

**Robot-Assisted Therapy for Upper Limb Rehabilitation in
Individuals with Stroke: Effectiveness, Role of Environment, and Evaluation
of a Novel “Assist-As-Asked” Protocol**

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ABSTRACT

A majority of stroke patients have impaired upper limb (UL) motor function following stroke and have difficulty in performing activities of daily living (ADL) independently. Task specific-high intensity exercises in an active, functional and highly repetitive manner over a large number of trials have been shown to enhance motor recovery, even in the chronic stages of stroke. However, the lack of resources and related costs have prevented conventional therapy to be replaced by intensive therapy. There are chronic stroke survivors who are not receiving any rehabilitation while still unable to or have difficulties in performing ADL independently. Developing a suitable and cost effective therapeutic solution for this subpopulation is much needed.

In order to determine the effectiveness of robot-assisted therapy (RT) in UL rehabilitation of stroke patients, we first systematically reviewed and analyzed the literature to find randomized controlled trials that employed robotic devices in UL rehabilitation of people with stroke. We found that when the duration/intensity of conventional therapy (CT) is matched with that of the robot-assisted therapy (RT), no difference exists between the intensive CT and RT groups in terms of motor recovery, ADL, strength, and motor control. However, depending on the stage of recovery, extra sessions of RT in addition to regular CT are more beneficial than regular CT alone in motor recovery of the hemiparetic shoulder and elbow of patients with stroke; the gains are similar to those that have been observed in intensive CT.

It has been shown that stroke patients with mild-to-moderate UL motor impairment benefit from training with a virtual reality rehabilitation system. However, during robot-assisted movements, it remains to be determined whether movements made in a virtual environment are similar to those made in a physical environment. Thus, we examined the role of training environment, whether virtual or physical, on robot-assisted reaching movements in chronic stroke and healthy

individuals, within a single session. Fifteen subjects participated in this study divided into three groups: 5 chronic stroke individuals able to perform a reaching task with no need for the robot assistance, 5 chronic stroke individuals who needed the robot assistance to complete the reaching task, and 5 healthy individuals. The task was to reach for six target buttons in two identical physical and virtual environments. The outcomes consisted of kinematic measures and a custom questionnaire to assess how participants perceived and experienced the reaching task in both environments. We found no differences between the two environments in terms of the outcome measures in any of the groups. We concluded that the choice of environment, whether physical or virtual, is not a key factor in designing a robot-assisted reaching protocol for stroke survivors.

We followed with a case study using an arm-based RT protocol to train reaching over 10 half-hour sessions in an individual with a long-term chronic stroke (20+ years). We analyzed the performance of the arm reaching movement with kinematic measures in two environments (physical and virtual) and evaluated the arm motor function using the Fugl-Meyer Assessment-Upper Extremity scale (FMA-UE). The results showed noticeable improvements in the subject's reaching performance accompanied by a small increase in FMA-UE score from 18 to 21. The improvements were also transferred into real life activities, as reported by the subject. This case study shows that even in long-term chronic stroke, improvements in motor function are still attainable with RT, while the underlying mechanisms of motor learning capacity or neuroplastic changes need to be further investigated.

Finally, we conducted a proof-of-concept study to identify clinical benefits and potential adverse effects of a novel, custom-developed RT protocol, named “Assist-As-Asked”, aiming at improving arm function of chronic stroke subjects with moderate-to-severe UL motor impairment and to investigate whether practicing in a physical or virtual environment would make any difference in

the outcomes of interest. Four chronic stroke subjects participated in 10 half-hour sessions to practice reaching six targets in both virtual and physical environments. The robotic arm provided gravity support, and with the “Assist-As-Asked” paradigm, helped subjects to complete movements when they requested it. Kinematics of the reaching movements and the subjects’ perception about the reaching practice in both environments were the primary outcome measures of interest. Change in scores of FMA-UE was the secondary outcome measure. Following the RT sessions, all the subjects noticeably improved their reaching performance, which was accompanied by 3-5 points improvement in FMA-UE score. There were no differences between the two environments in terms of kinematic measures even though subjects had different opinions about environment preference. We concluded that moderate-to-severe chronic stroke survivors may benefit from RT using the “Assist-As-Asked” paradigm. In designing an RT platform for moderate-to-severe chronic stroke survivors, the choice of environment, either physical or virtual, does not necessarily influence the outcome of therapy sessions.

RESUME

La majorité des patients qui ont subi un accident vasculaire cérébral (AVC) souffrent d'une altération de la fonction motrice du membre supérieur (MS) et ont de la difficulté à effectuer des activités de la vie quotidienne (AVQ) de façon autonome. Il a été démontré que des exercices réorientés sur la tâche à haute intensité offerts d'une manière active, fonctionnelle et de façon répétée sur plusieurs séances améliorent la récupération motrice, même dans les phases chroniques de l'AVC. Cependant, le manque de ressources et les coûts associés ont empêché le traitement conventionnel d'être remplacé par une thérapie intensive. Il y a des personnes ayant subi un AVC dans la phase chronique de récupération qui ne reçoivent plus de service de réadaptation pendant que ne peuvent toujours pas ou ont des difficultés à effectuer des AVQ de façon autonome. Il est donc important de développer une solution thérapeutique adaptée et économique pour cette sous-population.

Afin de déterminer l'efficacité de la thérapie assistée par un robot (RT) dans la réadaptation du MS chez les patients ayant subi AVC, nous avons d'abord systématiquement examiné et analysé la littérature pour identifier des essais contrôlés randomisés portant sur l'utilisation d'appareils de robotiques pour la réadaptation du MS des personnes ayant subi un AVC. Nous avons trouvé que lorsque la durée / intensité de la thérapie conventionnelle (TC) est comparée avec la thérapie assistée par un robot (RT), aucune différence n'existe entre les groupes intensifs de la TC et RT en termes de récupération motrice, de performance dans les AVQ, de force, et de contrôle du moteur. Cependant, dépendamment de la phase de récupération, des séances supplémentaires de la RT en plus de la TC sont plus bénéfiques que la TC seule pour la récupération motrice de l'épaule et du coude hémiparétiques des patients ayant subi un AVC; les bénéfices sont similaires à ceux qui ont été observés en TC intensive.

Il a été démontré que les patients ayant subi AVC avec un déficit moteur léger à modéré du MS bénéficient d'un entraînement avec un système de réadaptation en réalité virtuelle. Cependant, lors des mouvements assistés par robot, il reste à déterminer si les mouvements effectués dans un environnement virtuel sont similaires à ceux réalisés dans un environnement physique. Donc, nous avons examiné le rôle de l'environnement, soit virtuel ou physique, sur les mouvements assistés par un robot dans la phase chronique des personnes ayant subi un accident vasculaire cérébral et chez les individus sains, durant une seule séance. Quinze sujets ont participé à cette étude divisée en trois groupes: 5 individus atteints d'AVC chronique capables d'accomplir une tâche sans avoir besoin du robot, 5 individus atteints d'AVC chronique ayant besoin d'une assistance robotique pour accomplir la tâche et 5 individus en bonne santé. La tâche consistait d'atteindre six cibles dans deux environnements physiques et virtuels identiques. Les résultats comprenaient des mesures cinématiques et un questionnaire pour évaluer comment les sujets ont perçu et vécu la tâche d'atteinte dans les deux environnements. Nous avons trouvé qu'il n'y avait aucune différence pour les résultats entre les deux environnements et entre les groupes. Nous avons conclu que le choix de l'environnement, qu'il soit physique ou virtuel, n'est pas un facteur important dans la conception d'un protocole d'assistance avec un robot pour les personnes ayant subi un AVC.

Nous avons suivi avec une étude de cas en utilisant un protocole RT pour entraîner le bras) incluant plus de 10 séances d'une demi-heure chez un individu ayant subi un AVC chronique (20+ ans). Nous avons analysé la performance du mouvement du bras avec des mesures cinématiques dans les deux environnements (physique et virtuel) et la fonction motrice du bras a été évaluée en utilisant l'échelle *Fugl-Meyer Assessment-Upper Extremity* (FMA-UE). Les résultats indiquent des améliorations notables dans la performance du mouvement du bras du sujet, accompagnées d'une légère augmentation du score FMA-UE de 18 à 21. Les améliorations ont également été rapportées

par le sujet au niveau des activités de la vie de tous les jours. Cette étude de cas montre que même les patients ayant subi un AVC il y a longtemps peuvent améliorer de la fonction motrice du bras avec la RT. Les mécanismes sous-jacents de la capacité d'apprentissage moteur ou des modifications neuroplastiques doivent être examinés plus en détail.

Enfin, nous avons mené une étude de preuve de concept pour identifier les avantages cliniques et les effets indésirables potentiels d'un nouveau protocole RT personnalisé, appelé «Assist-As-Asked». Ce protocole vise l'amélioration la fonction du MS chez les sujets ayant subi un AVC chronique et ayant une déficience motrice modérée à sévère du MS. De plus, nous avons examiné si la pratique dans un environnement physique ou virtuel avait un impact au niveau des mesures ciblées. Quatre sujets ayant subi un AVC chronique ont participé à 10 séances d'une demi-heure. La tâche était de pratiquer l'atteinte de six cibles dans des environnements virtuels et physiques. Le bras robotisé a fourni un support gravitationnel et a utilisé un paradigme «Assist-As-Asked» (à aider les sujets à effectuer des mouvements lorsqu'ils le demandaient). Les principales mesures étaient la cinématique des mouvements du bras et la perception de la pratique du mouvement du bras des sujets dans les deux environnements. Le changement dans les scores du FMA-UE était la mesure secondaire. Après les séances de RT, tous les sujets ont nettement amélioré leur performance au niveau des mouvements du bras, accompagné d'une amélioration de 3-5 points du score FMA-UE. Il n'y avait aucune différence entre les deux environnements en termes de mesure cinématique, même si les sujets avaient divers opinions sur la préférence de l'environnement. Ces résultats nous permettent de conclure que les personnes ayant subi un AVC chronique modéré à sévère pourraient bénéficier de la RT en utilisant le paradigme «Assist-As-Asked». En concevant un protocole de RT pour les individus avec un AVC chronique

modéré à sévère, le choix de l'environnement, soit physique ou virtuel, n'influence pas nécessairement le résultat des séances de thérapies.

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To my beloved Mom and Dad to whom that I dedicate this work:

I will never forget your unconditional love. I am and will always be thankful to you.

PREFACE

Statement of Originality

The research works presented in this thesis are original works of the author and have not been published elsewhere except where specifically cited. Chapters 3, 4, 5 and 6 contribute to the advancement of knowledge in the field of robot-assisted therapy for upper limb rehabilitation of individuals with stroke, specifically on its effectiveness, role of environment, and evaluation of the “Assist-As-Asked” robot-assisted training protocol.

The research protocols of this work were approved by the Research Ethics Board (REB) of Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR). The research data presented in this thesis were collected at the Feil & Oberfeld Research Centre of the Jewish Rehabilitation Hospital, which is affiliated with McGill University and a site of CRIR.

Statement of Authorship

All the studies included in this thesis were designed, developed and conducted by me under the co-supervision of Dr. Philippe Archambault and Dr. Joyce Fung. As first author, I have been involved in all the work, such as research protocol design, subject recruitment, data collection, data processing, data analysis, reporting the results and critically discussing the findings, and documenting the research works in this manuscript. I was guided in the process by Dr. Philippe Archambault and Dr. Joyce Fung, who provided critical review of all the work included in this thesis and reviewed and approved the final version of all the manuscripts.

Thesis Format

This doctoral thesis is a manuscript-based thesis and contains four articles that have been published or submitted for publication. As part of the McGill regulation, besides the articles, this thesis

should have its own introduction, literature review and final summary section. Therefore, some materials from the articles are included in those sections.

Chapter One : INTRODUCTION

1.1 Rationale

Most people with stroke live with long-term disabilities, leading to serious social and economic impacts. A majority of patients have impaired upper limb (UL) motor function following stroke and have difficulty in independently performing activities of daily living (ADL) (Kwakkel et al. 2003; Prange et al. 2009). One of the challenging aspects of stroke rehabilitation is UL intervention. While the initial degree of stroke and paresis severity is a good predictor of UL function recovery (Jørgensen et al. 1995; Kwakkel et al. 2003; Wade et al. 1983), task-specific, high-intensity exercises in an active, functional, and highly repetitive manner over a large number of trials have been shown to enhance motor recovery, even in chronic stage of stroke (Fasoli et al. 2003). However, the lack of resources and related costs have prevented conventional therapy to be replaced by intensive therapy. Therefore, in stroke survivors who have reached their chronic stage, we are faced with a subpopulation of individuals with moderate-to-severe (MTS) UL motor impairments who are still suffering from decreased UL function, impairing their ability to perform daily activities independently, and are not receiving any rehabilitation services. Developing a suitable and cost effective therapeutic solution for this subpopulation is an important task.

Robot-assisted training/therapy (RT) is a promising tool for intensive practice of arm movements in stroke rehabilitation with some clear advantages over conventional treatment approaches; robotic devices can provide highly intensive and challenging practice, assistive/resistive/guiding force, task-specific and goal-directed movements, and movement reproducibility while allowing for kinematic/kinetic measurements. In addition, robots may allow patients to train more independently and with less supervision from a therapist (Kwakkel et al. 2008). However, the key to a successful use of RT is to integrate it with a proper practice environment to keep patients

actively engaged during the therapy session and have them adhere to the rehabilitation program; this environment can be either real or virtual. Virtual environment (VE) based rehabilitation systems greatly benefit from increasing patients' motivation, besides other advantages that they offer (Bayón-Calatayud et al. 2016). However, VE-based rehabilitation systems are mostly used in mild-to-moderate stroke patients (Saposnik and Levin 2011) because of their nature of not being able to provide direct movement assistance to MTS stroke patients with none/limited UL movement. A hybrid system in which a robotic device is coupled with a VE can take advantage of both systems' technical advancements and might benefit the MTS stroke patients. But a question rises about whether this is required in the case of MTS stroke or not; robots enable MTS stroke patients to complete the unsuccessful movements during therapy sessions that otherwise would be unattainable without external help and also can provide feedback about their performance; these are important motivation factors (Bejarano et al. 2016). In addition, there may not be a need for having a complex VE scene for chronic stroke patients with MTS motor impairments as higher repetition of simple tasks seems to be preferable than a task-oriented practice where patients have a hard time or are unable to complete the task (Fischer et al. 2007). Thus, in designing an RT system for helping MTS chronic stroke patients, the role of the robot may be more prominent than the VE itself. It remains to be investigated whether there is any advantage in coupling the robot with a VE than coupling it with a physical environment (PE) and whether movements made in the VE are like those made in the PE, when the task requirements are the same. To the best of our knowledge, most robotic rehabilitation setups have used VE and there is no study in the literature that investigated the effectiveness of robot-assisted upper limb reaching movement in a VE compared to a PE in individuals with stroke.

By considering all the above, we have developed a robot-assisted protocol aiming at improving arm function of chronic stroke subjects with MTS UL motor impairment. A novel “Assist-As-Asked” protocol is introduced in this new scheme where the robot only helps when the subject asks specifically for help. This thesis consists of 4 manuscripts, of which the first was a systematic review of the effectiveness of robot-assisted therapy in upper limb rehabilitation of stroke patients (Chapter Three). The subsequent research manuscripts (Chapters Four, Five and Six) examined whether robot-assisted practicing and training in a physical or virtual environment would make any difference in the outcomes of interest as well as evaluated feasibility and usability of our robot-assisted training system with the “Assist-As-Asked” protocol to determine whether our robot-assisted arm reaching protocol is beneficial in retraining the arm function of chronic stroke individuals with MTS UL motor impairment.

1.2 Objectives

The general objective of this research work was to investigate the effectiveness of robot-assisted therapy in upper limb rehabilitation of stroke subjects. To this aim, three specific objectives were defined as follows:

- 1- To systematically review the literature regarding the effectiveness of robot-assisted therapy in restoring upper limb motor function and improving activities of daily living in stroke patients. The first manuscript in Chapter Three covers this objective.
- 2- To investigate whether robot-assisted reaching training of stroke patients in chronic stage is affected by the choice of environment, whether physical or virtual. For this aim, two separate studies were done. Firstly, a single-session study was conducted (Chapter Four) to compare the robot-assisted reaching performance of healthy individuals and chronic stroke patients with mild-to-moderate and moderate-to-severe upper limb motor

impairment in physical and virtual environments. Secondly, a multi-session study was conducted (Chapter Six) to compare the robot-assisted reaching training over multiple sessions in moderate-to-severe chronic stroke patients. We hypothesized, for both studies, that there would be no difference in robot-aided arm reaching performance of stroke patients between physical and virtual environments.

- 3- To investigate a new robot-assisted training protocol, called “Assist-As-Asked”, in which the robot only provides assistance when the stroke patient specifically asks for it. Chapter Six presents the results of the proof-of-concept study on this new protocol in chronic stroke patients with moderate-to-severe upper limb motor impairment, while Chapter Five presents a case study that details the improvement in reaching performance in a long-term chronic stroke patient who benefitted from this new protocol.

Chapter Two : LITERATURE REVIEW

2.1 Stroke

Stroke or Cerebrovascular Accident (CVA) is a medical term used to describe a debilitating neurological condition caused by “the interruption of the blood supply to the brain, usually because a blood vessel bursts [i.e. hemorrhagic] or is blocked by a clot [i.e. ischemic]. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue.” (World Health Organization 2017). The absolute number of stroke survivors is progressively increasing; from 1995 to 2013, estimates for the number of people living with long-term effects of stroke in Canada increased from 261,000 to 405,000 and it is projected to reach around 700,000 by 2038 (Krueger et al. 2015). It is the leading cause of disability and depending on the magnitude and severity of the problem, stroke survivors experience a variety of motor, sensory and cognitive disabilities (Public Health Agency of Canada 2011). Using the *disability-adjusted life-years* (DALYs) as a measure of how many years of life are lost and lived with disability (with one DALY corresponding to one lost year of healthy life), stroke is the fourth leading cause of lost DALYs in adults worldwide; it is the leading cause of lost DALYs among adults between 45 and 69 years of age (Mukherjee and Patil 2011). Motor impairment following stroke is one of the main sources of long-term disability in the world.

A majority of stroke survivors experience problems in upper limb (UL) motor function, most commonly hemiparesis of the contralateral side (Winstein et al. 2016a). At 6 months post-stroke, i.e. the chronic stage, 26% of ischemic stroke survivors are still unable to independently perform activities of daily living (total or severe dependence on someone else based on a score of less than 60 on Barthel Index (Go et al. 2013; Hsieh et al. 2007; Mahoney 1965). In general, 30% to 66% of the chronic stroke survivors have impaired UL motor function (Veerbeek et al. 2016). Only

5%-20% of hemiplegic stroke survivors show complete recovery of arm function in their paretic arm at their chronic stage (Kwakkel et al. 2008). The UL motor impairments are manifested in muscle weakness and change in muscle tone as well as disrupted motor control, commonly seen as abnormal muscle synergies, disrupted inter-joint coordination, and decreased movement smoothness (Hatem et al. 2016). The fine motor skills needed in activities such as reaching and grasping, feeding, dressing and grooming are dependent on restoration of the UL motor function and its loss/lack directly affects independence of stroke survivors in performing activities of daily living (ADLs).

2.2 Stroke Recovery

How does a stroke survivor recover movement? To answer such a question, it is necessary to clarify the meaning of recovery before proceeding further. In addition, one must be familiar with the concept of neuroplasticity and that a human brain is plastic and can reshape itself in different circumstances and in response to trauma. Our focus here is only on understanding motor recovery process following stroke.

2.2.1 True Recovery versus Compensation

The term “recovery” is loosely used to simultaneously describe restitution of damaged cortical structures or functions (basic science researchers’ point of view) and also functional improvements regardless of the underlying mechanisms (clinicians’ point of view), i.e. whether restitution or adaptation processes have been responsible for the functional gains (Levin et al. 2009). Using the International Classification of Functioning (ICF) model of the World Health Organization, Levin, Kleim and Wolf differentiated *true recovery* from *compensation* at only two levels of the ICF, i.e. Body Function/Structure (impairment), and Activity levels. These are subcategories of the Health Condition. At the Health Condition level (top level), true recovery implies restitution/repair of

brain functions and structures to their original state which is not expected to happen in a stroke patient; instead true recovery can be defined as (re-)activation of surrounding areas around the infarct and also portion of the brain that is distantly connected to the infarct area (i.e. Diaschisis). Compensation at this level is defined as activation of alternative brain areas not seen in normal individuals. However, such a definition at this level can hardly be a distinguishable factor, even considering current brain imaging techniques; e.g. when a chronic stroke individual uses compensatory trunk movement to perform a reaching task, observation of an increased cortical activation in some brain areas can both reflect true neuronal recovery and compensation. There is no clinical measure available at this level.

On the other hand, true recovery and compensation can be better defined and distinguished at the ICF's Body Function/Structure (impairment) level. At this level, true recovery is defined as the reappearance of premorbid movement patterns such as improvements in muscle activation/coactivation patterns and spatiotemporal properties of interjoint coordination (i.e. to become more similar to premorbid ones), decrease in trunk compensatory movements in a reaching task, or decrease in spasticity. Compensation at this level can be a combination of *adaptive performance*, i.e. using alternative movement patterns in performing tasks, and *substitutive performance*, i.e. using different effector(s) to complete a task. Clinical measures such as the Fugl-Meyer Assessment (FMA) (Fugl-Meyer et al. 1975) and the Chedoke-McMaster stroke assessment (Gowland et al. 1993) allow clinicians to measure and monitor the impairment level but are not fine enough as kinematic measures and electromyography (EMG) recordings to show detailed movement patterns and compensations.

At the Activity level of the ICF, true recovery implies that for performing a task, the involved muscles and joints and their spatiotemporal movement patterns to be similar to those of normal

individuals. On the other hand, compensation implies using other body parts (rather than the usual ones) to perform a task. However, most clinical measures at the Activity level, such as the Action Research Arm Test (Lyle 1981; Yozbatiran et al. 2008), the Barthel Index (Mahoney 1965), the Functional Independence Measure (FIM) (McDowell 2006), or the Box and Block Test (Mathiowetz et al. 1985), fail to distinguish how the task is accomplished or whether there was a partial or full compensatory movement involved. There is a good reason for that; from the clinicians' point of view, the goal of stroke rehabilitation is to enable a stroke survivor to perform as many activities of daily living (ADL) as possible on their own; how the movements are done with the means being used are of less importance in clinical practice. The goal is not set on having a true recovery but on restoring function, whether by true recovery and/or compensation. For example, the current *Canadian Stroke Best Practice Recommendations* suggest initiation of discharge planning as soon as the stroke patient is admitted to each phase of care (Cameron et al. 2016) and therefore clinicians do their best to get stroke patients out of rehabilitation centres as soon as possible and mostly focus on ADL recovery whether done by compensation or true recovery. While compensatory movements might help completing a task, they might affect other body parts and posture as compensatory movements are not natural and optimal to the human body.

Throughout this thesis, we operationally define recovery at Body Function/Structure and Activity levels, in which detailed movement patterns are measurable by means of kinematics and EMG analyses. At the Health Condition level (top level), measuring/monitoring changes in brain activation alone does not indicate whether a true recovery has happened, or if a compensation is in place. Instead, it must be accompanied with detailed movement pattern measurements to

indicate whether the brain activation reflects a true recovery at the Body Function/Structure level or Activity level too or not.

2.2.2 Neuroplasticity

Neuroplasticity is an umbrella term for the ability of the nervous system to modify its structural and functional properties and neuronal connections in response to intrinsic and extrinsic stimuli (Cramer et al. 2011). These brain modifications can be described and analyzed in different levels such as molecular, cellular, genetics, neuronal morphology, and behavioural (Kolb and Gibb 2014) from which synaptic changes, i.e. changes in neural networks organization, are the primary form of plasticity related to behaviour. These plastic properties of the nervous system are the basis of its development. In a normal brain, three types of neuroplasticity have been identified: experience-independent, experience-expectant and experience-dependent (Kolb and Gibb 2014). During development, the genome cannot carry all the information related to all the neuronal connections in the brain. Instead, a rough neuronal structure of the brain is formed with overproduction of neuronal connections. This developmental process is referred to as the experience-independent plasticity. This overproduction of neuronal connections during experience-independent plasticity will be shaped later by internal and external stimuli which is the foundation of experience-expectant plasticity.

Experience-expectant plasticity is referred to the general development of the human brain through history and evolution to expect early universal stimulating experiences, such as visual stimulations, sound and body movements, for developing and tuning sensory and motor systems (Greenough et al. 1987). This type of plasticity is time sensitive (active during a ‘critical period’ in early life); Animal studies on cats have shown that during a relatively brief critical time window following birth, closure of one eye severely damages its visual performance when it is opened later (Winfield

1981; Hubel and Wiesel 1970). During this critical period, synaptic connections between neurons are produced in excessive amounts (“blooming”) and presence of the expected experiential stimuli determines survival of the formed synapses (i.e. “pruning” of the unwanted ones) (Greenough et al. 1987). In other words, synaptic connections are created and eliminated through use-dependent processes in this critical period and define the subsequent properties and functionalities of the brain in adulthood (Murphy and Corbett 2009).

While the first two plasticity terms are related to early development and are age-dependent, the experience-dependent plasticity is active in later development and adulthood. It is the core of behavioural development in humans. Experience-dependent plasticity refers to the changes of the existing cortical structure and function in response to stimuli (Kolb and Gibb 2014). One of the main modulators in experience-dependent plasticity is behavioural experience in which repetition shapes the properties of the associated cortical areas (Nudo 2013). Experience-dependent plasticity is shown in animal models during problem learning, expansion/shrinkage of topographic maps in response to experience, intense environmental manipulations, and in response to abnormal experiences and injury (Kolb and Gibb 2014).

While neuroplasticity is the basis for human development, it plays a critical role when an injury happens to the brain. The key note in plasticity is that it is the “experience” that shapes the blooming and pruning of the neuronal synapses in different brain regions.

2.2.3 Recovery by Type of Stroke (Ischemic vs Hemorrhagic)

Stroke is categorized into two types: ischemic (cerebral infarction) and hemorrhagic. The hemorrhagic strokes include intracerebral hemorrhage (ICH, bleeding directly into the brain) and subarachnoid hemorrhage (bleeding directly into the cerebrospinal fluid within the subarachnoid space) (Grysiewicz et al. 2008). The proportional frequency of stroke types is different around the

world. Ischemic stroke is the most prevalent type with 67%-81% of stroke cases (Feigin et al. 2003). Between 6% and 20% of stroke cases are ICH and 1%-7% are subarachnoid hemorrhage (Feigin et al. 2003). Compared to ischemic stroke, ICH results in higher mortality rates and more severe impairment in acute phase. The mortality rate of ICH is about 50% within the first month after stroke (Saulle and Schambra 2016).

A retrospective study compared functional recovery in 193 ICH and 871 ischemic stroke patients by using the FIM instrument (Kelly et al. 2003). The results showed that even though at admission to the rehabilitation program, the ICH patients were more functionally impaired than the ischemic patients, at discharge there were no significant differences between the two groups due to higher gains in FIM score in the ICH group. Therefore, care must be taken when studying motor recovery in acute and subacute stroke patients by subcategorizing the patients based on their stroke type. However, in the chronic stage of stroke, we do not expect ICH and ischemic stroke survivors to differ in their response to a rehabilitation program and have not found any research articles on this topic. Thereafter, throughout this thesis, while looking at motor recovery, we did not focus or emphasize on the stroke type of the patients.

