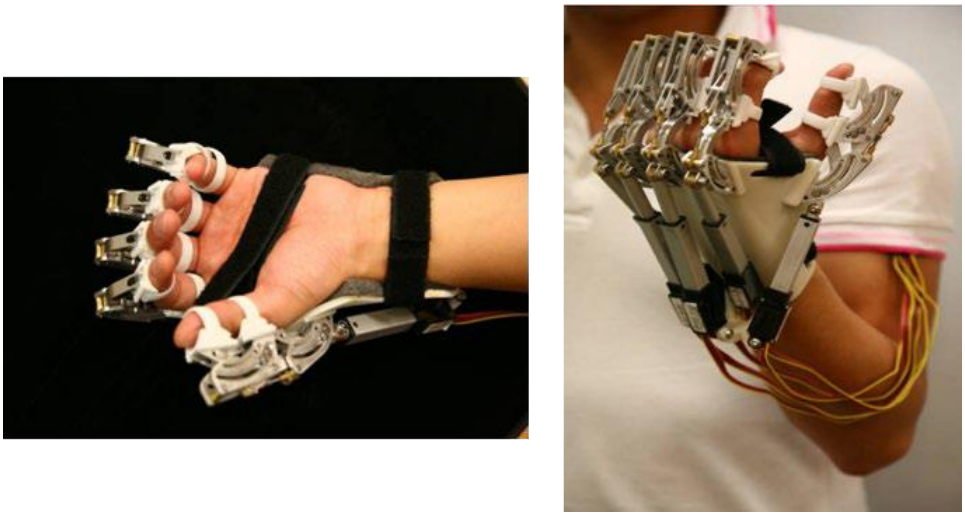


Figure 1-4. The Robotic hand rehabilitation training System: a system driven by electromyography (EMG), developed on the basis of a PolyJbot prototype. Adapted from [128]。

Hu et al. proposed a wrist rehabilitation system incorporating NMES alongside the EMG-driven robot [116, 142, 143], with EMG driving both the robot and NMES [102, 129, 130], where both NMES and robot were driven by EMG (i.e., EMG-driven NMES-robot) (Figure 1-5). In this way, the limitations of each method on its own were mitigated. As illustrated by previous studies, a robot is incapable of direct activation of the target muscles or of efficient minimization of compensatory contractions of other muscles or muscle groups. Meanwhile, using NMES alone could hardly achieve the desired accuracy in kinematics, such as speed and trajectories, as in the robot-assisted training. The related clinical trials suggested that the integration of NMES and robot could strengthen the benefits of both methods. The use of NMES-robot could the respective advantage of each technique diminished excessive muscular activity at the elbow and led to a longer sustainability of the motor improvements compared to those by pure-robot [131].

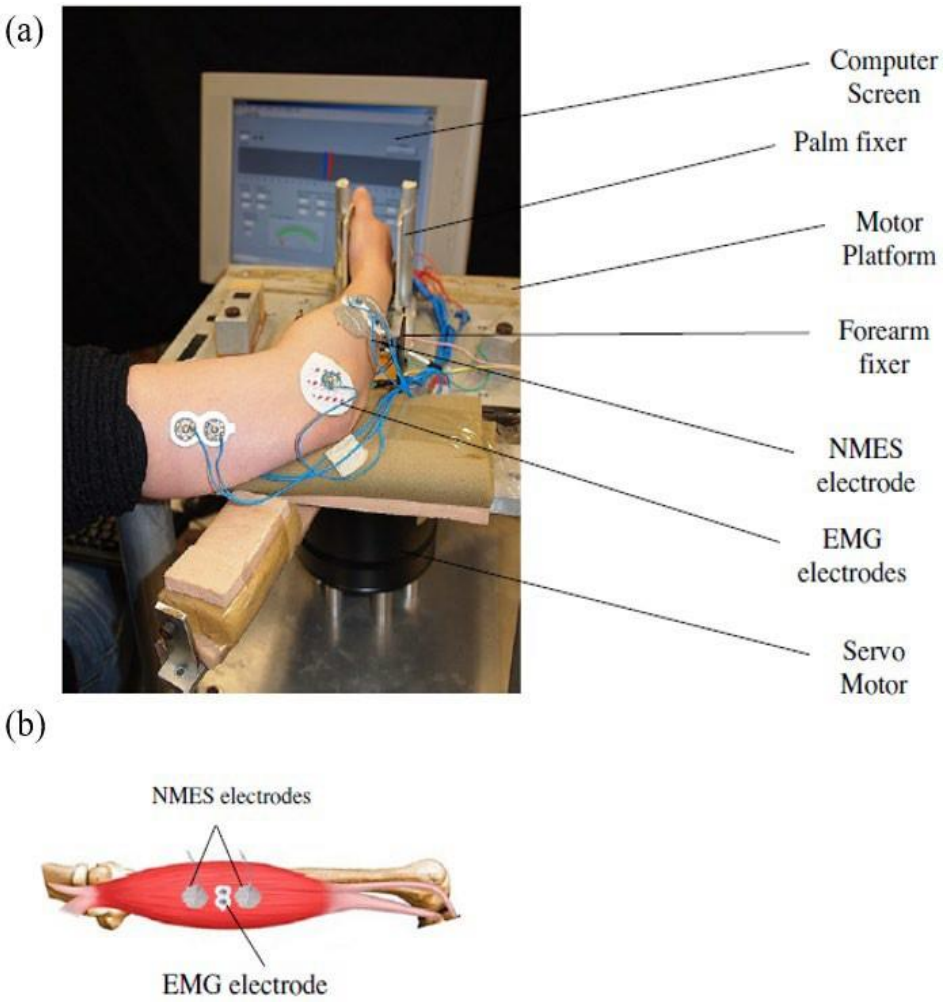


Figure 1-5. (a) The experimental setup of the integrated NMES-robot system; (b) Configuration of NMES and EMG electrodes. Adapted from [132].

Development of the EMG-based NMES-robot training system has been focused on making this system compatible with various physical training objectives at the elbow, wrist and fingers, with wearable and portable exoskeleton designs. One such design is the so-called Rehabilitation Sleeve, which consists of two mechanical modules, i.e. the wrist module and the elbow module, as shown in Figure 1-6. These modules can be worn either separately or jointly in one training session for the upper extremity. To make sure that they could be used by patients with various ergonomic

parameters, such as limb length and pronation angles away from the wrist neutral position, the modules were designed mechanically separate, since joints are stiff and muscles are spastic after a stroke [133]. Hence, stroke survivors can wear the new EMG-based NMES-robot device without difficulty, enabling the affected arm to carry out coordinated movements engaging multiple joints.

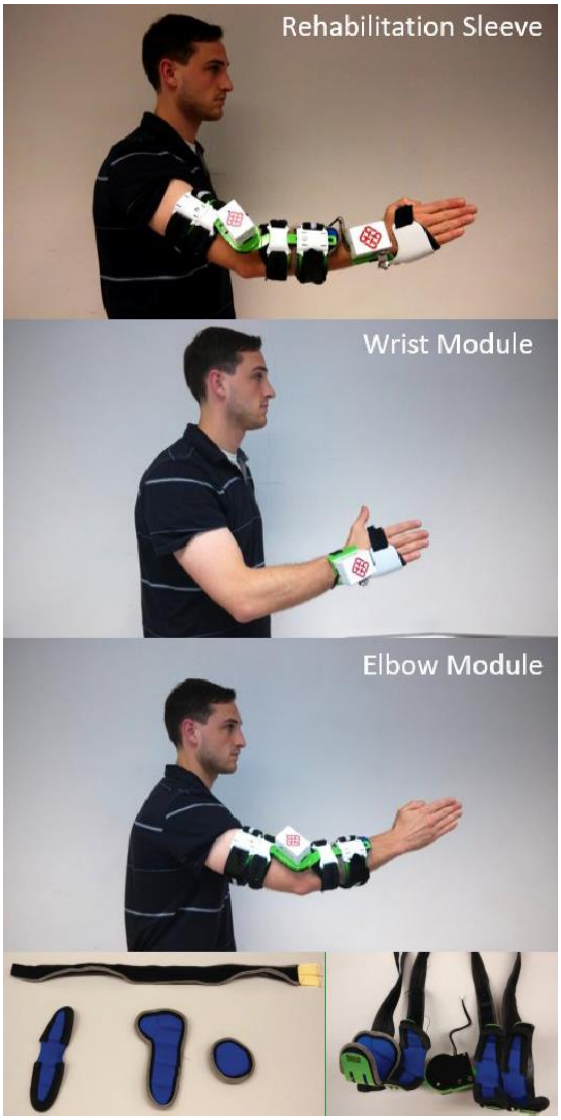


Figure 1-6. Developed EMG-driven integrated NMES-robotic training system with wearable and portable design, named the Rehabilitation Sleeve, which integrated the novel bracing system in the exoskeleton orthosis. Adapted from [134]

1.3 Objectives of the study

1.3.1 Research Gaps

At present, conventional therapeutic treatments for post-stroke upper limb rehabilitation in clinical practice are mainly manual-delivered. Nevertheless, the training effects of such treatments are falling short of clinical professionals' expectations [134-136] with numerous stroke patients leaving the hospital with dysfunctional upper limbs despite having received standard rehabilitation therapy in time [137].

Post-stroke rehabilitation requires continuous long-term treatments [138]. Enhanced functionality in the impaired upper limb is significantly aided by repetitive [28] and high-intensity practice [29], even in cases of chronic stroke where recovery usually plateaus [23]. Nevertheless, conventional manual therapies could hardly provide adequate or intensive practice in a consistent and precise manner for patients with upper limb impairments due to the lack of sufficient resources, which is an issue even in developed countries [139]. Furthermore, most manually treatments are time-consuming and labour-demanding, leading to tiredness at the side of physiotherapists, which makes the motion discontinuous, inaccurate, unstable and non-repetitive. Moreover, the therapist's experience and professional competence determine the motion control details such as movement track, speed and range of motion (ROM) [140]. For this reason, comprehensive characterizations of conventional treatment are infrequent and details are ignored by some studies when evaluating efficacy and outcomes [136]. Besides, there is also a considerable pressure to provide rehabilitation

in less-costly settings, despite the evidence that comprehensive intensive training may be superior to less-intense programs [19].

Furthermore, daily activities could be simulated through multi-joint practice alongside task-based training, which has been demonstrated to successful to achieve the conversion of motor improvements into meaningful limb functions [65]. However, it is difficult to manage the movements of different joints (e.g. fingers, wrist, and elbow joints) of the entire upper limb at the same time in conventional physical training adopting "one-to-one" manual-delivered therapies. Therefore, a pair of therapist-patient unit usually starts the training on the larger and more proximal joints, improving motor outcomes in the proximal segments rather than in the distal during the early rehabilitation after stroke. Under such circumstance, the finger, wrist and elbow flexors are frequently contracted following initial treatment, since the distal upper extremity has been kept in a rest position for a long time. The use of distal muscles is ignored in the instructions during the early stroke, and the muscle function is gradually replaced by the compensatory movement from the proximal muscles. Hence, the abnormal synergistic motion pattern, known as the 'learned non-use', is negatively reinforced during the chronic period, with compensatory movements being extended to this period [141].

Another reason for therapists' priority to treat in the proximal upper limb rather than that in the distal joint was due to the 'neuro-developmental' hypothesis [142], Some early related studies believed that a proximal to distal gradient of motor deficits would appear in patients after stroke [115, 143]. Current studies have challenged these

concepts, arguing that their scientific foundation is not robust enough [144-146]. Recent researches reported that the recovery process after a stroke is not monotonous with a specific training sequence [11]. Pineiro et al. discovered that the severity of motor deficits after stroke, indeed, is only related to the degree of corticospinal system damage [147]; while two other studies on the upper limb motor control reported that the segments in the entire upper extremity are similarly affected after stroke, without the gradient supposed in previous literature [148, 149]. Meanwhile, insufficient research has been conducted to determine how efficient various joint-supportive strategies were for upper extremity training after stroke, since standard treatments delivered manually cannot afford a motor control with the same training intensity on both proximal and distal joints. Thus, it is still unclear whether the enhanced joint-supportive strategy in task-based upper extremity training should be applied to the distal joints or the proximal ones.

The major difficulties in conventional stroke rehabilitation to achieve effective motor improvement and functional independence in the upper limb training could be summarized as follows:

1) Lack of intensive, repetitive practice in manually-delivered treatments;
2) Lack of coordinated management of upper limb motor tasks, particularly difficult to engage the distal joint movements, e.g., at the wrist and the fingers.
3) Lack of understanding of the optimal joint-supportive scheme in task-oriented training with multi-joint upper limb practices

1.3.2 Research Objectives

In this work, we designed to propose a more effective training strategy for upper limb rehabilitation after stroke, that is, the device-assisted multi-joint coordinated training.

Robots are valuable assistants in the labour-demanding post-stroke rehabilitation with controllable mechanical design and repeatable dynamic support in the physical training. Meanwhile, NMES could direct prompt and enhance the desired muscle contractions thus to improve motor coordination. A series of rehabilitation robots for multi-joint practices have been successfully designed in our previous works. Among them, an EMG-driven NMES-robotic hybrid system was adopted in this study where both NMES and robots were driven by voluntary evoked electromyography (EMG) from patients' paretic upper limbs. The robots could assist a stroke survivor to conduct upper limb tasks simulating daily tasks, e.g. coordinated arm reaching, hand grasping and releasing, with respective mechanical support to the elbow, wrist and fingers. There is evidence that voluntary effort was successfully engaged during training by the EMG-driven control strategy underlying such robots [57, 79]. The use of an NMES-robot system also allows a single trainer to instruct the multi-joint coordinated upper limb treatments with less labour work.

The objectives of the study are:

1) To evaluate the rehabilitation effectiveness of multi-joint coordinated upper limb practice assisted by an EMG-driven NMES-robot for stroke survivors in both the subacute and chronic stages.

2) To compare different joint supportive schemes using NMES-robots and identify the optimized scheme for upper limb rehabilitation.

1.3.3 Clinical Trials

The training effects and effectiveness are evaluated through three independent clinical trials with the common clinical assessments, i.e. MMSE, FMA, ARAT, MAS and FIM as specified in section **1.4**. In addition, a session-by-session EMG evaluation approach is applied in this study. EMG parameters were evaluated before each training session in order to trace the recovery progress of target muscles (i.e. the normalized EMG activation level) and the evolution of the muscle coordination (i.e. the normalized co-contraction index, CI between a pair of muscles) during the course of training.

The first study was aimed to investigate the training effects of the multi-joint coordinated upper limb training with assistance from an EMG-driven NMES-robot sleeve in subacute stroke patients, as well as to compare the effects with those achieved by conventional manual therapies. The study was a clinical randomized controlled trial with a 3-month follow-up.

The second study was aimed to investigate the training effects of the NMES-robot-assisted multi-joint coordinated upper limb training in chronic stroke patients. The study was a clinical trial with the single-group design.

In the third study, we hypothesized that different mechanical supportive strategies

to the joints in upper extremity might lead to distinguished recovery efficiency. The aim of this work was to investigate the training effectiveness of the multi-joint coordinated upper limb with robotic support to the distal (finger-palm) and to the proximal (wrist-elbow) segments in the task-oriented practices, and also to compare the training effects of the two supportive schemes. The study was also a clinical randomized controlled trial with a 3-month follow-up.

CHAPTER 2

EARLY STROKE REHABILITATION WITH MULTI-JOINT COORDINATED UPPER LIMB TRAINING ASSISTED BY AN EMG-DRIVEN NMES-ROBOTIC SLEEVE

2.1 Introduction

Less than 25% of stroke survivors experiencing upper extremity paralysis (UE) achieve near-to-normal motor recovery after survival from acute stroke episode, greatly affecting their daily living [10, 12]. Most motor recovery is believed to occur within the initial several days to weeks and plateaued within 6 months after stroke, i.e. in the subacute period [150]. Physical practice in this period can optimize the recovery progress by both spontaneous and learning-dependent processes, and result in maximized motor outcomes [151, 152]. Besides, the motor achievements from the subacute period are easier to be transferred into daily activities when compared with the treatments administrated in the chronic period (i.e., over 6 months after stroke) [153, 154]. One of the major reasons is that patients with newly acquired stroke have not been used to the learned non-use pattern by using intact limbs only for daily activities as observed in the chronic stroke commonly. Physical practice with high-intensity and precise repetition have been proven to speed up the motor restoration process in the early strokes [150, 155]. Besides, the involvement of voluntary effort from the residual neuromuscular pathways has been convinced to show better improvements with

higher efficiency when compared with the CPM trainings [57, 156]. Furthermore, management of coordination among different joints is more effective to translate the motor improvements into meaningful limb functions than repetitive practice with single joint [67].

However, conventional rehabilitation treatments for subacute stroke during hospitalization are usually 'one-to-one' manual-conducted by human therapists, usually time-consuming and labor-demanding [22]. As specified in **1.3.1,** current medical and healthcare system could hardly provide adequate repetitive and intensive rehabilitation treatments to persons with subacute stroke due to the shortage of professional manpower in the physical therapy industry [157]. It is always a difficulty for human therapists to instruct the coordinated upper limb motions with both proximal (i.e., the shoulder and the elbow) and distal joints (i.e., the wrist and the fingers) together in the clinical practice [158].

In our previous works, a series of exoskeletal robotics that adopt EMG-driven strategy for physical training at different UE joints have been designed [102, 118-121]. Residual electromyography (EMG) from the paretic muscles was used as markers of voluntary effort to control the robots to provide assistive torques for desired motions [102]. It has been found that that robot alone could not directly activate the desired muscles or muscle groups and could hardly limit the compensatory contraction in the other non-target muscles. However, the voluntary practice could improve the motor functions of the limb with longer

sustainability [79, 118]. Meanwhile, another prevalently used technique in stroke rehabilitation, the neuromuscular electrical stimulation (NMES), could apply programmed electrical currents directly to the paretic UE muscles, thereby generate limb movements [159]. The NMES could not only effectively prevent muscle atrophy and improve muscle strength, but also precisely stimulate the target muscles, as reported in systematic reviews [159, 160]. Based on other research, when the paralyzed or paretic muscle contracts, NEMS was also found to evoke sensorimotor feedback to the brain, and modulate the plasticity of the central nervous system [161]. Despite its advantages in stroke rehabilitation, the problem for using NMES alone is its kinematic inaccuracies, such as motion speed and trajectories. Hence, in the subsequent work, we integrated the NMES into the EMG-driven robots (i.e., the EMG-driven, NMES-robotic system) [102, 162-167].

In this study, we hypothesized that device-assisted post-stroke multi-joint coordinated training in the subacute stroke period could achieve the initiation of voluntary effort in the paretic arm and could enhance the muscular coordination across joints. An EMG-driven NMES-Robotic sleeve was adopted in this work to support the multi-joint coordinated training in stroke patients' paretic upper limbs. The training effectiveness was investigated through a randomized controlled trial in comparison with the conventional upper limb physical rehabilitation in hospital on persons with subacute stroke.

2.2 Methodology

2.2.1 EMG-Driven NMES-Robotic Sleeve

Figure 2-1 illustrates the EMG-driven NMES-Robot sleeve selected for the purposes of the present study. This sleeve enables four-stage performance of consecutive and iterative movements, namely, elbow extension, coordinated wrist extension and hand opening, wrist flexion, and elbow flexion. The movements permit simulation of multiple joint synchronization in movements of arm reaching and withdrawing in the context of everyday tasks. 180° elbow extension and 45° wrist extension constituted both the initial and final movement cycle positions. Furthermore, for the elbow joint and wrist, the maximum range of motion (ROM) was respectively established from 30° in flexion to 180° in extension and from 60° in flexion to 45° in extension. Application of the elbow and wrist ROMs on stroke patients in earlier studies [102, 119, 161] enabled assessment of how feasible they were. A bracing system that could adjust pressure application on skin to reduce device movement as the limb was moved repetitively was used for fixation of a patient's paretic arm in a solid exoskeleton orthosis [168]. The two autonomous servo motors MX 106 and ROBOTIS, with 8.4 Nm maximum stall torque regulated the motion of the mechanical exoskeleton for the elbow and wrist [161]. The implementation of the system involved the use of a hanging mechanism to lift the system-mounted paretic upper limb horizontally (Figure 2-1). During the early subacute phase, muscle weakness was more prevalent among stroke patients compared to spasticity like in the chronic phase, and shoulder muscle atrophy was a major cause of the inability of the majority of patients to even lift their paretic limbs without assistance. The patients with subacute stroke were aided by the

hanging mechanism to undertake the upper extremity activities using the system in the study. Throughout the movement stages, patients were visually guided by following a cursor moving on a computer screen at the same angular velocity for wrist and elbow motion.

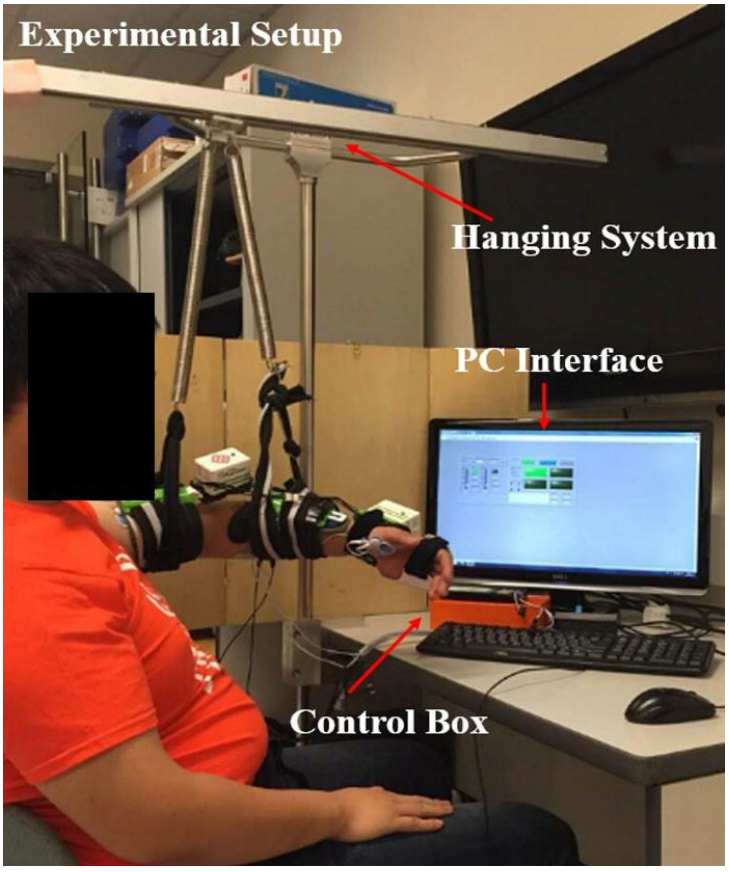


Figure 2-1. The training setup in a session assisted with the electromyography (EMG)-driven neuromuscular electrical stimulation (NMES)-robot sleeve, the visual feedback interface, and the hanging system.

Application of four-channel NMES was done on biceps brachii (BIC) and triceps brachii (TRI) when the elbow was flexed and extended, respectively, on flexor carpi radialis (FCR) when the wrist was flexed, and on the extensor carpi ulnaris (ECU) and extensor digitorum (ED) when the wrist was extended and the corresponding hand was open. A single channel surface NMES is sufficient for recruitment of both ECU and ED due to their anatomical proximity, with narrow muscle bellies on the dorsal forearm side [169]. Thus, for NMES as well as EMG detection, the two muscles were considered a muscle union (ECU-ED). BIC, TRI, FCR and ECU-ED enabled detection of the EMG, which controlled motor and NMES function. Figure 2-2 presents the manner in which the EMG and NMES electrodes were configured on each target muscle. The arrangement was also used in the earlier NMES-robot system to restore wrist function [170]. In order to minimize the stimulation artefact as the EMG was recorded, the positioning of the two pairs of EMG electrodes and NMES electrodes was done at right angles to one another on the target muscles [77]. Meanwhile, the shared zone of the muscle bellies was where the EMG and NMES electrodes were positioned for ECU-ED. Given that the majority of stroke survivors had trouble with opening and not with closing the hand [11, 22], and finger muscle tone could be more speedily improved by NMES on finger flexors, the movement of hand closing was not provided NMES or robotic assistance [22].

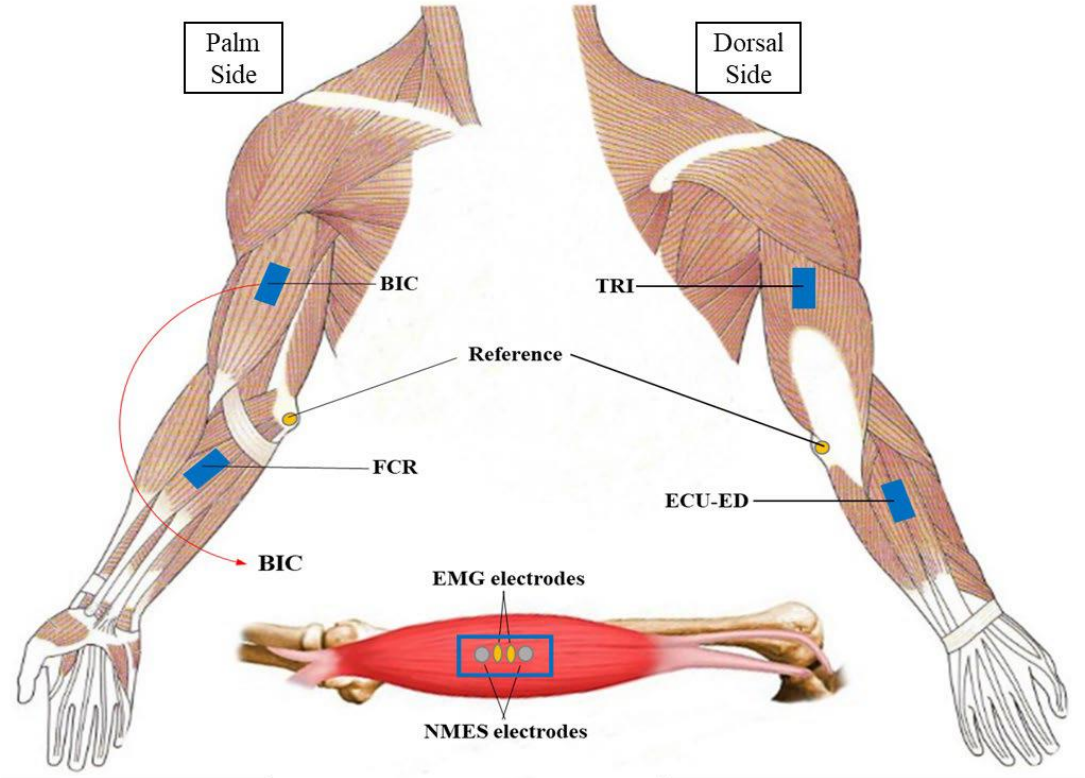


Figure 2-2. The electrode configuration on the target muscles, i.e. the biceps brachii (BIC), the triceps brachii (TRI), flexor carpi radialis (FCR), and the muscle union of the extensor carpi ulnaris and extensor digitorum (ECU-ED). The reference electrode was attached on the olecranon. The figure also illustrates the standard configuration of the electromyography electrodes and neuromuscular electrical stimulation (NMES) electrodes on a target muscle.

The target muscles emitted EMG signals that controlled robot and NMES module support, enabling patients to undertake activities involving phasic and consecutive movement of multiple joints. The present study employed EMG-induced control, meaning that, in every movement stage, after the EMG activation level of a driving muscle went beyond a pre-established limit (thrice the SD beyond the EMG baseline in the rest according to standard detection of elective EMG initiation in a muscle under contraction) [171], the motion of the associated joint motor maintained a fixed 10°/s velocity (flexion or extension in ROMs), which was a joint angular velocity that stroke patients in earlier studies found suitable [102, 170]. The voluntary EMG level beyond the triggering limit activated constant NMES as well, which was transmitted in 80-V square-wave pulses at 40 Hz stimulation frequency and 100μs individual pulse width to the driving muscle in the associated movement stage. After the driving muscle-derived EMG signals triggered the joint motors and NMES, patients did not have to make voluntary effort and the limb could carry out the remaining movement in the stage with assistance from the training system. Amplification of every EMG signal was performed with 1,000 gain (INA 333 amplifier, Texas Instruments Inc.), with filtering of band-pass from 10 to 500 Hz and sampling with 1,000 Hz for digitising purposes. The EMG activation levels were attained by full-wave rectifying and movement-averaging with 100 ms window of the EMG signals in the context of induction for motion activation.