2.2.4 Motor Recovery

2.2.4.1 Spontaneous Recovery

Recovery from stroke is a complex process which happens through a combination of spontaneous recovery and learning mediated processes. Following stroke/brain injury, the infarct area and surrounding tissues (*penumbra*) undergo a complex cascade of pathophysiological changes. The pathologic sequelae lead to functional impairments of the patient which its extent is dependent on several factors such as severity of the neurologic deficit, size and site of the lesion, and existence of prior lesions (Goldstein and Davis 1990). However, the remaining intact structures of the brain

become highly malleable to support recovery of some of the lost functions (Nudo 2013). The recovery starts with *spontaneous recovery*; the first few days following stroke, after the patient is stabilized, the brain starts rehabilitating itself. In the first 30 days following stroke, there is a dramatic recovery in motor function which is called spontaneous recovery due to the fact that it happens in absence of any specific rehabilitation intervention (Duncan et al. 1992). This period sometimes extends to 3 months post stroke in severe cases. The autonomous recovery might be due to several factors (Dancause and Nudo 2011). First, there is a sudden loss/reduction of activity in the portion of the brain that is distantly connected to the infarct area (called *Diaschisis*) and there is a belief that the brain tries to resolve this issue. Second, to perform daily tasks that are lost due to the cortical injury, compensatory movements are employed to achieve the same goals. Third, the brain starts local and distant rewiring following injury, i.e. plasticity. There is a critical period for this process similar to the experience-expectant plasticity; in this critical period, due to the injury to the brain, excessive production of synaptic connections begins and axonal sprouting re-initiates. Studies have shown that several forms of plasticity can be ongoing concurrently in response to a brain injury (Cramer et al. 2011). For instance, damage to part of the motor network can cause spontaneous intra-hemispheric changes (e.g. shifts in representational map of the hand area to the shoulder area or face area) and changes in inter-hemispheric balance (e.g. supra-normal activity of the intact hemisphere in respect to movement). Based on the amount and characteristics of the motor experience, this reshaping of the damaged brain can be adaptive, when associated with improvement in function, or maladaptive, when associated with negative results such as loss of function or increased injury (Nudo 2013). However, spontaneous recovery does not necessarily translate into a true recovery but can also result in a motor compensation or a combination of both true recovery and compensation (Murphy and Corbett 2009).

2.2.4.2 Rehabilitation during the Critical Period

If the same principles of experience-expectant plasticity in the developing brain apply to the critical period appearing following stroke, then lack of stimulation directed toward the motor cortex in the acute phase might result in permanent non-formation of new synaptic connections to replace the lost ones due to stroke (Adamovich et al. 2009; Kathleen et al. 2007). In other words, a question arises whether to start the rehabilitation program of a stroke patient as early as possible in the acute phase or not. Several studies on rats have shown that applying intensive forced therapy of the paretic limb too early after induced stroke results in poor motor recovery (Kwakkel et al. 2014). In humans, the benefits of starting constraint-induced movement therapy (CIMT) in the early months following stroke in sub-acute phase (2-3 months post-stroke) compared to delayed therapy (in chronic stage) is already established (Wolf et al. 2010), but the “Very Early Constraint-Induced Movement during Stroke Rehabilitation” study has shown that high-dose of CIMT delivered too early after stroke (in acute stage; starting days following stroke) not only does not help motor recovery but also results in poorer outcomes than standard CIMT and did not differ from the control group at 90 days follow-up (Dromerick et al. 2009). Similarly, the results of “A Very Early Rehabilitation Trial” study (Cumming et al. 2011) about very early mobilization of stroke patients (within 24 hours following stroke) has shown that increased amount of mobilization per day (higher dosage) reduced the odds of favourable outcome on the modified Rankin Scale (van Swieten et al. 1988) while increased frequency of mobilization per day (higher frequency) increased the odds of favourable outcome at 3 months post-stroke when compared to the usual care group (Bernhardt et al. 2016). In other words, the peri-infarct regions (regions surrounding the infarct area) cannot tolerate extra behavioural pressure (i.e. high dosage) in the early days or even weeks following stroke (Cramer 2009).

Rather than focusing on the intensive therapy during the acute phase of stroke, further studies need to be done on the use of early standard therapy which might not put that much of pressure on the cortex. A study on rats questioning the effect of rehabilitation starting time (three groups: 5-days, 14-days and 30-days) on functional outcome has shown that starting the rehabilitation at 5-days post-stroke resulted in the highest functional outcome, followed by the 14-days group. The 30-days post-stroke rehabilitation group did not differ from the control group, which did not receive any rehabilitation, in terms of motor function (Biernaskie et al. 2004). These results suggest that the efficacy of rehabilitation declines with time and the opportunity for rehabilitation might be totally lost if not applied in the right window time. In humans, a recent clinical trial in China focusing on ICH stroke patients has shown that starting rehabilitation within 48 hours of stroke improves functional outcomes at 6 months post-stroke when compared to starting the rehabilitation after 7 days (Liu et al. 2014). A clinical trial is underway to investigate administration of upper extremity therapy at different time points among stroke survivors to shed light on potential benefits of starting rehabilitation as early as possible (Dromerick et al. 2015). The results of such a study will better guide clinicians on when is the best and optimal time to deliver upper extremity motor training following stroke.

2.2.4.3 Rehabilitation-Induced Motor Recovery

Besides spontaneous recovery, rehabilitation plays a key role in regaining lost functions. Rehabilitation-induced motor recovery could be divided into two parts: one is true recovery through experience-dependent plasticity and the other one is compensatory movements.

Rehabilitation usually starts when brain edema, inflammation and *apoptosis* (delayed secondary cell death in the penumbra) are resolved and the stroke patient is stabilized by medical care (Dromerick et al. 2015). This usually means one to two weeks post-stroke. Current

standard/conventional upper limb rehabilitation practiced by occupational and physical therapists is mainly focused on neuromotor interventions based on two primary approaches: neurofacilitation and functional retraining (Nudo and Dancause 2013). Neurofacilitative approaches (or ‘named’ approaches), such as Bobath (also called neurodevelopmental therapy or NDT), Brunnstrom (also called movement therapy), Rood (sensorimotor approach), and proprioceptive neuromuscular facilitation (PNF) were developed based on neurophysiological principles and empirical assumptions that functional impairments are due to disruptions in central nervous system hierarchy and reflex motor control (Chen and Shaw 2014; Doss 2015; Pollock et al. 2014; Nudo and Dancause 2013). In the Bobath approach, the focus is on breaking the maladaptive or abnormal patterns of movement, normalizing the muscle tone and inhibiting spasticity while facilitating normal movement patterns. In the Brunnstrom approach, the therapist applies sensory stimulation and uses primitive reflexes and synergies to encourage return of voluntary movements. In the Rood approach, cutaneous sensorimotor stimulation is used to modify muscle tone and movements are activated and facilitated with the same sequencing that they occur in natural movement from basic to complex. In the PNF approach, muscles, nerves and sensory receptors of the affected limbs are manually stimulated in diagonal and spiral patterns to promote more functionally relevant movements. As a result, in neurofacilitative approaches, the therapist acts as a problem solver and decision maker by adjusting and applying the movement patterns while the patient remains relatively passive in this process (Pollock et al. 2014).

In contrast, functional retraining approaches are based on motor control and motor learning theories in which subjects should play an active role in the therapy. In these approaches, it is hypothesized that by practicing a task, the engrams (motor programs), that are disrupted and abolished due to the death of neurons can be restored or replaced with novel ones (Chen and Shaw

2014; Pollock et al. 2014; Nudo and Dancause 2013), similar to what happens in normal humans during motor task learning. Therefore, context-specific motor tasks are actively practiced by the patient while proper feedback is provided by the therapist. The task is then practiced for transferability. Here the concept of experience-dependent plasticity plays a key role.

While neurofacilitative approaches are widely being used in clinical practice, there is still a lack of high-quality research work on the effectiveness of conventional rehabilitation approaches; furthermore, there are no clear guidelines on which approach should be used. A meta-analysis assessing effectiveness of the aforementioned physical rehabilitation approaches concluded that while they are beneficial when compared to no treatment or usual care, none of them are more or less effective in improving ADL or motor function (Pollock et al. 2014). However, regarding the quality of the research papers pulled together in this meta-analysis, only less than half of them were considered of good quality. One of the reasons for the lack of high quality research work on conventional rehabilitation approaches is the technical challenges in designing such research (Nudo and Dancause 2013). In these approaches, the therapists, based on their own manual expertise, tailor the therapy program based on each patient's unique needs. This results in a high level of inter-subject and inter-therapist variability and therefore it would be very difficult to define standardized treatment protocols. Another reason is funding availability bias towards new and different treatment approaches, rather than for current conventional ones that are offered to all the stroke patients as part of their routine treatment plan (Cott et al. 2011). This results in evidence produced for isolated and partial treatments on a more focused impairment than the general treatment plan offered by conventional approaches.

Besides these two rehabilitation categories, new rehabilitation techniques based on scientific evidence from neuroscience and behavioural research or/and advancements in technology have

been being developed. These include non-invasive functional electrical stimulation (FES) of the nerves, brain stimulation using transcranial magnetic stimulation (TMS), CIMT, robotic rehabilitation and virtual reality. In the following sections, we will briefly go through CIMT as it illustrates motor recovery by using the affected UL. We later then focus on use of robotics in rehabilitation while covering some aspects of virtual reality in rehabilitation.

2.2.4.3.1 Constraint-Induced Movement Therapy

Use of CIMT in stroke patients was developed based on the ‘learned non-use’ theory which was derived from animal studies. While it was well known that monkeys would not use their unilateral deafferented limb in free situation even after spontaneous recovery happening in 2-6 months following forelimb deafferentation, Taub and his colleagues, based on the Munk’s original work (Munk 1909), hypothesized that the reason for this non-use could be that the monkeys’ attention is directed toward the unaffected limb; by restraining the unaffected limb, the animal then starts using the affected limb in a purposeful way and the non-use can be reversed (Knapp et al. 1963; Taub 1976; Taub et al. 1999). In stroke patients, while the neural injury is different from those resulting from deafferentation, learned non-use theory was thought to be one of the factors leading to the observation that some patients recover less than the others with similar lesion extent and location when they get to the chronic stage (Taub et al. 1999). Studies have shown that chronic stroke patients with mild-to-moderate motor deficits (sufficient voluntary movement control of extensors to overcome flexor synergies (Wolf et al. 1989)) benefit from CIMT; By restricting their unaffected arm (using a mitt or sling) for most of the waking hours over a couple of weeks (usually 2), while having them in a rehabilitation program applying task-oriented training with high number of repetitions, improvements in arm motor function, muscle tone, and arm-hand activities have been observed (Kwakkel et al. 2015; McIntyre et al. 2012).

Following success of CIMT in the chronic stage of stroke, this technique has also been investigated in the sub-acute and acute stages of stroke (Dromerick et al. 2009; Wolf et al. 2010; Stock et al. 2017). While the evidence is pointing toward its beneficial results in both sub-acute and chronic stages of stroke, applying CIMT too early in the acute phase was not superior to the standard care and it became detrimental when a higher dose was applied (as discussed in section 2.2.4.2).

Studies investigating the effects of CIMT on the neural system of stroke patients have shown that it results in cortical reorganization and experience-dependent plasticity. Following CIMT, TMS studies have shown increase and shift in motor related areas in the cortex and amplitude of motor evoked potentials correlated with clinical improvements (Liepert et al. 1998; Sawaki et al. 2008; Könönen et al. 2012), electroencephalography studies have shown marked changes in cortical activity (Miltner et al. 2016; Kopp et al. 1999) and fMRI (functional magnetic resonance imaging) studies have shown changes in cortical activity correlated with functional improvements (Laible et al. 2012; Könönen et al. 2012). But are the functional improvements and neuroplastic changes seen following use of CIMT of a compensatory origin or true recovery (refer to section 2.2.4.1)? Kitago and colleagues ran a pilot study on 10 chronic stroke subjects and showed that the observed functional improvements following CIMT are compensatory strategies developed by the patients rather than reduction in impairments or recovery of normal motor control (Kitago et al. 2013). In other words, functional improvements seen following CIMT did not originate from true recovery but were of a compensatory nature. The key lesson from this section is that functional improvements highlighted in many rehabilitation researches from clinical perspective do not necessarily mean that the patients' impairment levels have reduced; it might just mean that patients have developed workarounds (compensation) to complete their daily tasks.

2.2.4.4 Rehabilitation in Chronic Stroke

The response of the brain to rehabilitation changes over time. The critical period starts in the acute stage of stroke with highest sensitivity to training and continues into the sub-acute stage of stroke while fading away over time. During the critical time, the brain is highly sensitive to training (i.e. the nervous system responds better to training and practice) and over time this sensitivity gets reduced. For instance, a TMS study comparing the effects of CIMT in early (3-9 months post-stroke) and late (more than 12 months post stroke) stroke patients has found that while the early group showed greater improvements in motor ability in comparison to the late group, there was different brain reorganization occurring in the two groups; the late group had a larger shift and size increase in motor maps when compared to the early group (Sawaki et al. 2014). This can be justified with this postulation that when stroke patients get into their chronic stage, their learning mechanisms become like those of healthy adults, i.e. regular experience-dependent plasticity and motor learning mechanisms. This difference in plasticity is also observed in hemiparetic patients due to a subcortical stroke (Fujii and Nakada 2003); By using fMRI to monitor cortical reorganization of these patients over time, Fujii and Nakada observed that functional recovery is not a single continuous process but consists of two distinct phases of recovery with different neural mechanisms being involved. In the first phase, which typically ends within one month following stroke, the neural system tries to recover to its original state prior to stroke as much as possible. Patients who achieve a good level of functional recovery in this period (rapid recovery), show brain activation patterns similar to those of healthy individuals and no reorganization is seen in the contralesional hemisphere. These patients do not enter the second phase of recovery. However, those patients with slow recovery who did not achieve significant recovery within 1 month post-stroke, then enter the second phase of recovery. In this phase, the contralesional hemisphere also gets involved in the brain reorganization; attaining a good level of recovery becomes

dependent on successful reorganization of the contralesional hemisphere and on the recruitment of ipsilateral pathways. Early signs of bi-hemispheric activation following stroke means an early entrance into the second phase of recovery (Fujii and Nakada 2003).

The point here is that stroke recovery, even in chronic stage, does not stop and only its neurophysiological nature and rate might change. A meta-analysis of TMS and fMRI studies looking at the neural plasticity evidence following upper extremity training has shown that in the chronic stage of stroke, functional gains following activity-based therapies are accompanied by neuroplastic changes in the sensorimotor area of the lesioned hemisphere (Richards et al. 2008); greater functional recovery is associated with increased representation area and higher activation of the ipsilesional hemisphere. However, not all of the studies included in the meta-analysis reported the engagement of the lesioned hemisphere but instead reported the increased activation of the intact hemisphere following functional improvements (Richards et al. 2008). The most probable reason for this difference in plasticity could be that the lesion's site and size are critical factors in shaping the plastic changes following training. For instance, in individuals with high level of damage to sensorimotor area and its corticospinal tract following stroke, motor recovery is accompanied by increased activation of the contralesional hemisphere (intact hemisphere) (Fujii and Nakada 2003) rather than of the ipsilesional hemisphere probably due to the fact that the damage is so extensive or its location is in such a place that in the damaged hemisphere there are no spared pathways left to be recruited or there are no way to make new pathways by the central nervous system; the only resource left for movement control would be the intact hemisphere.

2.2.5 Prognosis of Recovery

A prospective study looking at 2213 individuals with first ischemic stroke admitted to an inpatient stroke rehabilitation program revealed that higher Functional Independence Measure (FIM) at

discharge was directly associated with higher FIM score (both motor and cognitive) at admission, longer stay at rehabilitation program, lower medical complications, and being younger (Ng et al. 2007). Interestingly, the functional status at discharge was not related to the stroke vascular territory. Among these factors, the length of rehabilitation stay is the only factor that can be adjusted and modified by the treatment/therapy team. The relationship between longer length of rehabilitation program and higher functional status at discharge has been interpreted in two ways (Ng et al. 2007). First, spending more time in an active rehabilitation program leads to higher gains in function. Second, only those patients that show improvements are kept in the rehabilitation program, otherwise they are discharged. However, the former explanation is aligned with the studies on dose-response relationship in stroke rehabilitation which have shown that more intensive therapy is associated with enhanced rate of motor recovery; additionally, no ceiling effect for intensity of therapy has been observed (Huang and Krakauer 2009; Kwakkel 2006; Langhorne et al. 1996; Lohse et al. 2014b). However, it should be noted that the stroke recovery is not a linear trend but generally it follows a non-linear, natural logarithmic, trend in which the largest improvements are seen early after stroke and as the time passes by the rate of recovery gets reduced (Figure 2-1) (Kwakkel et al. 2006; Langhorne et al. 2011). This natural logarithmic trend can be different for each stroke survivor. Fujii and Nakada was able to categorize patterns of functional recovery of stroke survivors into three distinct natural logarithmic categories: *rapid-good*, *slow-good* and *slow-poor* recovery (Figure 2-2) (Fujii and Nakada 2003). The stroke patients in *rapid-good recovery* group attained good functional recovery within 1 month post-stroke while the stroke patients in *slow-good recovery* group while had severe residual hemiparesis in the first month post-stroke, they attained good functional recovery within 3 months post-stroke. The stroke patients in *slow-poor recovery* had severe residual hemiparesis in the first month post-stroke and

continued to show significant functional deficits at the end of third month post-stroke (Fujii and Nakada 2003).

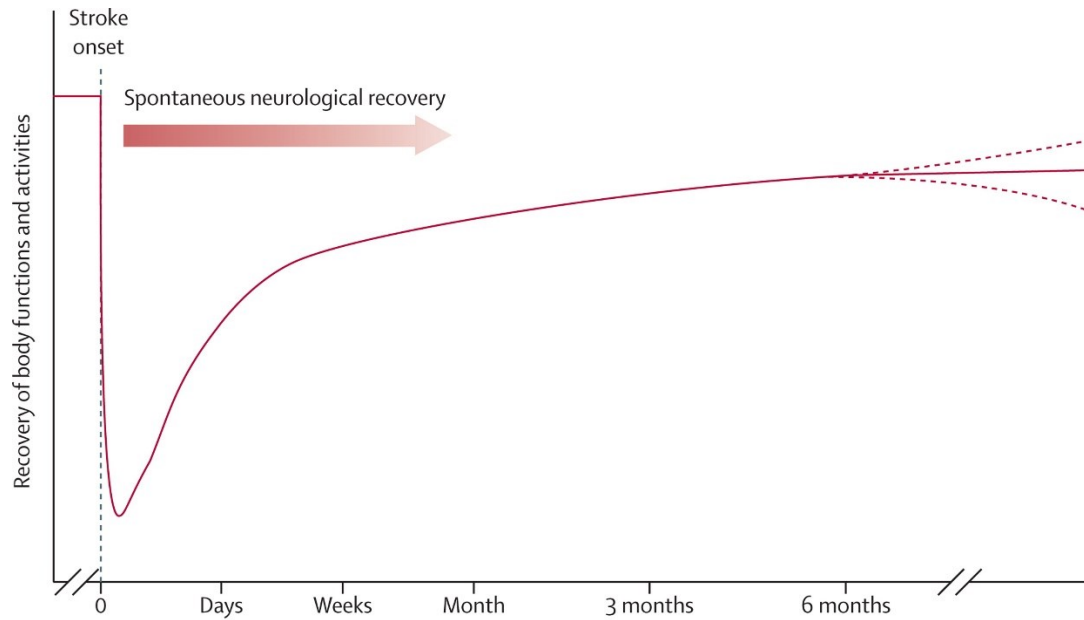


Figure 2-1: “Hypothetical pattern of recovery after stroke” (Langhorne et al. 2011). “Reprinted from The Lancet 377 (9778), Authors: ‘Peter Langhorne, Julie Bernhardt, Gert Kwakkel’, Title: ‘Stroke rehabilitation’, Pages: 1693-1702, © 2011, with permission from Elsevier. License number 4350830099368.”

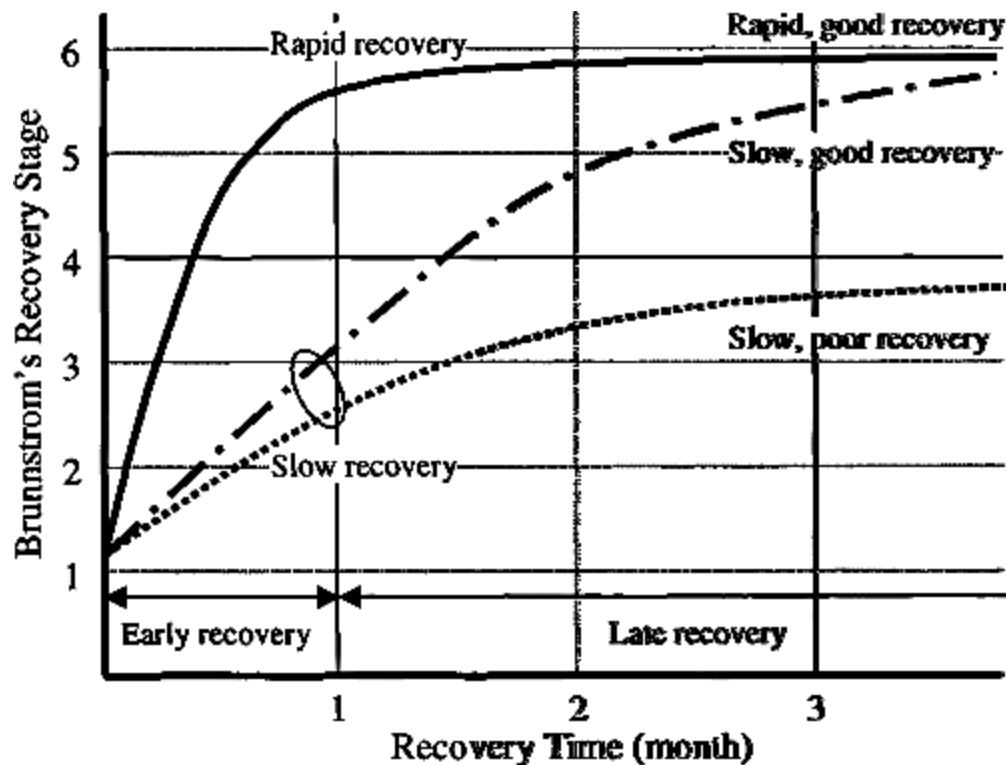


Figure 2-2: Three distinct categories of recovery rate: rapid-good, slow-good and slow-poor (Fujii and Nakada 2003). “Reproduced with permission of the Journal of Neurosurgery. Reprinted from ‘Yukihiko Fujii and Tsutomu Nakada’ (2003) ‘Cortical reorganization in patients with subcortical hemiparesis: neural mechanisms of functional recovery and prognostic implication’. Journal of Neurosurgery 98(1):64-73”.

2.3 Robot-Assisted Therapy/Training (RT)

In the medical subject headings (MeSH) database, *Robotics* is defined as “the application of electronic, computerized control systems to mechanical devices designed to perform human functions. Formerly restricted to industry, but nowadays applied to artificial organs controlled by bionic (bioelectronic) devices, like automated insulin pumps and other prostheses” (National Library of Medicine 2017). Use of robotic devices for upper limb stroke rehabilitation dates back to 1990s; Krebs, Hogan and their colleagues were the pioneers in building the well-known MIT-MANUS as an end-effector planar robot allowing patients to perform goal directed arm

reaching movements (Hogan et al. 1995; Fasoli et al. 2003). The device was later commercialized under the name of InMotion-ARM (InMotion 2.0) and became modular to incorporate a wrist training component (InMotion-WRIST) (Krebs et al. 2007b) and a hand training component (InMotion-HAND) (Masia et al. 2007). Since then, a survey on UL robotic devices in 2014 found and summarized a list of 129 robots that have been developed for UL rehabilitation (even though most of them are only at the research stage, with 15 of them having been commercialized) (Maciejasz et al. 2014).

As part of this thesis, we conducted a systematic review and meta-analysis of the literature to find evidence regarding the effectiveness of robot-assisted therapy in improving motor recovery and functional abilities of paretic upper-limb of stroke patients when compared to conventional therapy (see Chapter Three). Therefore, rather than focusing on RT studies for UL stroke rehabilitation in this chapter, we will review the benefits and importance of RT in stroke rehabilitation and some aspects of rehabilitation robotics design.

2.3.1 Benefits and Importance of Use of Robotics in Stroke Rehabilitation

Task-specific exercises involving high-intensity in an active, functional and highly repetitive manner over a large number of trials can enhance motor recovery even in chronic stages of a stroke (Fasoli et al. 2003). Studies on dose-response relationship in stroke rehabilitation have shown that more intensive therapy is associated with enhanced rate of motor recovery; additionally, no ceiling effect for intensity of therapy has been observed (Huang and Krakauer 2009; Kwakkel 2006; Langhorne et al. 1996). Despite these findings, conventional therapies are still unable to be delivered more intensively or frequently, often related to cost and labour limitations (Nef et al. 2009). The Canadian Stroke Best Practice guidelines (Hebert et al. 2016) recommend a minimum of 3 hours per day of direct task-specific therapy, five days per week, for inpatient rehabilitation

and a minimum of 45 minutes per day of active therapy per rehabilitation discipline, two to five days per week based on each patient's needs for at least 8 weeks, for outpatient rehabilitation. However, this minimum is often not reached within the current health care system in practice. Indeed, a study looking at the amount of time spent in physical activity in two inpatient rehabilitation units found that only 42% of session time (27 minutes out of 64 minutes session time in average) is spent on active task practicing and exercising (from which only 40% of this amount is related to UL training; i.e. 11 minutes out of 64 minutes or 17% of the session time) (Ada et al. 1998). A more recent study (from 7 sites around the United States and Canada) reported that average session duration is about 36 minutes (excluding rest breaks) but did not report the details of activities as the focus of the study was to quantify the amount of practice in terms of number of repetitions rather than its duration (Lang et al. 2009): the average number of repetitions of UL training tasks in each stroke rehabilitation session was around 32 repetitions of functional movements and 54 repetitions of active exercise (Lang et al. 2009). Such numbers are way lower than the hundreds of functional repetitions required for learning a new UL motor task in healthy individuals, as well as those reported in animal studies on rats and monkeys. In healthy animals, 400 to 600 repetitions per day are needed to alter cortical representations of motor areas for learning a new task (Lang et al. 2009), and in monkeys with induced stroke, 600 repetitions per day are required to induce neuroplastic changes for relearning a pellet retrieval task (Nudo et al. 1996).

Not only is it necessary to fill this gap between the recommended amount of practice per day and current practice in stroke rehabilitation, but it is also recommended to deliver extra dose of practice following stroke, as evidenced by more improvements with increasing active practice time (English and Veerbeek 2015). A recent scoping review, however, found that studies done on

delivering extra practice during stroke rehabilitation were structured in such a way that most often required full supervision of a qualified therapist, which is resource intensive and expensive, and therefore not sustainable in the current rehabilitation systems (Stewart et al. 2017). Use of equipment such as robotics to increase practice time and intensity, use of non-therapists to setup and operate the therapeutic equipment such as robots under supervision of a therapist are solutions that are recommended to overcome these shortcomings in practice (Stewart et al. 2017). Besides the lack of enough active practice, traditional “hands-on” interventions can, at times, result in repetitive strain injuries and excessive fatigue for therapists, thus leading to possible failure in delivering highly intensive and repetitive training (Hidler et al. 2005).