2.2.2 Participants

2.2.2.1 Subject Recruitment

The Human Subjects Ethics Subcommittee of Hong Kong Polytechnic University and the Cluster Clinical Research Ethics Committee of the Join Chinese University of Hong Kong-New Territories East granted approval for the research.

The stroke inpatients at the teaching hospital were subjected to screening and participants were selected from among those with motor impairments of the upper extremity who met the inclusion criteria below:

1) Unique unilateral brain lesion caused by stroke that occurred within four months;

2) Standard medical care and stable condition maintenance;

3) Capacity for comprehending the research aims and procedure and for complying with basic orders, based on evaluation through the Mini-Mental State Examination (MMSE > 21) [172];

4) Upper extremity motor dysfunction varying from severe to moderate, according to the Fugl-Meyer Assessment (15 < FMA < 45, with 66 highest score possible for upper extremity) [173];

5) Elbow, wrist and finger spasticity of less than 3, according to the Modified Ashworth Scale (MAS) ranging from 0 (no muscle tone increase) to 4 (rigidity in the affected area);

6) Passive ROM from 45° extension to 60° flexion and from 30° flexion to 180° extension for wrist and elbow, respectively;

7) Age range 18-78 years old [175, 176];

8) Identifiable voluntary EMG from target muscles, (i.e., above three times SD of EMG at resting status), which is consistent with muscle power evaluation > 1 in clinical diagnosis;

9) Medical condition stability to allow for more than one session of physical training

Patients who failed those criteria or those who were pregnant, suffered from severe aphasia or had a pacemaker implant were not included in the study.

The Randomized controlled trial conducted over a period of two years with three-month follow-up (3MFU) was the research design chosen for the study. The inclusion criteria were followed by a collaborative clinician to undertake the screening of post-stroke inpatients 7-10 days prior to training commencement. The training plan was explained to prospective participants, while those who were selected were asked to provide written consent prior to randomization, agreeing to take part in the training, which could involve the multi-joint coordinated training based on NMES-robot assistance or the traditional intervention. A computer-based random number generator that had the same 0.5 probability to issue the number "1" (experimental group) or "2" (control group) (Matlab 2015, Mathworks, Inc.) was used to arbitrarily divide the participants into two groups. Owing to training device availability, with a single set for each side, and the participants' duration of hospitalization, the participants were recruited in a more or less successive manner. Recruitment stopped when both sides of the robotic sleeves were engaged. The clinician who screened the patients also had to consider whether the device would be available for left or right hemiplegia in the training based on NMES-robot assistance. The flowchart of Consolidated Standards of Reporting Trials is illustrated in Figure 2-3 as it pertains to the training plan.

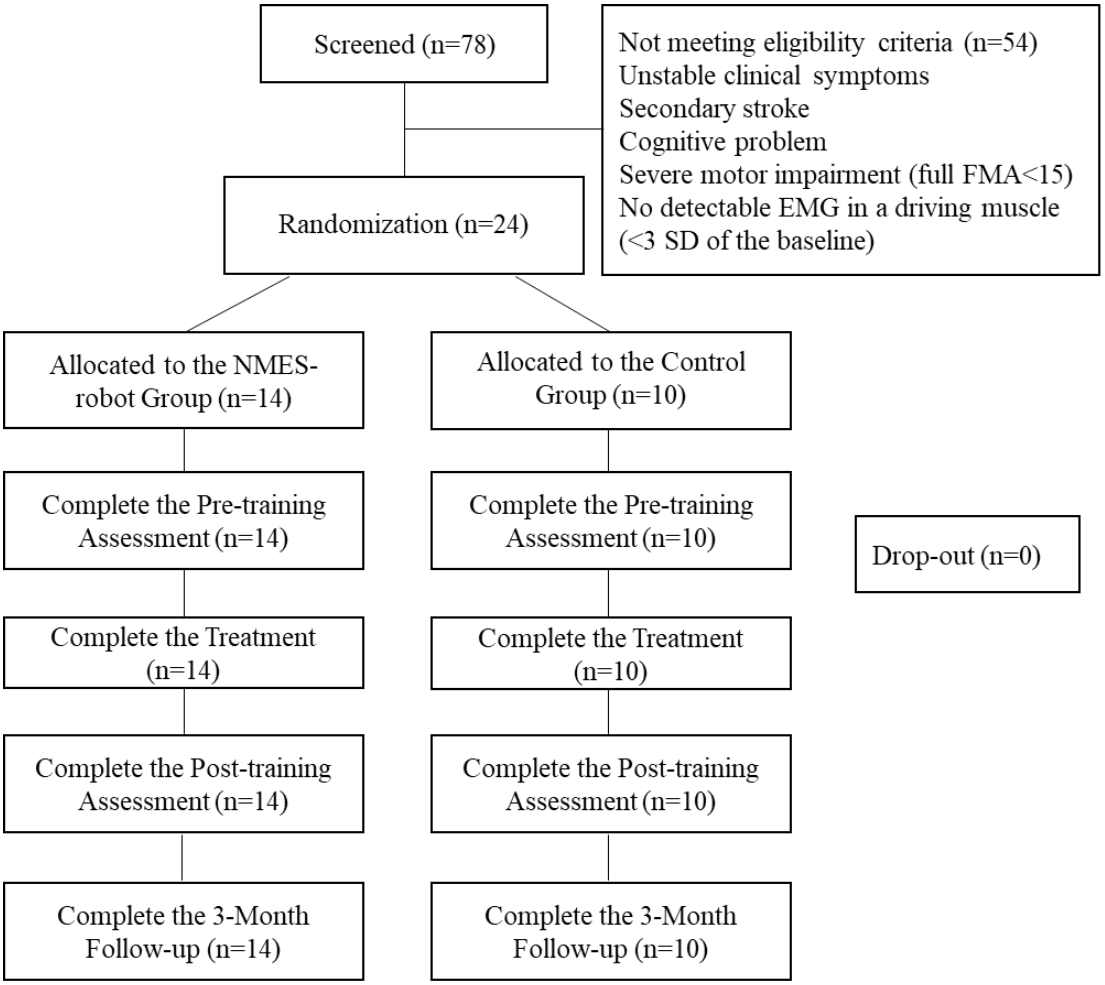


Figure 2-3. The Consolidated Standards of Reporting Trials flowchart of the experimental design.

2.2.2.2 Training Protocol

The participants in the experimental NMES-robot group underwent multi-joint coordinated upper extremity training with NMES-robot assistance over the course of 20 sessions, with one session every weekday. Every session required the participants to perform iterative limb movements with device support, namely, to extend their elbow and wrist, to open their hand and to flex their wrist and elbow. To prevent the muscles becoming fatigued, the participants were allowed to rest for 10 minutes after 20-minute practice. A balance was established between the training loads among the two groups and the session duration and frequency for upper extremity training. Thus, the duration of one training session for the experimental group was taken out of standard upper extremity training performed by human practitioners from the collaborative hospital (60 minutes Monday-Friday), involving muscle stretching, passive/assistive ROM and occupational treatments like feeding/eating and grooming practices. The device-assisted training was provided to the NMES-robot group for 40 minutes in a separate therapy room before being taken back for the remaining standard physical treatment. Owing to tiredness, the majority of NMES-robot group participants only performed muscle stretching and passive ROM for 10-15 minutes after the device-assisted training. Meanwhile, only standard upper extremity training was administered to the control group participants for 60 minutes in the common therapy room.

2.2.3 Evaluation of the Training Effects

2.2.3.1 Conventional Clinical Assessments

Several evaluation instruments were employed to functionally assess the paretic upper extremities of the participants. Thus, the FMA helps to measure sensorimotor functions according to performance in cases of post-stroke hemiplegia, and is based on a 0-66 complete score range, with 0-42 range for shoulder/elbow and 0-24 range for wrist/hand [173]. The Action Research Arm Test (ARAT) enables measurement of the capability of the hand for handling items of varying size, weight and form [177]. The Functional Independent Measurement (FIM) helps to assess activities of daily living (ADL) [178]. Last but not least, the MAS facilitates assessment of elbow, wrist and finger spasticity after stroke [174]. The performance of each of these evaluations was undertaken by an evaluator prior to training commencement, immediately upon completion of the 20 sessions, and at three months post-training. Furthermore, the evaluator had no knowledge about the training structure and communication between the participants and evaluator regarding the training was not permitted.

2.2.3.2 Session-by-Session Evaluation by EMG

Prior to the actual device-assisted training, the participants in the experimental group started every session with performance of a bare-arm assessment task. In keeping with earlier research on robot-assisted upper extremity training in cases of chronic stroke [102], the purpose of this task was to replicate the movement of the upper extremity during everyday activities, such as hand grasping and arm reaching/withdrawal, and determine how the motor function of the upper extremity was rehabilitated over the training sessions with no device support. The trainer's order to the participant and the sponge release by the assessed extremity at the

intended location were respectively the beginning and end points of EMG recording in every assessment task. There was awareness that initial lack of muscle strength could prevent participants with subacute stroke from using their affected extremity to perform the tasks without assistance in the first few sessions. Hence, a time restriction of 10 seconds was established, whereby participants were permitted to use their unaffected hand to support their affected extremity in task performance if the affected extremity could not perform the task independently within 10 seconds. Analysis was limited to the EMG signals occurring within the 10 seconds. From the initial session, none of the participants in the experimental group had trouble gripping the sponge and move their affected extremity horizontally. However, opening the hand to let go of the sponge and lifting the entire upper extremity vertically did present challenges to the participants. Hence, voluntary effort of finger extension was demanded from the participants, but effective hand release of the sponge was not. The time restriction of 10 seconds was primarily used in the case of the vertical tasks in the initial sessions, and during that interval, the participants had to make voluntary effort for task accomplishment by employing every strategy of muscle coordination in the affected upper extremity to enable recording of muscular patterns for a specific movement. It was observed that participants became frustrated by tiredness and lack of success in the case of longer attempt intervals, diminishing muscle exertion. By the final training session, no participant in the experimental group required the use of the unaffected extremity to perform the assessment tasks with the affected extremity anymore.

2.2.3.3 EMG Parameters

Two EMG parameters were used for quantitative cross-session monitoring of the muscle activation and coordination pattern changes during the evaluation in this work: (1) normalized EMG activation level of each muscle; and (2) normalized co- contraction index (CI) between the muscle pairs. The processing methods of the normalized EMG activation level was calculated as follows, i.e.,

$$\overline{EMG} = \frac{1}{T}\int_0^T EMG_i(t)dt, \qquad \text{(Eq. 2.1) [118, 119]}$$

where EMG was the EMG activation level of muscle *i*, $EMG_i(t)$ was the EMG linear envelope with respect to the maximal value recorded during the bare-arm evaluation tasks and maximum voluntary contractions in each session, and *T* was the length of the signal as did in previous works [118, 119]. In this work, the EMG activation levels in a session for an individual participant were further normalized with respect to the maximal EMG activation level of the participant recorded across the training sessions. This operation would show the tendency of the EMG activation level of a participant across the training session with the normalized values vary from 0 to 1, in order to minimize the variations among different participants as researchers encountered previously [118, 119].

The CI between a pair of muscles could be expressed as:

$$\mathrm{CI} = \frac{1}{T}\int_0^T A_{ij}(t)dt, \qquad \text{(Eq. 2.2) [118, 119]}$$

where $A_{ij}(t)$ represented the overlapping activity, i.e., Minimum[$EMG_i(t)$, $EMG_j(t)$], of the EMG linear envelopes for muscle *i* and *j*, and *T* was the length of the signal, $EMG_{i,j}(t)$ are the EMG envelopes as in *Eq. 2.1* [118, 119]. An increase of the CI values would represent an enlarged co-contraction phase of a muscle pair, and a decrease would suggest a separation in the co-contraction phase of the two muscles within the same joint or across multi joints. Similar normalization on the CI values in a session with respect to the maximal CI value across the sessions for individual participants was conducted as we did for the EMG activation levels. Monitoring the varying patterns of the EMG parameters across the 20 training sessions would provide a better understanding of the recovery progress of the affected upper limb functions.

2.2.4 Statistical Analysis

The Independent t-test was conducted to make sure that the two research groups were the same at baseline, indicating that the difference was statistically insignificant ($P>0.05$) on every clinical evaluation, namely, pre-assessments on FMA, MAS, ARAT and FIM scores [179]. The potential inter-group baseline discrepancy was attenuated even more by employing the pre-assessment as a covariate in two-way analysis of covariance (ANCOVA) regarding the inter-group differences in terms of independent factors and the time point on the clinical evaluations conducted before and after training and at 3MFU [179]. Meanwhile, the differences within the two

groups were investigated via one-way analysis of variance (ANOVA) at various time points with the Bonferroni post-hoc tests. One-way ANOVA also permitted examination of the EMG parameters, namely, EMG levels and CI values, throughout all training sessions to determine how rehabilitation progressed in the experimental group over the entire training program. The FMA and MAS clinical scores constituted the primary research outcomes, whilst secondary outcomes were given by the rest of the clinical scores and the EMG parameters. The reason for choosing FMA and MAS as primary outcomes was that, by contrast to the other scores, they were respectively indicative of multi-joint voluntary task-specified motor functions in the entire upper extremity and muscle spasticity difference between upper extremity joints. The results were statistically significant at 0.05, 0.01 and 0.001 levels.

2.3 Experiment Results

A number of 54 out of the 78 stroke inpatients who were subjected to screening in this study failed the inclusion criteria in one or more respects, such as not exhibiting stable clinical symptoms for ongoing and long-term physical training, having secondary stroke, exhibiting cognition deficits or aggravated motor dysfunction (full FMA<15), and lack of EMG detection in a driving muscle (less than thrice the SD of the baseline). Thus, the final research sample comprised 24 participants who met the inclusion criteria and who were distributed arbitrarily into two groups, namely, the NMES-robot group and the control group, consisting of 14 and 10 participants, respectively. Table 2-1 provides the participants' demographic

characteristics post-randomization.

Characteristics	Multi-Joint Training in Subacute Stroke	
	NMES-robot group (n=14)	Control (n=10)
Age (years)	54.6±11.3	64.6±3.43
Gender (female/male)	5/9	4/6
Lesion side (left/right)	11/3	9/1
Stroke Types (hemorrhagic/ischemic)	9/5	6/4
Time after Stroke (Min/Max days)	25/148	14/142

Table 2-1. Demographic data of the subacute participants after the randomization.

2.3.1 Motor improvement by clinical assessments

The FMA, ARAT, FIM and MAS clinical scores for the two groups are shown in Figure 2-4. These assessments were carried out before training commencement (pre-training assessment), immediately upon completion (post-training assessment) of training and at 3-month follow-up (3MFU). The means and 95% confidence interval of every clinical assessment alongside the two-way ANCOVA probabilities and anticipated effect sizes (EFs) pertaining to session and group, as well as the one-way ANOVA probabilities with EFs for session-related assessment within groups are provided in Table 2-2. Meanwhile, the probabilities and EFs for comparison between groups regarding assessment after training and at 3MFU by one-way ANCOVA, with baseline effect adjustment, are outlined in Table 2-3.

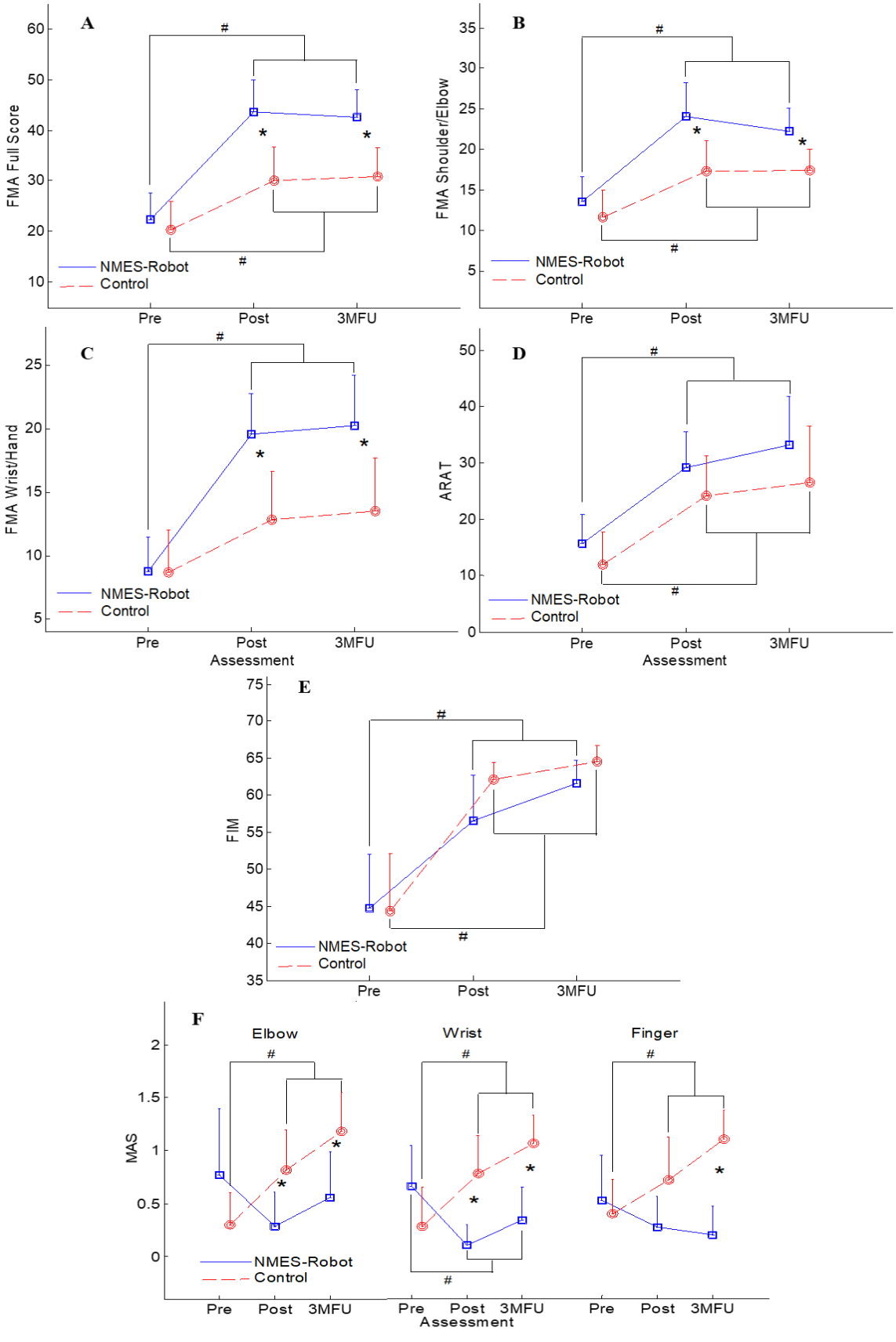


Figure 2-4. Overview of the results in clinical assessments.

Figure 2-4. Overview of the results in clinical assessments.

The clinical scores [evaluated before the first and after the 20th training session, as well as the 3-month follow-up (3MFU)] of the participants in both neuromuscular electrical stimulation (NMES)-robot and control groups: (A) Fugl-Meyer Assessment (FMA) full scores, (B) FMA shoulder/elbow scores, (C) FMA wrist/hand scores, (D) Action Research Arm Test (ARAT) scores, (E) Functional Independence Measurement (FIM), and (F) Modified Ashworth Scale (MAS) scores at the elbow, the wrist, and the fingers, presented as mean value with 2-time SE (error bar) in each evaluation session. The solid lines are for the NMES-robot group, and the dashed lines are for the control group. The significant inter-group difference is indicated by "*" ($P < 0.05$, one-way analysis of covariance), and "#" is used to indicate the significant intragroup difference ($P < 0.05$, one-way analysis of variance with Bonferroni post hoc tests).

Assessment	PRE	POST	3MFU	1-way ANOVA	2-way ANCOVA		
					P (*Partial*η^2)		
	Mean Value (95% Confidence Interval)			*P* (*Partial*η^2)	*Session*	*Group*	*S*G*
FMA Full (N-Robot)	22.3 (16.5-28.1)	43.6 (37.9-49.4)	42.5 (36.7-48.3)	0.001### (0.475)	0.000ΔΔΔ (0.615)	0.000ΔΔΔ (0.282)	0.003ΔΔΔ (0.160)
FMA Total (Control)	20.3 (14.2-26.4)	30.1 (24.0-36.2)	30.9 (24.8-37.0)	0.031# (0.227)			
FMA-SE (N-Robot)	13.6 (10.1-17.0)	24.1 (20.6-27.5)	22.3 (18.9-25.7)	0.000### (0.360)	0.000ΔΔΔ (0.401)	0.000ΔΔΔ (0.112)	0.029Δ (0.047)
FMA-SE (Control)	11.6 (8.2-15.0)	17.3 (13.9-20.7)	17.4 (14.0-20.8)	0.030# (0.229)			
FMA-WH (N-Robot)	8.7 (5.3-12.1)	19.6 (16.2-22.9)	20.2 (16.8-23.6)	0.000### (0.435)	0.000ΔΔΔ (0.551)	0.000ΔΔΔ (0.311)	0.001ΔΔΔ (0.184)
FMA-WH (Control)	8.7 (4.8-12.6)	12.8 (8.9-16.7)	13.5 (9.6-17.4)	0.176 (0.021)			
ARAT (N-Robot)	15.7 (8.8-22.6)	29.2 (22.3-36.1)	33.2 (26.3-40.1)	0.002## (0.268)	0.000ΔΔΔ (0.279)	0.284 (0.018)	0.912 (0.003)
ARAT (Control)	12.0 (4.0-20.0)	24.2 (16.2-32.2)	26.6 (18.6-34.6)	0.030# (0.229)			
FIM (N-Robot)	44.7 (38.8-50.6)	56.6 (50.7-62.5)	61.6 (55.7-67.5)	0.001### (0.311)	0.000ΔΔΔ (0.542)	0.117 (0.037)	0.418 (0.027)
FIM (Control)	44.3 (39.3-49.3)	62.1 (57.1-67.1)	64.6 (59.6-69.6)	0.000### (0.603)			
MAS-elbow (N-Robot)	0.8 (0.3-1.3)	0.3 (-0.2-0.8)	0.6 (0.1-1.0)	0.362 (0.051)	0.051 (0.087)	0.000ΔΔΔ (0.204)	0.001ΔΔΔ (0.201)
MAS-elbow (Control)	0.3 (-0.1-0.7)	0.8 (0.5-1.2)	1.2 (0.8-1.5)	0.005## (0.322)			
MAS-wrist (N-Robot)	0.7 (0.3-1.0)	0.1 (-0.2-0.4)	0.3 (0.0-0.7)	0.048# (0.145)	0.119 (0.064)	0.000ΔΔΔ (0.232)	0.000ΔΔΔ (0.241)
MAS-wrist (Control)	0.3 (-0.1-0.6)	0.8 (0.4-1.1)	1.1 (0.7-1.4)	0.009## (0.292)			
MAS-finger (N-Robot)	0.5 (0.2-0.9)	0.3 (-0.1-0.6)	0.2 (-0.1-0.5)	0.354 (0.052)	0.425 (0.026)	0.000ΔΔΔ (0.176)	0.005ΔΔ (0.152)
MAS-finger (Control)	0.4 (0.1-0.7)	0.7 (0.4-1.1)	1.1 (0.8-1.4)	0.025# (0.240)			

Table 2-2. Statistical results of the clinical scores in subacute study (1)

The mean and 95% confidence intervals for each measurement of the clinical assessments, and the probabilities with the estimated effect sizes of the statistical analyses. Differences with statistical significance are marked with superscripts beside the P values ("#" for one-way ANOVA intragroup tests, "Δ" for two-way ANCOVA tests on the group and session effects with the pre-assessment as the covariate). Significant levels are indicated as, 1 superscript for<0.05, 2 superscripts for≤0.01, and 3 superscripts for≤0.001.

Assessment	1-way ANCOVA on the Post- and 3MFU assessments between the groups	
	$Post_{Pre}$ P (Partial η^2)	$3MFU_{Pre}$ P (Partial η^2)
FMA		
Full Score	0.000*** (0.478)	0.005** (0.319)
Shoulder/Elbow	0.037* (0.190)	0.040* (0.186)
Wrist/Hand	0.000*** (0.538)	0.005** (0.322)
ARAT	0.417 (0.032)	0.455 (0.027)
FIM	0.123 (0.109)	0.169 (0.088)
MAS		
Elbow	0.003** (0.359)	0.004** (0.334)
Wrist	0.001*** (0.430)	0.002** (0.367)
Finger	0.074 (0.144)	0.000*** (0.507)

Table 2-3. Statistical results of the clinical scores in subacute study (2)

The statistical probabilities and the estimated effect sizes of the one-way analysis of covariance (ANCOVA) on the respective post-assessment and 3-month follow-up (3MFU) between the groups, by taking the pre-assessment as the covariate. Differences with statistical significance are marked with '*' beside the P values. Significant levels are indicated as, *for <0.05, ** for ≤0.01, *** for ≤0.001.

The extent to which the three assessment sessions varied in terms of FMA scores is indicated in Figure 2-4 (A-C). The factors of group and session differed significantly with regard to the FMA complete score and the FMA sub-scores for shoulder/elbow and wrist/hand (two-way ANCOVA, P<0.05, Table 2-2). Statistical significance was also noted for the interplay between the factors of group and session in relation to the three FMA scores (P<0.05, Table 2-2), with the highest and lowest significance being associated with the FMA wrist/hand (P=0.001, EFs=0.184) and the FMA shoulder/elbow (P=0.029, EFs=0.047), respectively (see Table 2-2). There was a significant increase in the FMA complete score at post-training assessment for both the experimental and control groups (Figure 2-4A), which was sustained at 3MFU assessment compared to pre-training assessment (P<0.05, one-way ANOVA with post-hoc tests), as indicated in Table 2-2. More specifically, at post-training assessment and 3MFU assessment, a significantly higher increase in the FMA complete score was exhibited by the experimental group

compared to the control group (one-way ANCOVA, P<0.01, Table 2-3). Meanwhile, there was no significant difference in the FMA shoulder/elbow and wrist/hand scores and the FMA complete score (Figure 2-4 B&C), although greater significance was exhibited by the FMA wrist/hand scores, with larger EFs in the group-session interplay (two-way ANCOVA, Table 2-2) as well as between groups at the post-training assessment and 3MFU assessment (two-way ANCOVA, Table 2-3). However, the control group did not display a significant increase in the FMA wrist/hand score at post-training assessment (P>0.05, one-way ANOVA), as shown in Table 2-2.

The ARAT scores obtained in the three assessment sessions for the experimental and control groups are provided in Figure 2-4D. Although the assessment time points were found to differ significantly (P<0.001, EFs=0.279, two-way ANCOVA, Table 2-2), the groups were not associated with any significant difference. Both groups exhibited a significant increase in the ARAT scores post-training (P<0.05, one-way ANOVA with Bonferroni *post-hoc* tests), which was sustained by 3MFU (P<0.05, one-way ANOVA with Bonferroni *post-hoc* tests).

Figure 2-4 (E) provides the Functional Independence Measurement scores that the two research groups obtained. Although the assessment time points were found to differ significantly (P<0.001, EFs=0.542, two-way ANCOVA, Table 2-2), the factor of groups was not associated with any significant difference. Furthermore, both the experimental and control groups exhibited significantly higher FIM scores at assessment after training and at 3MFU than at assessment before training (P≤0.001, one-way ANOVA with Bonferroni post-hoc test).