One of the novel and rapidly expanding technologies in post-stroke rehabilitation to enhance the recovery process and facilitate the restoration of function is the use of robotic devices. Robot-assisted therapies and/or trainings (RTs) enhance stroke rehabilitation as they can provide intense active assisted training to patients in a consistent and controlled fashion with minimum intervention from therapists and allow patients to train more independently (Kwakkel et al. 2008). Advanced robotic devices are able to provide consistent training and to measure performance with high reliability and accuracy (Dobkin 2004).

Compared to the research and development (R&D) in conventional therapy techniques, the cost, effort and time required for the R&D in rehabilitation robotics are significantly higher. Therefore, an important element in further development of therapeutic robots and robot-assisted therapy programs is to determine if RT is at least as effective as conventional therapy (CT), based on the scientific evidence extracted from literature. Based on the systematic review conducted (Norouzi-Gheidari et al. 2012) as part of this thesis, we concluded that when the duration/intensity of CT is matched with RT, there is no difference between RT and (intensive) CT groups in terms of motor

recovery, ADL, strength and motor control. Nonetheless, similar to the results obtained employing intensive CT, additional sessions of RT promote better motor recovery in upper extremity of stroke patients when compared to standard CT. In other words, the use of robotics by itself does not translate into better therapy for stroke survivors. Rather, robots deliver highly repetitive therapeutic tasks with minimal supervision of a therapist and these additional sessions of robot-assisted therapy improve motor recovery of hemiparetic shoulder and elbow of stroke patients.

Based on these findings (Norouzi-Gheidari et al. 2012), employing RT in clinical settings can be justified by several reasons. For instance, during intensive CT, the therapist might not be able to deliver the intensive program as planned and might not adjust it appropriately based on the patient's progress. This can be due to fatigue or other human-related factors. On the other hand, robots always deliver the therapeutic programs as planned and can be programmed to self-adjust based on the patient's progress. The repetitive nature of this form of therapy can be delegated to a properly designed robotic device which delivers high intensity therapeutic tasks and "highly reproducible motor learning experience" (Charles et al. 2005). Another reason is that RT seems more interesting and motivating to stroke patients than CT which might increase further collaboration, motivation and effort by the stroke patients in robot-assisted therapy sessions. In other words, even though RT and intensive CT may be equivalent in terms of functional gains, combining the two may lead to increased variety of therapeutic modalities for the patients. Last but not least, employing therapeutic robots may be cost-effective in the long-term; Wagner et al. (Wagner et al. 2011a, b) have shown that, even with the current high capital cost for robots, the total costs are not greater for RT compared to CT or intensive CT. The authors estimated that in a 60-minute RT session, only 15 minutes would involve direct patient contact with a therapist and

therefore one therapist can set up therapeutic programs in different workstations for several patients and monitor them at the same time (Wagner et al. 2011b). Nonetheless, there are limitations in use of RT. For example, most robotic devices discussed here are planar robots (two dimensional); they are mainly designed for shoulder and elbow movements and do not include wrist and prehension, which are frequently affected in stroke (Shumway-Cook and Woollacott 2007). In addition, the robot-assisted therapy exercises consist in motor rehabilitation-based techniques rather than function-based therapy. Furthermore, the “assist-as-needed” protocol that is used in many rehabilitation robotics studies may encourage patients to wait until the robot does the task for them. Here “assist-as-needed” describes a protocol in which the robot helps the patient to complete a task when the patient does not or cannot move his arm/hand further in reaching the goal of the task.

In general, depending on the stage of recovery, highly intense therapy either by a therapist or a robotic device is associated with higher recovery rate (Huang et al. 2009; Kwakkel 2006; Langhorne et al. 1996). However, patients in general receive limited therapy from therapists in rehabilitation settings (Dewey et al. 2007; Lang et al. 2007) due to resource constraints. Thus rehabilitation robotics could fill this gap by providing the opportunity for more intense practice with minimal supervision by the therapist (Dobkin 2004).

2.3.2 Training Modalities in RT

A training modality of a robot can be defined as the way the robot interacts with a stroke patient during a rehabilitation practice session. Based on the therapeutic approaches used in conventional therapy, four common modes of operations are usually developed in rehabilitation robotics. These training modes are *active*, *active-assisted*, *passive*, and *resistive* (Basteris et al. 2014). It should be noted that some of the modes (such as *active*, *passive*, *active-assisted*) are defined based on the

subject being at the epicentre of the practice (similar to conventional therapy) while others based on the robot's actions. So, an *active* training mode implies that the subject is actively moving his or her arm and the robot is completely passive (even though the robot can be used for measuring the subject's performance). On the other hand, a *passive* training mode means that the robot is actively moving the subject's arm through a prescribed movement pattern while the subject is being passive. In an *active-assisted* mode (also called *assist-as-needed*), the subject initiates the movement on his own but when he is unable to further complete the movement, the robot assists the subject by completing the rest of the movement while the subject is passive (systematic success in task completion). In a *resistive* training mode, the robot resists the subject's movement (to some predefined extent) so the subject is required to exert more force than normal to perform the movement.

Besides these training modalities that mimic conventional training, other modalities such as *assistive*, *path-guiding/corrective*, *passive-mirrored* and *electromyography-based (EMG)*, have also been developed in rehabilitation robotics. In an *assistive* mode, the subject should be active all the time while the robot assists the subject in some aspects of it such as providing weight support. In a *path-guiding/corrective* mode, the robot provides spring-like forces to restore the subject's movement when it is deviated from a pre-defined movement path or can create virtual walls around the pre-defined path to limit the subject's movement deviation. *Passive-mirrored* mode is found in bimanual robots in which the impaired side is moved passively based on the movements of the unimpaired side (therefore called *passive-mirrored*). Assisting the subject by activating the robot based on surface EMG activities of the subject's arm are also another training modality that have been developed. It should be noted that these modalities can be combined during training; for instance, a robot, while in resistive mode, also provides weight support or path

guidance. The choice of training modalities in RT sessions depends on how the robot is programmed/controlled and is decided by the therapist.

2.3.3 Mechanical Design of Robots in RT

Generally robots are categorized into two mechanical structures: *exoskeleton* type and *end-effector* type (Figure 2-3) (Micera et al. 2005). The difference between the two designs dictates different control mechanism for transferring the movements to the affected upper limb. An *exoskeleton* robot is a wearable machine that mirrors the human skeletal structure of targeted limbs and therefore movement of a robotic joint produces movement at the corresponding human joint. On the other hand, an *end-effector* robot has only one point of attachment usually at a distal UL part (holding the robot's manipulandum in the hand or attaching the forearm/wrist to the robot's end-effector) and movement of that body part by the robot moves other UL segments attached to it like a mechanical chain (Maciejasz et al. 2014; Laut et al. 2016). Design and construction of exoskeleton robots are more difficult than end-effector ones as an exoskeleton must be adjustable to fit different subjects, follow targeted UL joins and segments, and have multiple attachment points to UL segments. As there are more degrees of freedom in an exoskeleton compared to an end-effector, the control of exoskeletons is more difficult than that of end-effectors based on the intended training (Micera et al. 2005). On the other hand, an end-effector robot has a simpler structure and can easily be adapted to different subjects as there is only one point of attachment. That being said, the main advantage of exoskeletons over end-effectors is the ability to control movement of the attached joints independently (Laut et al. 2016). It is almost impossible to produce an isolated movement for an UL joint in an end-effector robot as any movement at the end-effector produces complex movements in the all the UL segments (Maciejasz et al. 2014).

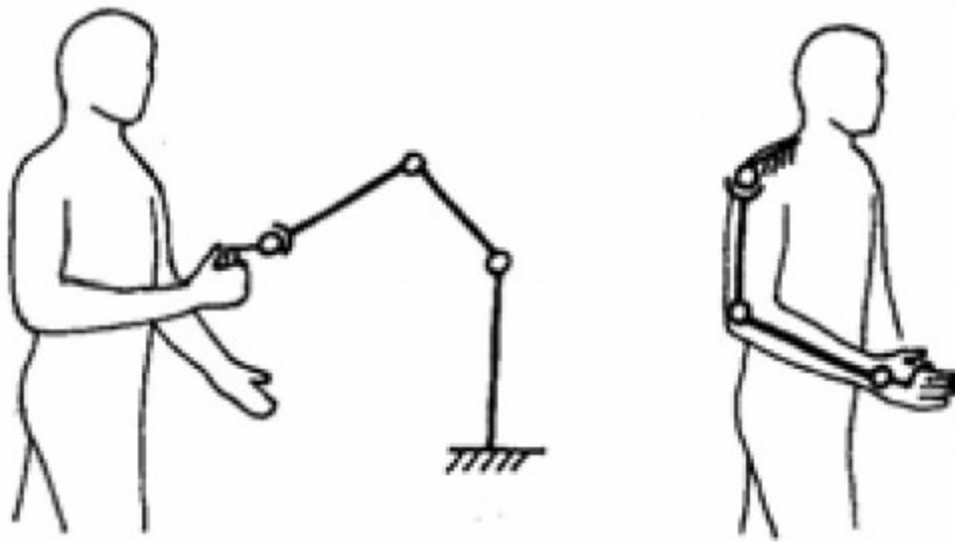


Figure 2-3: End-Effector (left) vs Exoskeleton (right) robotic type (Bergamasco et al. 2007). “Reprinted by permission from Springer Nature: Springer-Verlag Berlin Heidelberg, ‘Advances in Telerobotics’ edited by ‘Manuel Ferre, Martin Buss, Rafael Aracil, Claudio Melchiorri, Carlos Balaguer’ ©2003. License number 4350840539511”.

2.3.4 Use of RT in Stroke Rehabilitation

The author performed a systematic review and meta-analysis on the effectiveness of RT on stroke rehabilitation in upper limbs in 2011 (Chapter Three). Based on 12 RCT studies, we showed that when the duration/intensity of conventional therapy (CT) was matched with that of RT, no difference existed between the intensive CT and RT groups in terms of motor recovery, activities of daily living (ADL), strength, and motor control (Norouzi-Gheidari et al. 2012). However, depending on the stage of recovery, extra sessions of RT in addition to regular CT were more beneficial than regular CT alone in motor recovery of the hemiparetic shoulder and elbow of patients with stroke; the gains in motor control and muscle strength showed medium and large effect sizes, respectively, and the amount of gains were similar to those that have been observed in intensive CT (Norouzi-Gheidari et al. 2012).

Since that time, two other systematic review and meta-analyses were performed on effect of RT in UL rehabilitation of stroke patients. The Cochrane study by Mehrholz and colleagues in 2015 included 34 studies (32 RCTs and 2 cross-over) and concluded that RT improved ADL, arm function, and arm muscle strength when compared to CT (Mehrholz et al. 2015); however, the quality of the evidence was low to very low with small to medium effect size. Another meta-analysis involving 38 RCT studies showed that RT improved UL motor control and strength when compared to CT (Veerbeek et al. 2016). However, in terms of muscle strength, the effect size was small; and in terms of motor control, the authors only reported the mean difference and did not report the extent of its effect size. In terms of muscle tone, the results were in favour of CT with a small effect size. In terms of ADL, in contrast to findings of Mehrholz and colleagues (Mehrholz et al. 2015), RT did not benefit basic ADL more than CT (Veerbeek et al. 2016). Veerbeek and colleagues also performed a subgroup analysis comparing exoskeleton and end-effector robots (discussed previously in section 2.3.3) and found no significant effect for exoskeleton type in any of the outcome measures while finding significant effect for end-effector in motor control in favour of RT (Veerbeek et al. 2016).

In summary, we reviewed the efficacy of RT intervention in stroke rehabilitation and found that even though there is no difference between RT and CT with matched intensity, RT has a great potential in UL motor recovery of stroke patients. RT intervention may close the gap between the recommended amount of practice and current practice in stroke rehabilitation, by delivering extra dose of practice following stroke. In the following, we will review the use of virtual reality in stroke rehabilitation as most RT systems are integrated with virtual environments.

2.4 Virtual Reality

Similar to robotics, virtual reality is another emerging technology in motor recovery of upper limb in stroke patients and has been shown to induce cortical reorganization (You et al. 2005). Humans highly depend on their sense of vision as it provides around 70% of human sensing (Gulrez et al. 2008). Most of the VRs are built based on this notation: i.e. virtual environments (VEs) that subjects can navigate through and interact with solely based on visual information in real time. Besides auditory sensation, other human senses such as olfaction, somatosensation, or vestibular, while important, are more difficult to be simulated for deceiving the user's sensory receptors and are not as effective as visual simulations (Gulrez et al. 2008), even though use of haptic simulations coupled with VE has been on the rise. In general, two types of VEs are being used in VR systems: *immersive* (either fully or semi) and *non-immersive* (Bayón-Calatayud et al. 2016; Henderson et al. 2007). In immersive VEs, the users are immersed in a three-dimensional VE and can change their visual perspective through head or body movements (by using head mounted visual displays or virtual caves). The level of immersion depends on the VR system and can include motion platforms, surround sound systems and motion capture systems (such as the Computer-Assisted Rehabilitation Environment-CAREN system (Motekforce Link 2018)). A study by Martin and colleagues on arm reaching movements in three-dimensional space in an immersive VE showed that the VE immersion has no negative effect on the kinematic of the reaching movement and they are similar to those performed in physical environment (Martin et al. 2003). The velocity profiles are bell shaped with a single peak similar to the observations in physical environments (Dvorkin et al. 2006). On the other hand, non-immersive VR systems only use a two-dimensional display (e.g. a computer screen, a TV, or projecting on a screen) to show the VE. The commercial gaming systems usually use non-immersive VEs. As to whether there is a performance difference in

immersive versus non-immersive VE, Lathrop and Kaiser (Lathrop and Kaiser 2005) showed that when navigating in immersive and non-immersive VE, while participants were faster in navigating in immersive VE, there was no difference between the two VEs in terms of maintaining orientation. In addition, experienced gamers that participated in the study had higher absolute error in the immersive VE in comparison to the non-immersive one probably due to the acquired skills in playing in non-immersive game environments (Lathrop and Kaiser 2005).

Five elements intrinsic to VR training allow VR systems to be known as a powerful tool in rehabilitation: exposure (contextually relevant stimuli), distraction (from a painful or uncomfortable medical procedure), motivation (in doing the boring and repetitive tasks), measurement (Rizzo 2006) and safety (Johnson 2006). By creating a VE, therapists can create lifelike, highly motivating, and task-oriented environments in which patients can safely practice (Johnson 2006). The real-time interactive nature of VE when topped up with multi-sensory real-time feedback provides a unique training environment that allows practice of correction and control over different scenarios (that are sometimes impossible to be created in real world) by the patients. In the following sections, the latest evidence on VR effectiveness for UL stroke rehabilitation is discussed; then motivation and feedback as the main features of VR are covered.

2.4.1 VR Effectiveness

A 2007 systematic review and meta-analysis concluded that immersive VR is effective in improving motor function of the UL in stroke patients, compared to no therapy (level 1b evidence) or to conventional therapy (level 5 evidence) (Henderson et al. 2007). That being said, the conclusions regarding immersive VR were only based on one RCT with 10 stroke participants (5 in each group) and one single subject design at the time and therefore should be interpreted cautiously. More recent systematic reviews and meta-analyses had access to more research studies.

The 2014 meta-analysis by Lohse and colleagues (Lohse et al. 2014a) focused on how VR therapy affects outcomes according to the ICF and was able to differentiate between purpose-designed VE systems (20 studies) and commercial gaming (CG) systems (4 studies). The results showed overall benefit of VR therapy (both VE and CG studies combined) on ICF's Body Function and also Activity outcomes (medium effect size) when compared to conventional therapy. The research on ICF's Participation outcome was limited. While the authors could not find evidence of a difference between VE and CG, they could not draw any conclusion about it as the CG studies were too few and too small (Lohse et al. 2014a). A recent Cochrane review on VR concluded that the impact of VR on upper limb function and activity (composite measure) when compared to conventional therapy was not significant (22 studies were included), while its impact measured by the Fugl-Meyer Assessment-Upper Extremity Scale showed small significant effect when compared to conventional therapy (16 studies were included) (Laver et al. 2017). Having said that, use of VR as an additional intervention to augment standard care (10 studies were included) showed a medium significant effect on upper limb function (composite measure) (Laver et al. 2017). In addition, studies utilizing purpose-designed VEs (17 studies) showed significant benefits compared to conventional therapy while those utilizing CG systems (7 studies) did not; even though no significant subgroup differences between the two types of systems were found (Laver et al. 2017). The most recent VR meta-analysis (Aminov et al. 2018) concluded that VR therapy has small to medium effects on ICF's Body Function (27 studies) and also Activity (29 studies) outcomes while Participation (5 studies) outcome did not reach the significance level when compared to conventional therapy. These results were also reported earlier by Palma and colleagues (Palma et al. 2017). Similar to the above, these benefits were only observed in purpose-designed VE systems and not the CG systems (Aminov et al. 2018).

2.4.1.1 VR and Impairment Severity

Most of the studies on VR include stroke patients with mild-to-moderate impairment (Saposnik and Levin 2011) as probably more challenging severely affected patients cannot utilize VR effectively. In terms of severity of impairment, stroke patients with mild-to-moderate upper limb impairment benefited quite more from VR (small effect size) than those with moderate-to-severe impairment (Laver et al. 2017). Stroke patients with moderate-to-severe UL impairment do not benefit from VR rehabilitation probably due to the VR systems' nature of not being able to provide direct movement assistance to moderate-to-severe stroke patients with none/limited UL movement.

2.4.2 VR and Motivation

One goal in stroke rehabilitation is to encourage stroke subjects to move their arm beyond their usual limits of motion. To achieve this, a highly motivating scene with augmented feedback or rewards allows continuation of active training of patients, resulting possibly in increased quantity and quality of movement. Despite the lack of a common view about motivation between clinicians, it is commonly believed that motivation plays an important role in rehabilitation outcome (Maclean et al. 2000). It has been shown that highly motivated stroke patients take an active role in their rehabilitation program and also are keen to understand the goal and nature of the rehabilitation program (Maclean et al. 2000). This active engagement in the program is attributed to motivation while passivity is attributed to the lack of motivation (Colombo et al. 2012). The most common perceived barriers of stroke patients to physical exercise were reported to be physical impairments, lack of motivation and environmental factors (Nicholson et al. 2013; Damush et al. 2007). Furthermore, the most common perceived facilitators to physical exercise were reported to be motivation, social support and planned activities (Damush et al. 2007). In other words, motivation

plays a key role in participation of stroke patients in physical exercise. From the barriers and facilitators mentioned previously, motivation, environmental factors and planned activities can all be addressed in a VR system.

Some of the factors that affect patients' motivation are "the difficulty level of the motor task", repetitive nature of the task (high number of repetitions lowers motivation), awareness of the patients about the task goals, and level of feedback provided about patient's performance during/after the task (Colombo et al. 2012). The latter one, i.e. feedback, has been shown to play an important role on motivation.

2.4.3 Feedback in VR

Sensory information related to a motor behaviour can be divided into two general categories based on their relative timing to that motor behaviour: *feedforward* and *feedback* (Winstein 1991). Feedforward sensory information are those that are received prior to the movement and used for movement execution planning. On the other hand, sensory feedback information are received during and after the movement and can be categorized into two types: *intrinsic* and *extrinsic* feedback (Magill and Anderson 2016; Winstein 1991). Intrinsic feedback is the sensory feedback that is inherent to the action and naturally available from each one of the sensory system like visual, proprioceptive, kinesthetic, cutaneous, vestibular, and auditory signals. On the other hand, extrinsic feedback is the information provided about the action from an external source to the action performer and can be delivered concurrently, immediately following the action or in a delayed fashion (Magill and Anderson 2016; Winstein 1991). As this type of feedback is additional to intrinsic feedback, it is also called *augmented feedback*. When the extrinsic/augmented feedback is about the characteristics of the movement components, it is called *Knowledge of Performance* (KP) and when it is about the end results of the movement and how well it was done, it is called

Knowledge of Results (KR) (Sharma et al. 2016). Augmented feedback is an intrinsic part of any VR system and delivering both KR and KP to the task performer is aligned with motor learning principles. To better realize the difference between KR and KP, consider a VR system designed for stroke patients with partial movement to practice a reaching task to different targets. Following the completion of a trial, displaying the percentage of the movement completion to the target of interest is the KR of the reaching task. Displaying information about the speed and movement trajectory is the KP of the reaching task. Figure 2-4 summarizes what has been discussed about different levels and categories of feedback.

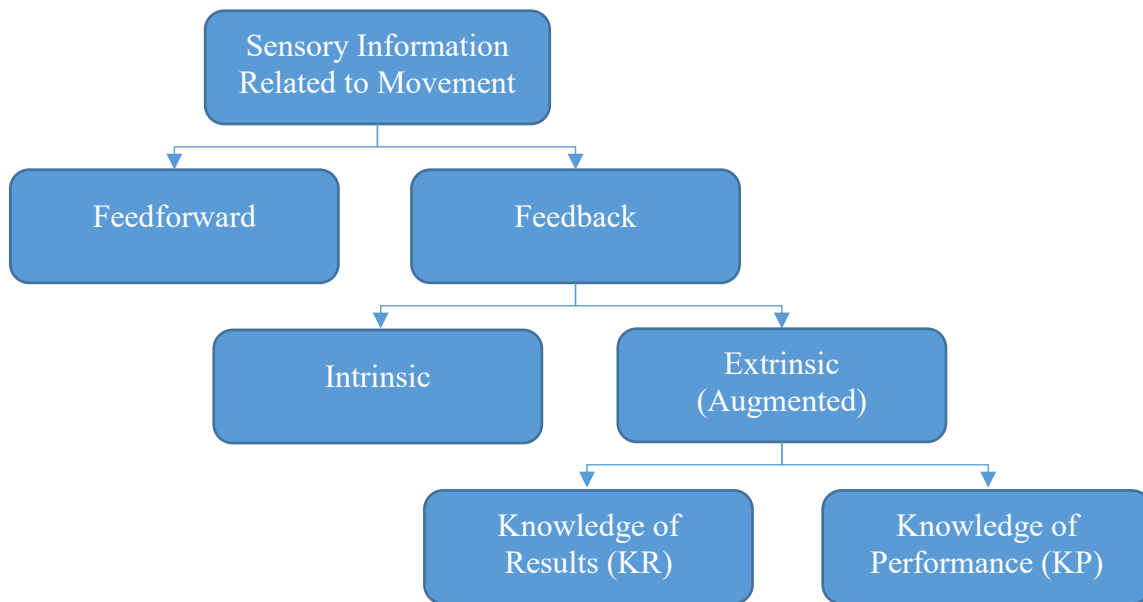


Figure 2-4: Sensory information related to a movement. Categorization of feedback is illustrated in this chart.

2.5 Summary

“If I can’t do it once, why do it a hundred times?” This quote is from a hemiplegic patient with severe UL impairment in reference to conventional therapy training and comparing it with practice in RT, by saying “I could actually do it!” (Reinkensmeyer and Housman 2007). It shows how

stroke patients with severe UL impairment lose their interest in training when they cannot complete a given task. Robots can help them in this regard as they are enablers; they let stroke patients move their arms beyond their usual limits of motion and therefore removes the feeling of disappointment due to not being able to perform a simple task such as reaching. In addition, RTs (with proper training protocol) encourage stroke patients to push themselves a bit more in every repetition. While for mild-to-moderate stroke patients, other treatment protocols and systems such as CIMT and VR are helpful, the only option left for stroke patients with moderate-to-severe UL impairment might be robotics. As discussed, the use of robotics by itself does not translate into better therapy for individuals with stroke; that being said, RT can deliver highly repetitive therapeutic tasks with minimal supervision of a therapist. Additional sessions of RT improve UL motor recovery. However, the key to a successful use of RT is to integrate it with a proper practice environment; this environment can be either real or virtual. When RT is combined with a VE and/or proper feedback, it might be the answer for retraining the stroke survivors with moderate-to-severe upper limb impairment. But it remains to be determined whether movements made in a virtual environment are similar to those made in a physical environment during RT. In the following chapters, we investigate the effectiveness of RT based on current evidence in the literature and then focus on effect of environment, whether physical or virtual, and a new RT protocol for this population.

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Chapter Three : EFFECTS OF ROBOT-ASSISTED THERAPY ON STROKE REHABILITATION IN UPPER LIMBS: SYSTEMATIC REVIEW AND META-ANALYSIS OF THE LITERATURE

3.1 Preface

In this manuscript, we examined the effectiveness of robot-assisted therapy based on the high-quality studies available at the time when this manuscript was published. This manuscript was published in Journal of Rehabilitation Research and Development (JRRD). As stated by the JRRD, “Contents of the Journal of Rehabilitation Research and Development are within the public domain.”. Therefore, no permission was required for including this manuscript in the thesis.

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3.2 Abstract

We systematically reviewed and analyzed the literature to find randomized controlled trials (RCTs) that employed robotic devices in upper-limb rehabilitation of people with stroke. Out of 574 studies, 12 matching the selection criteria were found. The Fugl-Meyer, Functional Independence Measure, Motor Power Scale, and Motor Status Scale outcome measures from the selected RCTs were pooled together, and the corresponding effect sizes were estimated. We found that when the duration/intensity of conventional therapy (CT) is matched with that of the robot-assisted therapy (RT), no difference exists between the *intensive* CT and RT groups in terms of motor recovery, activities of daily living, strength, and motor control. However, depending on the stage of recovery, extra sessions of RT in addition to regular CT are more beneficial than regular CT alone in motor recovery of the hemiparetic shoulder and elbow of patients with stroke; gains are similar to those that have been observed in intensive CT.

3.3 Introduction

According to the World Health Organization, a stroke, also known as a cerebrovascular accident (CVA), is a sudden ischemic or hemorrhagic interruption in the blood flow supplying oxygen and nutrients to brain tissue. This event results in brain cell death and, consequently, partial loss of neurological function (World Health Organization 2010). The occurrence of strokes has been progressively increasing. Currently, stroke is “the leading cause of adult disability in Western countries” (Carolei et al. 2002) and one of the most common causes of death in the world (World Health Organization 2004). The majority of people with stroke live with long-term disabilities leading to serious social and economic impacts. It is estimated that the direct and indirect cost of stroke care for the 6.5 million people living with the disability in the United States (American Heart Association 2009) was \$73.7 billion for 2010 (Lloyd-Jones et al. 2010). According to

“Tracking Heart Disease and Stroke in Canada” for 2009, stroke and heart diseases cost more than \$22.2 billion annually (Heart & Stroke Foundation 2009). These numbers will continue to rise as the population ages and people live longer.

Depending on the magnitude and severity of the problem, people with stroke experience a variety of motor, sensory, and cognitive disabilities. A majority of patients have impaired upper-limb (UL) motor function following stroke and have difficulty in independently performing activities of daily living (ADL) (Kwakkel et al. 2003; Prange et al. 2009). Therefore, one of the challenging aspects of stroke rehabilitation is UL intervention. Studies have shown that only 6 to 10 percent of people with stroke who have severe paralysis achieve a full recovery by 6 months (Wade and Hewer 1987), and only 18 percent of them regain full UL function (Nakayama et al. 1994). While the initial degree of stroke and paresis severity is a good predictor of UL function recovery (Jørgensen et al. 1995; Kwakkel et al. 2003; Wade et al. 1983), task-specific, high-intensity exercises in an active, functional, and highly repetitive manner over a large number of trials have been shown to enhance motor recovery, even in chronic stages of stroke (Fasoli et al. 2003). Studies on the dose-response relationship in stroke rehabilitation have shown that more intensive therapy is associated with enhanced rate of motor recovery; additionally, no ceiling effect for intensity of therapy has been observed (Huang et al. 2009; Kwakkel 2006; Langhorne et al. 1996). Despite these findings, traditional therapies are still not delivered more intensively or frequently, often because of cost and labor limitations (Nef et al. 2009). In addition, traditional “hands-on” interventions can, at times, result in repetitive strain injuries and excessive fatigue for therapists, thus leading to possible failure in delivery of highly intensive and repetitive training (Hidler et al. 2005). Moreover, major intra- and inter-individual variability exists in the application of manual therapy, leading to inconsistent outcomes.

One of the novel and rapidly expanding technologies in post-stroke rehabilitation for enhancing the recovery process and facilitating the restoration of function is robot-assisted therapy (RT). Rehabilitation robotics has some advantages over conventional treatment approaches. Advanced and intelligent robotic devices are able to provide consistent training and to measure performance with high reliability and accuracy (Dobkin 2004). Most importantly, robots may allow patients to train more independently and with less supervision from a therapist (Kwakkel et al. 2008).

Compared with the research and development in conventional therapy (CT) techniques, the cost, effort, and time required for the research and development in rehabilitation robotics are significantly higher. Therefore, an important element in further development of therapeutic robots and RT programs is determining whether RT is more effective than CT, based on the scientific evidence extracted from the literature. A systematic review is a rigorous methodology for gathering, synthesizing, and evaluating available scientific evidence (Oxman et al. 1993). Therefore, the main objective of this article was to systematically analyze the literature to find evidence regarding the effectiveness of RT compared with CT in improving motor recovery and functional abilities of the paretic UL of patients with stroke. The following question presents the goal of this review in PICO (population, intervention, comparison, and outcome) format: “In post-stroke individuals, does RT, as compared with CT, improve UL motor recovery and functional ability?”

3.4 Methods

3.4.1 Search Strategy

Eleven scientific databases were systematically searched through their online search engines; these databases were MEDLINE (Medical Literature Analysis and Retrieval System Online; 1947 to July 2, 2010), CINAHL (Cumulative Index to Nursing and Allied Health Literature; 1982 to July

2, 2010), EMBASE (Excerpta Medica Database; 1947 to July 2, 2010), Cochrane CENTRAL (Central Register of Controlled Trials; Issue 3, July 2010), Cochrane Database of Systematic Reviews (Issue 7, July 2010), REHABDATA (Disability and Rehabilitation Literature Database; July 2, 2010), OTseeker (Occupational Therapy Systematic Evaluation of Evidence; last updated May 28, 2010), DARE (Database of Abstracts of Reviews of Effects; July 2, 2010), Physiotherapy Evidence Database (PEDro) (July 2, 2010), AMED (Allied and Complementary Medicine Database; 1985 to July 2, 2010), and PsycINFO (Psychological Information Database; 1967 to July 2, 2010). No start date limit was set on the search criteria of the databases, but the end date was the first week of July 2010.

The following key words were used in the searches and the corresponding Medical Subject Headings (MeSH) terms were selected and “exploded” during the search. The general search strategy was as follows:

- Search 1: Cerebrovascular Accident, Cerebral Vascular Accident, CVA, Stroke* (combined by OR operator).
- Search 2: Hemiplegia, Hemiparesis, Paresis, Hemip* (combined by OR operator).
- Search 3: Robotics, Robot* (combined by OR operator).
- Search 4: Upper Extremity*, Upper Limb*, Arm* (combined by OR operator).
- Final Search: ((Search 1 OR Search 2) AND (Search 3 AND Search 4)).

In addition to the database searches, related reviews found during the search were examined and related publications included in the search results.

3.4.2 MeSH Terms Definition

Stroke is defined as “A group of pathological conditions characterized by sudden, non-convulsive loss of neurological function due to BRAIN ISCHEMIA or INTRACRANIAL HEMORRHAGES. Stroke is classified by the type of tissue NECROSIS, such as the anatomic location, vasculature involved, etiology, age of the affected individual, and hemorrhagic vs. non-hemorrhagic nature.” (PubMed MEDLINE: MeSH database, 2008).

Robotics is defined as “The application of electronic, computerized control systems to mechanical devices designed to perform human functions. Formerly restricted to industry, but nowadays applied to artificial organs controlled by bionic (bioelectronic) devices, like automated insulin pumps and other prostheses.” (PubMed MEDLINE: MeSH database, 1987).

Upper Extremity is defined as “The region of the upper limb in animals, extending from the deltoid region to the *HAND*, and including the *ARM*; *AXILLA*; and *SHOULDER*.” (PubMed MEDLINE: MeSH database, 2003).

3.4.3 Study Selection Criteria

The titles and abstracts of the studies found in the search were read independently by two of the reviewers. Based on the following criteria, suitable studies were included for the review. The reviewers had regular meetings about their findings, and in case of disagreement between the two reviewers, the third reviewer was consulted.

The inclusion criteria were:

- Participants were adult patients with stroke.
- Robot was used in the experimental protocol.
- RT was aimed at motor recovery, function, or control of the UL.

- Relevant outcomes measuring functional or motor recovery of the UL were used.
- Study was a randomized controlled trial (RCT).
- Control group received CT (either standard/usual care or intensive).
- Article was published in a peer-reviewed journal.

The exclusion criteria were:

- Studies that only compared two different RT techniques or devices.
- Robotic device was not used as a therapeutic tool.
- Pre-Post design studies.

The searches were not limited to the English language; articles published in languages other than English were examined by using their English abstracts or online translated versions of their abstracts.

3.4.4 Methodological Quality Assessment

The methodological quality of the chosen RCTs was evaluated using the PEDro scale (Physiotherapy Evidence Database 1999). Therapists and technicians who administer and supervise RT and CT know which subjects belong to the RT group and which ones to the CT group and are well aware of any assistance from the robotic device during the experimental sessions; therefore, it is very difficult in these studies to have a blinded therapist. In some studies, control groups were exposed to the robotic device in its passive mode (not assisting the patient), but even in these cases, non-assistance from the robot cannot be hidden from the person providing the intervention. Therefore, while the maximum score for the PEDro scale is 10, as the therapists and technicians providing the intervention cannot be blinded, the maximum possible score for the

PEDro scale in this case is 9. For this reason, studies with PEDro scores higher than 5 were considered of high quality in this review.

3.4.5 Data Extraction

The selected publications were reviewed and the following information was extracted from them:

- Descriptive information about subjects in the experimental and control groups
 - age, sex, number of subjects, stroke type, time from stroke onset, inclusion and exclusion criteria.
- Outcome measures
 - outcomes, mean and standard deviation of the changes in the outcome measures post-intervention.
- Intervention information in both groups
 - type of robot, intervention methodology, duration of the interventions.
- Statistically significant differences in outcome measures between RT and CT groups reported in the studies.

3.4.6 Data Analysis

Two outcome measures were selected for the analysis of motor and functional recovery of patients with stroke after RT in this review. The Fugl-Meyer (F-M) assessment (Fugl-Meyer et al. 1975; Gladstone et al. 2002) is a performance-based motor impairment index that measures motor recovery post-stroke. The F-M UL motor score is commonly used as the main outcome measure in rehabilitation robotics research. The Functional Independence Measure (FIM) (Keith et al. 1987) is a disability scale commonly used in RT research to assess abilities for ADL. Therefore, the primary outcome measures of interest for statistical analysis using data pooling were the UL

section of the F-M and the FIM. The statistical information about the changes in the F-M and FIM scores between admission and discharge were extracted, if available, or estimated from the selected RCTs. The effect size of each study was determined, and all of them were pooled together for calculating the summary effect size. In addition, 95 percent confidence intervals (CIs) were calculated. For this meta-analysis, we used Cochrane RevMan (version 5) software (The Cochrane Collaboration/The Nordic Cochrane Centre; Copenhagen, Denmark).

In addition, when available, Motor Power Scale (MPS) values, which measure strength in proximal muscles of the UL, and Motor Status Scale (MSS) values, which measure isolated movements of the UL, were pooled together.

3.5 Results

Figure 3-1 summarizes the selection process of the RCTs included in this review. From the systematic literature search, 574 records were retrieved from all the databases mentioned (286 records from EMBASE, MEDLINE, PsycINFO, and AMED after automatic removal of duplicate records by the Ovid search engine, 85 from CINAHL, 32 from the Cochrane databases, 3 from DARE, 30 from OTseeker, 100 from REHABDATA, and 38 from PEDro). By screening the titles and abstracts of these records, we selected only 44 relevant studies for further detailed review. Out of these 44 studies, 4 RCTs were excluded because RT groups were compared with control groups that received treatments other than CT (Table 3-4 in the Appendix), 14 of them were review studies (Table 3-5 in the Appendix), 8 did not meet the inclusion-exclusion criteria (Table 3-6 in the Appendix), and 6 presented preliminary results or were related to the included RCTs (Table 3-7 in the Appendix).

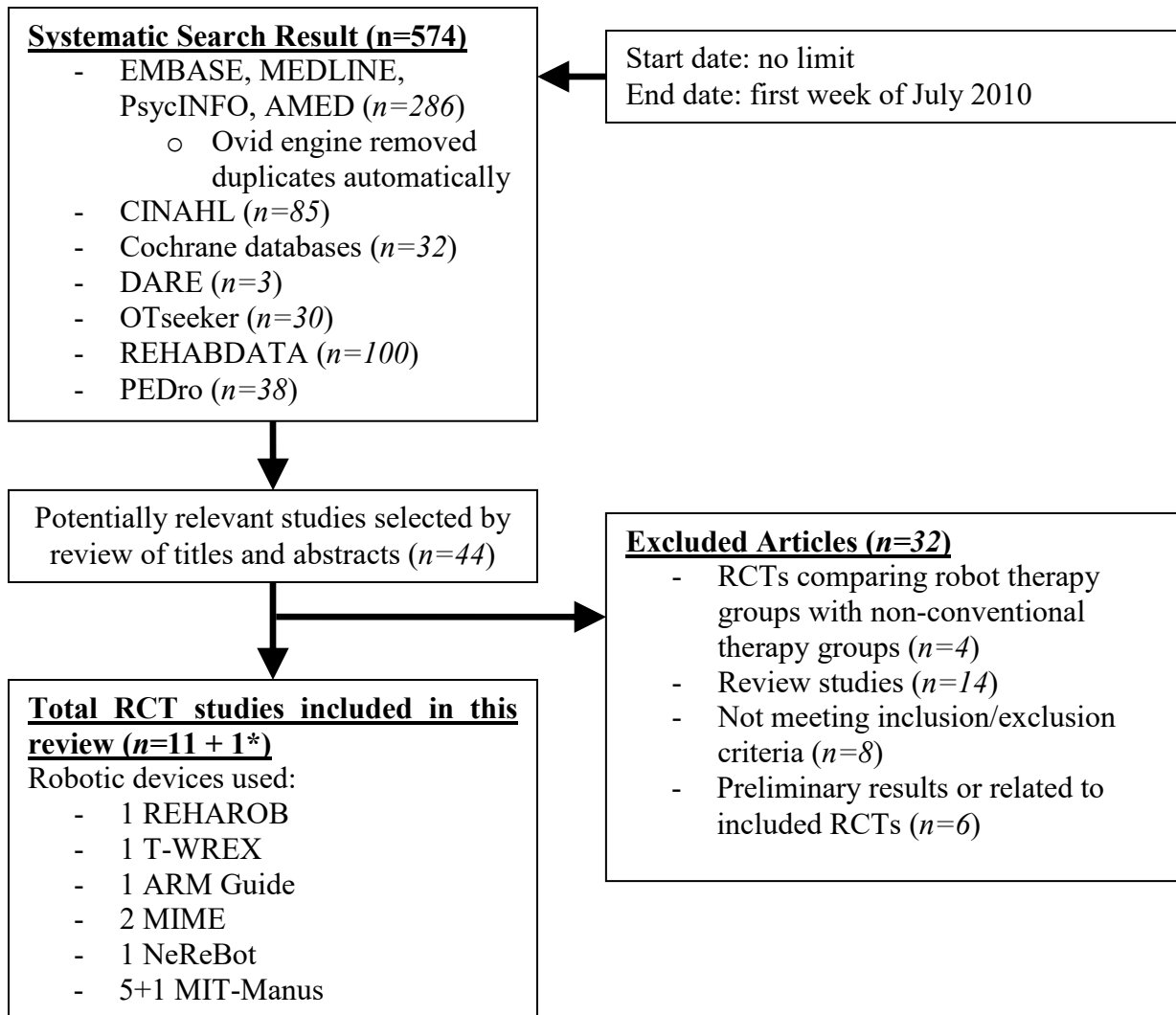


Figure 3-1: Flow diagram of selection process of randomized controlled trials (RCTs) included in this review. *One study is a follow-up of another included RCT.

Based on the inclusion-exclusion criteria, 11 RCTs (plus 1 follow-up study (Volpe et al. 1999) of another included RCT (Aisen et al. 1997)) were qualified for inclusion in this review. A summary of the included studies is shown in Table 3-1 with information about the participants, the robotic device, and the outcome measures that is of particular interest for this review.

The participants with stroke in these RCTs ranged from acute to chronic at the time of admission to the experiments. Six robotic instruments were used in these RCTs: REHAROB (Fazekas et al.

2007), T-WREX (Housman et al. 2009), ARM-Guide (Kahn et al. 2006b), MIME (Lum et al. 2002; Lum et al. 2006), NeReBot (Masiero et al. 2007b), and MIT-Manus (Aisen et al. 1997; Lo et al. 2010; Rabadi et al. 2008; Volpe et al. 2000; Volpe et al. 1999; Volpe et al. 2008). Most of the studies (and most robots) focused on the restoration of proximal UL function. One study compared three RT groups with CT to investigate the effect of bilateral RT (Lum et al. 2006); in our analysis, only the data from the unilateral RT group has been used. The other RCTs also focused on unilateral RT (except one (Lum et al. 2002) that incorporated bilateral therapy in addition to unilateral therapy inside the RT program).

Table 3-1: Characteristics of selected randomized controlled trials.

Study	N (sex)		Age (year) Mean $\pm$ SD (Range)		Months/ ^{weeks} / ^{day} Post-Stroke Mean $\pm$ SD or (Range)		Stroke Stage at Admission	Robotic Device	Outcome Measures of Interest
	RT(M/F)	CT(M/F)	RT	CT	RT	CT			
[Fazekas et al., 2007]	15(7/8)*	15(10/5)†	56.6 $\pm$? (28–82)	55.9 $\pm$? (28–77)	23.2 $\pm$? (1.2–87)	9.5 $\pm$? (1.1–44)	not stated (subacute/chronic)	REHAROB	F-M (s/e), FIM (self-care)
[Housman, Scott, and Reinkensmeyer, 2009]	14(11/3)	14(7/7)	54.2 $\pm$ 11.9	56.4 $\pm$ 12.8	84.5 $\pm$ 96.3	112.4 $\pm$ 128.5	chronic	T-WREX	F-M (UE)
[Kahn, Zygmant et al., 2006]	10(4/6)	9(7/2)	55.6 $\pm$ 12.2	55.9 $\pm$ 12.3	75.8 $\pm$ 45.5	103.1 $\pm$ 48.2	chronic	ARM Guide	Ch-McM (arm)
[Lum et al., 2002]	13(12/1)	14(8/6)	63.2 $\pm$ 3.6	65.9 $\pm$ 2.4	30.2 $\pm$ 6.2	28.8 $\pm$ 6.3	chronic	MIME	F-M (UE), FIM (self-care)
[Lum et al., 2006] ‡	10(9/1) 9(5/4) 5(2/3)	6(4/2)	62.3 $\pm$ 2.8 69.8 $\pm$ 4.0 72.2 $\pm$ 11.7	59.9 $\pm$ 5.5	[13.0 $\pm$ 2.1] wk [10.0 $\pm$ 1.9] wk [6.2 $\pm$ 1.0] wk	[10.6 $\pm$ 2.7] wk	sub-acute	MIME	F-M (UE), FIM (self-care), MSS, MPS
[Masiero, Celia et al., 2007]	17(10/7)	18(11/7)	63.4 $\pm$ 11.8	68.8 $\pm$ 10.5	[= 1 week]	[= 1 week]	acute	NeReBot	F-M (s/e/c, w/h), FIM (self-care)
[Aisen et al., 1997] ?	10(5/5)	10(6/4)	58.5 $\pm$ 8.3	63.3 $\pm$ 10.6	[2.8 $\pm$ 1.1] wk	[3.3 $\pm$ 1.2] wk	acute	MIT-Manus	F-M (UE), FIM (self-care), MSS, MPS
[Volpe et al., 1999] ?	6(4/2)	6(3/3)	54 $\pm$ 7.3	66 $\pm$ 4.9	"14.8 $\pm$ 4.4" d	"19.5 $\pm$ 7.8" d	?	MIT-Manus	F-M (s/e/c, w/h), FIM (self-care), MSS, MPS
[Volpe et al., 2000]	30(16/14)	26(14/12)	62 $\pm$ 11	67 $\pm$ 10.2	"14.0 $\pm$ 4.9" d	"15.8 $\pm$ 6.6" d	acute	MIT-Manus	F-M (s/e/c, w/h), FIM (motor), MSS, MPS
[Volpe et al., 2008]	11(8/3)	10(7/3)	62 $\pm$ 3	60 $\pm$ 3	[35 $\pm$ 7] wk	[40 $\pm$ 11] wk	chronic	MIT-Manus	F-M (s/e/c, w/h), MPS
[Rabadi et al., 2008]	10(5/5)	10(5/5)	79.5 $\pm$ 6.2	67.8 $\pm$ 12.7	"19.0 $\pm$ 4.7" d	"22.5 $\pm$ 18.2" d	acute	MIT-Manus	F-M (UE), FIM (motor), MSS, MPS
[Lo et al., 2010] §	49(47/2)	50(48/2) 28(27/1)	66 $\pm$ 11 (44–95)	64 $\pm$ 11 (28–86) 63 $\pm$ 12 (42–88)	3.6 $\pm$ 4.0 (0.6–19.8)	4.8 $\pm$ 4.0 (0.5–15.7) 6.2 $\pm$ 5.0 (0.5–23.6)	chronic	MIT-Manus	F-M (UE)

* 13 stroke and 2 traumatic brain injury. † 9 stroke and 6 traumatic brain injury. § 2 CT groups (top to bottom): Intensive Comparison Therapy and Usual Care.

‡ 3 RT groups (top to bottom): Robot-Combined, Robot-Unilateral, and Robot-Bilateral.

? [Volpe et al., 1999] is the follow-up study of [Aisen et al., 1997].

F-M: Fugl-Meyer, UE: Upper Extremity, s/e/c: Shoulder/Elbow/Coordination, w/h: Wrist/Hand; Ch-McM: Chedoke-McMaster Stroke Assessment;

FIM: Functional Independence Measure; MSS: Motor Status Scale; MPS: Motor Power Scale; RT: Robot Therapy; CT: Conventional Therapy; M: Male; F: Female

3.5.1 Summary of Robotic Devices

Among the wide variety of robotic devices that have been developed and used for stroke rehabilitation, those employed in the selected RCTs were the following:

- MIT-MANUS shoulder and elbow module is a two-degree-of-freedom robot allowing patients to perform reaching movements in the horizontal plane (Krebs et al. 1998). The wrist module of MIT-MANUS is a three-degree-of-freedom robotic device allowing

abduction-adduction, flexion-extension, and pronation-supination (Charles et al. 2005). The system also includes an antigravity module for vertical movements and a grasp-hand module for closing and opening movements (Lo et al. 2010). The device provides assistive or resistive forces as well as a passive mode, enabling patients to train their shoulder, elbow, and wrist.

- MIME, or “Mirror Image Movement Enabler,” is a robotic device with six degrees of freedom (Lum et al. 2002). MIME applies assistance or resistance forces to the patient’s paretic forearm. In bimanual mode, the robot helps patients move their affected arm in a pattern that mirrors that of the less affected arm.
- ARM-Guide, or “Assisted Rehabilitation and Measurement Guide,” is a four-degree-of-freedom robotic device developed by Kahn et al. (Kahn et al. 2001) that allows patients with stroke to reach along a linear track.
- T-WREX, or “Therapy Wilmington Robotic Exoskeleton,” was developed at the University of California-Irvine. T-WREX is a five-degree-of-freedom passive antigravity orthosis with a computer workstation (Sanchez et al. 2004). This device allows patients to exercise in a more functional way.
- NeReBot or “NEuro REhabilitation Robot,” (Fanin et al. 2003) is a three-degree-of-freedom robot, designed and built at Padova University. The robot system comprises a set of three nylon cables attached to a rigid orthosis, which is independently controlled by three direct-current motors.

3.5.2 Methodological Quality Assessment

The results of the methodological quality assessment using the PEDro scale are summarized in Table 3-2. The PEDro scores ranged from 2 to 7. All studies were considered high quality except

Fazekas et al. (Fazekas et al. 2007), which had a PEDro score of 2; as a result of the low PEDro score and also because the statistical information for the “between group comparisons” and “point estimates and variability” was not included, this study was excluded from further analysis. In two of the studies, some of the baseline values were not comparable between the groups. In Lum et al. (Lum et al. 2006), three robotic groups were compared with the control group; the baseline values of the Modified Ashworth Scale and MSS Synergy Scale for two of the robotic groups were different, and therefore, between-groups comparison was not performed for these two outcome measures. In the second study, Rabadi et al. (Rabadi et al. 2008), even though several baseline values were different between the groups, the confounding effects of baseline difference in age, stroke type, and some of the outcome measures were adjusted during the statistical analysis.

3.5.3 Quantitative Analysis

In order to compare the motor recovery in patients with stroke between RT and CT groups, nine of the selected studies used changes in F-M score, while one study used the Chedoke-McMaster measure for quantifying motor recovery (Kahn et al. 2006b); this study has therefore been excluded from the following analyses. In addition, changes in MPS and MSS scores were used in some of the studies (Aisen et al. 1997; Lum et al. 2006; Rabadi et al. 2008; Volpe et al. 2000; Volpe et al. 2008). Six of the studies used changes in the FIM to assess improvement in functional performance (Aisen et al. 1997; Lum et al. 2002; Lum et al. 2006; Masiero et al. 2007a; Rabadi et al. 2008; Volpe et al. 2000). Therefore, the focus of the quantitative analysis was on the F-M, FIM, MPS, and MSS measures.

Table 3-2: Quality assessment of selected randomized controlled trials using Physiotherapy Evidence Database (PEDro) scale: higher score implies higher quality.

Study	PEDro Items											PEDro Score
	Eligibility Criteria	Random Allocation	Concealed Allocation	Baseline Comparability	Blind Subjects	Blind Therapists	Blind Assessors	Adequate Follow-Up (Drop-out rate)	Intention-to-Treat Analysis	Between-Group Comparisons	Point Estimates and Variability	
(Fazekas et al. 2007)	No	Yes	No	No	No	No	Yes	No	No	No	No	2
(Housman et al. 2009)	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5
(Kahn et al. 2006b)	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5
(Lum et al. 2002)	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
(Lum et al. 2006)	Yes	Yes	No	No	No	No	Yes	Yes	No	Yes	Yes	5
(Masiero et al. 2007b)	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
(Aisen et al. 1997) & (Volpe et al. 1999)*	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	6
(Volpe et al. 2000)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7
(Volpe et al. 2008)	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
(Rabadi et al. 2008)	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	6
(Lo et al. 2010)	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6

* (Volpe et al. 1999) is the follow-up study of (Aisen et al. 1997).

When the effectiveness of RT versus CT is compared, two factors may affect the outcome measures of interest. The first factor is the duration/intensity of the therapy in the RT and CT groups (whether they are the same or the RT group received additional therapy) and the second one is the stage of stroke recovery (acute/subacute or chronic) of the participants in the studies. Table 3-3 categorizes the studies based on these two factors. Matching of duration/intensity in RT and CT groups for the studies shown in the first column of Table 3-3 refers to the same treatment

time per session and the same total number of sessions; in two of the studies (Lo et al. 2010; Rabadi et al. 2008) the same form of treatment was administered, and in one study (Lo et al. 2010), even the number of movements between the RT and CT groups was matched. All these parameters are referred as “duration/intensity” in the text. The data pooling analyses were run independently for each factor since, to our knowledge, no two-way meta-analysis technique exists.

Table 3-3: Study categorization based on two factors that affect outcome measures of interest.

Stroke Stage	Duration/Intensity of RT vs CT	
	Same	Additional
Acute/Subacute	Lum et al. Rabadi et al.	Aisen et al. Masiero et al. Volpe et al.
Chronic	Housman et al. Lo et al. Lum et al. Volpe et al.	Lo et al.
CT = conventional therapy, RT = robot-assisted therapy.		

Since the selected RCTs used different robotic devices, methodology, and subscales of outcome measures, we used the *random-effects* technique in the following meta-analyses to consider the potential effect of heterogeneity, i.e., potential variability among the selected RCTs. Also, in studies in which the standard deviation or mean of change of the outcome measures of interest has not been directly reported, calculated or estimated values were used in the meta-analyses. For illustration of the meta-analyses results, we included *forest plot* graphics in which the location of the filled square, its width, and its size represent the mean of change in the outcome measure of interest between RT and CT, its 95 percent CI, and the weight of each study in that meta-analysis, respectively. The width of the diamond in a forest plot shows the 95 percent CI for the pooled results of the meta-analysis. A study weight in each meta-analysis is determined based on the

mean, standard deviation, and number of subjects in that study compared with the other studies included in the meta-analysis.

3.5.4 Fugl-Meyer Meta-Analysis

In all the selected RCTs except one (Kahn et al. 2006b), the F-M measure was used for quantification of motor recovery. This study (Kahn et al. 2006b) used the Chedoke-McMaster measure and therefore was not included in the F-M meta-analysis. Three of the studies measured the F-M UL Total score (Aisen et al. 1997; Housman et al. 2009; Lo et al. 2010), while the others reported the F-M Proximal (shoulder/elbow/coordination) and the F-M Distal (wrist/hand) scores separately (Lum et al. 2006; Lum et al. 2002; Masiero et al. 2007b; Rabadi et al. 2008; Volpe et al. 2008; Volpe et al. 2000). The latter studies did not report any significant difference between the RT and CT groups in terms of change in the F-M Distal score. Therefore, in order to pool all the F-M measurements, we assumed that the changes in the F-M Total score were mostly due to changes in the F-M Proximal score. Based on this assumption, we pooled changes in the F-M Total and F-M Proximal together in this meta-analysis. In order to further remove any potential bias caused by this assumption, we used the standardized mean difference (SMD), rather than mean difference, to normalize the scales.

In order to compare the effectiveness of RT versus CT, we performed two separate meta-analyses. In the first meta-analysis, we formed two subgroups based on the comparability of the duration/intensity of the RT and CT (i.e., additional duration/intensity for the RT group or the same duration/intensity for RT and CT). The results are shown in Figure 3-2. One study (Lo et al. 2010) compared RT with two control groups (intensive CT that matched the duration/intensity of the RT and usual CT) and has therefore been included in both subgroups. The results show that when RT is used as additional therapy, the motor recovery in RT groups is significantly higher

than CT groups ($p = 0.004$), but when the CT duration/intensity is matched with the RT, the gain is not statistically significant.