The differences in MAS scores obtained for the experimental and control groups at

fingers, wrist and elbow in pre-training, post-training and 3MFU assessments are shown in Figure 2-4 (F). Two-way ANCOVA revealed significant variation between groups ($P<0.001$, EFs>0.176, Table 2-2) and the elbow, wrist and fingers were all associated with significant interplay between the group and evaluation time point factors ($P<0.01$, EFs>0.152, Table 2-2). The control group displayed significantly high MAS scores at the elbow, wrist and fingers at assessment after training, which stayed high at 3MFU assessment ($P<0.05$, one-way ANOVA with Bonferroni post-hoc tests, Table 2-2). On the other hand, the experimental group exhibited significantly reduced MAS scores, which stayed low at 3MFU assessment as well (one-way ANOVA, $P=0.048$, EFs=0.145, Table 2-2). By contrast, the MAS scores for elbow and fingers did not differ significantly in the case of the experimental group ($P>0.05$, one-way ANOVA, Table 2-2). Furthermore, when the MAS scores were compared between groups, the experimental group was found to have significantly lower MAS scores at elbow and wrist at assessment after training ($P<0.01$, EFs>0.359, one-way ANCOVA, Table 2-3), and at elbow, wrist and fingers at 3MFU assessment ($P<0.01$, EFs>0.334, one-way ANCOVA, Table 2-3).

2.3.2 *Muscular variation by EMG Parameters*

The manner in which the EMG parameters, namely, the EMG activation level and CI, behaved in the case of the experimental group throughout the training program is illustrated in Figure 2-5. It can be noted that the FCR was associated with significantly diminished EMG activation levels (Figure 2-5A, $P<0.05$, one-way ANOVA with Bonferroni post-hoc tests). The increase in the EMG activation levels that occurred in the initial couple of sessions reached its highest point about the third session, followed by a reduction in levels in the next 17 sessions, reaching a state of little or no change in the final five sessions. On the other hand, BIC, TRI and ECU-ED did not exhibit any fluctuations of significance. The manner in which the CI values behaved in various pairs of muscles in one or more than one joint is shown in Figure 2-5B. Thus, there was a significant decrease in the CI values of the pairs of muscles FCR&BIC and BIC&TRI throughout the training program ($P<0.05$, one-way ANOVA with Bonferroni post-hoc test). In the case of both these pairs, the CI values reached the highest point in the first eight training sessions before declining constantly in the next sessions and stabilizing in the final three training sessions. By contrast, the other pairs of muscles did not reveal CI value alterations of significance.

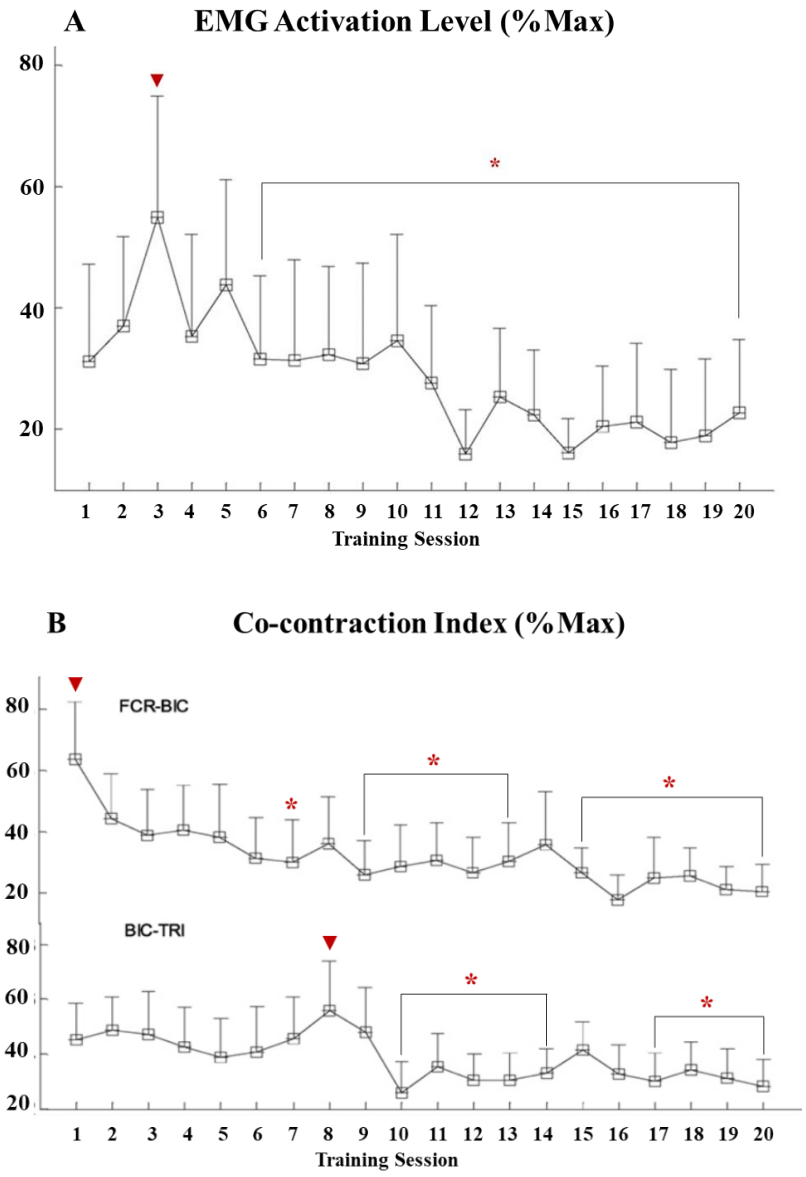


Figure 2-5. The variation of electromyography (EMG) parameters across the 20 sessions.

(A) the changes of the normalized EMG activation levels with significant decline observed in the flexor carpi radialis (FCR) muscle ($P<0.05$, one-way analysis of variance (ANOVA) with Bonferroni post hoc tests); (B) the significant decline of the normalized co-contraction Indexes (CI) values observed in the BIC&TRI and FCR&BIC muscle pairs ($P<0.05$, one-way ANOVA with Bonferroni post hoc tests). The values are presented as the mean value with 2-time SE (error bar) in each session (from our published work [130]).

2.4 Discussion

2.4.1 Functional Independence with Early Distal Motor Recovery

The present study has demonstrated that traditional recovery therapy and training involving coordination of multiple joints with NMES-robot assistance could both be effective in improving motor function in the paretic upper extremities in the early stage post-stroke. According to the ARAT and FIM scores, the two types of interventions yielded similar early effects, with the ARAT scores showing improvement especially in the hand, while the FIM scores indicated enhanced ADL autonomy. Furthermore, training involving coordination of multiple joints with NMES-robot assistance led to a rise in the ARAT scores, suggesting voluntary motor improvement in the fingers post-training, despite the fact that none of the tasks employed in this study targeted the finger joints particularly. However, in an earlier study [102], it was observed that training with NMES-robot assistance based on an intensive single-joint training program did not significantly enhance FIM scores in the case of chronic stroke patients. Nevertheless, the FIM scores obtained in the present study offered evidence for the efficiency of training with NMES-robot assistance based on an approach involving coordination of multiple joints for improving ADL of stroke patients in the early stage post-stroke. What is more, at three-month follow-up, the improvement was still maintained.

The FMA scores suggested that voluntary effort improvement in the motor function of the whole paretic upper extremity could be achieved by stroke patients through training involving coordination of multiple joints with NMES-robot

assistance. Meanwhile, motor function at the shoulder and elbow was enhanced not only by this intervention but also by standard recovery therapy, and the improvement was still observed at 3MFU. Nevertheless, compared to the control group, the experimental group was associated with higher FMA scores for the shoulder/elbow and wrist/hand. The improvement in the whole upper extremity, and particularly the shoulder (no actuated training assistance) in the case of the experimental group can be explained in terms of the engagement of the shoulder muscles in the task of arm lifting with the hanging system providing support, as well as in terms of the concomitant improvement in the neighbouring proximal joint when a joint muscle was engaged, as demonstrated in an earlier study [102] (i.e. elbow function was enhanced by wrist training and shoulder function was enhanced by elbow training). Furthermore, the FMA scores suggested that, by comparison to the control group administered traditional recovery therapy, the motor function of the wrist/hand was significantly enhanced by the training involving coordination of multiple joints with NMES-robot assistance. This could be explained in terms of the fact that 'one-to-one' recovery delivered by hand is less effective in improving motor function in the distal joints than in the proximal joints, such as shoulder and elbow. A proximal-to-distal sequence is adopted by the majority of training interventions delivered by hand and proximal joints tend to be prioritized over the distal joints in the early stage post-stroke, as discussed in Section 1.3.1 [180, 181]. The NMES-robot mechanism supported only straightforward flexion and extension in the case of one joint, but motors located at appropriate sites enabled more accurate engagement of the target joints, while computer programs enabled configuration of NMES to provide

coordinated movements of multiple joints. Moreover, in the early stage post-stroke, it is not generally possible to apply voluntary effort in the wrist extensors, which were ECU-ED in this case, through traditional rehabilitation treatment delivered by hand [181], whereas the wrist joint could be physically engaged directly with the employed EMG-driven NMES-robot sleeve, which also enabled coordination of motor practice in different joints, with the servo motors at the wrist and elbow providing mechanical support. The iterative sensorimotor experiences generated with NMES support stimulated voluntary effort as it increased participants' focus on the target muscles at the distal joints.

2.4.2 Motor Coordination with Spasticity Control in Subacute Stroke

Elbow, wrist and fingers all showed significant improvement in muscle tone (spasticity) following traditional recovery therapy. There are three explanations for this improvement. First of all, in keeping with the pathological sequence established by the Brunnstrom staging approach (see Section 1.1.2), spontaneous rehabilitation led to progressive development of muscle tone. Secondly, fatigue fostered greater offsetting muscular activity in the context of motor practice [102]. Thirdly, the conventional rehabilitation treatment enhanced motor stimulation in the flexors, without coordinated spasticity control. The outcomes of session-group interplay (see Table 2-2) indicated that muscle tone evolved differently in the experimental group than in the control group, despite the fact that the MAS scores for elbow and fingers in the former group were not significantly altered. Furthermore, training involving coordination of multiple joints with NMES-robot assistance was demonstrated to be efficient in releasing muscle spasticity at the wrist and retaining that effect at three

months, since elbow, wrist and fingers all exhibited decrease in muscle tone, which was especially pronounced at the wrist. The intensive practice that the experimental group undertook in a brief interval of time could explain this observed effect. The experimental group in this study was subjected to more intensive training compared to other clinical trials based on manual training, with one session of training every weekday for one month as opposed to three sessions weekly for 16 weeks [74], with other baseline effects potentially blurring discrepancies between groups. Likewise, the earlier study [102], where the wrist joint of chronic stroke patients was subjected to intensive training with NMES-robot support, also reported a significant spasticity relaxation in the finger joint muscles.

2.4.3 Cross-Session Recovery Revealed by EMG

The clinical scores and the EMG parameters were respectively indicative of enhancement in the motor function of the upper extremity and the rehabilitation progress throughout the training program in the experimental group. The fluctuation in the MAS scores for the wrist was congruous with the decrease in EMG activation levels of FCR suggestive of relaxation of wrist muscle spasticity. A stable condition was exhibited by the majority of participants following the fifteenth session. Furthermore, a correlation existed between FCR decrease and the reduction in the CI values of the FCR&BIC muscle pair, implying that the elbow-wrist simultaneous contraction patterns were relaxed. Thus, there was greater movement autonomy of these joints in the context of arm withdrawal/flexion. Moreover, improvement in flexor-extensor synchronicity and enhanced autonomy in muscle contraction over the course of the training program were reflected in the fact that the CI values of

BIC&TRI declined significantly. In the initial 3-4 sessions, there was a rise in the EMG activation levels of the FCR, while the CI values of BIC&TRI reached their highest point within the initial eight sessions, which was sensible since the majority of subacute stroke patients have weak muscles at the start of training, and subsequently a combination of spontaneous processes and physical training leads to improved muscle strength. The initial few training sessions are when adjustment to training occurs as well. According to the outcomes of the EMG parameters, muscle spasticity could be relaxed and control of movements within and across multiple joints of the upper extremity could be fostered, especially in the wrist, via training involving coordination of multiple joint with device support.

2.5 Periodic Summary

In this work, the multi-joint coordinated training strategy has been adopted in the UE physical practice assisted by the EMG-driven NMES-robotic sleeve among subacute stroke patients during their hospitalization stay. The training effectiveness of this novel strategy was evaluated through both clinical assessments (i.e., FMA, MAS, ARAT and FIM) and cross-session EMG parameters (i.e., EMG activation level and Co-contraction Index), and was further compared with that by routine/conventional treatments in rehabilitation unit. The device-assisted multi-joint coordinated training was effective to promote patients' voluntary motor functions in the entire paretic upper limbs as assessed by FMA (full score, shoulder-elbow and wrist-hand) and showed well control of muscle spasticity at wrist segments as assessed by MAS (wrist). Besides, these training outcomes were significantly better than those achieved by routine manual-delivered UE treatments. Besides, both the novel strategy and the routine treatments showed comparable UE motor

improvement in the function related tasks by ARAT and independence of daily activities by FIM. All the motor outcomes from the clinical assessments were maintained for 3 months. Furthermore, muscle activities of four target muscles (i.e. FCR, ECU-ED, BIC and TRI) have been traced through the session-by-session EMG evaluation. The results showed a significant release of muscle excessive contraction in the wrist flexor by EMG activation level (FCR) as well as the improvement of muscle coordination across multiple joints (FCR & TRI) and within single elbow joint (BIC & TRI) by CI values.

CHAPTER 3

TASK-ORIENTED UPPER LIMB TRAINING WITH MULTI-JOINT PRACTICE ASSISTED BY THE EMG-DRIVEN NMES-ROBOT IN CHRONIC STROKE

3.1 Introduction

Stroke causes long-term upper limb disability in adults [182] and requires continuous medical care for reducing the physical impairments in the paretic extremity. It has been found that the recovery of the proximal joints, e.g. the shoulder and the elbow, is always much better than the distal parts, i.e. wrist and hand, mainly due to the neurological recovery process (as illustrated in **1.1.2** and **1.2.1**) and the rehabilitation effects carried from subacute stroke period by conventional manual-delivered therapies. More than 60 percent of chronic stroke patients cannot well manage their affected hand into daily activities, without synchronously improved distal and proximal upper limb functions.

In conventional rehabilitation treatments, the spasticity control is usually lacked in the subacute phase, thereby leading to a most frequent pattern of flexor hypertonic posture in chronic stroke involving elbow, wrist and finger flexions (79% of patients affected at the elbow ,66% at the wrist and 67% in the fingers) [183]. Following the situation problems may be raised with pain, ankylosis, tendon retraction or muscle weakness and difficulties with wrist and finger extension worsen [184]. Beside weakness of the extensors and spasticity of the flexors in the paretic upper limb, the

muscular discoordination across multiple joints is another major difficulty in chronic stroke rehabilitation, which limits the potential of functional recovery with abnormal synergy patterns and loss of independent joint control [185]. The compensatory movement of the proximal muscles progressively substitutes the muscle function as the use of distal muscles is disregarded in the chronic instructions. Thereby, the motor recovery in the chronic period was regarded to be minimal or plateaued [23]. However, recent studies have reported enhanced functionality in the impaired upper limb is significantly aided by repetitive [28] and high-intensity practice [29], even in cases of chronic stroke [23]. Furthermore, systematic reviews have convinced that precise motor control across multiple joints can effectively convert motor improvements into meaningful limb functions in the chronic period [16, 66], especially with specific distal tasks (e.g., the wrist and fingers) [145]. Despite these findings, providing high-intensity and repetitive training is considered high-costly in clinical practice. And as we mentioned in **1.3.1**, it is hard for human therapists to manage the movements of different joints (e.g. finger, wrist, and elbow joints) with adequate intensive practice at the same time, especially for chronic stroke patients accustomed to 'learned non-use' (as defined in **1.3.1**) and compensatory movements.

In addition to affording consistent, high-intensive and precisely-repetitive physical practices with a long training duration [76], rehabilitation robots could also make it easier for movement control to be achieved on more than one upper limb joint through the use of various numbers of electrical motors of different dimensions and mechanical structure. The application NMES can improve limb functions by limiting

'learned disuse' that stroke survivors are gradually accustomed to managing their daily activities without using certain muscles, which has been considered as a significant barrier to maximize the recovery in the chronic period [180]. Post-stroke rehabilitation assisted with NMES has also been found to effectively prevent muscle atrophy and improve muscle strength [159, 160], and the stimulation also evokes sensory feedback to the brain during muscle contraction to facilitate motor relearning [186]. Therefore, the use of NMES-robot system could be an effective supplementary for chronic stroke upper limb rehabilitation. Nonetheless, previous clinical trial on chronic stroke assisted with the NMES-robot was under the single joint training scheme, the rehabilitation efficacy and the training effects of multi-joint practice assisted by the NMES-robotic sleeve in the chronic stroke has not been well studied.

In this study, we applied the NMES-robotic sleeve to cope with the chronic stroke physical practices, under the multi-joint coordinated training scheme. We hypothesized that multi-joint coordinated training assisted by the NMES-robotic sleeve could enhance paretic upper limb motor function in patients with chronic stroke. By contrast to the rehabilitation aims for subacute stroke to achieve the initiation of voluntary effort and to enhance the neurological motor recovery [22], the goals for chronic rehabilitation have been transferred to the optimization of motor independence in activities of daily living (ADLs). The training effectiveness was evaluated through a single-group clinical trial

3.2 Methodology

3.2.1 Experimental Setup

The NMES-robot sleeve used in this study was developed in previous work.

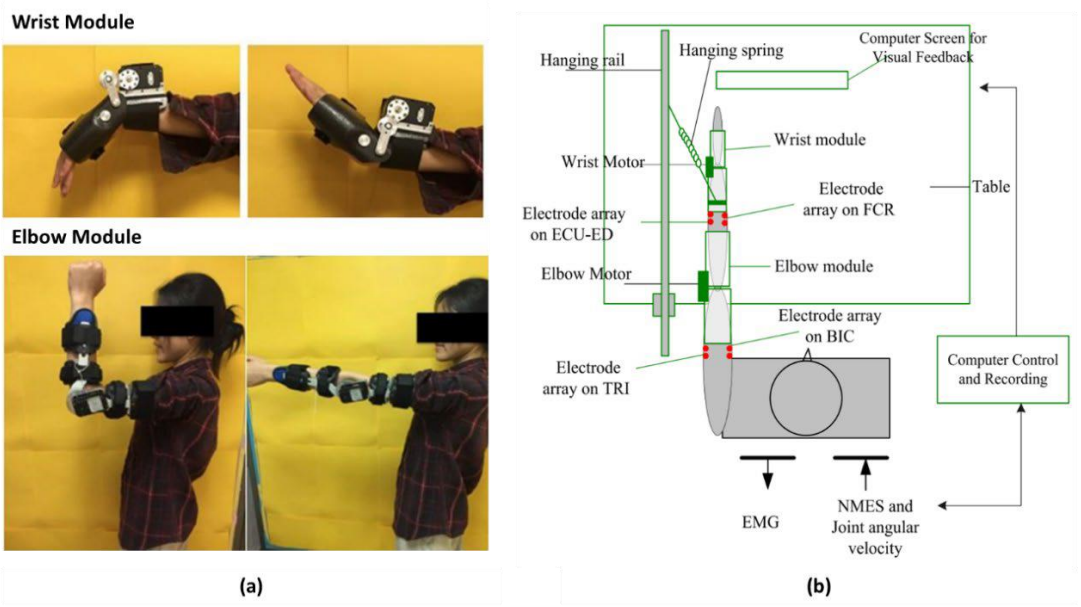


Figure 3-1. Overview of the experimental setup: a) a photo of a subject wearing the mechanical parts of the system; b) the schematic diagram of the experimental setup (Adapted from reference[129])

Figure 3-1 a shows the NMES-robotic sleeve, which consisted of two exoskeleton robotic modules respectively for the wrist and the elbow [130]. The two modules were not mechanically connected, in order to fit for participants with different ergonomic parameters (e.g. limb length and pronation angles away from the neutral position at the wrist), mainly due to joint stiffness and muscle spasticity after stroke [133]. Each mechanical module was controlled by an independent servo motor (MX 106, ROBOTIS, with a maximal stall torque of 8.4 Nm), and would support the joint perform flexion and extension motions with a constant velocity of 10°/s during the

training [133]. The orthosis of the wrist module only covered the palm at the hand side and set the fingers free for flexion and extension motions. The maximum ROM provided by the wrist module was from 45° extension to 60° flexion, while for the elbow it was from 30° flexion to 180° extension [129].

Four-channel NMES was applied on the muscles of BIC during elbow flexion, TRI during elbow extension, FCR for wrist flexion, and the last channel on both the ECU-ED muscle union, as we defined in **2.2.**, for wrist extension and the associated hand open (i.e., finger extension). The function of the motors and NMES was under the control of the EMG detected from the BIC, TRI, FCR and ECU-ED muscles. The configuration for the EMG and NMES electrodes on a paretic arm (i.e., BIC, TRI, FCR and ECU-ED in this work) is shown in Figure 3-1 b. which has also been adopted in our first study Figure 2-2**.** The EMG electrodes were also attached on the target muscle bellies, i.e. BIC, TRI, FCR, and the muscle union of ECU-ED. The reference electrode was attached on the olecranon. For the ECU-ED, the EMG and NMES electrodes are located on the common area of the muscle bellies of the two.

The EMG-triggered control of the NMES-robotic training system has been published in our previous studies and can be described as follows:

In each joint extension or flexion phase, the motors would be activated once the EMG activation level of a driving muscle exceeded a preset threshold (i.e., three times SD above the EMG baseline at rest [187]). NMES would be delivered to the upper limb extensor muscles simultaneously with the motor support only in the extension phase.

The assistance from both NMES and robot was under the control of the voluntary-evoked EMG signals from target muscles (i.e. BIC for elbow flexion; TRI for elbow extension; FCR for wrist flexion; ECU-ED for wrist extension and synchronized finger extension).

The experimental setup of the multi-joint coordinated upper limb training assisted by the NMES-robotic sleeve for chronic stroke patients was similar to that in the first study for subacute stroke patients, as shown in Figure 3-1 b [129]. It could assist a stroke survivor to perform the sequencing motions, i.e., (1) elbow extension, (2) synchronized wrist extension and hand open, (3) wrist flexion, and (4) elbow flexion, with the purpose to simulate the multi-joint coordinate arm-reaching daily tasks. The starting position of the motion cycle was set as elbow joint extended at 180° and the wrist extended at 45° respectively, which is also the end point for a motion cycle.

When using the NMES-robot sleeve in this work, the hanging system is also used for chronic stroke patients. There were two reasons: 1) most of the persons with chronic stroke could not afford the gravity of the system as well as the weight of their own upper limb with the long training duration, 2) chronic patients always experience muscle atrophy at the shoulder joint, some even suffer from shoulder dislocation [34]. The design was for a consideration of patients' safety and compensated the weight of both paretic upper limb and the robotic system during the training.

3.2.2 Participants

The study was approved by the Human Subjects Ethics Subcommittee of Hong Kong Polytechnic University. The study was a single-group clinical trial with a 3-month follow-up. Figure 3-2 shows the Consolidated Standards of Reporting Trials flowchart of the experimental design.

A total of 30 stroke patients were screened for the training from the local district near to the university during subject recruitment. 17 participants with upper limb dysfunction were finally recruited in this study satisfying the following inclusion criteria:

1) at least 6 months after the onset of a singular and unilateral stroke;

2) had enough cognition to understand the content or purpose of the study and follow simple instructions with MMSE > 21 [172];

3) motor impairments affected in the upper limb ranged from severe to moderate as assessed by the Fugl-Meyer Assessment (15 < FMA < 45, with a maximal score of 66 for the upper limb) [173];

4) the spasticity affected at the elbow, the wrist and the fingers below 3 as measured by the Modified Ashworth Scale [MAS, ranged from 0 (no increase in the muscle tone) to 4 (affected part rigid)][174];

5) the passive ROM of the subjects for the wrist was from 45° extension to 60° flexion and the ROM for the elbow was from 30° flexion to 180° extension;

6) aged from 18 to 78 years [175, 176];

7) had detectable voluntary EMG from the target muscles (i.e., above three times

of SD of the resting EMG), which is consistent with muscle power > 1.

Subjects were excluded if they did not meet the above inclusion criteria or had the following conditions: (1) currently pregnant, (2) severe shoulder pain, and (3) had an implanted pacemaker. There was no dropout of the participants after the subject recruitment. The recruited participants were informed of the aim and the content of the study. A participant was required to sign the written informed consents before the first training started.

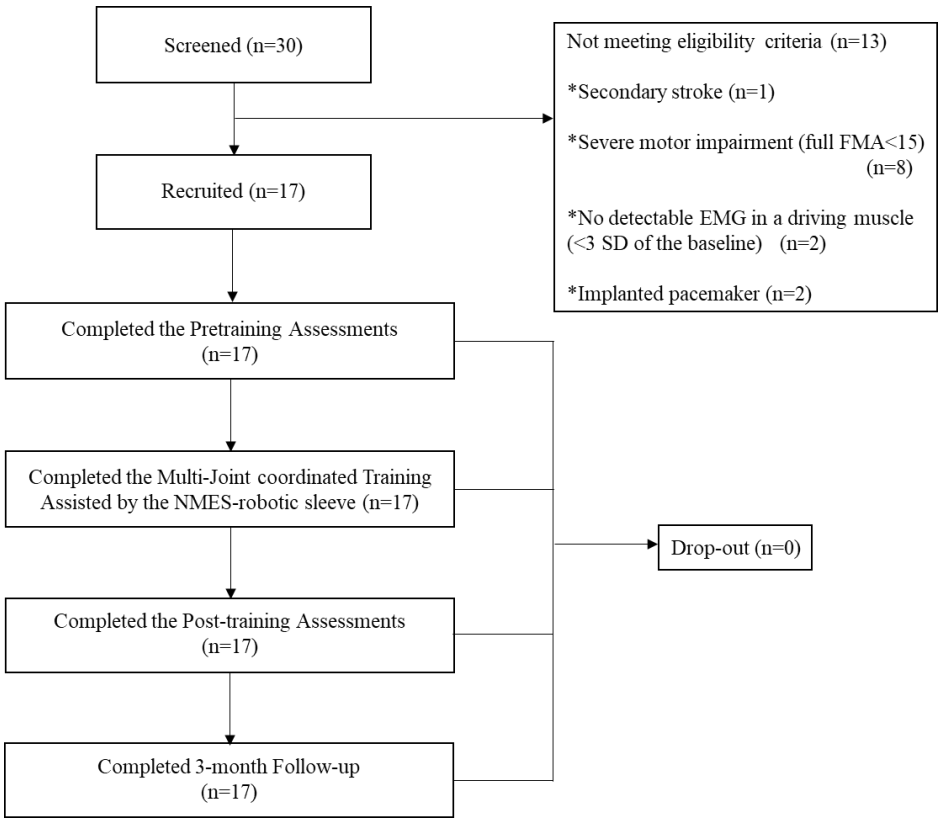


Figure 3-2. The Consolidated Standards of Reporting Trials flowchart of the experimental design.

3.2.3 Training Protocol

All participants received the multi-joint coordinated upper limb training, assisted with the NEMS-robot sleeve, which consisted of 20 training sessions with the intensity of 3-5 sessions/week, within 7 consecutive weeks.

3.2.3.1 Session-by-Session Pre-Training Evaluation Task

Before starting a training for an individual chronic stroke patient, we conducted the session-by-session pre-training evaluation in each training session/day. The EMG signals were recorded during the evaluation for offline processing.

1) The isolated maximum voluntary contraction (MVC) test was the first step for each participant on the following four muscles or muscle union: BIC, TRI, FCR and ECU-ED, with the EMG electrodes attached to the skin surface of the target muscle bellies. Each EMG electrode pair was in a separation of 2 cm between the two isolated electrodes as described in our previous work. A participant would be arranged to sit at a table with his/her impaired upper extremity placed on the table. When conducting the isolated MVC on the BIC and TRI muscles, a participant was instructed to position his/her paretic upper extremity with shoulder abducted at 70° and the elbow flexed at 90° held by an experimental operator. Then, he/her would be required to use his maximum effort to achieve elbow flexion and elbow extension respectively, for the EMG recording of BIC and TRI MVC EMG signals. While during the isolated MVC test on the FCR and ECU-ED muscles, the participant would be positioned with the affected upper extremity held with elbow

joint extended at 130°, and two respective wrist positions: flexed at 15° for maximum extension test and extended 15° for maximum flexion text. The MVC tests on each muscle of interest should be maintained for 5 seconds and each motion was repeated twice. Between the two consecutive repetitions of the muscle MVC test, participants were allowed to have a 2 min rest to prevent the muscle fatigue.

2) The second step for the pre-training test was the bare-arm evaluation task, which was conducted following the isolated MVCs on four muscles. The bare-arm evaluation task, as shown in Figure 3-3, had two parts, i.e., the horizontal task and the vertical task. All the motions of a participant in the test were instructed to be at a natural speed and completed solely by his/her paretic arm. In the horizontal task, a participant was required to use the affected limb to grasp a sponge (thickness 5 cm and weight 30 g) and transport it to the lateral side with a distance of 50 cm on a table; then, release the sponge. After that, the participant needed to pick up the sponge again and then transport it back to the original place, both the starting position and ending position are marked on the table. In the vertical task, the participant was required to complete the pick-up and release cycle vertically between two layers of a shelf on the table, that is, to grasp the sponge on the midline of the lower layer of the shelf, then lift it 17cm vertically and put it to the midline of the upper layer. Both the horizontal and vertical tasks were repeated twice for each with a 5 min break between two consecutive practices for the participant's rest to avoid the muscle fatigue.

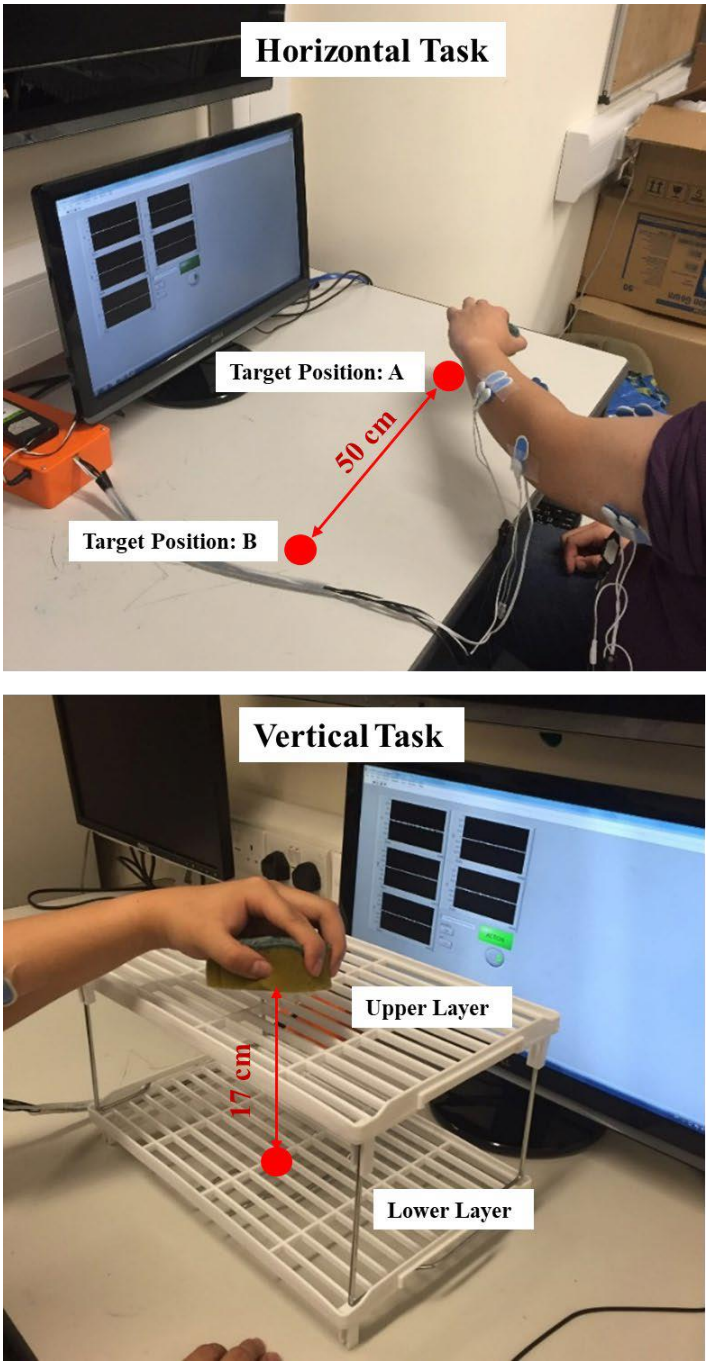


Figure 3-3. The configuration of bare-arm evaluation task, i.e. the horizontal task and the vertical task.

The EMG signal recording during the bare-arm test was defined to start with a participant's action to touch the sponge by fingers for grasping and to end with the participant's action to release the sponge back to the initial starting position. The EMG signals from the four target muscles or muscle union (BIC, TRI, FCR and ECU-ED) were first amplified with a gain of 1000 (amplifier: INA 333, Texas Instruments Inc.), filtered by a band-pass filter in the range from 10 to 500 Hz. Then the EMG signals were sampled with 1000 Hz by the data acquisition card and restored in the computer for off-line processing as we did in the previous study.

As we did in the first study, a 10-s maximum time limit was also applied in this test as follows: Only the EMG signals within the 10 s were included for analysis when a participant could not use his paretic arm to grasp the sponge or to lift up in 10 s. He or she would be allowed to use the intact hand for assistance in the task afterwards with no EMG recording. Successful hand release of the sponge was not required in this study, although the participants were required to make the voluntary efforts to extend the fingers. The EMG recording will be ended within 10s after a participant tried to release the sponge at the ending position. The 10-s maximum time limit was a supplementary guideline applied in this study, as the participants with chronic stroke suffered from hypertonic flexor patterns, and most of them could not release the sponge during the bare-arm test in the first several training sessions.

3.2.3.2 Task-oriented Training with the EMG-driven NMES-Robot

The multi-joint coordinated upper limb practices were designed to simulate normal activities of daily living for stroke survivors to regain meaningful upper limb motor functions, i.e. task-oriented practice.

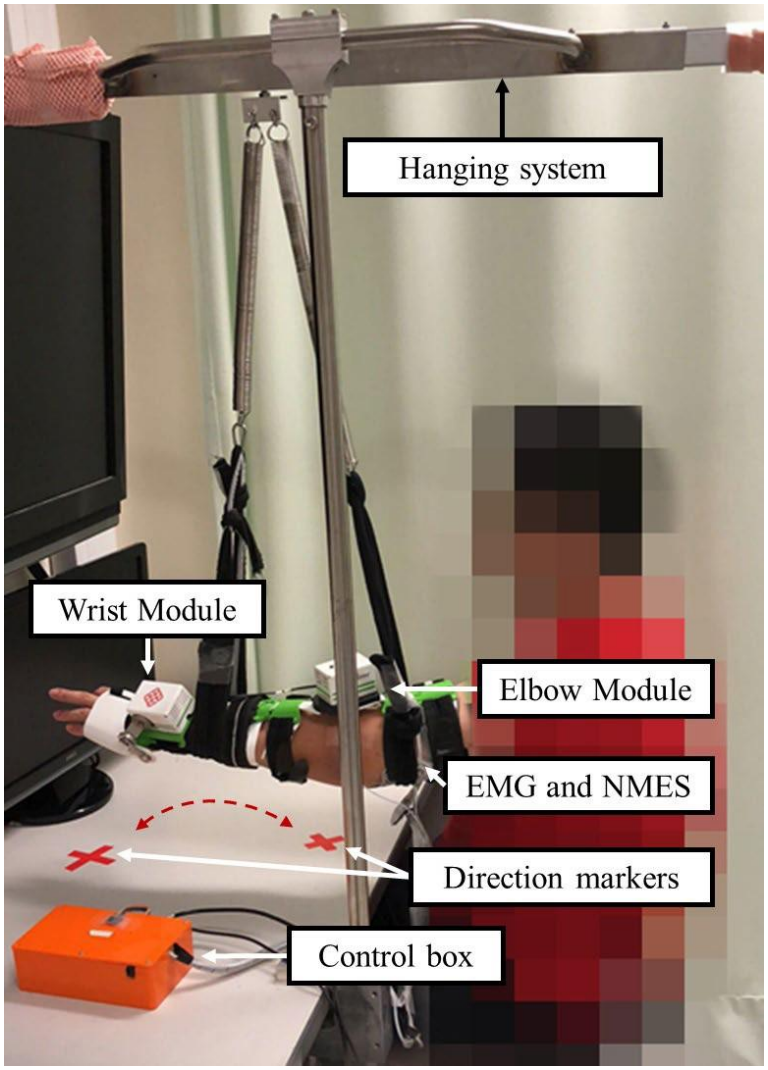


Figure 3-4. The task-oriented training setup with the EMG-driven NMES-robot.

In the beginning, the participants were arranged to sit in front of a table, with their paretic upper limbs suspended by a hanging system (Figure 3-4) supporting at the wrist and elbow joints, in order to offset the gravity effect of the NMES-robotic sleeve.

Subsequently, they were required to perform robot-assisted upper limb training in a vertical plane with sequenced and repeated motion tasks according to a visual cue on the screen for a total of 60 minutes: (1) elbow extension in forward reaching, (2) wrist extension and hand open, (3) wrist flexion and hand close, and (4) elbow flexion (withdrawing). To prevent muscle fatigue, participants were allowed to rest for 10 minutes after half an hour of training [103]. Furthermore, if the participants could not reach out at the elbow in the initial sessions, they were encouraged to try their best to complete the motion tasks.

3.2.4. Evaluation of Training Outcomes

3.2.4.1 Clinical Assessments

In this study, all participants underwent clinical assessments before, after training and three months later. The FMA for upper extremity (FMA-UE, full score 66) was used to evaluate the performance-based sensorimotor functions of the paretic upper limbs. Furthermore, to compare the motor functions between the proximal and distal segments, the FMA was sub-scaled into shoulder/elbow (42/66) and wrist/hand (24/66). The Action Research Arm Test (ARAT) was adopted mainly to evaluate motor functions with hand tasks, including holding/releasing objects in different shapes, sized and weights. Moreover, post-stroke spasticity at the fingers, the wrist and the elbow were assessed by applying the MAS. All the clinical assessments were conducted by a physiotherapist who was blinded to the training protocol. Communication between the participants and the assessor regarding training details was not allowed in the study.

3.2.4.2 EMG Parameters

In addition to the clinical assessments, session-by-session EMG evaluation before the device-assisted training was used to trace the underlying recovery progress across the 20 training sessions with MVCs and the bare-arm test, as stated previously.

Two EMG parameters were calculated for quantitative description of the cross-session variations in (1) muscle activation (the normalized EMG activation level of each target muscle) and (2) muscle coordination pattern [the normalized Co-contraction Index (CI) between a pair of muscles).

The processing methods for EMG parameters, i.e. EMG activation level and CIs, were the same as those in the first study: EMG activation level was described in *Eq. 2.1* and CI in a muscle pair could be expressed in *Eq. 2.2*. A further normalization was applied to both EMG parameters (EMG activation level and CI) of individual participants, with respect to the maximal and minimal values of the participants across the 20 training sessions, with the following expressions:

$$\overline{EMG_N} = \frac{\overline{EMG} - \overline{EMG_{min}}}{\overline{EMG_{max}} - \overline{EMG_{min}}} \qquad \text{(Eq. 3.1)}$$

Where EMGN was the normalized EMG activation level of muscle *i*, the $\overline{EMG_N}$ referred to the averaged EMG envelope value of muscle *i* in *Eq 2.1*, the $\overline{EMG_{min}}$ was the minimum value of the averaged EMG envelope across the 20 training sessions and the $\overline{EMG_{max}}$ was the maximum value of the averaged EMG envelope across the 20 training sessions.

$$\overline{CI_N} = \frac{CI - CI_{min}}{CI - CI_{max}}, \quad \text{(Eq. 3.2)}$$

Where, CI_N was the normalized CI value between a pair of muscle *i* and *j*; the CI referred to *Eq 2.2*, CI_{min} was the minimum value of the averaged overlapping activity of EMG linear envelopes, and CI_{max} was the maximum value of the averaged overlapping activity of EMG linear envelopes across the 20 training sessions. The purpose of this procedure was to illustrate the tendency of EMG parameters of an individual with normalized values to vary from 0 to 1 and to minimize the variations among different participants, as encountered previously.

3.2.5. Statistical Analysis

It was found that in our previous study that the clinical score and the EMG sample had a normal distribution, as assessed by the Lilliefors method with a significant level of 0.05 [103, 188]. One-way analysis of variance (ANOVA) with the repeated measures (Bonferroni *post hoc* tests) was conducted to determine the differences on the clinical assessments across different evaluation time point [i.e., the pre-, the post-, and the three-month follow-up (3MFU) assessments] and on the EMG parameters (i.e., the normalized EMG activation level and the CIs) across the 20 training sessions. The levels of statistical significance were indicated at 0.05 and 0.01 in this study.

3.3 Results and Discussions

A total of 17 chronic stroke patients fulfilled the inclusion criteria after the screening, and they were finally recruited in this study. All the participants completed the task-oriented training with multi-joint practice assisted by the EMG-driven NMES-robotic sleeve. The demographic data of the participants are shown in Table 3-1, while Table 3-2 summarizes statistical results of all the clinical scores measured in this study [i.e., the means and 95% confidence intervals of each clinical assessment together with the one-way ANOVA probabilities with effect sizes (EFs)]. It also illustrates the significant difference in clinical scores, which shows the FMA, ARAT and MAS scores evaluated at pre-, post-training assessments and the 3-month follow-up (3MFU). Figure 3-5 shows the muscles with significant variation of EMG parameters (i.e. EMG activation level and CI values) across the 20 training sessions in the upper limb.

Characteristics	Multi-Joint Training in Chronic Stroke (n=17)
Age (yrs)	57.1±6.54
Time after Stroke (yrs)	8.13±3.88
Gender (female/male)	7/10
Stroke side (left/right)	12/5
Type of stroke (hemorrhagic/ischemic)	3/14

Table 3-1. Demographic data of chronic patients participated in this study.

3.3.1 Training Effects by Clinical Assessments

Assessment	PRE	POST	3MFU	1-way ANOVA
	Mean Value (95% Confidence Interval)			*P* (*Partial* η^2)
FMA Total	27.77 (24.5-31.1)	38.9 (35.8-42.0)	42.4 (39.3-45.5)	$0.007^{\#\#}$ (0.243)
FMA-SE	19.23 (14.9-23.6)	27.62 (24.0-34.6)	29.85 (27.6-35.4)	$0.004^{\#\#}$ (0.262)
FMA-WH	8.54 (7.2-9.9)	11.31 (10.2-12.5)	12.54 (11.4-13.7)	0.079 (0.132)
ARAT	17.46 (13.6-21.3)	29.08 (25.8-32.3)	29.85 (25.6-34.1)	$0.047^{\#}$ (0.157)
FIM	62.31 (61.1-63.6)	66.38 (66.0-66.8)	65.69 (65.1-66.3)	$0.003^{\#\#}$ (0.282)
MAS-elbow	1.52 (1.2-1.8)	0.82 (0.6-1.0)	0.74 (0.5-0.9)	0.065 (0.141)
MAS-wrist	1.32 (1.2-1.5)	0.92 (0.8-1.1)	0.91 (0.7-1.1)	0.131 (0.107)
MAS-finger	1.37 (1.2-1.5)	0.91 (0.7-1.1)	0.94 (0.8-1.1)	0.143 (0.102)

Table 3-2. The statistical results for each measurement of the clinical assessments.

The means and 95% confidence interval, as well as the probabilities in one-way ANOVA with Bonferroni *post hoc* test. Differences with statistical significance (one- way ANOVA with Bonferroni post hoc tests) are marked with $^{\#}$ beside the P values. Significant levels are indicated as follows: $^{\#}$ for ≤ 0.05, and $^{\#\#}$ for ≤ 0.01.

As shown in Table 3-2, the FMA scores varied with respect to the whole arm as well as to distal and proximal segments. Significant difference was observed with respect to the factor of evaluation time points [i.e. the pre-training (pre), the post-training(post), and the 3-month follow up (3MFU)] in the FMA full score [P=0.007, effect size (EFs)=0.243, one-way ANOVA with Bonferroni *post hoc* test) and in the FMA shoulder/elbow score (P=0.004, EFs=0.262, one-way ANOVA with Bonferroni *post hoc* test). The significant increase in the FMA (full score and shoulder/elbow) indicated an improvement of voluntary motor control at the elbow and wrist joints of the paretic limb. Although the scores in FMA wrist/hand also increased after the training and at 3-month follow up, there was no intragroup significance in the statistical results.

Despite the loss of a significant increase in FMA wrist/hand, the ARAT illustrated markedly motor improvements by the significant increase (P=0.047, EFs=0.157, one-way ANOVA with Bonferroni *post hoc* test) in the evaluation items related to the finger, e.g. grasping, gripping and pinching movements. Besides, the assessments mainly related to the evaluation on the post-stroke functional independence of patient's daily activities, i.e. the FIM, also illustrated the significant increase (P=0.003, EFs=0.282, one-way ANOVA with Bonferroni *post hoc* test) in the post-training score and in the 3-month follow-up. The improvement as shown by ARAT and FIM was proof of the multi-joint coordinated training effectiveness to help chronic stroke patients achieve the functional recovery in their impaired upper limb. According to other robot-assisted studies as well as our previous research on the NMES-robot supported training on the

single wrist joint, the achievements in the ARAT and FIM were rarely observed. It is understood that in the chronic period after stroke, the neurological recovery in the injured central nervous system of patients has come to a plateau, as mentioned in Chapter 1. The aim of stroke rehabilitation treatment in this period, as indicated in stroke rehabilitation guidelines, is varied from the subacute goals (i.e. initiation of voluntary movement, equally intensive practice across multiple joints, and early muscle spasticity control) and concentrates more on the conversion of already gained motor recovery into meaningful daily activities. Therefore, in this study, the training outcomes achieved as shown in ARAT and FIM is more essential than that achieved in our first stage investigation on subacute stroke patients.

There was no significant change in the results of MAS scores at all three parts of the entire upper limb, i.e. the fingers, the wrist and the elbow, which indicates the stubborn hypertonic pattern in patients' upper limb at the affected side. Despite the negative performance evaluated by the clinical scale, we are more curious about the underlying recovery process in the muscular activities, as many clinical reports indicate a close contact between the release of flexor hypertonic pattern and functional upper limb movements. Hence, we made further investigation on chronic patients' muscular variation patterns, based on the EMG parameters achieved in each training sessions.

3.3.2 Training Effects by Cross-Session EMG Evaluations

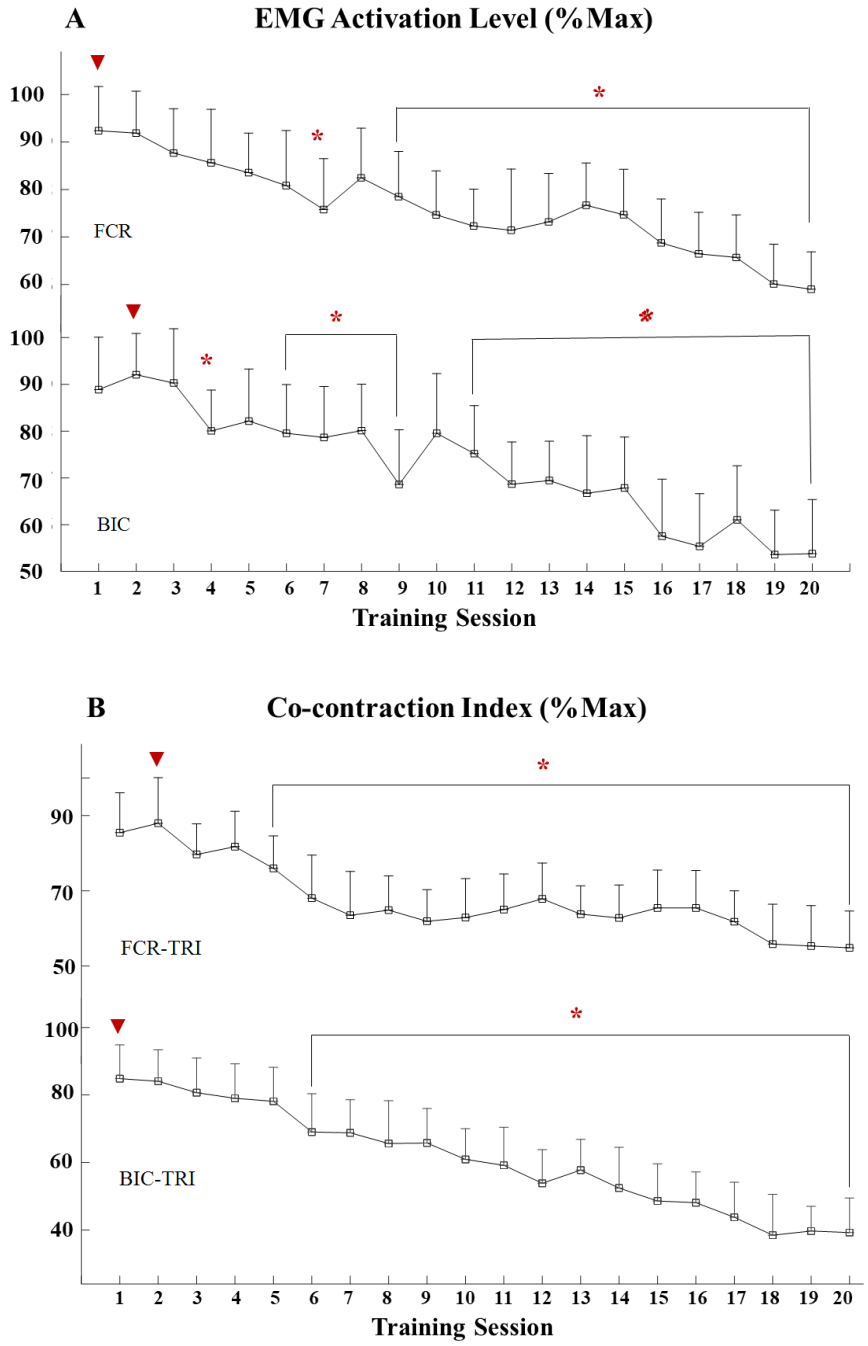


Figure 3-5. Significant variations in the EMG parameters as shown in the upper limb flexor muscles, i.e., the EMG activation level of FCR muscle and BIC muscle; and the CI values of FCR&TRI muscle pair and BIC&TRI muscle pair.

Figure 3-5 shows the muscles with significant muscular changes across the complete 20-session training progress. Significant variations were observed in the upper limb flexors, i.e. the FCR for wrist flexion and BIC for elbow flexion movements, while there was no significant variation in the extensors found in this study.

Both FCR and BIC muscles showed a release of hypertonic pattern with significantly decreased EMG activation level ($P<0.05$, one-way ANOVA with Bonferroni *post hoc* test). The results implied a recovery potential of the flexors o releases their muscle spasticity during the multi-joint coordinated training by the NMES-robot sleeve. A significant reduction was also found in the CI values of FCR&TRI muscle pair and BIC&TRI ($P<0.05$, one-way ANOVA with Bonferroni *post hoc* test). This finding is consistent with the improvement of movement independence with isolated joint control as patients performed in the FMA, ARAT evaluations. The variations in muscular activities also implied a change of accustomed compensatory motion patterns into near-to-normal motion control.

We also noticed that the reduction of EMG activation levels and CIs did not reach a plateau within the 20 training sessions as shown in **Figure 3-5**, which implied better recovery outcomes with longer training duration in the future studies.

3.4 Periodic Summary

In this work, the device-assisted multi-joint coordinated training strategy was adopted for the UE physical practice for patients with chronic stroke in the single-group clinical trial. Both the clinical assessments (i.e. FMA, MAS, ARAT and FIM) and cross-session EMG evaluation were used to illustrate the motor outcomes after the treatment. For the chronic patients, the novel training was effective to promote voluntary motor function in their paretic upper limbs especially at more relative proximal segments, i.e. the shoulder-elbow part, as assessed by FMA (full score and shoulder-elbow). The treatment also showed significant improvement of functional motions and independence of daily activities. All the motor achievements were maintained for 3 months after the treatment. There was no significant variation in the muscle tone after the treatment (post- and 3MFU assessment) as assessed by MAS at all three segments (finger, wrist and elbow). Meanwhile, the EMG parameters across 20 training sessions showed a significant release of muscle excessive contraction in both wrist flexor (FCR) and elbow flexor (BIC) by EMG activation level, as well as the improvement of muscle coordination across multiple joints (FCR & TRI) and within single elbow joint (BIC & TRI) by CI values.

CHAPTER 4

NMES-ROBOT-ASSISTED MULTI-JOINT COORDINATED UPPER LIMB TRAINING UNDER DIFFERENT JOINT-SUPPORTIVE SCHEMES IN CHRONIC STROKE

4.1 Introduction

As stated in the previous chapter, a particular challenge for current stroke rehabilitation is that most survivors with chronic stroke still sustain moderate to severe motor impairments in the wrist and hand for daily activities [10, 12], greatly affecting their functional independence and ability to perform activities of daily living (ADL) [17].

Significant motor recovery usually occurs within the first six months after the stroke onset [19] and is believed to be plateaued in the chronic period (i.e. six months after stroke onset) [138]. Therefore, rehabilitation resources are usually more concentrated in the early stage than in the chronic period after stroke conventionally. However, as specified in **Chapter 3**, we understand that repetitive [28] and high-intensity practice [29] can markedly contribute to functional improvement of the affected UE movement, even in patients with chronic stroke [23]. Furthermore, task-oriented training with coordinated practice among different joints in the upper limb has demonstrated to be effective of converting motor improvements into meaningful limb functions for daily activities after stroke [65].

Despite of the findings in our previous study indicating the training effectiveness of the NMES-robotic system to support multi-joint coordinated physical practice, inconsistent results were reported in early studies of robot-assisted therapy [35, 79, 84-87]. Earlier studies yielded inconsistent findings regarding the training outcomes of robot-assisted therapy. Most studies reported equivalent improvements after robot-assisted training compared with the manual delivered conventional treatments. Those studies involving voluntary effort reported better training outcomes with the assistance from rehabilitation devices while some others adopting CPM mode showed negative results [96-99]. Previous literature also reported different sustainability of the training effects with varied time length, i.e. Bovolenta reported less than 3 months' maintenance of effective training outcomes after one course of robot-assisted training [98], meanwhile Housman found the sustaining time could be longer than 6 months [81].

Beside of differences between the robots in their mechanical structures, one of the major reasons leading to the distinct rehabilitation results could be that the robot-assisted treatments have adopted different supportive strategies. As reported by Krebs et al., robotic assistance was applied on a single wrist joint but the treatment achieved additional motor improvements in the elbow-shoulder segments, while the elbow-shoulder parts were restricted to move in the training [101]. Similar motor improvements in the proximal joints relative to the target distal joints were also reported by Hu and colleagues when using electromyography (EMG)-driven robots to assist respective physical practices at the fingers and the wrist, and the motor

improvements achieved in both the proximal and the distal joints were maintained for three months after the training [102, 103]. The recovery occurring in the proximal joints when the physical training was restricted mainly to the distal joints was primarily due to the competitive interaction between the proximal and the distal joints in physical rehabilitation after stroke and the compensatory muscular activities in the proximal joint when moving the distal [104]. Mechanical supporting strategies could interfere with muscular synergies in the UE during physical training. Rare studies have investigated the varied training effects resulting from this aspect with the same robotic systems or under uniformed control algorithm.