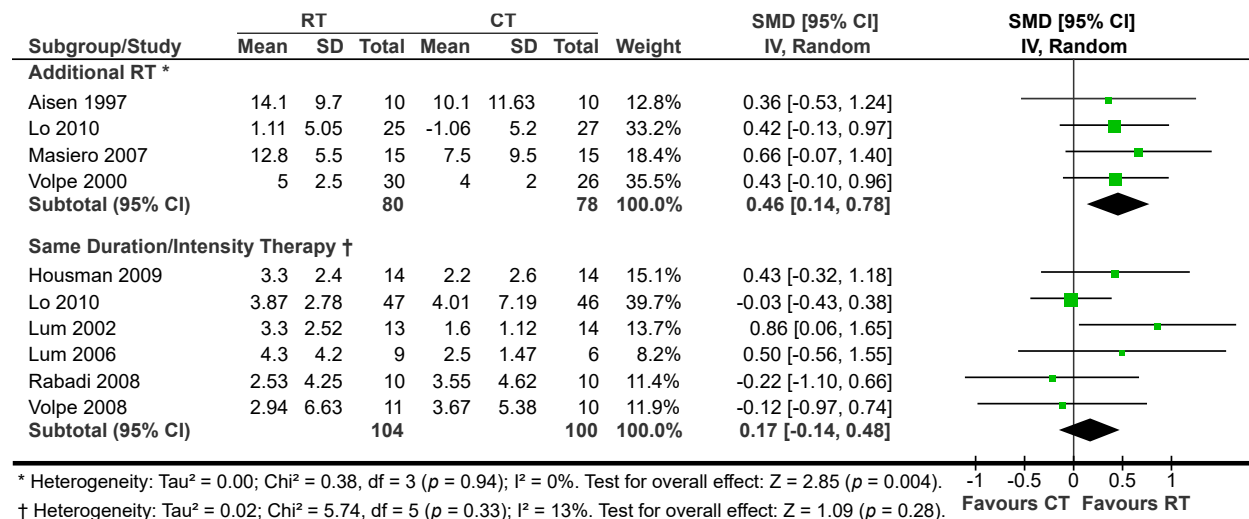


Figure 3-2: Results of changes in Fugl-Meyer (F-M) score between robot-assisted therapy (RT) and conventional therapy (CT). Two meta-analyses were performed based on relative duration/intensity of RT and CT. In these meta-analyses, standardized mean difference (SMD) of F-M Total score in (Aisen et al. 1997), (Housman et al. 2009), and (Lo et al. 2010) and SMD of F-M Proximal score in rest of studies were pooled together. CI = confidence interval, SD = standard deviation.

In the second meta-analysis, two subgroups were also formed, based on the stroke recovery stage of the participants (i.e., acute/subacute or chronic). However, as shown in Figure 3-2, the comparability of the duration/intensity of the RT and CT has a significant effect on the results. Therefore, meta-analyses were separately performed for the four factorial combinations in Table 3-3. The results are displayed in Figure 3-3 and reveal that in both early and late stages of stroke recovery when the duration/intensity of CT is matched with RT, motor recovery improvements are not statistically different between the two groups. However, the results do show that during the acute/subacute stage of stroke recovery, additional RT leads to significantly greater gains in F-M score than CT alone ($p = 0.01$). We could not perform any meta-analysis on effect of

additional RT during chronic stage because only one study was in this category (Lo et al. 2010). This study reported that gains were not statistically significantly different between additional RT and usual CT.

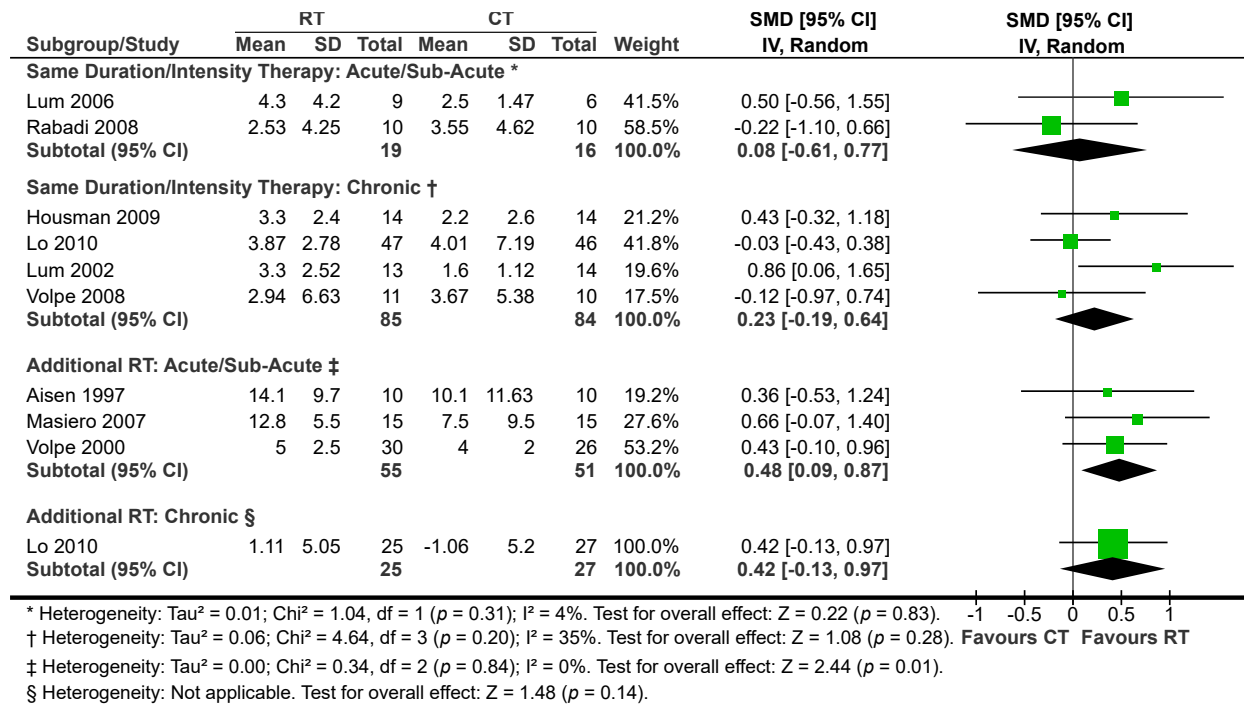


Figure 3-3: Detailed meta-analysis of changes in Fugl-Meyer score between robot-assisted therapy (RT) and conventional therapy (CT). Four subgroups based on stroke stage of participants and comparability of duration/intensity of RT and CT were formed. CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

3.5.5 Functional Independence Measure Meta-Analysis

The FIM scale has two subsections: Motor (including self-care, sphincter control, mobility/transfer, and locomotion) and Cognition (including communication and social cognition). FIM Total was measured in three of the RCTs (Aisen et al. 1997; Masiero et al. 2007b; Rabadi et al. 2008), two of which reported the FIM Motor scores as well (Masiero et al. 2007b; Rabadi et al. 2008). One study measured the FIM Motor (except for sphincter control) (Volpe et al. 2000), and two studies measured FIM self-care and transfer (Lum et al. 2006; Lum et al. 2002). Only three

studies measured the changes in FIM Cognition and reported that these changes were not different between the RT and CT groups (Masiero et al. 2007b; Rabadi et al. 2008; Volpe et al. 2000). We therefore assumed that the changes in the FIM Total and FIM Motor (or its subscales) could be pooled together for the purpose of this meta-analysis. In order to further remove any potential bias caused by this assumption, we used the SMD rather than mean difference to normalize the scales. Similar to the F-M meta-analysis, the studies for the FIM meta-analysis were placed in subgroups based on the comparability of duration/intensity of RT and CT (additional duration/intensity for RT or the same duration/intensity).

Figure 3-4 shows the results of this meta-analysis. The statistics of the pooled results in both subgroups indicate that no statistically significant difference existed between RT and CT in terms of improvement in ADL, whether applying additional RT or not.

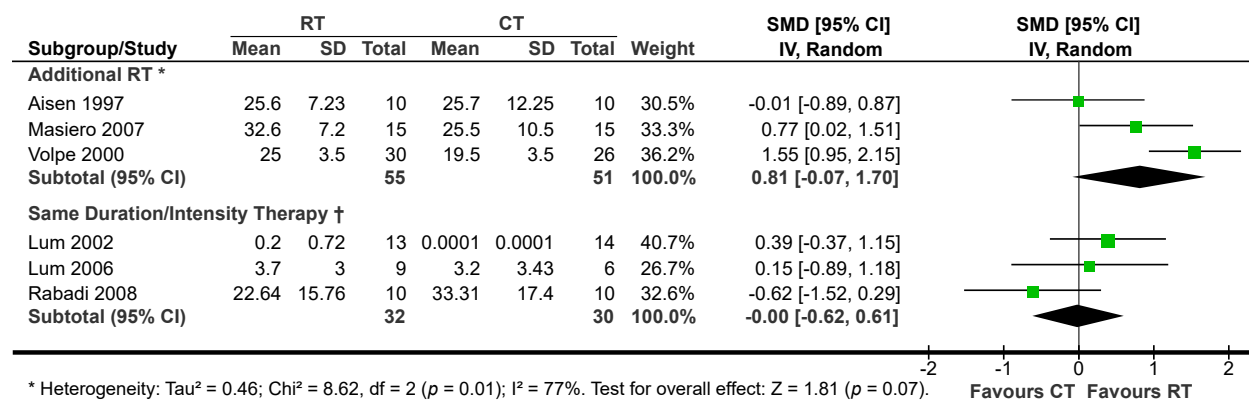
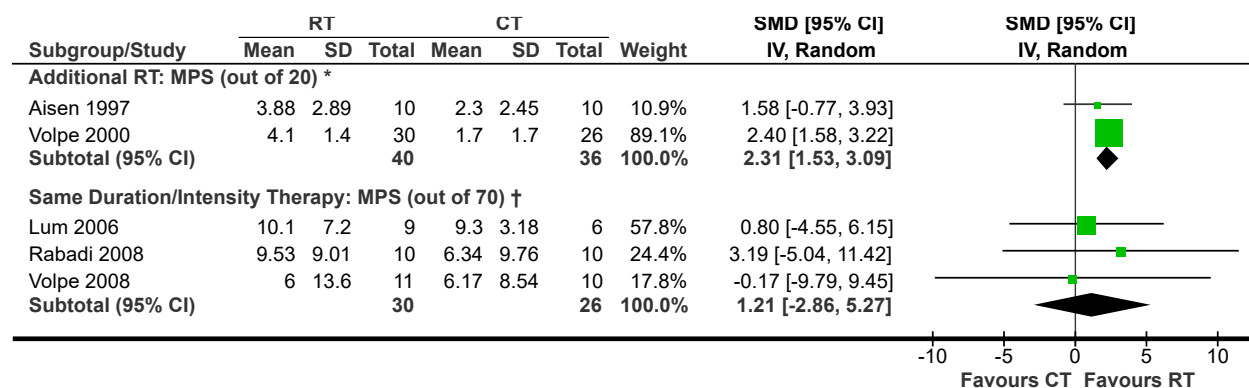


Figure 3-4: Meta-analysis of changes in Functional Independence Measure score between robot-assisted therapy (RT) and conventional therapy (CT) groups. CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

3.5.6 Motor Power Scale Meta-Analysis

Five studies used the MPS as one of the outcome measures. Two studies focused on strength in four proximal muscles of the paretic arm by assessing power in the elbow flexor and extensor (biceps and triceps) and shoulder flexor and abductor (anterior and lateral deltoid) muscles, with a

maximum score of 20 (Aisen et al. 1997; Volpe et al. 2000). However, three studies used the MPS to assess 14 movements at the scapular, shoulder, and elbow joints, with a maximum score of 70 (Lum et al. 2006; Rabadi et al. 2008; Volpe et al. 2008). Therefore, it was not possible to combine these two measurements in one group and two separate subgroups were formed. Fortunately, all the studies in the subgroup “MPS out of 20” looked at the effectiveness of additional RT and all the studies in the subgroup “MPS out of 70” were of the same duration/intensity for the RT and CT groups. Figure 3-5 shows the results of this data pooling. The mean difference has been used as the measures are the same in each subgroup. The results show that with additional RT, the gains in the MPS for 4 movements (out of 20) were significantly higher than with CT. However, no significant difference in MPS gains existed for 14 movements (out of 70) between same duration/intensity RT and CT.



* Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.42$, $df = 1$ ($p = 0.52$); $I^2 = 0\%$. Test for overall effect: $Z = 5.83$ ($p < 0.00001$).

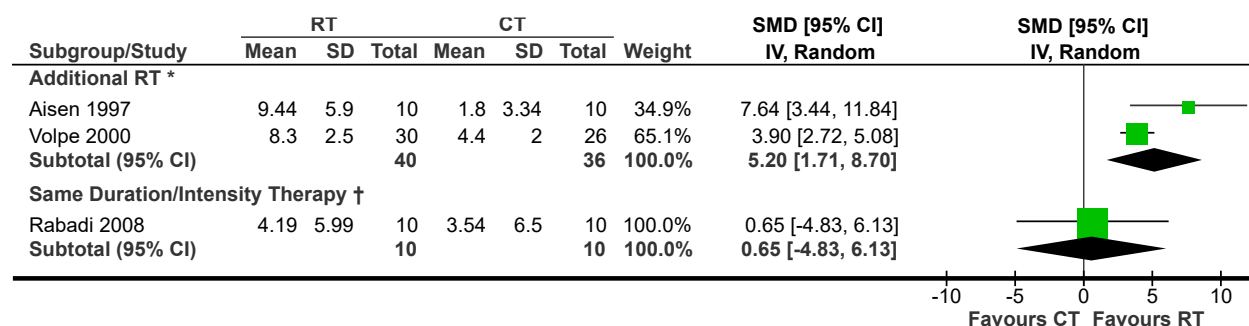
† Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.32$, $df = 2$ ($p = 0.85$); $I^2 = 0\%$. Test for overall effect: $Z = 0.58$ ($p = 0.56$).

Figure 3-5: Meta-analysis of changes in Motor Power Scale (MPS) score between robot-assisted therapy (RT) and conventional therapy (CT) groups. CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

3.5.7 Motor Status Scale Meta-Analysis

Four studies used the MSS as one of the outcome measures. One study measured MSS Synergy (Lum et al. 2006), while the other three measured MSS Shoulder/Elbow score and therefore the data could be pooled (Aisen et al. 1997; Rabadi et al. 2008; Volpe et al. 2000). However, two of

these studies (Aisen et al. 1997; Volpe et al. 2000) were additional RT and the other study (Rabadi et al. 2008) was same duration/intensity. Therefore, only the two additional RT studies (Aisen et al. 1997; Volpe et al. 2000) were pooled together in this meta-analysis (Figure 3-6). The results showed significant improvements in the MSS Proximal score in the RT group compared with the CT group when additional RT was employed. The single study with matched duration/intensity of RT and CT reported that the gain in the MSS Proximal score was not statistically significantly different (Rabadi et al. 2008).



* Heterogeneity: $\tau^2 = 4.51$; $\chi^2 = 2.82$, $df = 1$ ($p = 0.09$); $I^2 = 65\%$. Test for overall effect: $Z = 2.92$ ($p = 0.004$).

† Heterogeneity: Not applicable. Test for overall effect: $Z = 0.23$ ($p = 0.82$).

Figure 3-6: Meta-analysis of changes in Motor Status Scale score between robot-assisted therapy (RT) and conventional therapy (CT) groups. CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

3.5.8 Follow-up Meta-Analysis

In the analysis of the follow-up data, only the F-M measure was of interest to this review. Seven studies reported long-term follow-up data after the end of study. Four of the RCTs (Housman et al. 2009; Lum et al. 2006; Lum et al. 2002; Lo et al. 2010) measured the F-M score at 6 months posttreatment. The other studies measured the follow-up data after 3 months, 8 months, and 3 years (Volpe et al. 1999; Masiero et al. 2007b; Volpe et al. 2008). For data pooling, we selected only five studies with 6 to 8 month posttreatment data. Similar to the previous meta-analyses, the comparability of duration/intensity between RT and CT was considered. Four of the studies had the same duration/intensity and included a 6 month follow-up, while only one had additional RT

and measured the follow-up at 8-months posttreatment. Figure 3-7 shows the results of this meta-analysis. The results reveal that the F-M gains in RT groups were not significantly higher when compared with the matched duration/intensity CT groups. The single study (Masiero et al. 2007b) with additional RT reported that the difference in F-M gains at 8 months follow-up between the RT and CT groups was statistically higher following RT.

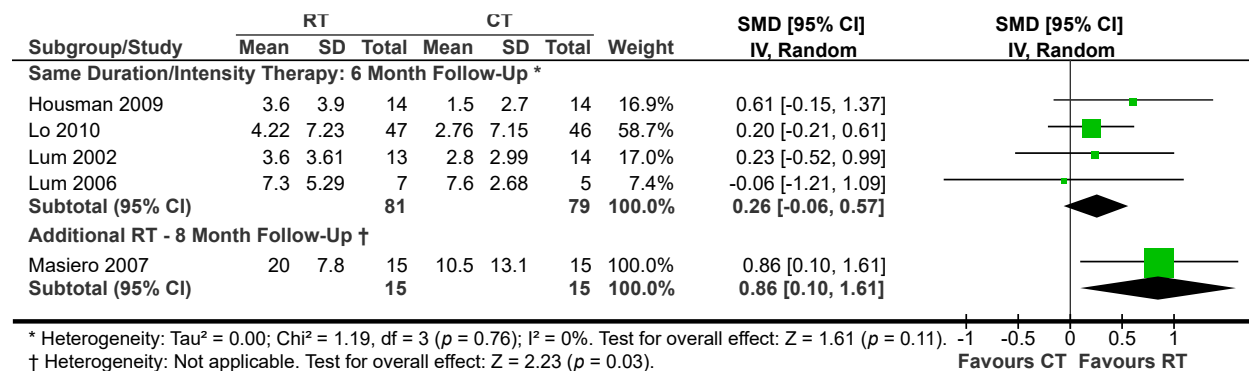


Figure 3-7: Meta-analysis of changes in Fugl-Meyer score between robot-assisted therapy (RT) and conventional therapy (CT) groups at 6- to 8-month follow-up. CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

3.6 Discussion

In this systematic review, the effect of RT in comparison with CT on improving motor recovery and functional abilities of the paretic UL of people with stroke was investigated through the use of several meta-analyses. The scope of this review is limited and does not include social robots. In summary, based on the high quality RCTs, the results suggest that when the duration/intensity of conventional rehabilitative care was matched with that of RT, no statistically significant difference existed in the F-M scores between the two groups. However, when RT techniques were applied in addition to CT, they significantly improved F-M scores after treatment compared with standard CT. The extra therapeutic duration/intensity may be the reason for this result; the high number of repetitive movements generated during RT is probably the key reason for this therapeutic effect.

The meta-analysis of the changes in F-M scores based on stroke stage indicated that, similar to what was discussed previously regarding when duration/intensity of CT was matched with that of RT, no statistically significant difference existed in motor recovery between CT and RT groups in both acute/subacute and chronic stages of stroke. However, when RT techniques were applied in addition to CT during the acute/subacute stage, significantly improved motor recovery occurred. As only one RCT (Lo et al. 2010) examined the effect of additional RT during the chronic stage of stroke, no meta-analysis could be performed and no conclusion could be drawn.

The meta-analysis of the 6 month follow-up of the F-M changes also shows that, in that case, no statistically significant difference existed in motor recovery between matched duration/intensity CT and RT. Again, as only one study examined the long-term effect of additional RT, no meta-analysis could be performed and no conclusion could be drawn (Masiero et al. 2007b). Similar to the previous results, the gains in strength, measured by the MPS, were not different between CT and RT groups when the duration/intensity of the therapies was matched and were different when additional RT was administered. Similar results were found for gains in motor control, measured by the MSS.

The F-M score used in these meta-analyses was either from the UL section or proximal UL (shoulder and elbow) section. Based on the studies that used F-M assessment at the distal level, no significant difference existed between the RT and CT groups in terms of change in F-M Distal subscore (wrist and hand level) (Lum et al. 2006; Lum et al. 2002; Masiero et al. 2007b; Rabadi et al. 2008; Volpe et al. 2008; Volpe et al. 2000). As a result, all the improvements in the F-M score from additional RT could be attributed to the proximal UL. The possible explanation for this difference is that almost none of the robotic devices discussed in this review were designed for motor improvements of the distal UL. The therapeutic program in these studies mostly focused on

the shoulder and elbow of the participants with stroke. In other words, the improvements were training specific. Likewise, the gains in both the MPS and MSS measures with additional RT were also in the proximal UL.

With regards to functional abilities (measured by the FIM), the performance of the RT groups was not different than the CT groups in both matched duration/intensity and additional RT groups. This can be explained by the fact that the focus of the RT programs was mainly on recovery of motor rather than functional abilities of the UL. Another important issue is the effect of bimanual RT in motor recovery after stroke. Only one RCT (Lum et al. 2006) investigated this factor and reported that the combined unimanual and bimanual RT program had greater gains in proximal F-M when compared with CT. Lack of RCTs dealing with this issue is evident.

All of the findings demonstrate that the effectiveness of rehabilitation robotics is similar to matched CT. It is worthwhile to clarify that when the duration/intensity of conventional rehabilitative care is matched with that of RT, this CT program is not the same as regular, standard care; it is an *intensive* CT program. Therefore, even though RT does not seem to lead to higher gains in UL function when matched with the same amount of extra CT (intensive CT), employing RT in clinical settings can be justified for several reasons. For instance, during intensive CT, the therapist might not be able to deliver the intensive program as planned and might not adjust it appropriately based on the patient's progress. This can be due to fatigue or other human-related factors. On the other hand, robots always deliver the therapeutic programs as planned and are programmed to self-adjust based on the patient's progress. The repetitive nature of therapy can be delegated to a properly designed RT program, which delivers high-intensity therapeutic tasks and a "highly reproducible motor learning experience" (Charles et al. 2005). Another reason is that RT seems more interesting and motivating to patients with stroke than CT, which might increase

collaboration, motivation, and effort by the patients with stroke in RT sessions. In other words, even though RT and intensive CT may be equivalent in terms of functional gains, combining the two may lead to increased variety of therapeutic modalities for patients. Last, but not least, there may be financial benefits when employing therapeutic robots in the long-term. For example, one therapist can setup therapeutic programs for several patients and monitor them at the same time. Nonetheless, there are limitations to the use of RT. For example, most robotic devices discussed here are planar robots (two-dimensional); they are mainly designed for shoulder and elbow movements and do not include wrist and prehension, which are frequently affected in stroke. In addition, the RT exercises are more motor-rehabilitation based techniques than function-based therapy. Furthermore, the “assist-as-needed” protocol that is used in many rehabilitation robotics studies may encourage patients to wait until the robot does the task for them.

In general, depending on the stage of recovery, highly intense therapy either by a therapist or a robotic device is associated with higher recovery rate (Kwakkel 2006; Langhorne et al. 1996; Huang et al. 2009). However, patients in general receive limited therapy from therapists in rehabilitation settings (Dewey et al. 2007; Lang et al. 2007) because of resource constraints. Thus, rehabilitation robotics fills this gap by providing the opportunity for more intense practice with minimal supervision by the therapist (Dobkin 2004).

3.7 Conclusions

This systematic review confirms that when the duration/intensity of CT is matched with RT, there is no difference between RT and (intensive) CT groups in terms of motor recovery, ADL, strength, and motor control. Nonetheless, similar to the results obtained employing intensive CT, additional sessions of RT promote better motor recovery in the UL of patients with stroke when compared with standard CT. In other words, the use of robotics by itself does not translate into better therapy

for people with stroke. Rather, robots deliver highly repetitive therapeutic tasks with minimal supervision of a therapist and these additional sessions of RT improve motor recovery of the hemiparetic shoulder and elbow of patients with stroke. Developing new function-based RT protocols, building robotic devices for rehabilitation of prehension and with more degrees of freedom, and conducting new RCTs that consider the factors discussed in this review are recommended for future studies.

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Author Contributions	
<i>Study concept and design</i>	N. Norouzi-Gheidari.
<i>Acquisition of data</i>	N. Norouzi-Gheidari, P. S. Archambault.
<i>Analysis and interpretation of data</i>	N. Norouzi-Gheidari.
<i>Drafting of manuscript</i>	N. Norouzi-Gheidari.
<i>Critical revision of manuscript for important intellectual content</i>	N. Norouzi-Gheidari, P. S. Archambault, J. Fung.
<i>Statistical analysis</i>	N. Norouzi-Gheidari.
<i>Obtained funding</i>	J. Fung, P. S. Archambault.
<i>Administrative, technical, or material support</i>	J. Fung, P. S. Archambault.
<i>Study supervision</i>	P. S. Archambault, J. Fung.
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3.9 Appendix

List of the excluded studies found during the systematic search with the reason of exclusion.

Table 3-4: Excluded RCT studies

Study	Reason for Exclusion
(Daly et al. 2005)	Control group received functional neuromuscular stimulation.
(Hesse et al. 2005)	Control group received electromyography-initiated electrical stimulation.
(Kutner et al. 2010)	Control group received Repetitive Task Practice.
(Takahashi et al. 2008)	Two groups differed according to the dose of active robotic assistance.

Table 3-5: Excluded review studies

Study	Reason for Exclusion
(Brewer et al. 2007)	Review Study
(Fasoli et al. 2004b)	Review Study
(Hesse et al. 2008)	Review Study
(Kahn et al. 2006a)	Review Study
(Krebs et al. 2000)	Review Study
(Krebs et al. 2002)	Review Study
(Krebs et al. 2007a)	Review Study
(Kwakkel et al. 2008)	Review Study
(Langhorne et al. 2009)	Review Study
(Mehrholtz et al. 2008)	Review Study
(Mehrholtz et al. 2009)	Summary of (Mehrholtz et al. 2008)
(Oujamaa et al. 2009)	Review Study
(Platz 2003)	Review Study
(Prange et al. 2006)	Review Study

Table 3-6: Excluded for other reasons

Study	Reason for Exclusion
(Casadio et al. 2009)	Pre-post design, no appropriate control group
(Colombo et al. 2005)	Comparing two robotic devices
(Dobkin 2009)	Not a clinical trial, Recommendations for future research
(Ellis et al. 2009)	Robotic device is not used as therapeutic tool
(Hu et al. 2009)	Comparing two robotic devices
(Mayr et al. 2008)	Cross-over design, comparing Robot Therapy with EMG-triggered neuromuscular electrical stimulation
(Patton et al. 2006)	Pre-post design, no control group
(Stein et al. 2004)	Comparing two robot-assisted techniques for therapy

Table 3-7: Excluded preliminary results of the included RCT studies or related to them

Study	Reason for Exclusion
(Burgar et al. 2000)	Preliminary results of (Lum et al. 2002)
(Fasoli et al. 2004a)	Same data as (Volpe et al. 2000), focusing on length of inpatient rehabilitation
(Housman et al. 2007)	Preliminary results of (Housman et al. 2009)
(Lo et al. 2009)	Preliminary results of (Lo et al. 2010)
(Masiero et al. 2006)	Preliminary results of (Masiero et al. 2007b)
(Masiero et al. 2007a)	Preliminary results of (Masiero et al. 2007b)

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Chapter Four : ROBOT-ASSISTED REACHING PERFORMANCE OF CHRONIC STROKE AND HEALTHY INDIVIDUALS IN A VIRTUAL VERSUS A PHYSICAL ENVIRONMENT: A PILOT STUDY

4.1 Preface

As we showed in the previous chapter, the use of robotics by itself does not translate into better therapy for people with stroke; nevertheless, RT can deliver highly repetitive therapeutic tasks with minimal supervision of a therapist. Additional sessions of RT improve motor recovery of the hemiparetic shoulder and elbow of patients with stroke. However, the key to a successful use of RT is to integrate it with a proper practice environment; this environment can be either real or virtual. As discussed, it has been shown that stroke patients with mild-to-moderate UL motor impairment benefit from practicing with a virtual reality rehabilitation system. However, during robot-assisted movements, it remains to be determined whether movements made in a virtual environment are similar to those made in a physical environment when the task requirements are the same. To the best of our knowledge, most robotic rehabilitation setups have used virtual environments and there is no study in the literature that investigates the effectiveness of robot-assisted upper limb reaching movement in a virtual environment compared to a physical one in patients with stroke. Therefore, in this chapter, we focus on the robot-assisted reaching differences between virtual and physical environments in a single session.