In this work, we hypothesized that robotic support to the distal joints would be more effective than to the proximal joints for the whole UE rehabilitation. As chronic stroke patients were usually in a stable status with rare spontaneous recovery, we designed to use both the EMG-driven NMES-robotic hand and the NMES-robotic sleeve to provide different training support when conducting the same motor tasks and to compare the training effectiveness of the two supportive schemes through a randomized controlled clinical trial, i.e. distal finger-palm support versus proximal wrist-elbow support.

4.2 Methodology

4.2.1 EMG-driven NMES-Robots

The two EMG-driven NMES-robots used in this work were wearable exoskeletons to support at hand/fingers (i.e., EMG-driven NMES-robotic hand) and to support at wrist-and-elbow segments (i.e., EMG-driven robotic sleeve), as shown in Figure 4-1. A and Figure 4-1. B.

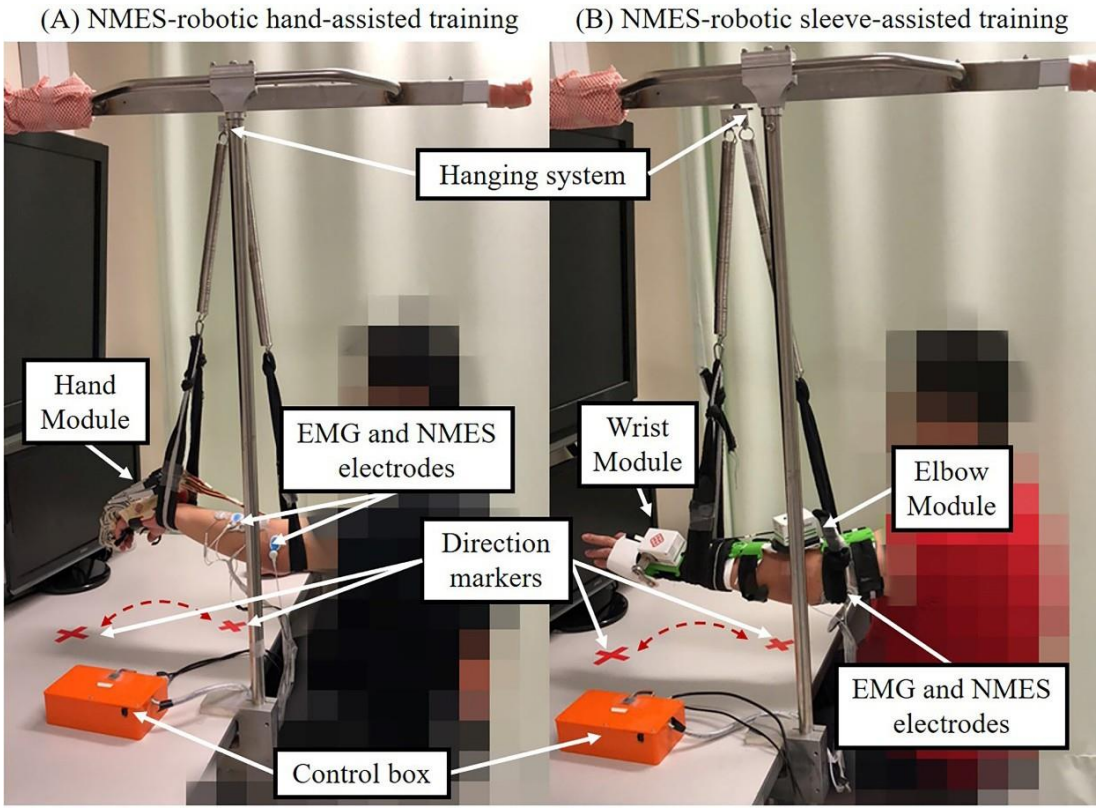


Figure 4-1. The experimental setup under different joint supportive schemes: (A) the EMG-driven NMES-robotic hand provides direct support on the distal fingers; (B) the EMG-driven NMES-robotic sleeve provides wrist-and-elbow training assistance (from our newly submitted Journal paper).

4.2.1.1 EMG-driven NMES-Robotic Hand

Figure 4-1. A shows the EMG-driven NMES-robotic hand, which consisted of a palm-wrist module fixed to the wrist and five individual finger assemblies. Each finger assembly was actuated by a linear actuator (Firgelli L12, Firgelli Technologies Inc.) [102]. For the index, the middle, the ring and the little fingers, the proximal section could rotate around the virtual centre located at the metacarpophalangeal (MCP) joint, whereas the distal section could rotate around the virtual centre located at the proximal interphalangeal (PIP) joint; as regards the thumb, it was designed to rotate around the virtual centre of its MCP joint [77]. Each finger assembly could provide a range of motion (ROM) of 55° for the MCP joint and 65° for the PIP joint. One channel NMES electrode pair (30 mm diameter; Axelgaard Corp., Fallbrook, CA, USA) was attached on the skin surface of the extensor digitorum (ED) muscle belly, being capable of providing square pulsed electrical current stimuli with a constant amplitude of 70 V, frequency of 40 Hz, and a manually adjustable pulse width in the range of 0-300μs (set at the minimum intensity to achieve a fully extended position of the fingers for each individual). No electrical stimulation for finger flexion was used because when the hand is open the muscles are weak while when the hand is closed there is a likelihood of increased spasticity in the majority of patients with chronic stroke. The EMG electrode pairs (Blue Sensor N, Ambu Inc., with a contact area of 20 mm × 30 mm) were attached on the skin surface of the muscle bellies of ED and flexor digitorum (FD), with centre separation of 2 cm. For the ED muscle, the EMG electrodes were placed perpendicularly to the NMES electrode pair, adopted as an

empirical configuration to have relatively low stimulation artefact during EMG signal capturing as we specified previously.

In each motion phase (i.e. finger flexion or extension), the finger assembly motors would move with a constant velocity (22°/s at MCP and 26°/s at PIP joint) once the EMG activation level of a driving muscle exceeded a preset threshold (i.e., three times the standard deviation (SD) above the EMG baseline at rest, by following the standard detection of the onset of voluntary EMG in a contracting muscle [189]). The NMES would be delivered to the ED muscle simultaneously with the motor support just in the finger extension phase. The voluntary-evoked EMG signals from the target muscles (i.e. FD for finger flexion and ED for finger extension) controlled the assistance from both the robot and NMES [102, 103].

4.2.1.2 EMG-driven NMES-Robotic Sleeve

Figure 4-1.B shows the NMES-robotic sleeve, which consisted of two exoskeleton robotic modules for the wrist and the elbow, respectively [130]. Due to post-stroke joint stiffness and muscle spasticity, the modules were not mechanically connected to ensure that they fitted participants with different ergonomic parameters (e.g. limb length and pronation angles away from the neutral position at the wrist) [133]. Each mechanical module was controlled by an independent servo motor (MX106, ROBOTIS), and would support the joint perform flexion and extension motions with a constant velocity of 10°/s during the training [133]. The orthosis of the wrist module only covered the palm at the hand side and set the fingers free for flexion

and extension motions. The maximum ROM provided by the wrist module was from 45° extension to 60° flexion, while for the elbow it was from 30° flexion to 180° extension [129]. Two channel NMES electrode pairs were attached on the muscle bellies of the triceps brachii (TRI) and the extensor carpi radialis (ECR), with the same setting for stimuli parameters (i.e., amplitude, frequency and pulse) as for the NMES-robotic hand training. Moreover, as in the case of the NMES-robotic hand training, electrical stimuli were not delivered to the biceps brachii (BIC) and flexor carpi radialis (FCR) (i.e. the flexors) due to the muscle weakness in the UE extensors and potential spasticity in the UE flexors for the chronic stroke patients. The EMG electrode pairs were placed on the muscle bellies of BIC, the TRI, the FCR and the ECR. The configuration of EMG and NMES electrodes on the extensors (i.e. TRI and ECR) was the same as that in NMES-robotic hand training.

The control algorithm for the assistance from the robotic sleeve and NMES was also similar to the NMES-robotic hand, and involved using the voluntary EMG signals detected from the target muscles for the related joint motion control (i.e. BIC for elbow flexion, TRI for elbow extension, FCR for wrist flexion and ECR for wrist extension) [130].

4.2.2 Subject Recruitment

After obtaining the approval from the Human Subjects Ethics Subcommittee of the university, we screened chronic stroke patients from local districts and then arranged the treatments with the two EMG-driven NMES-robots in a rehabilitation

laboratory. The study design was a randomized controlled trial with a three-month follow-up for comparing the motor improvements on the upper limb with two different supporting schemes, namely, support to the distal joints (fingers) by EMG-driven NMES-Robotic hand and support to the more proximal joints (wrist- elbow) by EMG-driven NMES-Robotic sleeve. Figure 4-2 illustrates the Consolidated Standards of Reporting Trials flowchart of the experimental design.

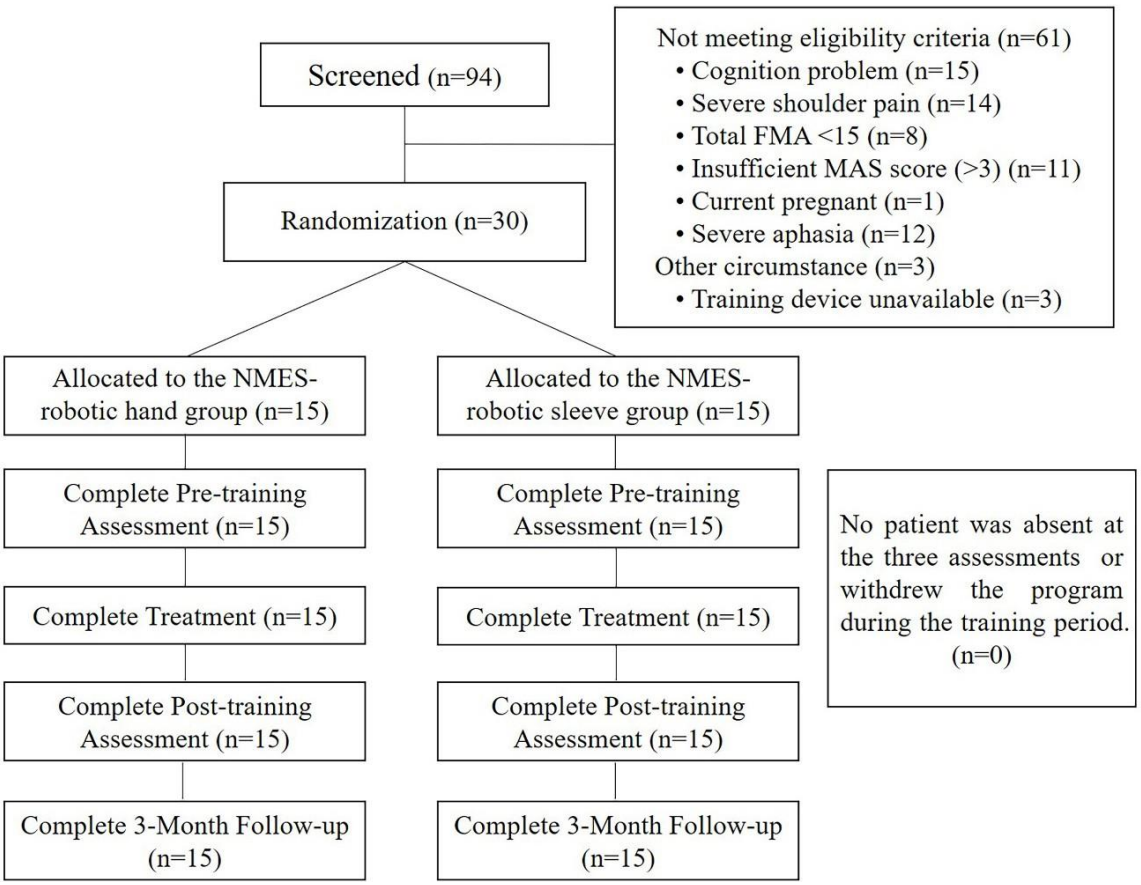


Figure 4-2. The Consolidated Standards of Reporting Trial flowchart of this clinical randomized controlled trial on chronic stroke patients.

The 94 patients with chronic post-stroke UL motor deficits who were subjected to screening all complied with the applied inclusion criteria: (1) age range 18-78 years

old prior to stroke [190, 191]; (2) evidence of acquiring an unilateral brain lesion due to stroke at least six months, without other diagnosed neurological deficits or secondary onset; (3) had enough cognition to understand the content or purpose of the study and follow simple instructions, as assessed by the Mini-Mental State Examination (MMSE>21) [192]; (4) motor impairments affected in the UL ranged from severe to moderate, measured by the Fugl-Meyer Assessment for upper extremity (15<FMA<45, with a maximal score of 66) [193]; (5) spasticity affected at the elbow, the wrist and the fingers during enrollment ranged ≤3, as assessed by the Modified Ashworth Scale [MAS, ranged from 0 (no increase in the muscle tone) to 4 (affected part rigid)] [174]; (6) had detectable voluntary EMG from the target muscles (i.e., above three times SD of the resting EMG), which is consistent with muscle force >1 [102]. The patients were also excluded if they were pregnant at the time, had severe aphasia or had a pacemaker implant, participants were not included.

In the end, 30 patients with chronic stroke were recruited in this study and later randomly assigned into two group, namely, assistance by the EMG-driven NMES-Robot on the fingers (NMES-robotic hand group, n=15) and on the wrist-elbow segments (NMES-robotic sleeve group, n=15). The recruited participants were informed of the aim of the study, and they were also informed about what the training programs would entail. Table 4-1 shows the demographic and clinical information of the participants after the randomization.

Characteristics	Training Assisted by NMES-ROBOTS		P value
	Hand group (n=15)	Sleeve group (n=15)	
Age (yrs) [a]	57.3±8.87	57.7±5.93	0.886
Time since stroke (yrs)[a]	8.26±4.17	7.87±3.07	0.773
Gender (male/female)[b]	12/3	10/5	0.682
Stroke side [b]	7/8	7/8	1.000
Type of stroke [b] (hemorrhagic/ischemic)	8/7	6/9	0.715

Table 4-1. Demographic data of all the chronic patients participated in this study, with training by different joint supportive schemes.

No significant intergroup difference for the baseline of both groups (P>0.05): (1) a for independent t-test; (2) b for Fisher's exact test.

4.2.3 Training Design

Both groups received repetitive task-oriented motion practice with participants' voluntary effort on their entire affected UE, assisted by the two EMG-driven NMES-robots. The two groups did not differ much in terms of training duration and intensity. All the participants received the same 20-session robot-assisted UE practice consisting sequenced and repeated motion tasks to simulate daily activities of multi-joint coordinated arm-reaching and arm-withdrawing. Each training session contains two sections of 30 mins' training and 10 mins break between the two consecutive sections. Participants were provided with 5 training sessions per week (in the working days) and complete the 20 sessions in 5 weeks.

4.2.3.1 Protocol for Hand-Support Practice

In the beginning, the participants were arranged to sit in front of a table, with their

paretic upper limbs suspended by a hanging system (Figure 4-1. A) supporting at the wrist and elbow joints, in order to offset the gravity effect of the NMES-robotic hand. This design was justified by the fact that most of the participants had difficulty sustaining the weight of both their paretic limbs and the robotic system without support, especially in the first several training sessions. Subsequently, they were required to perform robot-assisted vertical UE training with sequenced and repeated motion tasks according to a visual cue on the screen for a total of 60 minutes: (1) elbow extension in forward reaching, (2) wrist extension and hand open, (3) wrist flexion and hand close, and (4) elbow flexion (withdrawing). To prevent muscle fatigue, participants were allowed to rest for 10 minutes after half an hour of training [103]. Furthermore, if the participants could not reach out at the elbow in the initial sessions, they were encouraged to try their best to complete the motion tasks.

4.2.3.2 Protocol for Sleeve-Support Training

During the sleeve-assisted training, the paretic upper limbs of the participants were also suspended by the hanging system (Figure 4-1. B) to resist the gravity effect of the NMES-robotic system. Similar to the robotic hand group, the motion tasks that the participants in the robotic sleeve group had to perform involved sequenced and repeated arm reaching and withdrawing movements as prompted by the visual cues on the computer screen. Each training session lasted for a total of 60 minutes, with a 10-minute break between two consecutive 30-minute intervals to avoid muscle fatigue [130].

The main objective of the motion tasks was to simulate arm reaching-grasping and withdrawing motions in the daily activities. Markers on the table (Figure 4-1) were labelled for the participants to recognize the targeting positions of the hand in the horizontal plane during the motions.

4.2.4 Training Outcome Evaluation

1) Clinical Assessments

In this study, all participants underwent clinical assessments before, after training and three months later. The FMA for upper extremity (FMA-UE, full score 66) was used to evaluate the performance-based sensorimotor functions of the paretic upper limbs. Furthermore, to compare the motor functions between the proximal and distal segments, the FMA was sub-scaled into shoulder/elbow (42/66) and wrist/hand (24/66). The Action Research Arm Test (ARAT) was adopted mainly to evaluate motor functions with hand tasks, including holding/releasing objects in different shapes, sized and weights. Moreover, post-stroke spasticity at the fingers, the wrist and the elbow were assessed by applying the MAS. All the clinical assessments were conducted by a physiotherapist who was blinded to the training protocol. Communication between the participants and the assessor regarding training details was not allowed in the study.

2) Session-by-Session EMG evaluation

In addition to the clinical assessments, session-by-session EMG evaluation before

the device-assisted training was used to trace the evolution of the muscle coordination and the recovery progress of each target muscle across the 20 training sessions with maximum voluntary contractions (MVC) and a bare arm test, as practiced previously [187, 194]. The test was similar to the motion tasks in the formal training but without support by NMES-robot, consisting of horizontal arm reaching, hand grasping, hand opening, and arm withdrawing tasks, and was repeated three times [102, 103, 129, 130]. EMG signals from BIC, TRI, ECR-ED unit, and FCR-FD unit were collected for off-line processing. In the context of the investigation of EMG activities in the forearm for both groups, the EMG electrode pairs were located on the common area of the two muscle bellies of ECR-ED and FCR-FD due to the close anatomical proximity between the ECR and ED muscles and between the FCR and FD muscles. All EMG signals were amplified with a gain of 1000 (amplifier: INA 333, Texas Instruments Inc.), band-pass filtered from 10 to 500 Hz, and then sampled with 1000 Hz for digitization, as was done previously [103, 130].

Two EMG parameters were adopted for quantitative description of the cross-session variations in (1) muscle activation (normalized EMG activation level of each muscle) and (2) muscle coordination pattern (normalized co-contraction index, CI between the muscle pairs). The processing calculation methods have been specified in ***2.2.3.*** The increase in CI values was potentially indicative of aggravation of muscle coordination patterns of a muscle pair with broadened overlapping area, while a decrease in CI values was indicative of separation in the co-contraction phase of the two muscles with the reduced overlapping area.

In this study, a further normalization as specified in ***3.2.4*** was applied to both EMG parameters (EMG activation level and CI) of individual participants, with respect to the maximal and minimal values of the participants across the 20 training sessions. The purpose of this procedure was to illustrate the tendency of EMG parameters of an individual with normalized values to vary from 0 to 1 and to minimize the variations among different participants, as encountered previously [118, 119].

4.2.5 Statistical Analysis

The two groups did not differ significantly in terms of the baseline of the demographic data (i.e., age, sex, duration from stroke onset, side of paresis, P>0.05, independent t-test, Table 4-1) and all clinical scores (i.e., pre-assessments on FMA, ARAT and MAS, P>0.05, independent t-test, Table 4-2). The results of clinical assessments were first analyzed using the two-way analysis of covariance (ANCOVA), with respect to the factors of 1) treatment (i.e. NMES-robotic hand training and sleeve training) and 2) the evaluation time point [i.e., the pre-, the post-, and the three-month follow-up (3MFU) assessments], by taking the pre-assessment as a covariate, in order to further minimize the possible baseline difference between the groups [179]. When a significant difference with respect to the time points was found, one-way analysis of variance (ANOVA) was conducted to determine the intra-group differences with the *post hoc* Bonferroni tests. Subsequently, the between-group comparisons on the clinical scores at the respective post- and 3MFU were evaluated by one-way ANCOVA with the pre-assessment as a covariate (Table 4-3). It was not necessary to use the

initial values for EMG parameters (i.e. EMG activation level and CI values) for ANCOVA, mainly due to the normalization mentioned above and due to the fact that the initial values were usually the peak among the 20 training sessions. Two-way ANOVA was first applied with respect to the group factor and the factor of training times (i.e. 20 sessions). Subsequently, one-way ANOVA was performed to investigate the variation across the 20 training sessions with Bonferroni correction in the *post hoc* tests. If significant group difference was found by two-way ANOVA with respect to the group factor, the independent t-test would be applied at different training sessions for the investigation of intergroup differences. The levels of statistical significance were indicated at 0.05, 0.01, and 0.001 in this study.

4.3 Experimental Results

All participants, either trained by using the NMES-robotic hand (n=15) or the NMES-robotic sleeve (n=15) completed the 20-session treatments. Table 4-2 summarizes all clinical scores measured in this study, namely, the means and 95% confidence interval of each clinical assessment together with the one-way ANOVA probabilities with the effect sizes (EFs) for the intra-group evaluation with respect to the assessment sessions, and the two-way ANCOVA probabilities with EFs with respect to session and group. Table 4-3 summarizes the probabilities and EFs of the between-group comparison on the respective post- and 3MFU assessments by one-way ANCOVA with the adjustment of the baseline effect.

4.3.1 Training Outcomes by Clinical Assessments

Assessment	PRE	POST	3MFU	1-way ANOVA	1- way ANCOVA		
					P (*Partial* η^2)		
	Mean Value (95% Confidence Interval)			*P* (*Partial* η^2)	*Session*	*Group*	*S*G*
FMA Total (Hand)	28.9 (22.6-35.1)	42.2 (35.9-48.5)	45.3 (39.0-51.5)	$0.001^{\#\#\#}$ (0.274)	$0.000^{\Delta\Delta\Delta}$ (0.567)	0.879 (0.000)	0.920 (0.002)
FMA Total (Sleeve)	32.4 (25.9~38.9)	44.8 (38.3-51.3)	47.5 (41.0-54.0)	$0.004^{\#\#}$ (0.229)			
FMA-SE (Hand)	20.0 (16.0-24.0)	28.5 (24.4-32.5)	30.6 (26.6-34.6)	$0.001^{\#\#\#}$ (0.270)	$0.000^{\Delta\Delta\Delta}$ (0.550)	0.793 (0.001)	0.825 (0.005)
FMA-SE (Sleeve)	21.7 (17.8-25.6)	30.7 (26.8-34.6)	31.5 (27.6-35.4)	$0.001^{\#\#\#}$ (0.271)			
FMA-WH (Hand)	8.9 (6.3-11.4)	13.7 (11.2-16.3)	14.7 (12.1-17.2)	$0.005^{\#\#}$ (0.222)	$0.000^{\Delta\Delta\Delta}$ (0.362)	0.695 (0.002)	0.698 (0.009)
FMA-WH (Sleeve)	10.7 (7.3-14.0)	14.1 (10.8-17.5)	16.1 (12.7-19.4)	0.075 (0.116)			
ARAT (Hand)	15.6 (8.8-22.4)	26.5 (19.7-33.3)	26.9 (20.1-33.7)	$0.036^{\#}$ (0.147)	$0.000^{\Delta\Delta\Delta}$ (0.396)	0.430 (0.08)	0.938 (0.002)
ARAT (Sleeve)	20.8 (13.6-28.0)	31.9 (24.7-39.1)	33.3 (26.1-40.5)	$0.034^{\#}$ (0.149)			
MAS-elbow (Hand)	1.5 (1.1-2.0)	0.9 (0.4-1.3)	0.7 (0.3-1.2)	$0.033^{\#}$ (0.149)	$0.000^{\Delta\Delta\Delta}$ (0.191)	0.591 (0.003)	0.388 (0.023)
MAS-elbow (Sleeve)	1.1 (0.7-1.5)	0.8 (0.4-1.2)	0.7 (0.3-1.0)	0.288 (0.058)			
MAS-wrist (Hand)	1.5 (1.1-1.9)	0.6 (0.2-1.0)	0.3 (-0.1-0.7)	$0.001^{\#\#\#}$(0.295)	$0.000^{\Delta\Delta\Delta}$ (0.518)	$0.00^{\Delta\Delta\Delta}$ (0.319)	$0.01^{\Delta\Delta\Delta}$ (0.149)
MAS-wrist (Sleeve)	1.3 (0.9-1.8)	0.9 (0.5-1.4)	0.9 (0.4-1.3)	0.272 (0.060)			
MAS-finger (Hand)	1.3 (0.9-1.7)	0.5 (0.0-0.9)	0.4 (0.0-0.8)	$0.004^{\#\#}$ (0.231)	$0.000^{\Delta\Delta\Delta}$ (0.367)	$0.001^{\Delta\Delta\Delta}$ (0.136)	0.067 (0.063)
MAS-finger (Sleeve)	1.4 (0.9-1.9)	1.0 (0.5-1.5)	0.9 (0.5-1.4)	0.319 (0.053)			

Table 4-2. Statistical results of the clinical scores in chronic stroke patients undertaking different supportive schemes (1)

The means and 95% confidence intervals for each measurement of the clinical assessments, and the probability with the estimated effect sizes of the statistical analyses. Differences with statistical significance are marked with superscripts beside the P values ("#" for one-way ANOVA intragroup tests, "Δ" for two-way ANCOVA tests on the group and session effects with the pre-assessment as the covariate). Significant levels are indicated as, 1 superscript for <0.05, 2 superscripts for ≤0.01, and 3 superscripts for≤0.001.

Assessment	1-way ANCOVA on the Post- and 3MFU assessments between the groups	
	***Post*_Pre** P (*Partial* η^2)	***3MFU*_Pre** P (*Partial* η^2)
FMA		
Full Score	0.865 (0.001)	0.9090 (0.000)
Shoulder/Elbow	0.601 (0.010)	0.601 (0.010)
Wrist/Hand	0.996 (0.000)	0.8070 (0.002)
ARAT	0.721 (0.005)	0.458 (0.021)
MAS		
Elbow	0.686 (0.006)	0.661 (0.007)
Wrist	0.686 (0.006)	0.000*** (0.557)
Finger	0.003** (0.289)	0.008** (0.234)

Table 4-3. Statistical results of the clinical scores in chronic stroke patients undertaking different supportive schemes (2)

The statistical probabilities and the estimated effect sizes of the one-way analysis of covariance (ANCOVA) on the respective post-assessment and 3-month follow-up (3MFU) between the groups, by taking the pre-assessment as the covariate. Differences with statistical significance are marked with '*' beside the P values. Significant levels are indicated as, * for <0.05, ** for ≤0.01, *** for ≤0.001.

The clinical scores of FMA, MAS and ARAT scores in both groups were illustrated in Table 4-2, 4-3 and Figure 4-3. As the results of FIM scores were almost near to normal score in most recruited patients, there was no indication of the changes in their functional independency in the study. The clinical assessments were also evaluated three times as we did in previous studies, i.e. before the first training (pre-assessment), right after the last training (post-assessment) and 3 months later after the last training (i.e. 3MFU).