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4.2 Abstract

Objective: The aim of this study was to examine the role of environment, whether virtual or physical, on robot-assisted reaching movements in chronic stroke and healthy individuals, within a single session.

Design: Fifteen subjects participated in this study divided into three groups: 5 chronic stroke individuals able to perform a reaching task with no need for the robot assistance, 5 chronic stroke individuals who needed robot assistance to complete the reaching task and 5 healthy individuals. The task was to reach for six target buttons in two identical physical and virtual environments. The outcomes consisted of specific kinematic measures (amount of movement completion without robot assistance, mean speed, peak speed, straightness, and shakiness) and a custom questionnaire to assess how the stroke subjects perceived and experienced the reaching task in both environments.

Results: There were no differences between the two environments in terms of the outcome measures in any of the groups.

Conclusion: The choice of environment, whether physical or virtual, is not a key factor in designing a robot-assisted reaching protocol for stroke survivors. Other related factors, such as cost, amount of therapist supervision and space requirements, should get more consideration in this respect than the type of environment itself.

4.3 Introduction

The absolute number of stroke survivors is progressively increasing; from 1995 to 2013, estimates for the number of people living with long-term effects of stroke in Canada increased from 261,000 to 405,000 and it is projected to reach around 700,000 by 2038 (Krueger et al. 2015). It is the

leading cause of disability and depending on the magnitude and severity of the problem, stroke survivors experience a variety of motor, sensory and cognitive disabilities (Public Health Agency of Canada 2011). At 6 months post stroke, i.e. the chronic stage, 26% of ischemic stroke survivors are still unable to independently perform activities of daily living (Go et al. 2013) and 30% to 66% of the chronic stroke survivors have impaired upper extremity motor function (Veerbeek et al. 2016). Therefore, one of the challenging aspects of stroke rehabilitation is upper extremity intervention. Virtual Reality (VR) and robotics are two novel technologies in the field of rehabilitations that are shown to be an effective tool in stroke rehabilitation when compared to conventional therapy (Lohse et al. 2014a; Norouzi-Gheidari et al. 2012).

With about 70% of human sensory receptors being located in the eye, humans highly depend on their sense of vision (Gulrez et al. 2008). Most virtual environments (VEs) are built based on this notation: virtual scenes that subjects can navigate through and interact with, solely based on visual information. By feeding visual information to the human sensory system, VR has been shown to be effective in promoting motor recovery of upper limb in individuals with stroke compared to no therapy (level 1b evidence) and conventional therapy (level 5 evidence) (Henderson et al. 2007). Therapists can create lifelike, highly motivating, and task-oriented VEs in which patients can safely practice (Johnson 2006). Training patients with stroke in a VE allows them to interact with VE and get real-time feedback. A highly motivating scene keeps patients engaged in the course of training (Maclean et al. 2000).

It remains to be determined whether movements made in a VE are similar to those made in a physical environment (PE), when the task requirements are the same. A recent study compared upper limb training of stroke subjects in a VE and PE (without using a robotic device) and found that even though there was no overall effect of the environment, there were some subtle differences

in arm movements between the two environments (Subramanian et al. 2013); shoulder horizontal adduction toward the lower-middle target and shoulder flexion range toward the upper-ipsilateral target were higher post training in subjects trained at VE compared to PE. It has been discussed that even though the task is similar, there may be perceptual issues (such as limited field of view in VE and absence of certain depth cues) that make people (even healthy individuals) behave differently in the two environments. In another study (Liebermann et al. 2009), a single session reaching task in 3 dimensional (3D) PE and 2 dimensional (2D) VE was performed by healthy and stroke subjects and the results showed that the (compensatory) trunk movement speed was less in VE than PE in both healthy and stroke. Also the total trunk displacement in stroke subject was less in VE than PE. However, the arm movement of stroke subjects in VE was jerkier, lengthier and longer and had higher arm torsion when compared to PE. The authors argued that different cognitive factors due to the difference in perception of the 2D VE and the 3D PE might be the cause of this difference in arm movement between the two environments (Liebermann et al. 2009).

Robot-assisted therapies enhance stroke rehabilitation as they provide intense active assisted training to patients in a consistent and controlled fashion with minimum intervention from a therapist (Norouzi-Gheidari et al. 2012). Advanced robotic devices are able to provide consistent training and to measure performance with high reliability and accuracy (Dobkin 2004). Most importantly, robots may allow patients to train more independently or with less supervision from a therapist (Kwakkel et al. 2008). However, the key to a successful use of robot-assisted therapy is to integrate it with a proper practice environment; this environment can be either real or virtual. To the best of our knowledge, most robotic rehabilitation setups have used VE and there is no study in the literature that investigated the effectiveness of robot-assisted upper limb reaching movement in a VE compared to a PE in patients with stroke.

In this pilot study, a robotic arm was coupled with a VE that mimics a physical world scene. Healthy and stroke individuals performed the same 3D reaching task both in VE and PE in a single session. The goal of this study was to investigate the extent to which the robot-aided reaching performance of stroke subjects differed when done in VE versus in PE. Therefore, it was hypothesized that there would be no difference in robot-aided arm reaching performance of stroke subjects between PE and VE, by having a VE that simulated a PE more realistically and a robot arm that minimized unwanted arm movements, resulting in a more controlled arm reaching movement compared to non-assisted reaching.

4.4 Methods

4.4.1 Subjects and Setting

In this study, 10 chronic stroke subjects and 5 healthy subjects were recruited, all from the Greater Montreal region in Canada. The stroke subjects were categorized into two groups; those who were able to perform the reaching task, described later in the text, without the help of a guiding force (GF) provided by the robot arm (“No-GF”); and subjects who required robotic assistance for completion of the reaching task (“With-GF”). There were five subjects in each group. All the stroke subjects were right-handed with right-side hemiparesis and were capable of understanding verbal instructions in either French or English. None of the subjects had hemispatial neglect or any visual problem which was not corrected by eyewear, any upper limb surgery, any pain interfering with arm function (the Shoulder Pain section of the Chedoke-McMaster (C-M) stroke assessment (Gowland et al. 1993) was between stages of 1 and 4), any neurological or neuromuscular conditions other than stroke, or any structural changes secondary to stroke (passive range of motion of the elbow and shoulder restricted more than 20°). These three groups are identified through the text as “Healthy”, “No-GF” and “With-GF”. The “No-GF” and “With-GF” groups were between

43.8–71.0 and 48.1–71.5 years, respectively, and 8.0–17.5 months and 1.5–20 years post-stroke with C-M Upper Extremity Arm score range of 5–7 and 3–4, respectively. The “Healthy” group were in the age range of 20–37. The study was done at the Laboratory of Advanced Technology in Rehabilitation of the Jewish Rehabilitation Hospital in Laval, Canada. A local research ethics committee approved this research study and all the subjects provided their informed consent.

4.4.2 Instrumentation and Safety

In this study, the HapticMaster (MOOG Inc. FCS) robotic arm (van der Linde et al. 2002) was used as the primary tool for providing anti-gravity and guiding force (GF) to the subjects when needed and also for measuring the subjects’ arm movements in three dimensional (3D) space. This product is still investigational. The HapticMaster is a three degree-of-freedom (DOF), programmable endpoint robot which spans a workspace of approximately 1 m³. It has low friction and is equipped with force and position sensors (Figure 4-1A). Custom-made software was written to create pre-defined and feedback-controlled 3D force fields. A forearm splint, in which the subject’s arm is placed, is linked to the robot arm through a universal joint providing three rotational DOF (passive). The robot arm runs at a fixed update rate of 2500 Hz which guarantees a smooth and realistic experience by users. The force can be measured and applied with a precision of 0.01 N and the position measurements are accurate to 0.012 mm.

The robot arm assisted the arm movements of subjects in 3 ways. A) Virtual Tunnel: before the start of the reaching movement, a virtual tunnel (radius: 4 cm) was created, linking the starting position to the target of interest, thus preventing unwanted deviation of the subjects’ arm movement from the ideal straight line path. B) Gravity Support: It always provided gravity support by not letting the subject’s forearm drop. C) “Assist-As-Asked” Paradigm: When a subject asked for help to complete a movement, the robot arm provided a guiding force to assist the subject in

completing the reaching task; when assistance was turned on, the robot produced a virtual spring, with elastic constant of $k = 400 \text{ N/m}$. The spring was then moved at a constant velocity of 5 cm/s towards the selected target, thus smoothly helping the subject in reaching that target. The maximum amplitude of the guiding force was set at 150 N . The experimenter was near the subject at all times and the robot arm was equipped with software and hardware safety switches, so that the subject or the experimenter could rapidly turn it off. Pain and fatigue were monitored during the experiment.

4.4.3 Experimental Setup and Procedure

Subjects were required to perform the same reaching task in both PE and VE (Figure 4-1) in a single session. Each subject was seated on a chair, either in front of a vertical board when performing in PE, or a screen when performing in VE. The affected forearm, i.e. right, was attached to the forearm brace of the robot arm. In order to maintain an upright posture and limit the trunk movements during the experiment, a seat belt was used to restrain the subject's trunk to the chair. Based on a pseudo-randomization, subjects either started the experiment in PE followed by VE, or vice versa.

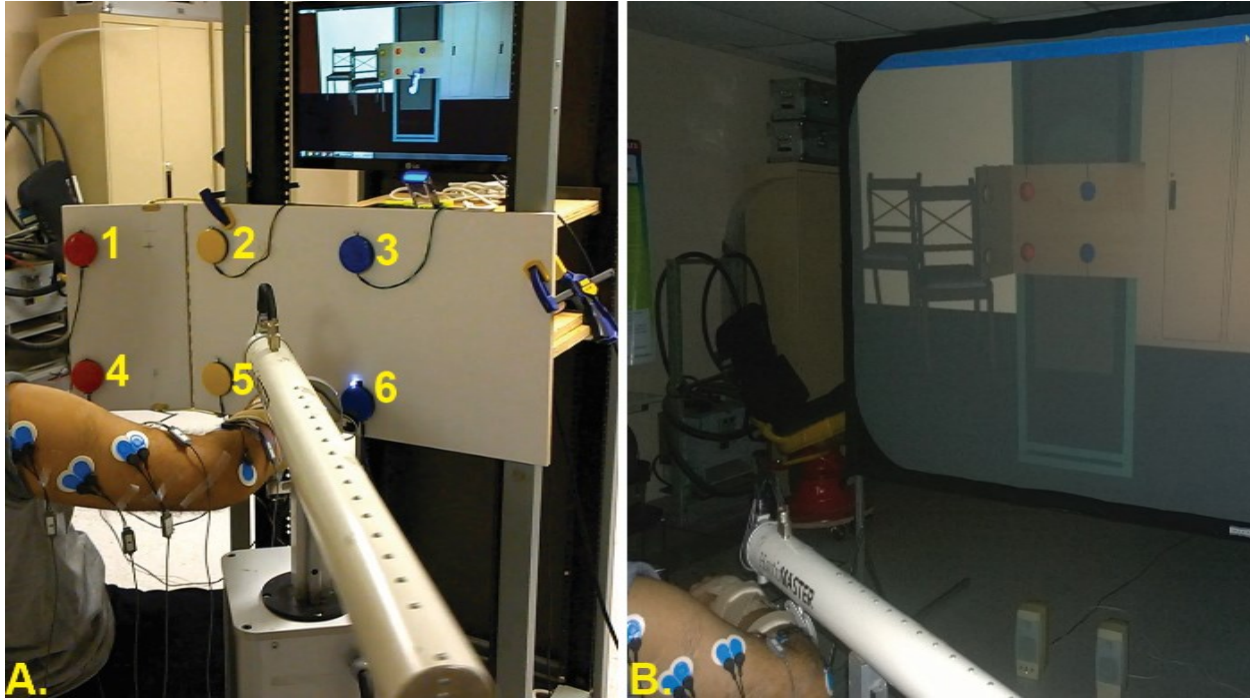


Figure 4-1: A. The Physical Environment (with LED of target 6 being on) and B. The Virtual Environment

The experiment in PE consisted of a reaching task to six buttons/targets placed on two rows, each with three buttons with a diameter of 6 cm (Figure 4-1A). The targets were numbered 1, 2, and 3 from left to right on the top row and 4, 5, and 6 on the bottom row. These six targets were attached to a hinged wooden board. The board was placed so that the middle and right targets (2, 3, 5 & 6) were placed in front of the subject, parallel to the coronal plane; the leftmost buttons (1 & 4) were angled at $\sim 130^\circ$. This arrangement of buttons was preferred, in order to account for the shorter range of motions when reaching for objects placed contralateral to the moving arm. The top and bottom rows of targets were spaced 25 cm apart; the left- and the right-side buttons were placed 15 cm and 30 cm away from the middle buttons, respectively. An LED was placed on top of each button. The height of the experiment board was adjusted in a way that the middle bottom target (#5) was at the level of the subject's xiphoid process of the sternum. Then, based on the subject's right arm length, the experiment board was moved at a distance from the subject so that 150° of

elbow extension was required in order to reach the middle bottom target. The starting position was set at the 14 cm in front of the xiphoid process of the sternum. This configuration allowed different upper limb muscle group activations when reaching for the 6 targets; it covered flexion, extension and abduction in different directions.

The VE mimicked the PE: a wooden board with six call buttons in the virtual scene (Figure 4-1B). The virtual environment was created by projecting images at 120 Hz to a projection screen, providing a 3D perspective view of the experimental scene. The VE was calibrated to have the same metrics as for the PE. The position of the robot arm's end effector was displayed as a hand in the VE. Movements of the robot arm and hand were reproduced onto the 3D VE on a one-to-one scale.

The robot arm assisted the arm movements of subjects in both environments, based on the subject's need. The robot arm created a virtual tunnel (radius: 4 cm) from the starting position to the target of interest, thus preventing unwanted deviation of the subjects' arm movement from the ideal straight-line path and also providing gravity support by not letting the subject's forearm fall. It could also provide a guiding force to assist the subjects in completing each reaching task, at their own request.

In either environment, subjects were instructed to move at a comfortable speed and to reach and press the target buttons while not producing any compensatory trunk movements during the experiment; the experimenter was monitoring every trial and if an excessive compensatory movement was observed, that trial was repeated. For subjects having difficulty in reaching any of the targets, when they could not move their arm further during a reaching trial, they asked for the robot's assistance by saying the word "force". At this point, the experimenter turned on the guiding force so that the robot would assist in completing the rest of the reaching movement; this happened

only in the With-GF group. In PE, one of the LEDs above the targets was pseudo-randomly turned on to indicate the reach target. In VE, the target button was visually highlighted. There were 5 reaching trials to each button, for a total of 30 trials in each environment. In PE, the movement end was indicated in the recording when the target button of interest was physically touched by the subject. In VE, as there was no physical target button present, the robot arm stopped the subject when the target of interest was reached in the VE and a “click” sound was played, similar to that of a physical button. When the subject reached the target button, either with or without help of the robot arm, the percentage of the movement distance that the subject was able to complete without assistance from the robot was displayed as feedback on a monitor placed above the experiment board in PE and displayed on the screen in VE. After completion of a reaching trial, the robot arm actively moved the subject’s hand back to the starting position.

4.4.4 Outcome Measures and Data Analysis

To analyse the movement, the trajectory data were digitally low-pass filtered using a Butterworth filter with a cut-off frequency of 6 Hz (dual-pass). Then several kinematic metrics from the trajectory data were extracted. The analyses were only focused on the portion of movement that was solely performed by the subject, without assistance from the robot. The kinematic metrics were: 1) movement completion, defined as the ratio of the straight-line distance completed by the subject over the target distance from starting position; 2) mean speed over the path line (i.e. trajectory); 3) peak speed; 4) straightness; and 5) shakiness. Considering a straight line as the ideal

travel path for a reaching task¹, straightness was defined as the ratio of the straight line over the path line in the reaching movement; the straightness measure has a value between 0% and 100% with higher values meaning the reaching trajectory being closer to the straight line. Shakiness was defined as the number of acceleration profile zero crossings over the path line. A lower shakiness value represents a smoother movement in terms of being less jerky. Subjects in the With-GF group, similar to the other two groups, were only instructed to reach to the targets (the only set goal); as a result, when they reached close to their movement limit, they started struggling to go further. This made the last five percent of the movement very different from the other parts of the trajectory. Therefore, in the With-GF group, the last five percent of the trajectory in terms of distance was excluded from the movement analysis. The movement completion measure was primarily used for the With-GF group to show how much of the reaching task was performed without the robot's assistance; the other two groups were able to complete the reaching task and had a movement completion of 100%. The relationship between the movement completion and the straightness and shakiness outcome measures as well as the movement duration and those two outcome measures in the With-GF group was also examined by performing Pearson's correlation analyses.

A repeated measures ANOVA was used to assess whether there were any significant differences between the two environments in terms of kinematic measures by modelling the 2 environments and 6 targets as the within-subject factors and the 3 groups as the between-subject factor all

¹ It should be noted that when the starting hand position is lower than the target, healthy subjects usually choose a slightly curved trajectory (more vertical displacement than forward displacement of the hand at the beginning of the movement). This might be done to reduce gravity torque and consequently, muscle fatigue. However, as movements of both stroke and healthy participants are compared to the same ideal straight line, the difference in straightness between the two groups can still be measured, even though the healthy participants may not themselves follow a straight line.

combined in a full factorial model. If there were any significant interaction present between the factors, simple effect tests were performed. The significance level was set at $p < 0.05$.

Along with the kinematic metrics, a custom questionnaire was developed to assess how the stroke subjects perceived and experienced the reaching task in both environments using a modified version of the Intrinsic Motivation Inventory (modified-IMI) (McAuley et al. 1989) combined with a modified Short Feedback Questionnaire (modified-SFQ) (Kizony et al. 2005). The modified-IMI consisted of ten questions divided into five scales: Interest/Enjoyment, Perceived Competence, Effort/Importance, Pressure/Tension, and Value/Usefulness. The modified-SFQ consisted of two questions about Repeating the experiment and Comfort of the experiment. There were also three questions about which environment they preferred, which one was easier for them and whether they felt fatigued. All stroke subjects, i.e. both No-GF and With-GF groups, filled out this questionnaire. As this was a within subject design, the Wilcoxon signed-rank test, a non-parametric statistical hypothesis test, was used for analysing the results of the modified-IMI and modified-SFQ questions.

4.5 Results

Figure 4-2 shows typical trajectories for the three study groups; i.e. “Healthy”, “No-GF” stroke, and “With-GF” stroke. The black lines represent the subjects’ self-movement without any robotic assistance. The green (lighter) lines in the With-GF group represent the portion of movement completed with the robot’s assistance. A higher level of movement variability in the moderate-to-severe stroke subjects (With-GF group) is quite evident while in the mild stroke subjects (No-GF group), movement variability is close to what can be observed in the healthy individuals. The kinematic metrics were used to quantify the movements. Table 4-1 summarizes the mean and standard error of each metric in both environments for each group. If there was a

main effect or an interaction was significantly present, it is also mentioned; in case of interaction, the presence of a related main effect is ignored.

Table 4-1: Summary of the statistical analysis performed on the outcome measures

Outcome Measures	Healthy		No-GF Stroke		With-GF Stroke		Effect of Environment Factor	Significant Interactions / Main Effects
	PE	VE	PE	VE	PE	VE		
Mean Speed over Path Line (cm/s)	18.98 ± 2.92	17.37 ± 3.17	22.35 ± 2.92	22.23 ± 3.17	10.79 ± 2.92	11.27 ± 3.17	F(1,12)=0.31 p = 0.589	Target x Group F*(8.29,49.77)=2.66 p = 0.015
Peak Speed (cm/s)	29.42 ± 4.70	26.43 ± 4.91	36.10 ± 4.70	35.86 ± 4.91	23.19 ± 4.70	22.30 ± 4.91	F(1,12)=1.58 p = 0.233	Target x Group F*(7.53,45.16)=2.22 p = 0.046
Straightness (%)	98.07 ± 4.01	97.92 ± 2.51	93.71 ± 4.01	93.95 ± 2.51	73.11 ± 4.01	77.07 ± 2.51	F(1,12)=0.46 p = 0.509	Group F(2,12)=18.06 p = 0.000
Shakiness (#/cm)	0.11 ± 0.15	0.12 ± 0.15	0.17 ± 0.15	0.14 ± 0.15	0.55 ± 0.15	0.61 ± 0.15	F(1,12)=1.40 p = 0.264	Target x Group F*(7.48,37.42)=4.04 p = 0.002

* Huynh-Feldt degree of freedom adjustment for lack of sphericity

No statistically significant differences in the reaching performances between PE and VE were found in any of the groups. Not only the main effect of the environment factor was not significant, but also its interaction with the other two factors, i.e. target and group, was not significant meaning that neither reaching a different target nor being in a different group had any effect on lack of meaningful difference in reaching performance between the two environments.

That being said, significant interactions between the groups and reach targets were observed in almost all outcome measures, as shown in Table 4-1. Therefore, simple effect analyses were run on the data (Table 4-2). Figure 4-3 illustrates the performance of each group when reaching different targets and shows both group-wise and target-wise reaching performance in one graph; the corresponding statistically significant results are reported in the text.

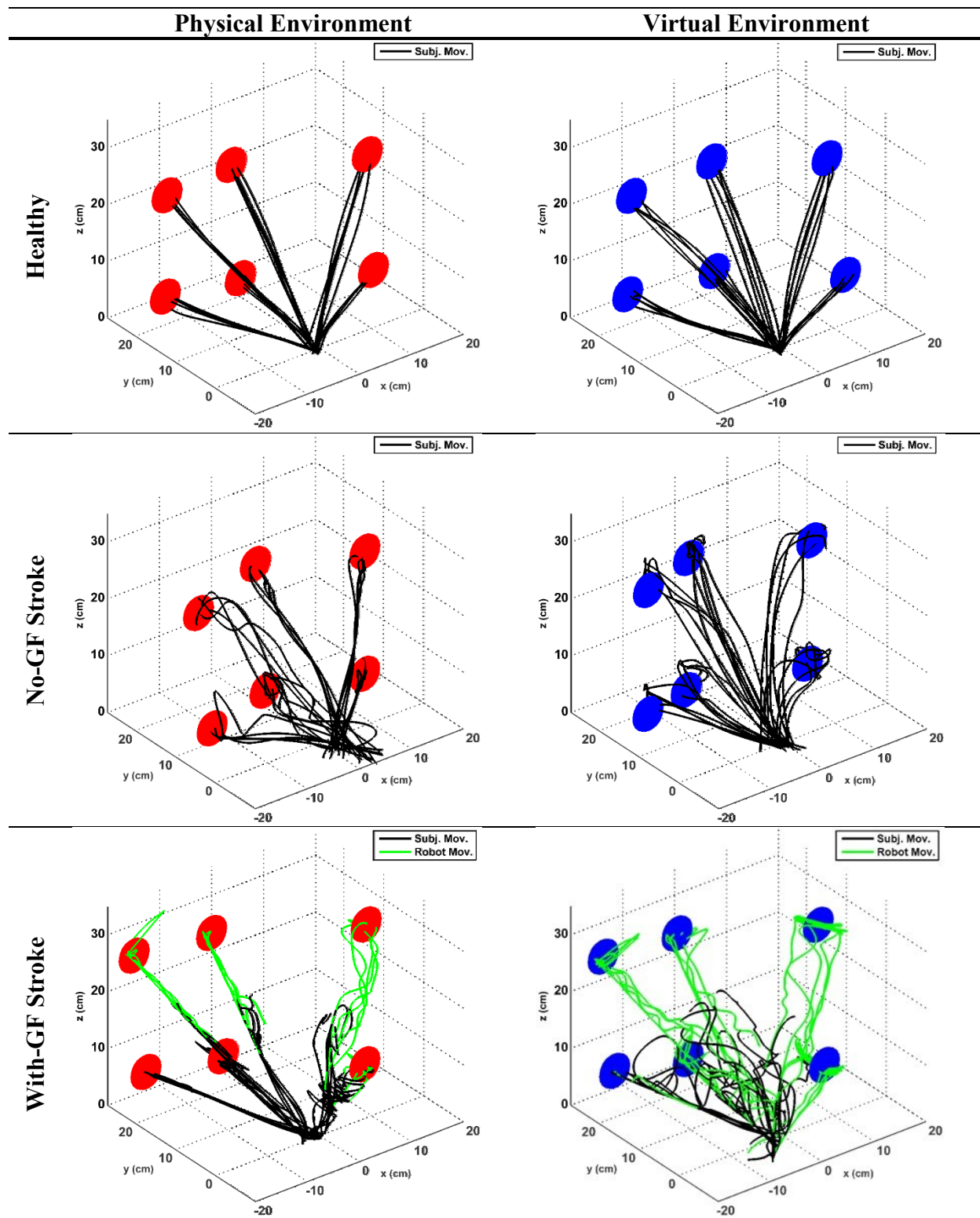


Figure 4-2: Typical trajectories for Healthy, No-GF and With-GF groups in both environments

4.5.1 Group Differences

In terms of mean speed, the No-GF group was significantly faster than the With-GF group in targets 1, 2, 3, 5 & 6. As for peak speed, the No-GF group was statistically faster than the With-GF group only in targets 1 and 2. In general, the No-GF group had the highest mean and peak speed, followed by the Healthy group and then the With-GF group. Higher peak speed in the Healthy group compared to the With-GF group is well aligned with what has been previously reported (Kamper et al. 2002).

Both Healthy and No-GF groups displayed significantly higher straightness values than the With-GF group in reaching each target. While the average straightness for the Healthy group was higher than the No-GF group for all the targets, this difference was not statistically significant. In terms of Shakiness, in all the targets except target 4, the With-GF group had significantly higher values (less smooth) than the other two groups. Both Healthy and No-GF groups had similar shakiness values with their absolute mean difference being less than 0.04 (#/cm) in all the targets.

4.5.2 Target Differences

Comparing the targets, all the groups in general had higher mean and peak speed when reaching target 1 than for all the other targets followed by targets 2, 3, 4 and 5, respectively. In reaching target 6, the mean and peak speed had the lowest values compared to all the other targets. There was an exception in this order regarding targets 3 and 4 in which the order varied between them, i.e. the speed ordering was either 1, 2, 3, 4, 5 and 6 or 1, 2, 4, 3, 5, and 6. This difference in mean and peak speed between targets was significant in most of the comparisons.