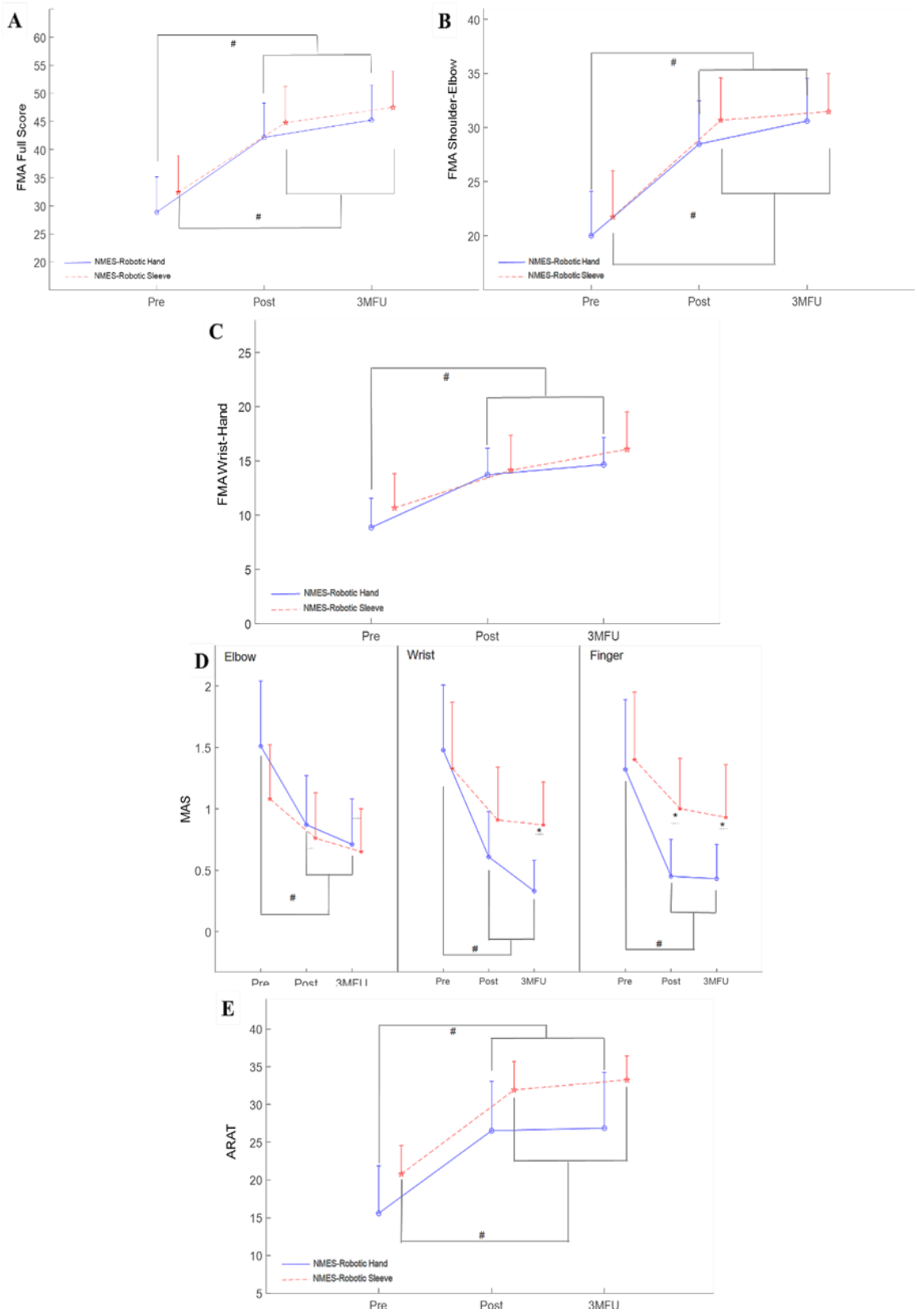


Figure 4-3. Overview of the significant changes in different clinical scores.

Significant difference was observed only with respect to the factor of evaluation time points in the FMA full score, the FMA shoulder-elbow and FMA wrist-hand sub-scores (two- way ANCOVA, P<0.05, Table 4-2). Although the values in FMA full score [NMES-robotic hand group: P=0.001, EFs=0.274, one-way ANOVA with Bonferroni post hoc test; and NMES-robotic sleeve group: P<0.005, EFs=0.229, one-way ANOVA with Bonferroni post hoc test, Figure 4-3 (A)] and FMA shoulder-elbow [NMES-robotic hand group: P=0.001, EFs=0.271, one-way ANOVA with Bonferroni post hoc test; and NMES-robotic sleeve group: P=0.001, EFs=0.271, one-way ANOVA with Bonferroni post hoc test, Figure 4-3 (B)] were significantly increased in both two groups after the treatments and the results were maintained for at least 3 months, the FMA wrist-hand scores [P<0.01, EFs=0.222, one-way ANOVA with Bonferroni post hoc test, Table 4-2, Figure 4-3 (C)] were only increased in the NMES-robotic hand group but absent in the NMES-robotic sleeve group (P>0.05). The results indicated better motor improvement of distal UE segments with direct support from the NMES-robotic hand.

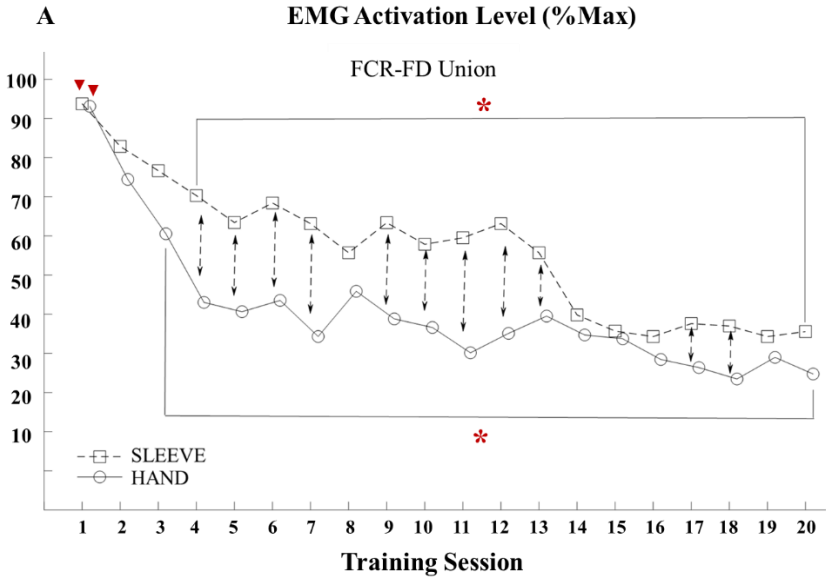
Significant differences in the MAS scores were observed with respect to the evaluation time points by two-way ANCOVA (Table 4-2) at elbow (P<0.001, EFs=0.191), wrist (P<0.001, EFs=0.518) and fingers (P<0.001, EFs=0.367). The significant reduction of MAS at all three parts (i.e., the elbow, the wrist and the fingers) were also observed in the NMES-robotic hand group only [elbow (P < 0.05, EFs=0.149, wrist (P < 0.001, EFs=0.295, fingers (P < 0.01, EFs=0.231), one-way ANOVA with Bonferroni post hoc tests, Figure 4-3 (D)], with significant between-

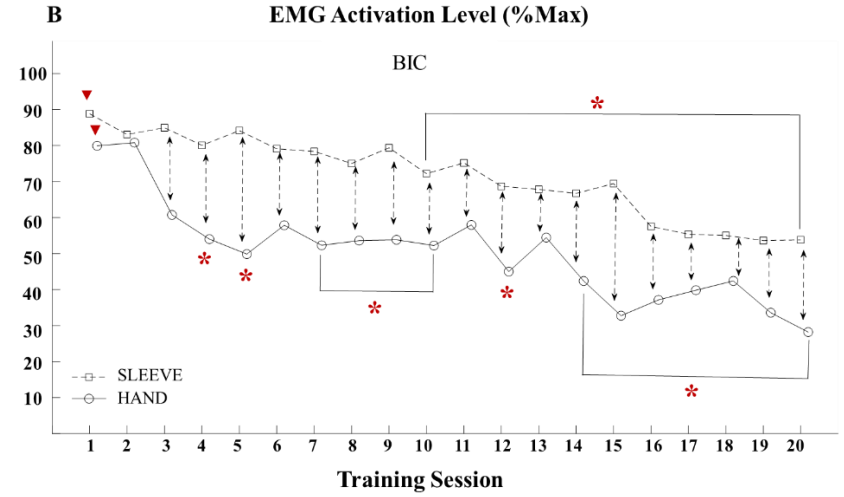
group differences in values of MAS wrist at post-training assessment (P<0.01, EFs=0.289, one-way ANCOVA) and 3MFU assessment (P<0.01, EFs=0.234, one-way ANCOVA) and in values of MAS finger at 3MFU (P<0.001, EFs=0.557, one-way ANCOVA). The results illustrated more effective release of muscle spasticity in the entire upper limb with the NMES-robotic support to the distal segments. All the achievements could be maintained for 3 months as well.

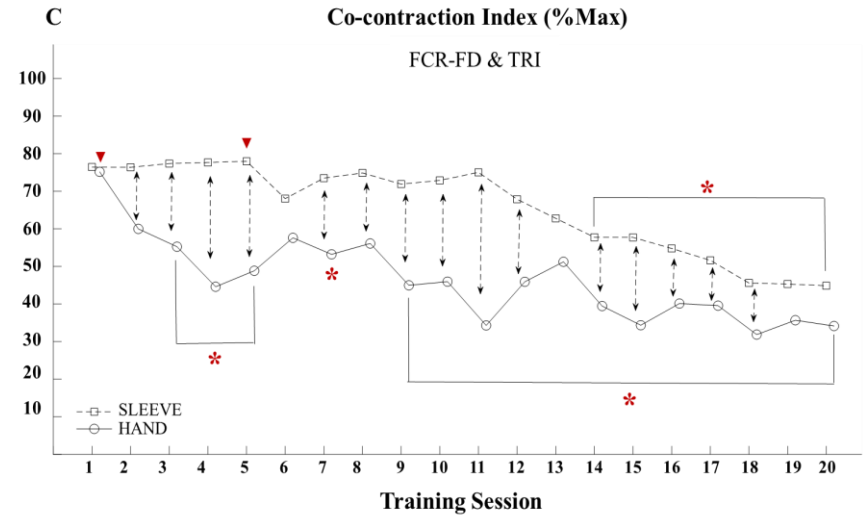
For the ARAT scores, both groups showed similar patterns with no between-group difference with respect to group factor (P>0.05, two-way ANCOVA) in this measurement. Significant differences were observed with respect to the evaluation time points by two-way ANCOVA [elbow (P<0.001, EFs=0.191), wrist (P<0.001, EFs=0.518) and fingers (P<0.001, EFs=0.367), Table 4-2]. Furthermore, after the training, both groups exhibited significant increment compared to the pre-training values, and the elevation was maintained until three months later when evaluation was (NMES-robotic hand group: P<0.05, EFs=0.147; and sleeve group: P<0.05, EFs=0.149, one- way ANOVA with Bonferroni *post hoc* test, Table 4-2).

4.3.2 Training Outcomes by EMG Evaluation

Figures 4-4 (A) to (D) illustrated the significant variation patterns of EMG parameters (i.e. the normalized EMG activation levels and the normalized CI values) across the 20 training sessions in both the NMES-robotic hand group and sleeve group.


A
EMG Activation Level (%Max)
FCR-FD Union
100
90
80
70
60
50
40
30
20
10
SLEEVE
HAND
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Training Session


B
EMG Activation Level (%Max)
BIC
100
90
80
70
60
50
40
30
20
10
SLEEVE
HAND
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Training Session


C
Co-contraction Index (%Max)
FCR-FD & TRI
100
90
80
70
60
50
40
30
20
10
SLEEVE
HAND
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Training Session

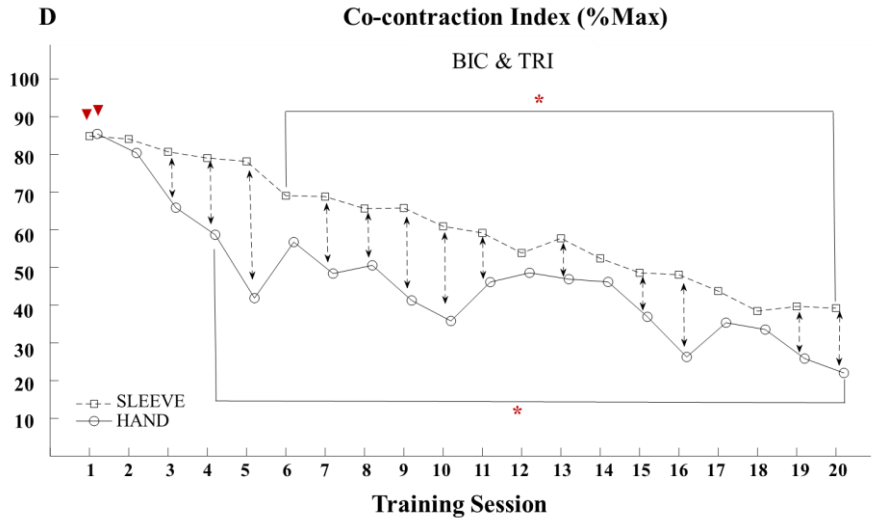


Figure 4-4. The variation of electromyography (EMG) parameters recorded across the 20 training sessions.

The significant variations of the EMG parameters in the comparison of both supportive schemes (i.e., finger-hand support in the Hand group and wrist-elbow support in the Sleeve group). Dotted double arrow presents the significant between-group difference (t-test, P<0.05) in each training session. '▼' illustrates the peak of the EMG parameters through 20 training sessions. '*' demonstrates the significant intragroup differences in each group (1-way ANOVA with Bonferroni post hoc test, P<0.05)

Both groups exhibited significant decrease in the EMG activation level at the FCR-FD muscle union (NMES-robotic hand group: P<0.05, EFs=0.436; and NMES-robotic sleeve group: P<0.05, EFs=0.151) and the BIC muscle (NMES-robotic hand group: P<0.05, EFs=0.375; NMES- robotic sleeve group: P<0.05, EFs=0.112) by one-way ANOVA with Bonferroni post hoc test. As regards the between-group comparison, Figure 4-4 (A) indicates that, from the fourth training session, the NMES-robotic hand group exhibited significantly lower EMG activation values of FCR-FD muscle union (P<0.05, t-test). Moreover, the values of BIC were also significantly lower in the NMES-robotic hand group (P<0.05, t-test) from the third

training session and remained lower until the twentieth session, as shown in Figure 4-4 (B).

Figure 4-4 (C) and (D) demonstrated the variation patterns of CI values across the 20 training sessions. A significant decrease in CI values was observed in both groups in the muscle pairs FCR-FD&TRI ($P<0.05$, one-way ANOVA with Bonferroni *post hoc* test) and BIC&TRI ($P<0.05$, one-way ANOVA with Bonferroni post hoc test), respectively. In terms of the between-group comparison, the NMES-robotic hand group exhibited significantly lower CI values ($P<0.05$, t-test) than the sleeve group from the second to the fifteenth training session in the FCR-FD&TRI muscle pair [Figure 4-4. (C)]. Additionally, the NMES-robotic hand group had significantly lower CIs from the third to the twentieth training session in the BIC&TRI muscle pair [Figure 4-4. (D)].

4.4. Discussion

The study compared two different supporting schemes for chronic upper limb rehabilitation by using the EMG-driven NMES-robots, namely, support to the elbow and wrist versus support to the fingers. The results obtained revealed that the two training schemes with different supporting strategies led to upper limb motor recovery with improved clinical scores and session-by-session evaluated EMG parameters in all participants.

4.4.1 *Motor Improvements with Functional Independence*

The increase of FMA score and its subscores demonstrated the voluntary motor improvements achieved by the two different joint supporting strategies, as well as the

improvements in the related upper limb segments, namely, distal (wrist-hand) and proximal (elbow-shoulder) parts. Both supporting strategies significantly improved the overall upper limb motor functions after the training. We also noticed that, compared to pre-assessment, the averaged FMA full scores in robotic hand group increased by 46.1% right after the treatment (post-assessment) and by 56.8% at three-month follow-up, when the ratio was 38.2% (post-assessment) and by 46.7% (3MFU) in the robotic sleeve group. This suggested that motor improvements continued in both groups over a period of three months after treatment completion. For the FMA-SE, the average scores increased by 42.4% (post-assessment) and 54% (3MFU) in the robotic hand group, with the ratio of 41.1% (post-assessment) and by 44.8% (3MFU) in the robotic sleeve group. The motor improvements in the FMA-SE subscores for the robotic hand group confirmed that robotic support at the distal fingers could also benefit the proximal joint recovery (i.e. shoulder/elbow) and the motor gain achieved was comparable to that for the robotic sleeve group where direct robotic supports were provided to the proximal joint, similar to the observations reported in the literature [101, 103]. In this work, proximal improvement in the robotic hand group was determined to be due to the compensatory contraction of proximal UE muscles during the recruitment of distal muscles in NMES-robotic hand training and due to the competitive interaction between distal and proximal muscles during the sequenced motion tasks, as mentioned earlier [104]. For the evaluation of the distal UE by FMA-WH subscores, the average scores increased by 54.8% in the robotic hand group and by 32.4% in the robotic sleeve group at post-assessment. A further increase by 65.4% in the robotic hand group and by 50.6% in the sleeve group was reported at three-

month follow-up. However, significant improvement across three evaluation time points (i.e. pre-assess, post-assess and 3MFU) at wrist-hand was achieved only in the robotic hand group and not in the sleeve group, as shown in Figure 4-3. The results suggested that direct support to the finger joints was more effective to achieve distal motor improvements than support to more proximal (i.e. wrist-elbow) joints, and the improvement could continue in the three months after the training.

The improvements in the ARAT scores were consistent with the observations obtained by FMA scores. The ARAT results suggested that both treatments could improve the voluntary motor functions in the whole upper limb, with an emphasis on daily tasks involving finger functions [177, 195]. The improvement for both groups could last for three months after the training. Although FMA-WH improvement was not significant for the robotic sleeve group, the significant improvements in the ARAT also suggested the distal improvements achieved by the sleeve training. However, besides evaluating hand grasping and fingers gripping functions, the ARAT assessments tested the positioning of extremities and the choice of objects with varied weights as well. These evaluation items were related to the motor function of proximal upper limb segments [177], which could benefit from the treatment of the wrist-elbow parts. Furthermore, we found increased scores in the subscale items of lifting upper extremities and placing hand to various pericranial positions in both groups, although the robotic sleeve group achieved higher scores. This was due to the fact that ARAT uses a specific time limit to define the level of deficits [195]. The between-group differences in the items were not significant but higher scores showed a trend of better smoothness of the movements after training by the NMES-robotic sleeve.

4.4.2. Motor Improvements with Spasticity Control

The MAS scores showed the descending trend of muscle tone in both groups by supporting different UE segments. The decline of muscle tone was not significant in the robotic sleeve group according to the MAS scores at all three parts (i.e. the fingers, the wrist and the elbow). Meanwhile, the use of the NMES-robotic hand led to the significant release of muscle spasticity, which could be maintained for three months after training. Significant between-group differences were observed at the wrist (only in the 3MFU) and at the fingers (in both the post-assessment and 3MFU) with markedly declined muscle tone in the robotic hand group. The MAS results suggested that direct robotic assistance at the finger joints could more effectively release the spasticity at the distal. Another possible reason for the better performance in MAS of the whole upper limb by the robotic hand group than the sleeve group was that the participants exerted more voluntary effort in the arm-reaching tasks than the sleeve group when the elbow and wrist were not actuated. Maximized involvement of voluntary effort in post-stroke limb practice has been found to be an important factor related to the significant release of muscle tone with long-term effects as we specified in ***2.1***. Furthermore, it was common that persons with chronic stroke had better proximal limb functions than the distal. When the distal joints (e.g., the fingers in this work) were assisted by the NMES-robotic hand to perform the tasks they could not achieve (e.g., hand open) by themselves, they would be promoted to practice.

4.4.3. Muscular Activities and Muscle Coordination by EMG Parameters

The session-by-session EMG evaluation demonstrated the recovery progress in

the muscle coordination across the 20 training sessions for both groups, by monitoring the activation and coordination patterns among the four individual muscles/muscle unions (i.e. BIC, TRI, FCR-FD and ECR-ED).

Significant decreases of muscle activation levels of UE flexors (FCR-FD and BIC) were observed in both groups. In the NMES-robotic hand group, FCR-FD and BIC decreased rapidly by 50% and 32%, respectively, over the first four sessions, and decreased by a further 19% and 31.9%, respectively, from the fifth to the twentieth session. By contrast, the NMES-robotic sleeve group showed a gradual decrease by 50% (FCR-FD) over 14 sessions and by 32% (BIC) over 16 sessions. In this work, the EMG activation level of FCR-FD muscle union (major flexor in the distal UE segments, i.e. fingers and wrist) and BIC muscle (major flexor in the more proximal UE, i.e. elbow) in the NMES-robotic hand group decreased significantly faster than that in the NMES-robotic sleeve group across most of the 20 training sessions, as shown in Figure 4-4. The results did not only indicate the reduced spasticity of the related joints in both groups [196] but also illustrated that the release of spasticity in the entire UE was more effective by supporting to distal joints (i.e. fingers) than that by supporting to the more proximal parts (i.e. wrist-elbow). It was consistent with the variation of MAS scores in the elbow, the wrist and the fingers in both two groups. It also manifested the differences between the two training schemes by supporting to the distal and more proximal UE. Furthermore, the decrease in the EMG activation level could also be attributed to the reduction in excessive muscle activities of FCR-FD and BIC muscles during the bare arm test for arm reaching, withdrawing and hand grasping motions [197]. The faster decrease of EMG

activation levels by supporting the distal UE segments could be a reason for better performance in the FMA scores and its subscores for patients in the NMES-robotic hand group. Joints commonly exhibited excessive co-contractions after stroke [22]. The significant reduction of CI values in FCR-FD&TRI indicated the release of their co-contraction patterns and implied the improved isolation of the distal joint (i.e. wrist) movements from the more proximal joint (i.e. elbow). The improvements could reflect evolutionary and more independent motion patterns during the bare test and clinical assessments of ARAT and FMA. Meanwhile, the significant decrease of CI values in BIC&TRI showed the release of co-contraction patterns in the elbow joint and indicated the promotion of arm reaching and withdrawing movements through elbow extension and flexion. Compared to the sleeve group, the NMES-robotic hand group exhibited fasted reduction of CI values in FCR-FD&TRI and BIC&TRI. With supporting to the distal segments during the training, CI values associated with FCR-FD&TRI decreased rapidly by 40.7% over the first four training sessions, while the CI values associated with FCR-FD&TRI declined by 40.3% over 19 training sessions. The CI values in NMES-robotic hand group were significantly lower than those in the sleeve group through the first 15 training sessions. As for BIC&TRI, the CIs also decreased more rapidly in the group with support to the distal UE than with support to more proximal parts. The values decreased by 51% over the first five training sessions in the NMES-robotic hand group but decreased only by 7.9% at the same evaluation point (5th session) in the NMES-robotic sleeve group. Therefore, compared to a provision of support to the more proximal parts, the provision of support to the distal joints could lead to more

effective improvement in the release of muscle co- contraction during the UE rehabilitation.

In the study, we noticed that the recovery process did not reach a plateau within the 20 training sessions with the acceleration of EMG activation levels in the FCR-FD and BIC for both groups, and similar patterns could be found in the CIs of the FCR-FD&TRI and BIC&TRI in both groups as well. In an earlier study, it was suggested that a plateau of little or no change in performance was indicative of the fact that learning of a skilled movement had come to an end [198]. Hence, the results of EMG parameters could suggest that further improvement in the recovery of the upper limb at both distal and proximal segments could be obtained through additional training.

4.5 Periodic Summary

In this work, a comparison between training effectiveness of different supportive schemes was made adopting the multi-joint coordinated physical practice assisted by the two EMG-driven NMES-robotic devices (i.e. the NMES-robotic sleeve and the NMES-robotic hand). This trial was conducted among chronic stroke patients. Clinical assessments (i.e., FMA, MAS, ARAT and FIM) and cross-session EMG evaluation (EMG activation level) were used for the outcome measurement as we adopted in previous two trials. Both the treatments could achieve significant and comparable voluntary motor recovery in the proximal UE segments as assessed by FMA (full score and shoulder-elbow). While, only external assistance directly to the finger-hand by the NMES-robotic hand could improve the voluntary motor functions

at the distal UE segments as assessed by FMA (wrist-hand). For the control of muscle spasticity in the chronic stroke period, assistance to the wrist-elbow could hardly achieve the release of muscle tone with the treatment by the NMES-robotic sleeve, while assistance to the finger-hand could significantly reduce the muscle tone at all 3 UE segments (finger, wrist and elbow). Significant reduction was observed at wrist segment in the 3MFU and at fingers in both post- and 3MFU assessment. Both the treatments could promote patients' UE functions with daily tasks as assessed by ARAT. For further investigation, the muscle activities were evaluated in the both groups. The result illustrated the release of muscle excessive motions at both flexors in the entire UE (i.e. FCR-FD union and BIC) by EMG activation level, and also the improvement of muscle coordination across multiple joints (FCR-FD & TRI) and within single elbow joint (BIC & TRI) by CI values. It also showed a more rapid speed of evolutionary process by providing direct support to the finger-hand when compared to that by support to the wrist-elbow.

CHAPTER 5

CONCLUSIONS

Device-assisted multi-joint coordinated can effectively promote upper limb motor function for independent activities of daily living in both subacute and chronic stroke patients. In this study, the clinical effects and rehabilitation effectiveness of such training were investigated through three independent clinical trials.

In the first clinical RCT, the clinical effects of multi-joint coordinated upper limb training assisted by an EMG-driven NMES-robot in subacute stroke patients were compared with those of conventional rehabilitation treatment. Both treatments achieved significant motor recovery and enhanced functional independence of upper limb activities, with comparable clinical results for ARAT and FIM. The superiority of the NMES-robot-assisted multi-joint training consisted mainly in the significantly greater improvement of voluntary motor performance, as assessed through FMA scores, and better spasticity control in the entire upper limb, especially at the wrist and hand joints, as assessed through MAS scores. This could be because conventional treatments are mainly delivered manually on a “one-to-one” basis and are thus unable to simultaneously manage the distal and proximal joints in the subacute stroke phase. Moreover, most manually delivered training programs follow a proximal-to-distal training sequence, thereby involving little effort for the distal segments in the early period after stroke. By contrast, motor practice using the NMES-robot could provide highly intensive repetitions directly on the wrist joint,

and movements across multiple joints could be precisely coordinated through the settled computer program. Moreover, assistance from NMES-robot could provide a repetitive sensorimotor experience and enable subjects to concentrate more on target muscles at the distal joints, thus facilitating the voluntary effort. Furthermore, the muscle spasticity released after NMES-robot-assisted training was in contrast to the significantly increased muscle tone in conventional treatments. This resulted from the higher frequency of physical practice with assistance from the NMES-robot in an equivalent training duration, given that training frequency is reportedly highly related to spasticity control. The results from EMG parameters in the NMES-robot training group were consistent with MAS performance, and also indicated reduced excessive muscle contraction and enhanced muscle coordination within and across different joints, particularly at the wrist. All motor improvements achieved in NMES-robot-assisted multi-joint training were maintained for 3 months.

In the second trial on chronic stroke, the rehabilitation outcome of multi-joint coordinated training assisted by an NMES-robot differed from that in the subacute phase. Patients in chronic stroke usually remain on a plateau, with little spontaneous recovery of the central nervous system and less response to a monotonous training protocol. Nevertheless, significant motor recovery, as measured by the clinical scores and EMG parameters, was achieved after multi-joint coordinated training assisted by the NMES-robotic sleeve. Compared to the first trial among subacute patients, this study in chronic stroke showed significant increase in FMA full score and shoulder/elbow but lacked the improvement at the wrist-hand as illustrated by FMA

wrist/hand. Despite of this, the ARAT still demonstrated enhanced functional muscle coordination with fine precision and joint stability related to the fingers, for example, grasping, gripping, and pinching movements, and the FIM indicated enhanced independence in activities of daily living (ADL). It was commonly observed in other robot training studies on chronic patients that the motor achievements after training are difficult to be transferred into functional use for performing ADL [87]. Nonetheless, the clinical results in this study indicated that multi-joint coordinated training assisted by an NMES-robot could effectively convert motor improvements into meaningful limb motions in chronic stroke patients. Proximal joints (i.e., shoulder/elbow) gained more than distal ones (i.e., wrist/fingers), mainly due to the accustomed compensatory activities of patients' early stroke experiences. Although the decreased MAS scores were not significant, the marked reduction in CIs of the FCR&TRI (cross-joint) and BIC&TRI (within-joint) muscle pairs illustrated an underlying improvement of muscular coordination after training. A significant decrease was also observed in the EMG activation level of the upper limb flexors, namely, FCR for the wrist and BIC for the elbow, indicating a potential release of muscle spasticity. It may be concluded that the compensatory motion pattern in practicing daily tasks gradually changed after multi-joint coordinated training assisted by an NMES-robot. This represents a meaningful recovery for chronic stroke patients, which some rehabilitation theories have termed "motor re-education" [32]. All motor improvements achieved through training were maintained for 3 months.

In the last part of this study, through a clinical RCT, we compared two different

supportive schemes using EMG-driven NMES-robots, namely, elbow-wrist support versus finger–palm support, which adopted two most popular robot designs at current.

We recruited chronic stroke patients as they have overcome the flaccid paralysis period and could better adapt to different forms of UE physical practice than subacute patients. The FMA exhibited comparable motor improvements in the shoulder and elbow segments after training using both the distal (i.e., finger–palm) and proximal (i.e. shoulder-elbow) supportive schemes, whereas significant improvements in the wrist and hand segments were only observed in the distal supportive scheme. The results indicated that external support to the distal upper limb joints could achieve motor improvement in the adjacent proximal joints; this was consistent with the findings reported in our previous study on single-joint robot-assisted wrist training [102]. However, support to the proximal segments did not affect distal motor recovery. In addition, both the distal and proximal supportive schemes were able to improve muscle coordination, with an emphasis on functional ADL as revealed by an increased ARAT score. However, in the proximal supportive scheme, this increased ARAT score was highly related to evaluation items with arm positioning movements, whereas in the distal supportive scheme it mainly resulted from improved hand (grasping) and finger (gripping) movements. This indicates a differentiated motor control recovery process in different joint supportive schemes. Moreover, muscle spasticity in the paretic upper limb was effectively released after distal supportive training, as revealed by the MAS (finger, wrist, and elbow) score,

whereas no significant improvement was observed in the proximal supportive scheme. Significantly decreased EMG activation levels in the upper limb flexors and decreased CIs indicated improvements in spasticity control and muscular coordination (within the elbow joint or across the wrist-elbow joints) in both supportive schemes. However, the distal supportive scheme was found to be more effective than the proximal supportive scheme due to its faster response to muscle activity. Furthermore, none of the EMG parameter changes in these two schemes reached a plateau during the 20 training sessions, implying a recovery potential with a longer training duration in chronic stroke patients. A key contribution of the study was the suggestion that the provision of direct support to the distal joints was more effective than the provision of support to the proximal joints in the case of chronic stroke patients. This finding could help rehabilitation professionals and patients with chronic stroke to achieve optimal motor recovery with limited resources.

Although the movements provided by the NMES-robot systems for a joint were simple flexion and extension, the target joints could be more precisely exercised with the aid of well-positioned motors and NMES and could be organized into well-coordinated movements with computer programs. In this study, the clinical effects and rehabilitation effectiveness of multi-joint coordinated training assisted by an EMG-driven NMES-robot for upper limb rehabilitation in both the subacute and chronic phases after stroke have been successfully investigated. This study also demonstrated that multi-joint coordinated practice with direct support to distal upper limb segments could achieve a superior rehabilitation prognosis in chronic stroke.

APPENDICES

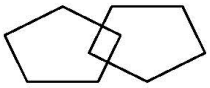
Appendices 1: Clinical Assessments

1.1 Mini-Mental State Exam (MMSE)

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: ***Ask the questions in the order listed. Score one point for each correct response within each question or activity.***

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

1

Source: www.medicine.uiowa.edu/igec/tools/cognitive/MMSE.pdf Provided by NHCQF, 0106-410

Instructions for administration and scoring of the MMSE

Orientation (10 points):

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

Registration (3 points):

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

Attention and Calculation (5 points):

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):

- Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
- Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.
- Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

(Folstein, Folstein & McHugh, 1975)

Interpretation of the MMSE

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Sources:

- Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. *JAMA*. 1993;269(18):2386-2391.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
- Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. *Hosp Pract*. 1987;22(1A):99, 103, 106, 110.
- Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922-935.

https://www.uml.edu/docs/Mini%20Mental%20State%20Exam_tcm18-169319.pdf

1.2 Fugl-Meyer Assessment for Upper Extremity (FMA-UE)

Rehabilitation Medicine, University of Gothenburg

FUGL-MEYER ASSESSMENT **ID:**
UPPER EXTREMITY (FMA-UE) **Date:**
Assessment of sensorimotor function **Examiner:**

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S: The post-stroke hemiplegic patient. A method for evaluation of physical performance. Scand J Rehabil Med 1975, 7:13-31.

A. UPPER EXTREMITY, sitting position					
I. Reflex activity			**none**	**can be elicited**	
Flexors: biceps and finger flexors **Extensors**: triceps			0 0	2 2	
		Subtotal I (max 4)			
II. Volitional movement within synergies, without gravitational help			**none**	**partial**	**full**
Flexor synergy: Hand from contralateral knee to ipsilateral ear. From extensor synergy (shoulder adduction/ internal rotation, elbow extension, forearm pronation) to flexor synergy (shoulder abduction/ external rotation, elbow flexion, forearm supination). **Extensor synergy:** Hand from ipsilateral ear to the contralateral knee	Shoulder Elbow Forearm	retraction elevation abduction (90°) external rotation flexion supination	0 0 0 0 0 0	1 1 1 1 1 1	2 2 2 2 2 2
	Shoulder Elbow Forearm	adduction/internal rotation extension pronation	0 0 0	1 1 1	2 2 2
		Subtotal II (max 18)			
III. Volitional movement mixing synergies, without compensation			**none**	**partial**	**full**
Hand to lumbar spine	cannot be performed, hand in front of SIAS hand behind of SIAS (without compensation) hand to lumbar spine (without compensation)		0	1	2
Shoulder flexion 0°-90° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion abduction or elbow flexion during movement complete flexion 90°, maintains 0° in elbow		0	1	2
Pronation-supination elbow at 90° shoulder at 0°	no pronation/supination, starting position impossible limited pronation/supination, maintains position complete pronation/supination, maintains position		0	1	2
		Subtotal III (max 6)			
IV. Volitional movement with little or no synergy			**none**	**partial**	**full**
Shoulder abduction 0 - 90° elbow at 0° forearm pronated	immediate supination or elbow flexion supination or elbow flexion during movement abduction 90°, maintains extension and pronation		0	1	2
Shoulder flexion 90°- 180° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion abduction or elbow flexion during movement complete flexion, maintains 0° in elbow		0	1	2
Pronation/supination elbow at 0° shoulder at 30°-90° flexion	no pronation/supination, starting position impossible limited pronation/supination, maintains extension full pronation/supination, maintains elbow extension		0	1	2
		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 reflex markedly hyperactive or at least 2 reflexes lively maximum of 1 reflex lively, none hyperactive		0	1	2
		Subtotal V (max 2)			
		Total A (max 36)			

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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	full
Stability at 15° dorsiflexion elbow at 90°, forearm pronated shoulder at 0°	less than 15° active dorsiflexion dorsiflexion 15°, no resistance is taken maintains position against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 90°, forearm pronated shoulder at 0°, slight finger flexion	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Stability at 15° dorsiflexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	less than 15° active dorsiflexion dorsiflexion 15°, no resistance is taken maintains position against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Circumduction	cannot perform volitionally jerky movement or incomplete complete and smooth circumduction	0	1	2
	Total B (max 10)			

C. HAND support may be provided at the elbow to keep 90° flexion, no support at the wrist, compare with unaffected hand, the objects are interposed, active grasp		none	partial	full
Mass flexion from full active or passive extension		0	1	2
Mass extension from full active or passive flexion		0	1	2
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	2
B – thumb adduction 1-st CMC, MCP, IP at 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	2
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	2
D – cylinder grip cylinder shaped object (small can) tug upward, opposition in digits I and II	cannot be performed can hold cylinder but not against tug can hold cylinder against a tug	0	1	2
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	2
	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	none
Tremor		0	1	2
Dysmetria	pronounced or unsystematic slight and systematic no dysmetria	0	1	2
		> 5s	**2 - 5s**	**< 1s**
Time	more than 5 seconds slower than unaffected side 2-5 seconds slower than unaffected side maximum difference of1 second between sides	0	1	2
	Total D (max 6)			

TOTAL A-D (max 66)	

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H. SENSATION, upper extremity blind-folded, compared with unaffected side		**anesthesia**	**hypoesthesia dysesthesia**	**normal**
Light touch	upper arm, forearm	0	1	2
	palmar surface of the hand	0	1	2
		absence less than 3/4 correct	**3/4 correct considerable difference**	**correct 100% little or no difference**
Position small alterations in the position	shoulder	0	1	2
	elbow	0	1	2
	wrist	0	1	2
	thumb (IP-joint)	0	1	2
			Total H (max12)	

J. PASSIVE JOINT MOTION, upper extremity				**J. JOINT PAIN** during passive motion, upper extremity		
Sitting position, compare with unaffected side	only few degrees (less than 10° in shoulder)	decreased	normal	pronounced constant pain during or at the end of movement	some pain	no pain
Shoulder						
Flexion (0° - 180°)	0	1	2	0	1	2
Abduction (0°-90°)	0	1	2	0	1	2
External rotation	0	1	2	0	1	2
Internal rotation	0	1	2	0	1	2
Elbow						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Forearm						
Pronation	0	1	2	0	1	2
Supination	0	1	2	0	1	2
Wrist						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Fingers						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Total (max 24)				**Total** (max 24)		

A. UPPER EXTREMITY	/36
B. WRIST	/10
C. HAND	/14
D. COORDINATION / SPEED	/ 6
TOTAL A-D (motor function)	/66

H. SENSATION	/12
J. PASSIVE JOINT MOTION	/24
J. JOINT PAIN	/24

https://neurophys.gu.se/digitalAssets/1520/1520773_fma-ue-protocol-english-updated-20150315.pdf

1.3 Action Research Arm Test (ARAT)

ACTION RESEARCH ARM TEST

Patient Name: _____

Rater Name: _____

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

Carroll D. "A quantitative test of upper extremity function."
J Chronic Diseases. 1965;18:479-491.

Crow JL, Lincoln NNB, Nouri FM, De Weerdt W. "The effectiveness of EMG biofeedback in the treatment of arm function after stroke.
International Disability Studies. 1989;11:155-160.

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.**

1.4 Functional Independent Measurement (FIM)

APPENDIX D
Functional Independence Measure (FIM) Instrument

	ADMISSION	DISCHARGE	FOLLOW-UP
Self-Care			
A. Eating			
B. Grooming			
C. Bathing			
D. Dressing - Upper Body			
E. Dressing - Lower Body			
F. Toileting			
Sphincter Control			
G. Bladder Management			
H. Bowel Management			
Transfers			
I. Bed, Chair, Wheelchair			
J. Toilet			
K. Tub, Shower			
Locomotion			
L. Walk/Wheelchair			
M. Stairs			
Motor Subtotal Score			
Communication			
N. Comprehension			
O. Expression			
Social Cognition			
P. Social Interaction			
Q. Problem Solving			
R. Memory			
Cognitive Subtotal Score			
TOTAL FIM Score			

LEVELS		
	Independent 7 Complete Independence (Timely, Safely) 6 Modified Independence (Device)	**NO HELPER**
	Modified Dependence 5 Supervision (Subject = 100%+) 4 Minimal Assist (Subject = 75%+) 3 Moderate Assist (Subject = 50%+) **Complete Dependence** 2 Maximal Assist (Subject = 25%+) 1 Total Assist (Subject = less than 25%)	**HELPER**
Note: Leave no blanks. Enter 1 if patient is not testable due to risk.		

https://www.strokengine.ca/pdf/FIMappendixD.pdf

1.5 Modified Ashworth Scale (MAS)

Modified Ashworth Scale

The Modified Ashworth Scale (MAS) measures resistance during passive soft-tissue stretching. It is a quick and easy measure that can help assess the efficacy of treatment. The following conventions prevail:

- The MAS is performed in the supine position (this will garner the most accurate and the lowest score as any tension anywhere in the body will increase spasticity)
- Because spasticity is "velocity dependent" (the faster the limb is moved, the more spasticity is encountered), the MAS is performed while moving the limb at the "speed of gravity"; this is defined as the same speed at which a non-spastic limb would naturally drop (fairly fast)
- The test is performed a maximum of three times for each joint; if more than three times, the short-term effect of a stretch can influence the score
- The MAS is performed prior to goniometric testing; goniometric testing provides a stretch, and the short-term effect of a stretch can influence the score

Scoring

0 = Normal tone, no increase in tone
1 = Slight increase in muscle tone, manifested by a catch and release or minimal resistance at the end of the range of motion (ROM) when the affected part(s) is moved in flexion or extension
1+ = Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2 = More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3 = Considerable increase in muscle tone, passive movement difficult
4 = Affected part(s) rigid in flexion or extension

Positions

The positions used for an MAS assessment are as follows:

Score_____Elbow. *Start position:* Elbow fully flexed, forearm neutral. Movement: Extend elbow from maximum possible flexion to maximum possible extension. (Triceps would be in the same position, opposite direction.)

Score_____Wrist. *Start position:* Elbow as straight as possible, forearm pronated. Movement: Extend the patient's wrist from maximum possible flexion to maximum possible extension.

Score_____Fingers. *Start position:* Elbow as straight as possible, forearm neutral. All fingers are done at once. Movement: Extend the patient's fingers from maximum possible flexion to maximum possible extension.

Score_____Thumb. *Start position:* Elbow as straight as possible, forearm neutral, wrist neutral. Movement: Extend the thumb from maximum possible flexion (thumb against index finger) to maximum possible extension (in anatomical position, "abducted").

Score_____Hamstrings. *Start position:* Prone so that ankle falls beyond end of the plinth, hip in neutral rotation. Movement: Extend the patient's knee from maximum possible flexion to maximum possible extension

Score_____Quadriceps. *Start position:* Prone so that ankle falls beyond end of the plinth, hip in neutral rotation. Movement: Flex the patient's limb from maximum possible flexion to maximum possible extension

Score_____Gastrocnemius. *Start position:* Supine, ankle plantarflexed, hip in neutral rotation and flexion. Movement: Dorsiflex the patient's ankle from maximum possible plantarflexion to maximum possible dorsiflexion not more than three consecutive times and rate the muscle tone.

Score_____Soleus. *Start position:* Supine, ankle plantarflexed, hip in neutral rotation and flexion and with the knee flexed to ~15°. Movement: Dorsiflex the patient's ankle from maximum possible plantarflexion to maximum possible dorsiflexion.

Reprinted with permission from Peter G. Levine. Testing spasticity: the Modified Ashworth Scale. June 2, 2009. http://physical-therapy.advanceweb.com/Article/Testing-Spasticity-The-Modified-Ashworth-Scale.aspx. and Bohannon R, et al. Interrater reliability of a Modified Ashworth Scale of muscle spasticity. *Phys Ther.* 1987;67(7):206-207.

https://www.med-iq.com/files/noncme/material/pdfs/DOC%201--Modified%20Ashworth%20Scale.pdf

Appendices 2: CONSENT FORM

Consent Form

I, _____ (name of subject), hereby consent to participate as a subject for the project entitled "Biomechatronic System Using Electromyography (EMG)-driven Neuromuscular Electrical Stimulation (NMES) for Upper Limb Rehabilitation".

- I have understood the experimental procedures presented to me.
- I have given an opportunity to ask questions about the experiment, and these have been answered to my satisfaction.
- The testing should not result in any undue discomfort, I realize that I can discontinue the experiment with no reasons given and no penalty received during the experiment.
- I realize the experiment will possibly benefit my upper limb motor functions.
- I agree that the PI and the project research members, who obtained the authorization from the PI, can use my experimental data for this project study.
- I realize that the results of this experiment are the properties of The Hong Kong Polytechnic University
- I realize that the results of this experiment may be published, but that my own results will be kept confidential.

Subject name: _____ Signature: _____ Date: _____

Witness: _____ Signature: _____ Date: _____

Investigator: QIAN QIUYANG Signature: _____ Date: _____

同意書

我，_____(受試者姓名), 在此同意作為受試者參加"上肢互动机械训练系统"的研究。

- 我已明白到這個測試的所有步驟。
- 我已給予機會詢問有關該測試的問題, 並已獲得滿意的回答。
- 如果實驗給我帶來不適, 我已明白在實驗中我可以隨时終止測試而無需給予任何理由, 或由此而受到任何懲罰。
- 我已明白這個實驗的結果有可能可以改善我的上肢运动功能。
- 我同意本項目負責人及其受權的項目研究人員使用我的實驗記錄以作此項目的研究。
- 我已知道這個測試的結果屬香港理工大學。
- 我已知道這個測試的結果可被發表, 但有關我個人的結果將獲得保密。

受試者姓名_____簽署_____日期_____

作證人姓名_____簽署_____日期_____

研究員姓名 钱秋阳 簽署_____日期_____

REFERENCE

[1] Warlow C.P., van Gijn J., Dennis M.S., et al. Stroke: practical management, 3ed. Oxford: Blackwell Publishing, 2008.

[2] Helicon S. Brain Basics: Preventing Stroke: Helicon, 2016.

[3] Corbyn Z. A growing global burden. Nature. 2014;510(7506): S2-S3.

[4] The World Health Report 2003: shaping the future, WHO, 2003. http://www.who.int/whr/2003/en/overview_en.pdf. Accessed7 Sept 2010.

[5] Ovbiagele B., Goldstein L.B., Higashida R.T., et al. Forecasting the future of stroke in the United States a policy statement from the American Heart Association and American Stroke Association. Stroke. 2013;44(8): 2361-75.

[6] Hospital Authority Statistical Report. Hospital Authority (2012–2013), Hong Kong. http://www.ha.org.hk/ho/corpcomm/Statistical%20Report/2012-13.pdf. Accessed 2 June 2014.

[7] Hospital Authority Statistical Report. Hospital Authority (2014–2015), Hong Kong. http://www.ha.org.hk/haho/ho/stat/HASR1415_3.pdf. Accessed 30 Jan 2018.

[8] Lloyd-Jones J.D., Adam M.R., Brown B.T., et al. Heart Disease and Stroke Statistics-2010 Update: A Report from the American Heart Association. Circulation. 2010;121(7): e46–e215.

[9] Go A.S., Mozaffarian D.L, Roger V.L., et al. Heart disease and stroke statistics-2014 update: A Report from the American Heart Association. Circulation. 2014;29(3): e28-e29.

[10] Dobkin B.H. Rehabilitation after Stroke. The New England Journal of Medicine 2005;352(16): 1677-84.

[11] Langhorne P., Bernhardt J. Stroke Care 2: Stroke rehabilitation. The Lancet. 2011;377(9778): 1693-702.

[12] Kwakkel G., Kollen B.J., van der Grond J., et al. Probability of Regaining Dexterity in the Flaccid Upper Limb: Impact of Severity of Paresis and Time Since Onset in Acute Stroke. Stroke. 2003;34(9): 2181-6.

[13] Kong K.H., Karen S.C., Jeanette L. Recovery of upper limb dexterity in patients more than 1 year after stroke: Frequency, clinical correlates and predictors.

NeuroRehabilitation. 2011;28(2): 105-11.

[14] Nakayama J.H., Raaschou H., Olsen T. Recovery of upper extremity function in stroke patients: the Copenhagen stroke study. Archives of Physical Medicine and Rehabilitation. 1994;75(4): 394–8.

[15] Kwakkel G., Wagenaar R.C., Kollen B., et al. Predicting disability in stroke: A critical review of the literature. Age Aging. 1996: 479-89.

[16] Kwakkel G., Wagenaar R.C., Twisk J.W., et al. Intensity of leg and arm training after primary middle cerebral artery stroke: a randomized trial. Lancet. 1999;354(9174): 191-6.

[17] Marie-Hélène M., Spencer S.J., Chan V., et al. Corticospinal Excitability as a Predictor of Functional Gains at the Affected Upper Limb Following Robotic Training in Chronic Stroke Survivors. Neurorehabilitation and Neural Repair. 2014;28(9): 819-27.

[18] Donnan G.A., Fisher M., Macleod M, et al. Stroke. The Lancet. 2008; 371(9624): 1612-23.

[19] Good D.C., Bettermann K., Reichwein R.K. Stroke Rehabilitation. Neurorehabilitation. 2011;17(3): 545-67.

[20] Sterling P. Neuroscience: How neurons compute direction. Nature. 2002; 452(6914): 375-6.

[21] Dai L., Wang T. The clinical application of neuromuscular facilitation techniques in the hemiplegic rehabilitation of the upper limb. Chinese Journal of Rehabilitation Medicine. 2004;19(11): 827-9.

[22] Raghavan P. Upper limb motor impairment after stroke. Physical Medicine & Rehabilitation Clinics of North America. 2015;26(4): 599–610.

[23] Kwakkel G., Kollen B.J., Twisk J.W. Impact of time on improvement of outcome after stroke. Stroke. 2006;37(13): 2348-53.

[24] Kwakkel G. Impact of intensity of practice after stroke: Issues for consideration. Disability and Rehabilitation. 2006;28(14): 823-30.

[25] Kwakkel G., Wagenaar R.C. Effect of duration of upper- and lower-extremity rehabilitation sessions and walking speed on recovery of interlimb coordination in hemiplegic gait. Physical Therapy. 2002;82(5): 432-48.

[26] Ween J.E., Alexander M.P., D' Esposito M. Factors predictive of stroke outcome in a rehabilitation setting. Neurology. 1996;47(2): 388-92.

[27] Kwakkel G., van Peppen R., Wagenaar R.C., et al. Effects of augmented exercise therapy time after stroke: a meta-analysis. Stroke. 2004;35(11): 2529–39.

[28] Hung C.S., Hsieh Y.W., Wu C.Y., et al. The effects of combination of robot-assisted therapy with task-specific or impairment-oriented training on motor function and quality of life in chronic stroke. Polymyalgia Rheumatica. 2016;8(8): 721-9.

[29] Harris J.E., Eng J.J. Strength training improves upper-limb function in individuals with stroke: a meta-analysis. Stroke. 2010;41(1): 136-40.

[30] Sasmita A.J., Ling P.K. Harnessing neuroplasticity: modern approaches and clinical future. The International Journal of Neuroscience. 2018;4: 1–17.

[31] Rakic P. Neurogenesis in adult primate neocortex: an evaluation of the evidence. Nature Reviews Neuroscience. 2002;3(1): 65–71.

[32] Lennon S., Ashburn A. The Bobath concept in stroke rehabilitation: a focus group study of the experienced physiotherapist's perspective. Disability and Rehabilitation. 2000;22(15): 665-74.

[33] Gowland C, Stratford P, Ward M, et al. Measuring Physical Impairment and Disability with the Chedoke-McMaster Stroke Assessment. Stroke. 1993;24(1): 58-63.

[34] Brunnstrom S. Movement Therapy in Hemiplegia: A Neurophysiological Approach. New York, New York: Harper & Row, 1970.

[35] Amirabdollahian F., Loureiro R., Gradwell E., et al. Multivariate analysis of the Fugl-Meyer outcome measures assessing the effectiveness of GENTLE/S robot-mediated stroke therapy. Journal of NeuroEngineering and Rehabilitation. 2007;4(1): 4.

[36] Hsueh I.P., Lee M.M., Hsieh C.L. The Action Research Arm Test: is it necessary for patients being tested to sit at a standardized table? Clinical Rehabilitation. 2002;16(4): 382-8.

[37] Pangman V.C., Sloan J., Guse L. An Examination of Psychometric Properties of the Mini-Mental Status Examination and the Standardized Mini-Mental Status Examination: Implications for Clinical Practice. Applied Nursing Research. 2000;13(4): 209–13.

[38] Harrell L.E., Marson D., Chatterjee A., Parrish J.A. The Severe Mini-Mental

Status Examination: A New Neuropsychologic Instrument for the Bedside Assessment of Severely Impaired with Alzheimer's Disease. Alzheimer Disease and Associated Disorders. 2000;14(3): 168–75.

[39] Page S.V., White S. Portable upper extremity robotics is as efficacious as upper extremity rehabilitative therapy: a randomized controlled pilot trial. Clinical Rehabilitation. 2013;27(6): 494-503.

[40] Lee V.D. The responsiveness of the Action Research Arm test and the Fugl-Meyer Assessment scale in chronic stroke patients. Journal of Rehabilitation Medicine. 2001;33(3): 110–3.

[41] Sanford J., Moreland J. Reliability of the Fugl-Meyer Assessment for Testing Motor Performance in Patients Following Stroke. Rehabilitation Measures Database. 1993: 73.

[42] Ansari N.N., Naghdi S., Arab T.K., Jalaie S. The interrater and intrarater reliability of the Modified Ashworth Scale in the assessment of muscle spasticity: limb and muscle group effect. NeuroRehabilitation. 2008;23(3): 231–7.

[43] Chumney D., Nollinger K., Shesko K., et al. Ability of Functional Independence Measure to accurately predict functional outcome of stroke-specific population: Systematic review. The Journal of Rehabilitation Research and Development. 2010;47(1): 17–30.

[44] Kimberly M., Christian A.P., Richard F. T. Learning and memory: basic principles and model systems. Neural Plasticity: cellular and molecular mechanisms of neural plasticity. In: Textbook of Neural Repair and Rehabilitation, 2ed. Kwakkel G., Miller R. Cambridge: Cambridge University Press, 2014.

[45] Gareth T. Long-term Potentiation and long-term depression. Neural plasticity: cellular and molecular mechanisms of neural plasticity. In: Textbook of Neural Repair and Rehabilitation, 2ed. Kwakkel G., Miller R. Cambridge: Cambridge University Press, 2014.

[46] Chechik G.M., Ruppin E.I. Synaptic pruning in development: a computational account. Neural computation. 1998;10(7): 1759–77.

[47] Huttenlocher P.R., Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. The Journal of Comparative Neurology. 1997;387(2): 167-78.

[48] Carey J.R., Kimberley T.J., Lewis S.M., et al. Analysis of fMRI and finger tracking training in subjects with chronic stroke. Brain. 2002;125(4): 773-88.

[49] Frost S.S., Friel K.M., Plautz E.J., et al. Reorganization of Remote Cortical Regions After Ischemic Brain Injury: A Potential Substrate for Stroke Recovery. Journal of Neurophysiology. 2003;89(6): 3205-14.

[50] Carmichael S.T. Cellular and molecular mechanisms of neural repair after stroke: making waves. Annals of Neurology. 2006;59(5): 735-42.

[51] Kozlowski D.A., James D.C., Schallert T. Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions. Journal of Neuroscience. 1996;16(15): 4776-86.

[52] Humm J.L. Kozlowski D.A., Bland S.T., et al. Use-dependent exaggeration of brain injury: is glutamate involved? Experimental Neurology. 1999;157(2): 349-58.

[53] Cramer S.C., Nelles G., Benson R.R., al. e. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke. 1997;28(12): 2518-27.

[54] Jaillard A., Martin C.D., Garambois K. A longitudinal fMRI stroke study. Brain. 2005;128: 1122-38.

[55] Teasell R., Bayona N.A., Bitensky J. Plasticity and reorganization of the brain post stroke. Topics in Stroke Rehabilitation. 2005;12(3): 11-26.

[56] Bernhardt J.M., Collier J.M., Legg L.A. Very early versus delayed mobilization after stroke. The Cochrane Database of Systematic Reviews. 2009;1: CD006187.

[57] Lynch D., Ferraro M., Krol J., et al. Continuous passive motion improves shoulder joint integrity following stroke. Clinical Rehabilitation. 2005;19(6): 594-9.

[58] Kutner N.G., Zhang R., Butler A.J., et al. Quality-of-life change associated with robotic-assisted therapy to improve hand motor function in patients with subacute stroke: a randomized clinical trial. Physical Therapy. 2010;90(4): 493–504.

[59] Ng K.L., Gibson E.M., Hubbard R. et al. Fluoxetine maintains a state of heightened responsiveness to motor training early after stroke in a mouse model. Stroke. 2015;46(10): 2951–60.