In terms of straightness, the target-wise comparisons showed no significant differences in the Healthy group nor in the No-GF group when reaching the different targets. However, there were some significant differences in terms of straightness within the With-GF group when reaching

different targets; the least straight reaching path was toward targets 5 and 6. The straightest path achieved by the With-GF group was in reaching toward targets 3 and 4. Targets 1 and 2 had the middle values of the straightness measure. In Figure 4-3, the straightness graph also shows the average movement completion by the With-GF group before asking for robot help. Correlation between the movement completion and straightness measures was negative and showed a high value of coefficient of determination ($R^2=0.82$); target 4 was excluded in this calculation as it was the only target that the With-GF group did not differ statistically from Healthy and No-GF groups in terms of movement completion, mean speed, peak speed and shakiness.

In terms of shakiness measure, the Healthy and No-GF groups had similar range of values when reaching different targets. In the With-GF group, target 4 had the lowest shakiness value ($p<0.035$ for all the targets except target 2). Then targets 1, 2 and 3 had lower shakiness values than targets 5 and 6. Target 6 had the highest shakiness value in the With-GF group ($p<0.05$).

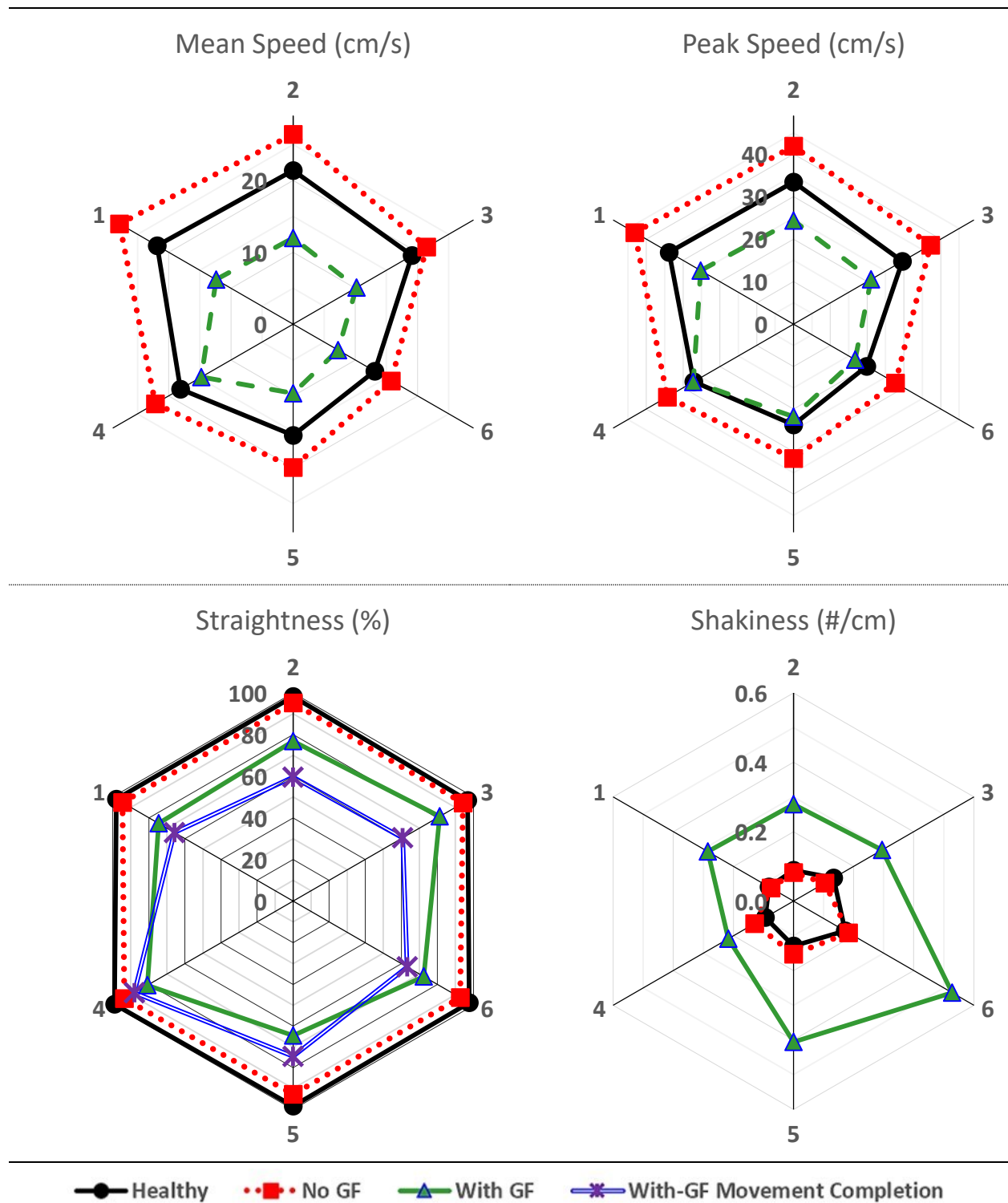


Figure 4-3: Mean speed, peak speed, straightness, and shakiness outcome measures of each group in reaching the targets of interests are shown. The amount of movement completion by the With-GF group is also embedded in the straightness chart. Note that the target locations in these radar charts are not in the exact location as the experiment.

Table 4-2: The simple effects analysis of the outcome measures based on group comparisons. Only statistically significant results are shown.

Measure	Unit	Groups	Within	Mean Diff.	Std. Err.	p Val.
Mean Speed	cm/s	N-W	T1	15.5	5.2	.012
			T2	14.4	5.1	.015
			T3	11.3	4.3	.021
			T5	10.3	4.4	.037
			T6	8.6	3.1	.017
Peak Speed	cm/s	N-W	T1	17.9	7.9	.043
			T2	17.5	7.9	.047
			T3	16.1	7.9	.063
Straightness	%	H-W		22.9	4.1	.000
		N-W		18.7	4.1	.002
Shakiness	#/cm	H-W	T1	-0.20	0.07	.019
			T2	-0.19	0.05	.004
			T3	-0.16	0.03	.001
			T5	-0.28	0.08	.006
			T6	-0.36	0.07	.000
		N-W	T1	-0.21	0.08	.022
			T2	-0.20	0.05	.004
			T3	-0.19	0.04	.000
			T5	-0.25	0.08	.013
			T6	-0.35	0.07	.001

H: Healthy Group, N: No-GF Group, W: With-GF Group, T: Target, #: No of Zero Crossings, Diff.: Difference, Std. Err.: Standard Error, p Val.: p Value (significance probability)

4.5.3 Subjective Perception Differences

A Wilcoxon signed-rank test was used to analyze the questionnaires and showed that there was no statistically significant difference between the two environments in terms of the subjective experience of the stroke subjects (Table 4-3). All expressed positive feedback in terms of enjoyment and interest and were completely comfortable in both environments except one subject who felt uncomfortable in both environments even though enjoying the experiment. The same subject did not want to repeat the experiment in any of the environments and another subject felt the same regarding VE. All other subjects wanted to repeat the reaching task in either environment. All the stroke subjects were satisfied with their performance in both environments except one

subject who was not satisfied with their perceived performance in VE. Only two of the stroke subjects put “some effort” to complete the activities in both environments while the rest put “a lot of effort”. All of them felt “no pressure” or “some pressure” in doing the tasks in both environments except one subject who felt being under “a lot of pressure” to do the task in PE (the same subject who felt uncomfortable). All of them felt that the activity was equally useful for their affected arm in either PE or VE, except for one subject who thought it is not useful at all and another subject who thought it was less useful in VE. In terms of environment preference, four subjects chose PE and three chose VE, with the rest choosing either environments as equal. In terms of the environment being easier for the reaching task, four of them chose both environments as equal and the rest were divided between PE and VE. Finally, five subjects reported feeling fatigue; two in PE and three in VE.

Table 4-3: The results of the Wilcoxon signed-rank test on subjective view of the stroke patients

Questionnaire Items	Z	P Value
Interest/Enjoyment	0.00	1.00
Perceived Competence	-1.63	0.10
Effort/Importance	-1.41	0.16
Pressure/Tension	-1.89	0.06
Value/Usefulness	-0.96	0.34
Repeating	-1.60	0.11
Comfort	-1.00	0.32

4.6 Discussion

In this study, the main goal was to identify whether the choice of the environment during a reaching task (with or without assistance) has any effect on the movement variables. Fifteen individuals participated in this study consisting of three groups: five healthy individuals, five chronic stroke individuals with no need of assistance, and five chronic stroke individuals who needed assistance

to complete the reaching task. The results strongly suggest that there are no differences in terms of the movement variables (speed, straightness, and shakiness) between the two environments for any of the three groups of this study. This can be explained by a study on healthy subjects comparing reaching tasks in real vs virtual environment in presence/absence of visual/haptic feedback (Ebrahimi et al. 2016); the results showed that the subjects' performance were similar in both environments when the subjects had visuo-haptic feedback in VE. In this design, besides the presence of visual feedback in VE, the robot arm provided haptic feedback at the end point for the users by stopping them when the virtual button was reached. Also, both PE and VE shared the same haptic feedback in terms of forearm attachment to the robot arm.

In this study, chronic stroke subjects with mild-to-moderate and moderate-to-severe arm impairment were recruited. Similar results were observed during a multi-session study comparing VE and PE in a reaching task performed by chronic stroke individuals without robotic assistance. The authors also reported no overall effect of the environment on the end point tangential velocity nor on the precision kinematic variables (Subramanian et al. 2013) even though other differences were reported. In another study, an intensive 2-weeks arm and finger training of two chronic stroke groups were compared; one training in a conventional (physical) setting performing repetitive task practice-based approaches and the other in a robotically-assisted VE with haptic guidance training tasks, similar to those of the conventional group (Fluet et al. 2015). The authors did not find any significant difference in terms of peak velocity between the two environments but found gains in peak velocity of the group being trained in the robotically-assisted VE were statistically higher but still not caught up with the baseline values of the conventional group (baseline imbalance). It should be noted that both latter studies were intervention studies performed over multiple sessions and were in nature different from this experimental design. Also, in this study, the presence of the

robot arm may have removed the reliance of stroke subjects on compensatory trunk movements; it may have allowed them to perform the reaching task without risk of sudden fall of the arm by providing when-needed anti-gravity support and guiding force, and let them move their arm in a virtual tunnel to minimize extra deviation of the movement from optimal path.

Besides finding no difference in terms of movement variables between the two environments, analysis of subjective experience of the stroke subjects revealed no difference between the two environments as well. There was no common environment preference as the subjects were divided almost equally between choosing VE or PE. Even feeling fatigued or choosing an easier environment was similar between the two environments. This shows that not only the movement pattern was the same in both VE and PE but also the subjects' experience was similar as well.

Task-oriented (task-specific) training (TOT) has been shown to be an effective approach for regaining upper extremity motor function post stroke (Mathiowetz 2015; Rensink et al. 2009; Schweighofer et al. 2012; Winstein and Wolf 2008). In TOT, a challenging functional task is broken down into several modules and the therapist and the patient work on re-/learning of each module of the task; it involves physical/real objects and is goal directed (Winstein and Wolf 2008). Emphasis on the use of real objects is the foundation of TOT. However, in practicing a reaching task such as the one used in this study, the trajectory of the reaching is in nature independent of the chosen environment. Therefore, we suggest that in a reaching task, TOT can be used either in physical or virtual environments and the choice of the environment does not interfere with the principles of TOT in this specific task. Efforts have been made to come up with task-oriented rehabilitation robotics (TOR) complying with principles of TOT (Johnson et al. 2007 ; Schweighofer et al. 2012; Timmermans et al. 2014).

The lack of difference in the movement variables between the environments was not dependent on the group; whether there were healthy subjects or chronic stroke subjects with or without need of robot assistance. However, these groups performed differently in the reaching task. A surprise finding was a generally higher speed of the No-GF group compared to the Healthy group. They also had higher speed compared to the With-GF group. However, this general higher speed of the No-GF group during reaching movement was done with lower straightness but similar level of shakiness when compared to the Healthy group. That being said, the movement straightness and shakiness of the No-GF group was significantly better than the With-GF group. This implies that a different mechanism of reaching is developed during stroke recovery. In a previous robot-assisted therapy study, observations of higher peak speeds in chronic stroke compared to subacute stroke and healthy individuals had been attributed to the development of pathologic patterns in chronic stroke (Mazzoleni et al. 2013). Several studies have indicated that chronic stroke subjects can increase paretic arm velocity during a reaching task in order to improve their quality of movement (DeJong et al. 2012; Mandon et al. 2016; Massie and Malcolm 2012; van Vliet and Sheridan 2007). This might be the reason why the No-GF group produced faster movements that resulted in a normal level of shakiness as of the Healthy group but still due to residual impairments this faster movement was not as straight as that of the Healthy individuals.

In the With-GF group, target 4 was a special case among all the targets; it was in the lower ipsilateral position of the subjects. Reaching this target required minimal elbow extension and shoulder abduction from the starting position compared to the other targets; a movement that is aligned with flexor synergy seen in stroke subjects with upper extremity motor impairment (Cailliet 2003; Roh et al. 2013). Therefore, subjects in the With-GF group had their best reaching performance toward this target with the least difference from Healthy subjects in terms of the

movement speed, straightness and shakiness compared to all the other targets. It was the only target in which the With-GF group did not differ statistically from Healthy and No-GF groups in terms of movement completion, mean speed, peak speed and shakiness.

The difference in the straightness measure in reaching toward different targets by the With-GF group had a high negative correlation with the movement completion. This meant that as the subjects in the With-GF group tried to go further distance toward a target, their reaching movement became less straight. This phenomenon was not observed in the Healthy or No-GF group where the movement was 100% completed by the subjects and also in the With-GF group when reaching toward target 4 where they got very close to it in such a way that the movement completion was not statistically different from the other two groups (average of the movement completion was 88% at target 4). While straightness was negatively related to the amount of movement completion in the With-GF group, there was no relationship between the shakiness and the movement completion measures in this group. Instead, shakiness was more related to the movement duration in the With-GF group; the highest shakiness value was during reaching attempt toward target 6 (never reached by the subjects without robot assistance) which lasted only for 2.5 seconds in average (the lowest reaching attempt time), while the least shakiness value was during reaching attempt toward target 4 (with the best achievement in the With-GF group) which lasted 4.3 seconds in average. The correlation analysis showed a moderately high value of coefficient of determination ($R^2=0.72$) for this negative relationship. In other words, higher level of shakiness in a movement resulted that movement to be attempted for a lesser time by the subject. This finding is aligned with another study in which a similar shakiness index, defined as the number of peaks in the tangential velocity profile, was shown to be (negatively) predictive of the regained function (Frisoli et al. 2012).

There were several limitations in this pilot study. There were only fifteen subjects participating in this study divided into three groups. While the results are well aligned, due to this low number of subjects, the obtained results may not be generalizable to the chronic stroke population. In addition, this result is only based on a robot-assisted protocol and should not be expanded to a non-robotically aided reaching tasks and also other functional tasks that require manipulation of objects like grasping. As each subject only participated in one single session, information about treatment effect of PE or VE setting or their effectiveness and retention in long run cannot be concluded. Running a multi-session study to compare the training effect in PE vs VE is recommended as a next step.

In summary, this pilot study shows that the choice of environment, whether physical or virtual, is not a key factor in designing a robot-assisted reaching protocol for stroke survivors. The choice of environment should be based on other related factors such as cost, amount of therapist supervision and space requirements, and not the type of environment itself.

4.7 Acknowledgments

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Chapter Five : ARM RE-TRAINING USING ROBOTICS IN PHYSICAL AND VIRTUAL ENVIRONMENTS: CASE STUDY REPORT OF A SUBJECT WITH LONG-TERM CHRONIC STROKE

5.1 Preface

In the previous manuscript, we looked at the effect of environment in a single session of robot-assisted training and showed that the training environment is not crucial at least in a single session of training. In this chapter, we proceed to validate the assist-as-asked RT protocol for longer term training, i.e. multiple sessions of training. A long-term chronic stroke patient with moderate-to-severe upper limb used our assist-as-asked robot-assisted training protocol in both environments over ten sessions. A condensed version of this manuscript was published as a short proceeding paper in “International Conference on Virtual Rehabilitation (ICVR) 2017” and is copyrighted by IEEE. In compliance with IEEE copyrighted materials, the following notice is included here:

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5.2 Abstract

To investigate the utility and benefits of robot-assisted training (RT) for stroke rehabilitation, we conducted a case study using an arm-based RT protocol to train reaching over 10 half-hour sessions in an individual with a long-term chronic stroke (20+ years). We analyzed the performance of the arm reaching movement with kinematic measures in two environments (physical and virtual) and evaluated the arm motor function using the Fugl-Meyer Assessment-Upper Extremity scale (FMA-UE). The results showed noticeable improvements in the subject's reaching performance accompanied by a small increase in FMA-UE score from 18 to 21. The improvements were also transferred into real-life activities, as reported by the subject. This case study shows that even in long-term chronic stroke, improvements in motor function are still attainable with RT, while the underlying mechanisms of motor learning capacity or neuroplastic changes need to be further investigated.

5.3 Introduction

Regaining upper extremity motor function is one of the main goals of stroke rehabilitation. The concept of neuroplasticity has opened new doors in neurorehabilitation practice in individuals with stroke. The key finding is that the frequency and intensity of therapy should be high enough to induce cortical changes in the central nervous system (CNS) of the person with stroke, leading to re-learning of the task in practice (Cramer et al. 2011; Krupinski et al. 2014). Robot-assisted training/therapy (RT) is a promising tool for intensive practice of arm movements in stroke rehabilitation (Norouzi-Gheidari et al. 2012). However, as a first step, the utility and benefits of RT need to be established in individuals with long-term chronic stroke, who are presumed to have less potential for experience-dependent neuroplasticity.

We have developed a robot-assisted protocol aimed at improving arm function of chronic stroke subjects with upper extremity (UE) motor impairments. The “Assist-As-Asked” paradigm is introduced in this new scheme where the robot only provides assistance when the subject specifically asks for it. The system is coupled with two environments, one physical and one virtual, which are equivalent and allow the practice of the same arm reaching movements. The main objective of this case study was to investigate whether an individual with a long-term chronic stroke can benefit from RT and improve their UE function even after long-term disuse. The secondary objective of this case study was to investigate whether the subject would perform differently in a physical environment (PE) than in a virtual environment (VE) during RT sessions.

5.4 Methods

5.4.1 Participant Description and Setting

The subject who participated in this study was a 48-year-old female who had an ischemic stroke in 1994 (21 years before the RT sessions). The stroke manifested as hypo density of the left anterior middle cerebral artery regions and the left frontal lobe. This resulted in right hemiparesis. At the time of participation in this study, her score in the arm section of the Chedoke-McMaster (C-M) (Gowland et al. 1993) stroke assessment was 3, with spasticity in the right elbow and wrist flexors. Her score on the UE section of the Fugl-Meyer Assessment (FMA-UE) (Fugl-Meyer et al. 1975) was 18. She did not have any hemispatial neglect or visual problems; she had not undergone any upper limb surgery and was not experiencing any pain interfering with the UE function. Being right-handed before the stroke, she had learnt to carry out most daily activities with only the left UE after the stroke. During the time of study, the subject did not participate in any other therapy or research. The study was conducted at the Laboratory of Advanced Technology in Rehabilitation of the Jewish Rehabilitation Hospital in Laval, Canada, a research site of the Montreal Centre for

Interdisciplinary Research in Rehabilitation (CRIR). The CRIR research ethics committee approved the research and the subject provided her informed consent.

5.4.2 Instrumentation

The HapticMaster (MOOG Inc. FCS) robotic arm (van der Linde et al. 2002) was used to deliver RT: a three degree-of-freedom, programmable endpoint robot which spans a workspace of approximately one m³. It has low friction and is equipped with force and position sensors (Figure 5-1). A forearm splint, in which the participant's arm was placed, was linked to the robot arm through a universal joint providing three rotational degrees-of-freedom (passive). We programmed this robotic arm to create a virtual tunnel (radius: 4 cm) between the starting position and the targets of interest. The virtual tunnel provided gravity support and prevented unwanted deviation of the subject's arm movement from the ideal straight-line path. We also programmed the robot to provide physical assistance for completing the reaching movement, when specifically requested by the subject ("Assist-As-Asked" paradigm). The robot then produced a force acting as a spring with its endpoint situated on the target of interest. The device was also used for measuring the subject's arm movements in three-dimensional (3D) space. The robot arm's update rate of 2.5 kHz guaranteed a smooth and realistic experience by the user. The force application and measurement and the position measurement had a precision of 0.01 N and 0.012 mm, respectively. The experimenter was near the subject at all times during RT and the robot arm was equipped with software and hardware safety switches, so that the subject or the experimenter could rapidly turn it off.

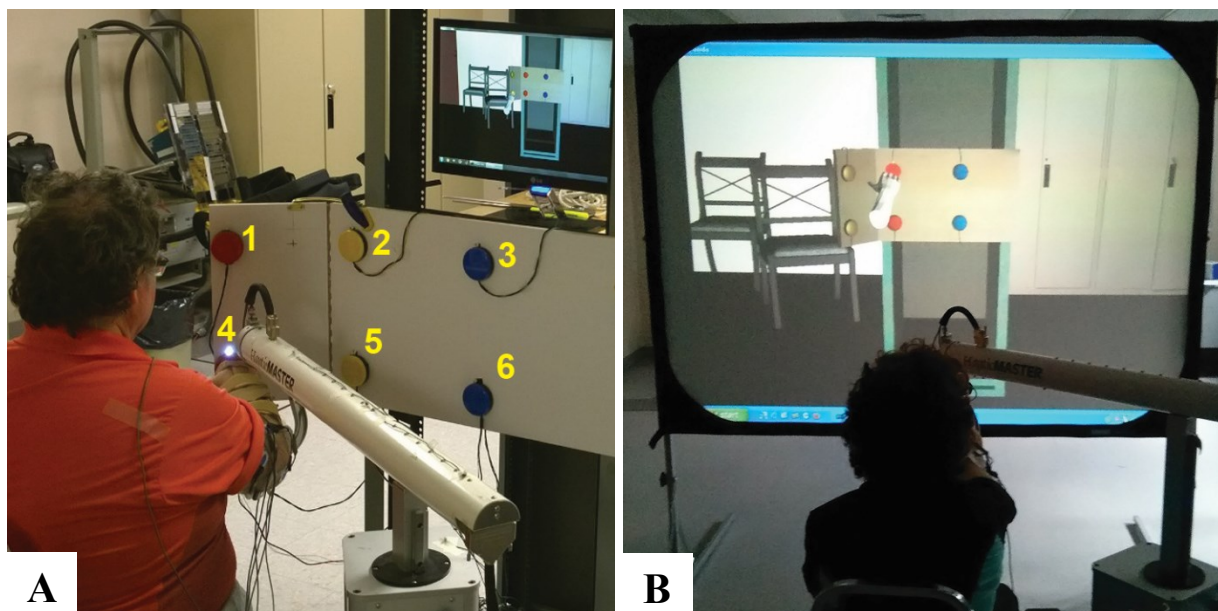


Figure 5-1: A. The Physical Environment (with LED of target 4 being on) and B. The Virtual Environment

5.4.3 Procedures

The training consisted of reaching six targets in both PE and VE in ten sessions over the course of a month. The subject was seated on a chair, either in front of a vertical board when performing in PE, or a screen when performing in VE. In PE, the six buttons/targets were attached to a hinged wooden board in two rows, each with three buttons with a diameter of 6 cm (Figure 5-1A). The targets were numbered 1, 2, 3 from left to right on the top row and 4, 5, 6 on the bottom row. The board was placed so that the middle and right targets were placed in front of the subject, parallel to the coronal plane; the leftmost buttons were angled at $\sim 130^\circ$. The targets at the top and bottom rows were 25 cm apart; the left- and the right-side buttons were placed 15 cm and 30 cm away from the middle buttons, respectively. A light emitting diode (LED) was placed on top of each button. The height of the experiment board was adjusted in a way that the middle bottom target was at the level of the subject's sternum. Then, based on the subject's right arm length, the experiment board was placed at a distance from the subject so that 150° of elbow extension was

required in order to reach the middle bottom target. This configuration allowed different upper limb muscle group activations when reaching for the 6 targets; it covered flexion, extension and ab/adduction in different directions. VE mimicked PE: a virtual scene that showed the wooden board with six call buttons (Figure 5-1B). The VE was created by projecting images at 120 Hz to a projection screen, providing a 3D perspective view of the experimental scene. It was calibrated to have the same metrics as for PE. The position of the robot arm's end effector was displayed as a hand in VE. By moving the robot arm, the hand movement was projected onto the 3D VE on a one-to-one scale.

In each session, the affected forearm of the subject, i.e. right, was attached to the forearm brace of the robot arm. Based on a randomization protocol, the subject either started the experiment in PE followed by VE, or vice versa, in each session. The subject was instructed to move at a comfortable speed and to reach and press the target buttons while not producing any compensatory trunk movements during the experiment. In PE, one of the LEDs above the targets was pseudo-randomly turned on to indicate the reach target of interest. In VE, the target call button was visually highlighted. During each one of the ten sessions, there were 5 reaching trials to each button, for a total of 30 trials in each environment, summing up to 60 trials per session. In PE, the movement end was marked as when the target button of interest was physically touched by the subject. In VE, as there was no physical target button present, the robot arm stopped the subject when the target of interest was reached and a “click” sound was played, similar to that of a physical button. In each reaching trial, when the subject could not go further on her own, she asked for help and the robot arm provided physical assistance to help her complete the movement. When she reached the target button, the percentage of the movement distance that she completed without assistance from the robot was displayed as feedback on a monitor placed above the experiment board in PE and

displayed directly on the screen in VE. After completion of a reaching trial, the robot arm actively moved her hand back to the starting position.

5.4.4 Outcome Measures and Data Analysis

To monitor the changes in UE motor function of the subject following RT, we used the FMA-UE. The FMA-UE was measured at the first session prior to the start of the experiment and at the last session following the completion of the experiment. To analyze the movement, we extracted several kinematic metrics from the trajectory data of each session and focused on the portion of movement solely done by the subject, without any robotic assistance. The kinematic metrics were: 1) movement completion ratio, defined as the ratio of the straight-line distance between the starting point and the closest point to the target that was achieved by the subject over the distance between the starting point and the target; 2) mean speed over the path line (i.e. trajectory); 3) straightness; and 4) jerkiness. Considering a straight line as the ideal travel path for a reaching task², straightness was defined as the ratio of the straight line over the path line in the reaching movement; the straightness measure has a value between 0% and 100% with higher values meaning the reaching trajectory being closer to the straight line. Such computation does not account for the movement completion ratio and may thus be limited in its ability to distinguish between movements that are fully or partially completed by the subject. We therefore adjusted the straightness measure by multiplying it by the movement completion ratio to remove this confounding effect. “Jerkiness”

² It should be noted that when the starting hand position is lower than the target, healthy subjects usually choose a slightly curved trajectory (more vertical displacement than forward displacement of the hand at the beginning of the movement). This might be done to reduce gravity torque and consequently, muscle fatigue. However, as movements of both stroke and healthy participants are compared to the same ideal straight line, the difference in straightness between the two groups can still be measured, even though the healthy participants may not themselves follow a straight line.

was defined as the number of zero crossings in the acceleration profile over the path line. A lower jerkiness value represents a smoother movement, with fewer starts and stops.