[60] Zeiler S.J. The interaction between training and plasticity in the poststroke brain. Current Opinion in Neurology. 2013;26(6): 609–16.

[61] Hallett M. Plasticity of the human motor cortex and recovery from stroke. Brain Research Reviews. 2001;36(2): 169-74.

[62] Boroojerdi B., Ziemann U., Chen R, et al. Mechanisms underlying human motor

system plasticity. Muscle Nerve. 2001;24(5): 602-13.

[63] Coq J.D., Xerri C. Tactile improverishment and sensorimotor restriction deteriorate the forepaw cutaneous map in the primary somatosensory cortex of adult rats. Experimental Brain Research. 1999;129(4): 518-31.

[64] Cramer S.C. Functional magnetic resonance imaging in stroke recovery. Physical Medicine & Rehabilitation Clinics of North America. 2003;1(4): s47-s55.

[65] Kwakkel G., Kollen B.J., Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. Restorative Neurology and Neuroscience. 2004;22(3): 281-99.

[66] Govender P., Kalra L. Benefits of occupational therapy in stroke rehabilitation. Expert Review of Neurotherapeutics. 2007;7(8): 1013-9.

[67] Grimaldi G., Manto M. Functional impacts of exoskeleton-based rehabilitation in chronic stroke: multi-joint versus single-joint robotic training. Journal of NeuroEngineering and Rehabilitation. 2013;10(1): 113.

[68] Feys H., De Weerdt W., Verbeke G., et al. Early and repetitive stimulation of the arm can substantially improve the long-term outcome after stroke: a 5-year follow up study of a randomized trial. Stroke. 2004;35(4): 924–9.

[69] Selzer M., Clarke S., Cohen L.G. Textbook of Neural Repair and Rehabilitation. Cambridge: Cambridge University Press, 2006.

[70] Evidence-Based Review of Stroke Rehabilitation. Heart & Stroke Foundation Canadian Partnership for Stroke Recovery. http://www.ebrsr.com/sites/default/files/documents/v18-SREBR-ExecutiveSummary-2.pdf. Assessed 2 Jan 2018.

[71] Saladin L.K. Cerebrovascular disease: stroke. In: Fredricks CM, Saladin LK, editors. Pathophysiology of the motor systems: Principles and clinical presentation. Philadelphia: F.A. Davis; 1996: 486–512.

[72] Wolf S.L. Electromyographic biofeedback applications to stroke patients. A critical review. Physical Therapy. 1983;63(9): 1448–59.

[73] Carr J.H. Assumptions underlying physical therapy intervention: theoretical and historical perspectives. In: Carr J.H., Shepherd R.B., Gordon J., Gentile A.M., Held J.M. Movement Science Foundations for Physical Therapy in Rehabilitation, 2ed. London, England: Heinemann, 1987.

[74] Wolf S.L., Winstein C.J., Miller J.P., et al. Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 months after stroke. The Journal of the American Medical Association. 2006;296(17): 2095-104.

[75] Sterr A., Saunders A. CI therapy distribution: theory, evidence and practice. NeuroRehabilitation. 2006;21(2): 97–105.

[76] Pignolo L. Robotics in neuro-rehabilitation. Journal of Rehabilitation Medicine. 2009;41(12): 955-60.

[77] Hu X.L., Tong K.Y., Wei X.J., et al. The effects of poststroke upper limb training with an electromyography(EMG)-driven hand robot. Journal of Electromyography and Kinesiology. 2013;23(5): 1065-74.

[78] Schmit B.D., Dewald J.P., Rymer W.Z. Stretch reflex adaptation in elbow flexors during repeated passive movements in unilateral brain-injured patients. Archives of Physical Medicine and Rehabilitation. 2000;81(3): 269-78.

[79] Volpe B.T., Ferraro M., Lynch D. Robotics and other devices in the treatment of patients recovering from stroke. Current Atherosclerosis Reports. 2004;6(4): 314-9.

[80] Tong R.K., Ng M.F., Li L.S. Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: A randomized controlled trial. Archives of Physical Medicine and Rehabilitation. 2006;87(10): 1298-304.

[81] Fasoli S.E., Krebs H.I., Stein J., et al. Robotic therapy for chronic motor impairments after stroke: follow-up results. Archives of Physical Medicine and Rehabilitation. 2004;85(7): 1106-11.

[82] Butefisch C., Hummelsheim H., Denzler P., et al. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. Journal of the Neurological Sciences. 1995;130(1): 59-68.

[83] Krebs H.I., Volpe B.T., Aisen M.L., et al. Increasing productivity and quality of care: robot-aided neuro-rehabilitation. Journal of Rehabilitation Research and Development. 2000;37(6): 639-52.

[84] Dipietro L., Ferraro M., Palazzolo J., et al. Customized interactive robotic treatment for stroke: EMG-triggered therapy. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2005;13(3): 325–34.

[85] Lambercy O., Dovat L., Yun H., et al. Effects of a robot-assisted training of grasp and pronation/supination in chronic stroke: a pilot study. Journal of NeuroEngineering

and Rehabilitation. 2011;8(1): 63.

[86] Chang W.H., Kim Y.H. Robot-assisted therapy in stroke rehabilitation. Journal of Stroke. 2013;15(3): 174–81.

[87] Mehrholz J., Pohl M., Platz T., et al. Electromechanical and robot assisted arm training for improving activities of daily living, arm function and arm muscle strength after stroke. Cochrane Database of Systematic Reviews. 2015;7(11): CD006876.

[88] Krebs H.I., Hogan N., Aisen M.L., et al. Robot-aided neurorehabilitation. IEEE Transactions on Rehabilitation Engineering. 1998;6(1): 75-87.

[89] Reinkensmeyer D.J., Kahn L.E., Averbuch M., et al. Understanding and treating arm movement impairment after chronic brain injury: progress with the ARM Guide. Journal of Rehabilitation Research & Development. 2000;37: 653-62.

[90] Burgar C.G., Shor P.C., Van der Loos H.F. Development of robots for rehabilitation therapy: the Palo Alto VA/Stanford experience. Journal of Rehabilitation Research & Development. 2000;37: 663-73.

[91] Lum P.S., Burgar C.G., Shor P.C. Evidence for improved muscle activation patterns after retraining of reaching movements with the MIME robotic system in subjects with post-stroke hemiparesis. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2004;12(2): 186-94.

[92] Daly J.J., Hogan N., Perepezko E.M., et al. Response to upper-limb robotics and functional neuromuscular stimulation following stroke. Journal of Rehabilitation Research & Development. 2005;42(6): 723-36.

[93] Basmajian J.V., Gowland C.A., Finlayson M.A., et al. Stroke treatment: comparison of integrated behavioral physical therapy vs. traditional physical therapy programs. Archives of Physical Medicine and Rehabilitation. 1987;68(5): 267-72.

[94] Takahashi C.D., Der-Yeghiaian L., Le V., et al. Robot-based hand motor therapy after stroke. Brain. 2008;131(2): 425–37.

[95] Lambercy O.L., Yun H., Wee S.K., et al. Effects of a robot-assisted training of grasp and pronation/supination in chronic stroke: a pilot study. Journal of NeuroEngineering and Rehabilitation. 2011;8: 63–71.

[96] Prange G.B., Jannink M.J., Groothuis-Oudshoorn CG, Hermens H.J., IJzerman M.J. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. Journal of Rehabilitation Research & Development. 2006;43: 171-84.

[97] Kwakkel G., Kollen B.J., Krebs H.I. Effects of Robot-Assisted Therapy on Upper Limb Recovery After Stroke: A Systematic Review. Neurorehabilitation and Neural Repair. 2008;22(2): 111-21.

[98] Bovolenta F., Agosti M., Faenza M., et al. Robot-based rehabilitation of the upper limb in stroke patients: A longitudinal observational study. Gait & Posture. 2011;33(1): S54.

[99] Sale P., Bovolenta F., Agosti M., et al. Short-term and long-term outcomes of serial robotic training for improving upper limb function in chronic stroke. International Journal of Rehabilitation Research. 2014;37(1): 67-73.

[100] Hesse S., Mehrholz J., Werner C. Robot-assisted upper and lower limb rehabilitation after stroke: Walking and arm/hand function. Deutsches Arzteblatt International. 2008;105(18): 330-6.

[101] Krebs H. I., Volpe B. T., Williams D., et al. Robot-Aided Neurorehabilitation: A Robot for Wrist Rehabilitation. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2007;15(3): 327-35.

[102] Hu X.L., Tong K.Y., Ho S., et al. Wrist rehabilitation assisted by an Electromyography-Driven Neuromuscular Electrical Stimulation (NMES)-Robot after stroke. Neurorehabilitation and Neural Repair. 2015;29(8): 767-76.

[103] Nam C.Y., Rong W., Li W.M., et al. The effects of upper-limb training assisted with an Electromyography-Driven Neuromuscular Electrical Stimulation Robotic Hand on Chronic Stroke. Frontiers in Neurology. 2017;14(8): 679.

[104] Takeuchi N., Izumi S. Maladaptive plasticity for motor recovery after stroke: mechanisms and approaches. Neural Plasticity. 2012;2012: 359728.

[105] Knutson J.S., Fu M.J., Sheffler L.R., et al. Neuromuscular Electrical Stimulation for Motor Restoration in Hemiplegia. Physical Medicine & Rehabilitation Clinics of North America. 2015;26(4): 729-45.

[106] DeSantana J.M., Walsh D.M., Vance C., et al. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. Current Rheumatology Reports. 2008;10(6): 492-9.

[107] Kern H., Carraro U., Adami N. Home-based functional electrical stimulation rescues permanently denervated muscles in paraplegic patients with complete lower motor neuron lesions. Neurorehabilitation and Neural Repair. 2010;24(8): 709-21.

[108] Etoom M., Khraiwesh Y. Neuromuscular Electrical Stimulation for Lower Limb in Chronic Stroke. Archives of Physical Medicine and Rehabilitation. 2018;99(8): 1689-90.

[109] Lake D.A. Neuromuscular Electrical Stimulation: An overview and its application in the treatment of sports injuries. Sports Medicine. 1992;13(5): 320-36.

[110] Seneviratne C., Then K.L., Reimer M. Post-stroke shoulder subluxation: a concern for neuroscience nurses. Axone. 2005;27(1): 26–31.

[111] Sujith O. Functional electrical stimulation in neurological disorders. European Journal of Neurology. 2008;15(5): 437–44.

[112] Spiegel J., Tintera J., Gawehn J. Functional MRI of human primary somatosensory and motor cortex during median nerve stimulation. Clinical Neurophysiology. 1999;110: 47-52.

[113] Chae J., Yu D. Neuromuscular stimulation for motor relearning in hemiplegia. Critical Reviews in Physical and Rehabilitation Medicine. 1999;11: 279–97.

[114] Depietro L., Ferraro M., Palazzolo J.J., et al. Customized interactive robotic treatment for stroke: EMG-triggered therapy. IEEE Transaction of Neural System and Rehabilitation Engineering. 2005;13(3): 325-34.

[115] Bard G., Hirschberg G.G. Recovery of voluntary motion in upper extremity following hemiplegia. Archives of Physical Medicine and Rehabilitation. 1965;46: 567–72.

[116] Hogan N., Krebs H.I., Srikrishna P., et al. MIT-Manus: A workstation for manual therapy and training. Proc. IEEE Workshop on Robot and Human Communication, 1992.

[117] Volpe B., Krebs H.I., Hogan N., et al. A novel approach to stroke rehabilitation: robot-aided sensorimotor stimulation. Neurology. 2000;54(10): 1938-44.

[118] Hu X.L., Tong K.Y., Song R., et al. A comparison between electromyography-driven robot and passive motion device on wrist rehabilitation for chronic stroke. Neurorehabilitation and Neural Repair. 2009;23(8): 837-46.

[119] Hu X.L., Tong K.Y., Song R., et al. Variation of muscle coactivation patterns in chronic stroke during robot-assisted elbow training. Archives of physical medicine and rehabilitation. 2007;88(8): 1022-9.

[120] Hu X.L., Tong K.Y., Song R., et al. Quantitative Evaluation of Motor Functional

Recovery Process in Chronic Stroke Patients during Robot-Assisted Wrist Training. Journal of Electromyography and Kinesiology. 2008;19(4): 639-50.

[121] Hu X.L., Tong K.Y., Li R., Xue J.J., Ho S., Chen P.N. Post-stroke wrist rehabilitation assisted with an intention-driven Functional Electrical Stimulation (FES)-Robot system. IEEE International Conference on Rehabilitation Robotics. 2011;2011: 1-6.

[122] Rosen J., Fuchs B.M., Arcan M. Performances of hill-type and neural network muscle models: Towards a myosignal based exoskeleton. Computers and Biomedical Research. 1999;32(5): 415-39.

[123] Rosen J., Brand M., Fuchs M.B., et al. A myosignal-based powered exoskeleton system. IEEE Transactions on Cybernetics. 2001;31(3): 210-2.

[124] Lee S.Y. Power assist control for leg with HAL-3 based on virtual torque and impedance adjustment. IEEE International Conference on Systems, Man and Cybernetics. 2002.

[125] Cheng H.S., M.S.J., Lin K.C. Improving elbow torque output of stroke patients with assistive torque controlled by EMG signals. Journal of Biomechanical Engineering. 2003;125: 881-6.

[126] Basteris A., Nijenhuis S.M., Stienen A.H., et al. Training modalities in robot-mediated upper limb rehabilitation in stroke: a framework for classification based on a systematic review. Journal of NeuroEngineering and Rehabilitation. 2014;10(11): 111.

[127] Boissy P., Carlotti M.M., Gravel D., Arsenault B.A. Maximal grip force in chronic stroke subjects and its relationship to global upper extremity function. Clinical Rehabilitation. 1999;13: 354.

[128] Tong K.Y., Pang P. K., Hu X.L., et al. An Intention Driven Hand Function Task Training Robotic System. Annual International Conference of the IEEE Engineering in Medicine and Biology. 2010: 3406-9.

[129] Rong W., Li W., Pang M., et al. A Neuromuscular Electrical Stimulation (NMES) and robot hybrid system for multi-joint coordinated upper limb rehabilitation after stroke. Journal of NeuroEngineering and Rehabilitation. 2017;14: 34.

[130] Qian Q.Y., Hu X.L., Lai Q., Ng S.C., Zheng Y.P., Poon W.S. Early Stroke Rehabilitation of the Upper Limb Assisted with an Electromyography-Driven Neuromuscular Electrical Stimulation-Robotic Arm. Frontiers in Neurology. 2017;4(8): 447.

[131] Knutson J.S., Fu M.J., Sheffler L.R., et al. Neuromuscular Electrical Stimulation for Motor Restoration in Hemiplegia. Physical Medicine & Rehabilitation Clinics of North America. 2015;26: 4.

[132] Hu X.L., Tong K.Y., Li R., et al. The effects of electromechanical wrist robot assistive system with neuromuscular electrical stimulation for stroke rehabilitation. Journal of Electromyography and Kinesiology. 2012;22(3): 431-9.

[133] Hu X.L., Tong K.Y., Tsang S.F., Song R. Joint-angle-dependent neuromuscular dysfunctions at the wrist in persons after stroke. Archives of Physical Medicine and Rehabilitation. 2006;87(5): 671-9.

[134] Brown T.B., Parmer G., Durant R., et al. Health professional shortage areas, insurance status, and cardiovascular disease prevention in the reasons for geographic and racial differences in stroke (REGARDS) study. Journal of Health Care for the Poor and Underserved. 2011;22(4): 1179–89.

[135] Cailliet R. The Shoulder in Hemiplegia. Philadelphia: F.A. Davis, 1980.

[136] Carr J.H., Shepherd R. B. A motor relearning programme for stroke. 2nd ed., US ed. Oxford: Heinemann Medical Books; Rockville M.: Aspen Publishers, 2002.

[137] Kollen B.J., Lennon S., Lyons B., et al. The effectiveness of the Bobath Concept in stroke rehabilitation. Stroke. 2009;40(4): e89-e97.

[138] Horn S.D., DeJong G., Smout R.J., et al. Stroke rehabilitation patients, practice, and outcomes: is earlier and more aggressive therapy better? Archives of Physical Medicine and Rehabilitation. 2005;86(12): 101-14.

[139] Woo J., Chan S.Y., Sum M.W., et al. Inpatient stroke rehabilitation efficiency: influence of organization of service delivery and staff numbers. BMC Health Services Research. 2008;8(1): 86.

[140] Barra J., Oujamaa L., Chauvineau V., et al. A symmetric standing posture after stroke is related to a biased egocentric coordinate system. Neurology. 2009;72(18): 1582-7.

[141] Gillen G. Stroke rehabilitation: a function-based approach: St. Louis, Missouri: Elsevier, 2016.

[142] Bobath B. Adult Hemiplegia: Evaluation and Treatment, third edition. Oxford, England: Heinemann, 1990.

[143] Colebatch J., Gandevia S.C. The distribution of muscular weakness in upper motor neuron lesions affecting the arm. Brain. 1989;112: 749-63.

[144] Milot M.H., Spencer S.J., Chan V., et al. A crossover pilot study evaluating the functional outcomes of two different types of robotic movement training in chronic stroke survivors using the arm exoskeleton BONES. Journal of NeuroEngineering and Rehabilitation. 2013;19(10): 112.

[145] Giuliana G., Mario M. Functional impacts of exoskeleton-based rehabilitation in chronic stroke: multi-joint versus single-joint robotic training. Journal of NeuroEngineering and Rehabilitation. 2013;10: 113.

[146] Cordo P., Wolf S., Lou J-S, et al. Treatment of Severe Hand Impairment Following Stroke by Combining Assisted Movement, Muscle Vibration, and Biofeedback. Journal of Neurologic Physical Therapy. 2013;37(4): 194-203.

[147] Pineiro R.S., Smith S, Flitney D, et al. Relating MRI changes to motor deficit after ischemic stroke by segmentation of functional motor pathways. Stroke. 2000;31: 672–9.

[148] Lang C.E., Beebe J.A. Relating movement control at 9 upper extremity segments to loss of hand function in people with chronic hemiparesis. Neurorehabilitation Neural Repair. 2007;21: 279–91.

[149] Beebe J.A., Lang C.E. Relationships and responsiveness of six upper extremity function tests during the first 6 months of recovery after stroke. Journal of Neurologic Physical Therapy. 2009;33(2): 96–103.

[150] Good D.C., Bettermann K., Reichwein R.K. Stroke Rehabilitation. NeuroRehabilitation. 2011;17(3): 545-67.

[151] Zeiler S.R., Krakauer J.W. The interaction between training and plasticity in the poststroke brain. Current opinion in neurology. 2013;26(6): 609-16.

[152] Ng K.L., Gibson E.M., Hubbard R., et al. Fluoxetine Maintains a State of Heightened Responsiveness to Motor Training Early After Stroke in a Mouse Model. Stroke. 2015;46(10): 2951-60.

[153] Tomori K., Nagayama H., Ohno K., et al. Comparison of occupation-based and impairment-based occupational therapy for subacute stroke: a randomized controlled feasibility study. Clinical rehabilitation. 2015;29(8): 752-62.

[154] Flöel A., Werner C., Grittner U., et al. Physical fitness training in Subacute Stroke (PHYS-STROKE)-study protocol for a randomized controlled trial. Trials.

2014;15: 45.

[155] Harris J.E., Eng J.J. Strength Training Improves Upper-Limb Function in Individuals with Stroke: A Meta-Analysis. Stroke. 2010;41(1): 136-40.

[156] Ng K., Zhang R., Butler A.J., et al. Quality-of-life change associated with robotic-assisted therapy to improve hand motor function in patients with subacute stroke: a randomized clinical trial. Physical therapy. 2010;90(4): 493-504.

[157] Brown T.M., Parmar G., Durant R.W., et al. Health Professional Shortage Areas, Insurance Status, and Cardiovascular Disease Prevention in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Journal of Health Care for the Poor and Underserved. 2011;22(4): 1179-89.

[158] Yang C.L., Lin K.C., Chen H.C., et al. Pilot comparative study of unilateral and bilateral robot-assisted training on upper-extremity performance in patients with stroke. The American Journal of Occupational Therapy. 2012;66(2): 198.

[159] Knutson J.S., Fu M.J., Sheffler L.R., Chae J. Neuromuscular Electrical Stimulation for Motor Restoration in Hemiplegia. Physical medicine and rehabilitation clinics of North America. 2015;26(4): 729-45.

[160] Seneviratne C., Then K.L., Reimer M. Post-stroke shoulder subluxation: a concern for neuroscience nurses. Axone. 2005;27(1): 26-31.

[161] Hu X.L., Tong K.Y., Wei X.J., et al. The effects of post-stroke upper-limb training with an electromyography (EMG)-driven hand robot. Journal of Electromyography and Kinesiology. 2013;23(5): 1065-74.

[162] Tong K.Y., Ng F.W., Li L., et al. Gait training of patients after stroke using an electromechanical gait trainer combined with simultaneous Functional Electrical Stimulation. Physical therapy. 2006;86(9): 1282-94.

[163] Mccabe J.P., Dohring M.E., Marsolais E.B., et al. Feasibility of combining gait robot and multichannel functional electrical stimulation with intramuscular electrodes. Journal of Rehabilitation Research and Development. 2008;45(7): 997-1006.

[164] Ng F.W., Tong K.Y., Li L.S.W. A pilot study of randomized clinical controlled trial of gait training in subacute stroke patients with partial Body-Weight support electromechanical gait trainer and functional electrical stimulation: six-month follow-up. Stroke. 2008;39(1): 154-60.

[165] Staubli P., Nef T., Klamroth-Marganska V., et al. Effects of intensive arm training with the rehabilitation robot ARMin II in chronic stroke patients: four single-

cases. Journal of NeuroEngineering and rehabilitation. 2009;6(1): 46.

[166] Takahashi C.D., Der-Yeghiaian L., Le V., Motiwala R.R., Cramer S.C. Robot-based hand motor therapy after stroke. Brain. 2008;131: 425-37.

[167] Vette A.H., Masani K., Kim J.Y., Popvic M.R. Closed-loop control of Functional Electrical Stimulation-assisted Arm-Free standing in individuals with spinal cord injury: a feasibility study. Neuromodulation: Technology at the Neural Interface. 2009;12(1): 22-32.

[168] Hu X.L., Tong K.Y., Hu J.Y., et al. Wearable robotic device with bracing system with moisture and pressure management for comfortable rehabilitation, US patent application. 2013:14093066.

[169] Boyaci A., Topuz O., Alkan H., et al. Comparison of the effectiveness of active and passive neuromuscular electrical stimulation of hemiplegic upper extremities: a randomized controlled trial. International Journal of Rehabilitation Research. 2013;36(4): 315-22.

[170] Hu X.L., Tong K.Y., Li R., Xue J.J., Ho S.K., Chen P. The effects of electromechanical wrist robot assistive system with neuromuscular electrical stimulation for stroke rehabilitation. Journal of Electromyography and Kinesiology. 2012;22(3): 431-39.

[171] Kamen G, Gabriel D. Essentials of Electromyography. Amherst: University of Massachusetts, 2010.

[172] Folstein M., Folstein S., McHugh P. Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;12(3): 189-98.

[173] Fugl-Meyer A.R., Jaasko L., Leyman I., et al. The post-stroke hemiplegic patient. A method for evaluation of physical performance. Scandinavian Journal of Rehabilitation Medicine. 1975;7(1): 13-31.

[174] Ashworth B. Preliminary trials of carisoprodol in multiple sclerosis. Practitioner. 1964;192: 540-2.

[175] Feigin V.L., Lawes C. M., Bennett D.A., et al. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. The Lancet Neurology. 2003;2(1): 43-53.

[176] Traylor M., Rutten-Jacobs L.C.A., Holliday E.G., et al. Differences in common genetic predisposition to ischemic stroke by age and sex. Stroke. 2015;46(11):3042-7.

[177] Mcdonnell M. Action Research Arm Test. Australian Journal of Physiotherapy. 2008;54(3): 220.

[178] Meškauskaitė I., Krutulytė G., Šakalienė R. Evaluation of responsiveness of the Barthel index, Function independence measure, Rivermead mobility index, and Motor assessment scale applied for patients after stroke. Neurologijos Seminarai. 2011;15(47): 38-43.

[179] Liu S., Lebeau J., Tenenbaum G. Does exercise improve cognitive performance? A conservative message from Lor's Paradox. Frontiers in Psychology. 2016;7: 1092.

[180] Chae J., Yu D. Neuromuscular stimulation for motor relearning in hemiplegia. Critical Reviews in Physical and Rehabilitation Medicine.1999;11: 279-97.

[181] Gillen G., Ann B. Stroke Rehabilitation: A Function-Based Approach, 4ed. Mosby: Columbia University, Medical Center, 2015.

[182] Saunders D.H., Sanderson M., Hayes S., et al. Physical fitness training for stroke patients. The Cochrane Database Systematic Reviews. 2016;24(3): CD003316.

[183] Wissel J., Schelosky L.D., Scott J., et al. Early development of spasticity following stroke: A prospective, observational trial. Journal of Neurology. 2010;257(7): 1067–72.

[184] Duncan P.W., Zorowitz R., Bates B., et al. Management of adult stroke rehabilitation care: A clinical practice guideline. Stroke. 2005;36(9): e100–e143.

[185] Doan Q.V., Brashear A., Gillard P.J., et al. Relationship between disability and health related quality of life and caregiver burden in patients with upper limb poststroke spasticity. Polymyalgia Rheumatica. 2012;4(1): 4-10.

[186] Sujith O.K. Functional electrical stimulation in neurological disorders. European Journal of Neurology. 2008;15(5): 437-44.

[187] Rong W., Tong K.Y., Hu X.L., et al. Effects of electromyography-driven robot-aided hand training with neuromuscular electrical stimulation on hand control performance after chronic stroke. Disability and Rehabilitation. 2015;10(2): 149-59.

[188] Razali N.M., Wah Y.B. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. Journal of Lifetime Data Analysis. 2011;2((1): 21–33.

[189] Rong W., Tong K.Y., Hu X.L., Ho S.K. Effects of electromyography-driven

robot-aided hand training with neuromuscular electrical stimulation on hand control performance after chronic stroke. Disability and Rehabilitation. 2015;10(2): 149-59.

[190] Feigin V.L., Lawes C.M., Bennett D.A., Anderson C.S. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and casefatality in the late 20th century. Lancet Neurology. 2003;2(1): 43-53.

[191] Traylor M., Rutten-Jacobs L., Holliday E., et al. Differences in common genetic predisposition to ischemic stroke by age and sex. Stroke. 2015;46(11): 3042-7.

[192] Folstein M., Folstein S., McHugh P. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;12(3): 189-98.

[193] Fugl-Meyer A., Jaasko L., Leyman I., Olsson S., Steglind S. The post-stroke hemiplegic patient.1. A method for evaluation of physical performance. Scandinavian Journal of Rehabilitation Medicine. 1975;7(1): 13-31.

[194] Castelein B., Cagnie B., Parlevliet T., et al. Optimal Normalization Tests for Muscle Activation of the Levator Scapulae, Pectoralis Minor, and Rhomboid Major: An Electromyography Study Using Maximum Voluntary Isometric Contractions. Archives of Physical Medicine and Rehabilitation. 2015; 96(10): 1820-7.

[195] Yozbatiran N., Der-Yeghiaian L., Cramer S.C. A Standardized Approach to Performing the Action Research Arm Test. Neurorehabilitation and Neural Repair. 2008;22(1): 78–90.

[196] Bakheit A., Maynard V.A., Curnow J., et al. The relation between Ashworth scale scores and the excitability of the α motor neurons in patients with post-stroke muscle spasticity. Journal of Neurology, Neurosurgery, and Psychiatry. 2003;74(5): 646–8.

[197] Flament D., Shapiro M.B., Kempf T., et al. Time course and temporal order of changes in movement kinematics during learning of fast and accurate elbow flexions. Experimental Brain Research. 1999;129(3): 441–50.

[198] Geogopoulos A.P. On Reaching. Annual Review of Neuroscience. 1986; 9: 147-70.