5.5 Results

The subject attended all ten RT sessions and did not report any pain, fatigue, or adverse effects during the training. We observed evident changes in movement completion by the subject: during the first session, the subject had difficulty in completing the reaching task towards targets 1, 2, 3, and 6 and needed the robot's assistance to complete the task. In the last session, she could independently reach to all the targets. This progression/improvement is illustrated in Figure 5-2 in which the black lines represent the subject's self-movement trajectories without any robotic assistance and the green (lighter) lines represent the portion of movement completed with the robot's assistance.

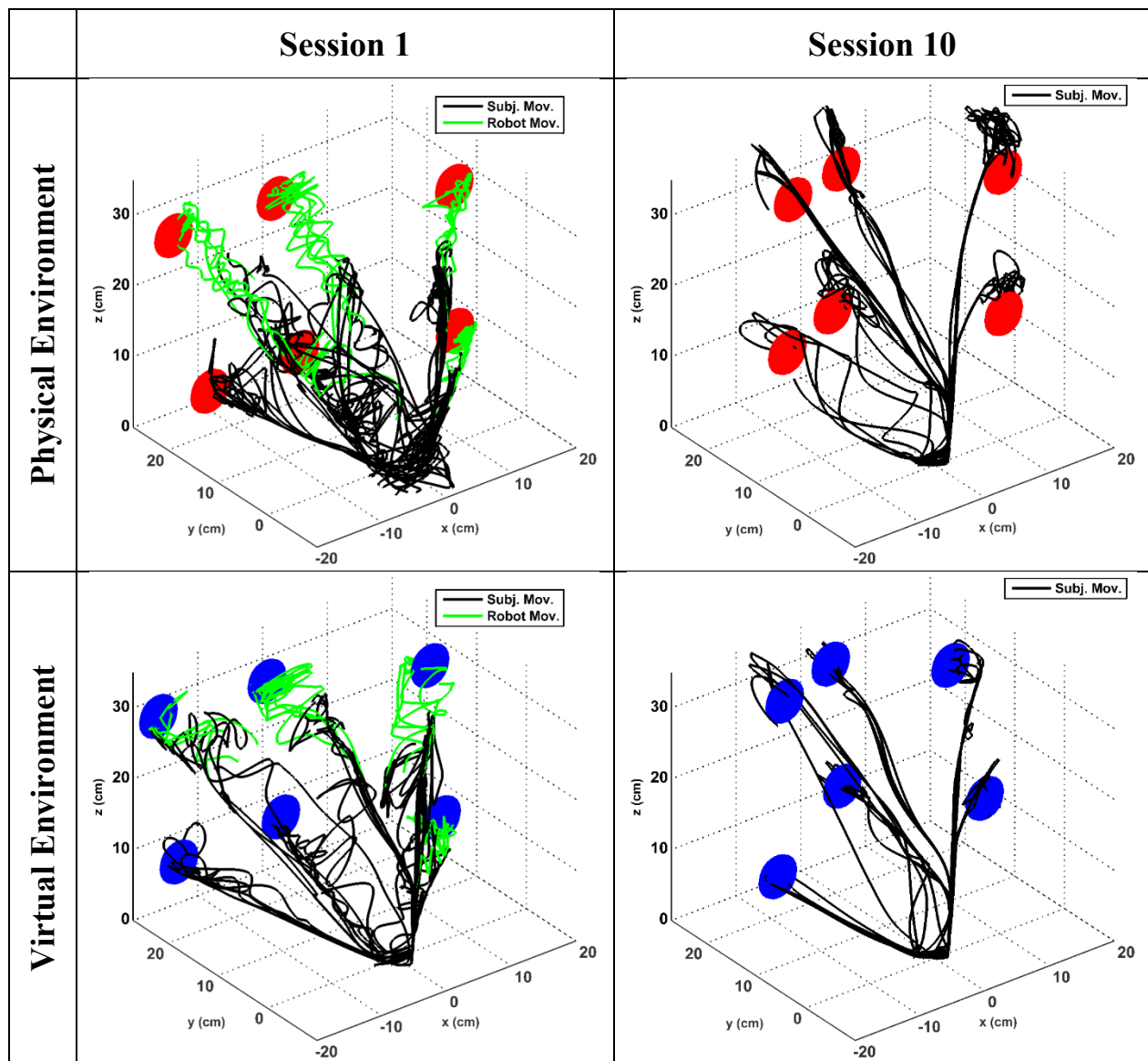


Figure 5-2: Movement trajectories for session 1 and session 10 in both environments. Black lines represent the trajectories performed by the subject (no robot assistance). After 10 sessions of practice, the improvements in reaching without robot assistance are quite evident. No noteworthy difference can be seen between the two environments in terms of reaching trajectories.

Figure 5-3 illustrates the subject's movement completion ratio when reaching toward each one of the six targets of interest in both environments in each session of practice. Clear improvements in the subject's reaching movements can be observed in both environments. In the same figure, the jerkiness measure is also plotted on the second axis to display its relationship with the subject's movement completion ratio. In targets 1, 2, 3, and 6, there was a progressive increase in the movement jerkiness until the subject reached a plateau. Following that, the jerkiness value started to decrease in the following sessions.

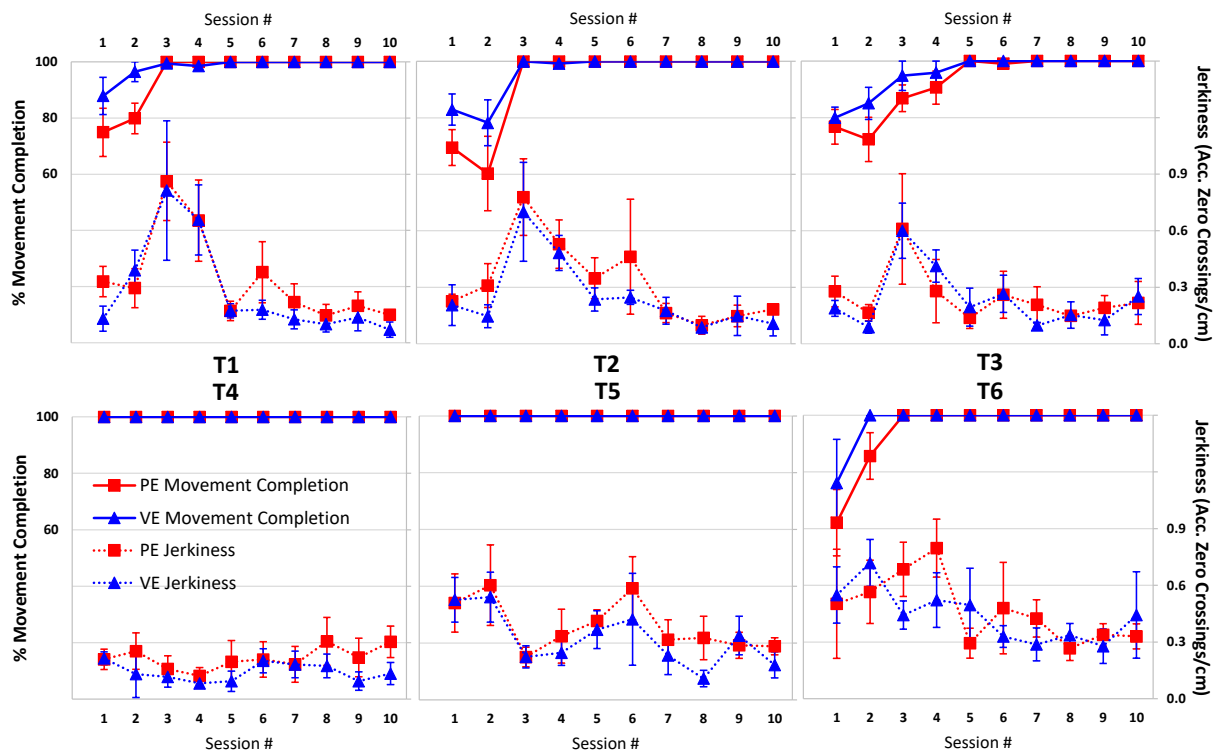


Figure 5-3: Movement completion ratio and jerkiness for each session. The error bars represent 95% confidence interval. T1 to T6 indicate target numbers. PE and VE represent Physical and Virtual environments. Acc.: Acceleration.

Changes in mean speed and straightness measures over the 10 sessions of practice are shown in Figure 5-4. The mean speed over the 10 sessions did not vary much and while the values differed among the targets, there was no clear trend. On the other hand, the straightness measure did vary across the sessions. However, similar to the jerkiness measure, there was a trend in targets 1, 2, 3 and 6 showing increase of straightness toward the last 3-4 sessions of the RT. We did not find any meaningful differences between the two environments in terms of kinematic measures (figures 2-4); some of the differences between PE and VE were negligible and others were inconclusive.

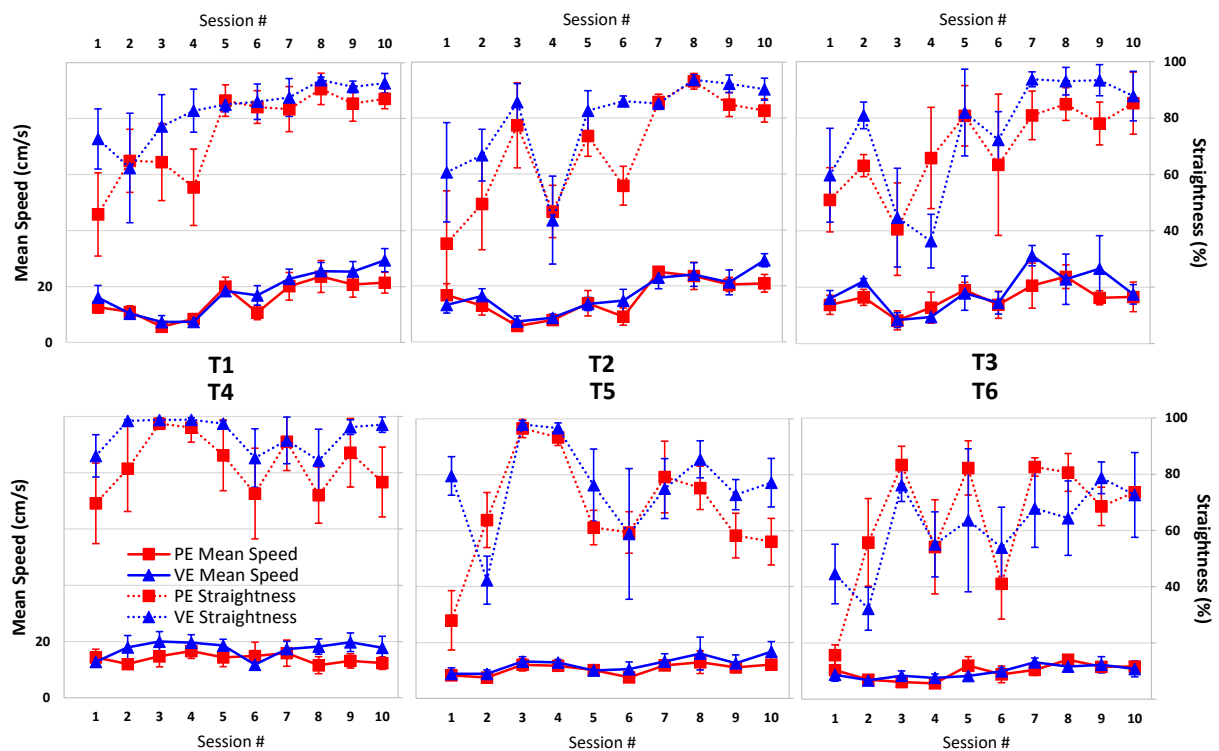


Figure 5-4: Mean speed and straightness for each session. The error bars represent 95% confidence interval. T1 to T6 indicate target numbers. PE and VE represent Physical and Virtual environments.

The FMA-UE improved by 3 points, from 18 prior to the experiment to 21 at the end of last session. At the sixth session, the subject reported (with a lot of emotion) that while she had not been able to push the elevator button with her right hand in the last 20 years following her stroke, she has become able to do it; we checked this with her on the last session and she said she has become very comfortable in doing it. She mentioned that this has been the most effective therapy she had experienced and she wanted to know if there was a way she could continue the robot-assisted therapy sessions.

5.6 Discussion

This study clearly demonstrates that even in long-term chronic stroke cases, RT can be used as an effective tool for regaining some UE motor function. The subject in this study had been dealing with stroke consequences in the last 20+ years and still benefited from RT. The improvements seen during the reaching practice were transferred to real life activities. In the current health care system, rehabilitation services are not offered for such cases; usually individuals with stroke are left on their own when they reach a chronic stage and their motor recovery plateaus (Page et al. 2004). RT could greatly benefit stroke patients in chronic stages even with little or no residual movements.

One of the reasons that might have contributed to the success of the subject to fully complete the reaching task was the minimization of fatigue by means of the robot. Indeed, the robot arm assisted the subject in two ways: by providing anti-gravity support to the UE and by assisting the subject in completing her reaching movements as soon as she asked for it. Therefore, the subject never reported any fatigue or pain during the practice sessions.

While improvements in kinematic measures were evident and measurable, the FMA-UE only improved by 3 points, which was below the minimal detectable change (MDC) of 5.2 (Lin et al.

2009) and/or minimal clinically important difference (MCID) of 7 (Sivan et al. 2011). A recent study, however, has shown that the MCID can be accepted at 4 (Lundquist and Maribo 2016). As we only focused on training the arm, not the wrist and hand, this may explain the lack of major improvement in FMA-UE score. Moreover, the tests in FMA-UE do not differentiate between the two aspects of movement: strength and motor control (Kitago et al. 2015). Therefore, it might not be a clear representative of the improvements by the subject achieved with RT.

We only performed one baseline (pre) measurement of FMA-UE and did not perform multi-baseline evaluations because of two reasons. First, the participant was in long-term chronic stage of stroke (20+ years post-stroke) and therefore we expected a stable and non-varying baseline in terms of motor impairment level for her. Second, the robotic arm was able to provide precise kinematic and kinetic data on the subjects' reaching movements at every session. Kinematic measurements are sensitive to small and more specific changes in UE movements, and since they are recorded by precise and accurate equipment they are not dependent on an experimenter's observations. In other words, the FMA-UE measure was accompanied and supported by a more precise, accurate and sensitive measurement and therefore we did not perform any other FMA-UE measures besides the pre- and post- measures.

It has been shown that there is a limited time window for enhanced neuroplasticity between 1-3 months post-stroke due to spontaneous reorganization and increased responsiveness to training and an enriched environment (Zeiler and Krakauer 2013). Outside of this sensitive time window, this heightened level of responsiveness to treatment would fade away. It is suggested that the neural mechanisms underlying motor learning in chronic stages are somewhat similar to those in healthy adults where no cortical reorganization or repair takes place (Zeiler and Krakauer 2013); whether

this is the case or whether experience-dependent neuroplastic changes can occur in chronic stages of stroke should be investigated by neuroimaging studies of motor improvements.

The subject reached a plateau in her motor performance at different sessions for different targets. In the sessions leading to a plateau, there was a clear increase in jerkiness. Following the plateau, the jerkiness started decreasing. Due to a lack of neuroimaging studies, the underlying neurological mechanism responsible for these improvements in the kinematic measures are still unknown (Buma et al. 2016). However, the theory of sub-movements blending during a motor recovery in stroke has shown that during post-stroke recovery, the criterion for refinement of movement patterns is not constrained to improving smoothness measures such as jerkiness but more toward gaining back the function; following the regain of the function, the jerkiness improves (Rohrer et al. 2002). In other words, jerkiness exhibits a non-monotonic behaviour during motor recovery. However, other kinematic measures such as straightness exhibit monotonic behaviour during the course of recovery, where they reach a plateau (Rohrer et al. 2002). This can be observed in our case for the straightness measure. For the targets where the subject was already able to complete the movement at the first session, i.e. 4 and 5, the straightness varied across sessions and no improvement could be seen. However, for the targets where the subject re-learned to complete the movement with the help of RT (i.e. targets 1, 2, 3 and 6), a clear trend of improvement in the straightness measure can be seen, even though it was still variable. Therefore, the lesson that can be learned is that the decision to stop the training of a movement should not be based only on the movement plateau but also on improvements of other outcomes such as jerkiness. Tracking these changes is possible by RT (Bosecker et al. 2010).

Lastly, we did not find any noticeable and/or meaningful differences in terms of the movement variables (speed, straightness, and jerkiness) between the two environments. This can be explained

by a study on healthy subjects comparing reaching tasks in physical vs virtual environment in presence/absence of visual/haptic feedback (Ebrahimi et al. 2016) in which the results showed that the subjects' performance was similar in both environments when the subjects had visuo-haptic feedback in VE. In our study, besides the presence of visual feedback in VE, the robot arm provided haptic feedback at the endpoint for the subject by stopping her when the virtual button was reached. Also, both PE and VE shared the same haptic feedback in terms of forearm attachment to the robot arm.

5.7 Acknowledgments

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Chapter Six : CHANGES IN ARM KINEMATICS OF CHRONIC STROKE INDIVIDUALS FOLLOWING ROBOT-ASSISTED TRAINING IN VIRTUAL AND PHYSICAL ENVIRONMENTS: A PROOF-OF-CONCEPT STUDY

6.1 Preface

So far in Chapter Four, we showed that in a single session of practice with the “Assist-As-Asked” RT protocol, the training environment is not crucial. In Chapter Five, we conducted a case study of a long-term chronic stroke to validate the assist-as-asked RT protocol. In this chapter, we present the results of a proof-of-concept study on chronic stroke patients with moderate-to-severe upper limb who used our assist-as-asked robot-assisted training protocol in both environments over multiple sessions of training. We investigated both the feasibility and benefits of this new protocol and also verified the effect of environment in robot-assisted training. This manuscript is potentially acceptable by the Journal of NeuroEngineering and Rehabilitation pending resubmission of a revised manuscript. The revised manuscript (6.2 - 6.8) was submitted on July 30, 2018 and is currently under review.

Citation: This manuscript is submitted to the *Journal of NeuroEngineering and Rehabilitation* (Manuscript ID: JNER-D-17-00249R2; accepted pending revision).

6.2 Abstract

Background: The main goal of this proof-of-concept study was to identify clinical benefits and potential adverse effects of a custom-developed robot-assisted training protocol, named “Assist-As-Asked”, aiming at improving arm function of chronic stroke subjects with moderate-to-severe upper extremity motor impairment. The secondary objective of this study was to investigate the feasibility of this training protocol in both physical and virtual environments.

Methods: A sample of convenience of four chronic stroke subjects participated in 10 half-hour sessions. The task was to practice reaching six targets in both virtual and physical environments. The robotic arm provided gravity support and used the “Assist-As-Asked” paradigm (helped subjects to complete movements when asked by them). Changes in the kinematics of the reaching movements were the primary outcome measures of interest. The subjective perception of the subjects about the reaching practice in both environments and change in scores of Upper Extremity section of Fugl-Meyer Assessment were the secondary outcome measures.

Results: Subjects noticeably improved their reaching performance, which was accompanied by 3-5 points improvement in Fugl-Meyer Assessment-Upper Extremity score. None of the subjects reported any adverse events. There were no differences between the two environments in terms of kinematic measures even though subjects had different opinions about the environment preference.

Conclusion: Moderate-to-severe chronic stroke survivors may benefit from robot-assisted training using “Assist-As-Asked” paradigm. In designing a robot-assisted training platform for moderate-to-severe chronic stroke survivors, choice of environment, either physical or virtual, may not necessarily influence the outcome of therapy sessions.

6.3 Background

Motor impairment following stroke is one of the main sources of long-term disability in the world. When looking at the *disability-adjusted life-years* as a measure of how many years of life are lost and lived with disability, stroke is the fourth leading cause in adults worldwide; it is the leading cause of lost disability-adjusted life-years among adults between 45 and 69 years of age (Mukherjee and Patil 2011). At 6 months post-stroke, only 5%-20% of hemiplegic stroke survivors show complete recovery of arm function while 30%-66% show no sign of function in their paretic arm (Kwakkel et al. 2003). While the intensity of therapy and increase in number of repetitions have been shown to directly impact stroke recovery (Kwakkel 2006; Langhorne et al. 1996), lack of resources and related costs have prevented conventional therapy to be replaced by intensive therapy. Therefore, in stroke survivors who have reached their chronic stage, we are faced with a subpopulation of individuals with moderate-to-severe (MTS) upper limb (UL) motor impairments who are still suffering from decreased UL function, impairing their ability to perform daily activities independently, and are not receiving any rehabilitation services. Developing a suitable and cost effective therapeutic solution for this subpopulation is an important task.

The notion of “one-size-fits-all” does not apply in neurorehabilitation of stroke; different treatment protocols and therapeutic techniques should be tailored individually based on each patient’s needs, physical capabilities, condition, performance and even biomarkers. Robotic systems benefit from elements that place them in a better position to provide required therapy for regaining of motor function in MTS stroke patients and its evaluation; elements such as providing highly intensive and challenging practice, assist-as-needed protocol, task-specific and goal directed movements, and movement reproducibility while allowing for kinematic/kinetic measurements. Properly designed robot-assisted therapy (RT) systems that target the requirements of MTS stroke patients

can be exploited in clinical settings and even in home settings (Sivan et al. 2014) to provide an intensive therapy which is more effective than conventional therapy; studies have shown that RT (which takes much less time and effort of a therapist compared to conventional therapy) is as effective as dose-equivalent intensive conventional therapy (Norouzi-Gheidari et al. 2012) and sometimes even more effective when designed properly, e.g. RT with three dimensional (3D) tasks (Reinkensmeyer et al. 2012).

To achieve the high number of repetitions required for regaining motor function, keeping patients actively engaged during the therapy session and having them adhere to the rehabilitation program is of the utmost importance. Motivation plays a key role in this regard. Virtual environment (VE) based rehabilitation systems greatly benefit from this concept, i.e. increasing patients' motivation, besides other advantages that they offer (Bayón-Calatayud et al. 2016). However, VE-based rehabilitation systems are mostly used in mild-to-moderate stroke patients (Saposnik and Levin 2011) because of their nature of not being able to provide direct movement assistance to MTS stroke patients with none/limited UL movement. A hybrid system in which a robotic device is coupled with a VE can take advantage of both technical advancements and might benefit the MTS stroke patients. But a question arises about whether this is necessary in the case of MTS stroke or not; robots enable MTS stroke patients to complete the unsuccessful movements during therapy sessions that otherwise would be unattainable and also can provide feedback about their performance; these are important motivation factors (Bejarano et al. 2016). In addition, there is no need for having a complex VE scene for chronic stroke patients with MTS motor impairments as higher repetition of simple tasks seems to be preferable than a task-oriented practice where patients have a hard time or are unable to complete the task (Fischer et al. 2007). So, in designing an RT system for helping MTS chronic stroke patients, the role of robot may be more prominent than the

VE itself. Therefore, there is a question as to whether there is any superiority coupling the robot with a VE than coupling it with a physical environment (PE) and whether movements made in the VE are similar to those made in the PE, when the task requirements are the same.

While there is a shift in rehabilitation from Impairment-Oriented Training to Task-Oriented Training (Rensink et al. 2009), an RT study showed that in MTS chronic stroke individuals, training the arm and hand in a task-oriented training was not superior than training the arm alone (an impairment-oriented training approach) in terms of restoring the UL functionality (Krebs et al. 2008). A recent randomized controlled trial on chronic stroke individuals with moderate UL motor deficit also reported that a structured task-oriented training is not superior to a dose-matched (or even a lower dose of) usual and customary occupational therapy (Winstein et al. 2016b). In other words, in an MTS chronic stroke patient, at least some basic elements of motor control need to be restored, i.e. restoring the patient's UL function into mild-to-moderate motor impairment level, before starting a task-oriented training. Based on this concept, an impairment-oriented training approach in sub-acute stroke individuals with severe arm paresis has been shown to be effective in improving UL motor function (Platz et al. 2005) and the authors suggested that the severity of the paresis should be a key factor in choosing the therapeutic approach.

By considering all the above, we have developed a robot-assisted protocol aiming at improving arm function of chronic stroke subjects with MTS upper extremity motor impairment. The “Assist-As-Asked” paradigm is introduced in this new scheme where the robot only helps a subject when the subject asks specifically for help. As a prerequisite for a large-scale randomized controlled trial, a feasibility study was required to identify clinical benefits, potential adverse effects, and whether practicing in a physical or virtual environment would make any difference in the outcomes of interest. Therefore, we performed this study on four subjects

matching the inclusion/exclusion criteria to evaluate the system's usability and to determine whether our robot-assisted arm reaching protocol is beneficial in retraining the arm function of chronic stroke individuals with MTS UL motor impairment. In addition, we evaluated the users' perceptions about the system in both environments in terms of motivation and preference. We expected that our robot-assisted protocol would improve chronic stroke subject's motor performance over the course of the training and hypothesized that the choice of environment would not affect the kinematics of the reaching task.

6.4 Methods

6.4.1 Subjects and Setting

Within the limited time period of this proof-of-concept study, we recruited a sample of convenience of 4 chronic stroke subjects from the Greater Montreal area in Canada. In a preparatory test, these stroke subjects required robotic assistance for completion of the reaching task. All the stroke participants were right-handed with right-side hemiparesis and capable of understanding verbal instructions in either French or English. None of the subjects had hemispatial neglect or any visual problem which was not corrected by eyewear, any upper limb surgery, any pain interfering with the arm function (the Shoulder Pain section of the Chedoke-McMaster stroke assessment (C-M) (Gowland et al. 1993) was between stages of 1 and 4), any neurological or neuromuscular conditions other than stroke, or any structural changes secondary to stroke (passive range of motion of the elbow and shoulder restricted more than 20°). Table 6-1 shows the characteristics of the four stroke subjects who participated in this study. The study was done at the Laboratory for Advanced Technology in Rehabilitation of the Jewish Rehabilitation Hospital in Laval, Canada. All subjects provided their informed consent, as approved by the local ethics committee.

Table 6-1: Characteristics of chronic stroke individuals participated in this study.

P. #	Gender	Age (years)	Time since Stroke (years)	C-M	FMA-UE	Type of Stroke	Side of Hemiparesis
1	M	53.1	1.6	3	15	Ischemic	Right
2	M	59.8	2.7	3	13	Hemorrhagic	Right
3	F	49.0	20.9	3	18	Ischemic	Right
4	M	53.2	6.6	3	14	Ischemic	Right

P. #: Participant No.; M: Male; F: Female; C-M: Chedoke-McMaster stroke assessment; FMA-UE: Upper Extremity section of Fugl-Meyer Assessment

6.4.2 RT Protocol

The HapticMaster (MOOG Inc.) robotic arm (van der Linde et al. 2002) was used as the primary tool for providing anti-gravity and guiding force to the subjects when needed and also for measuring the subjects' arm movements in 3D space. The HapticMaster is a three degree-of-freedom, programmable endpoint robot which spans a workspace of approximately 1 m³, with low friction and is equipped with force and position sensors (Figure 6-1). The system can be programmed to create pre-defined and feedback controlled 3D force fields. A forearm splint, in which the subject's arm is placed, is linked to the robot arm through a universal joint providing three rotational degrees-of-freedom (passive). The robot arm runs at a fixed update rate of 2500 Hz which guarantees a smooth and realistic experience by users. The force can be measured and applied with a precision of 0.01 N precision and the position measurements are accurate to 0.012 mm.

The robot arm assisted the arm movements of subjects in 3 ways. A) Virtual Tunnel: before the start of the reaching movement, a virtual tunnel (radius: 4 cm) was created, linking the starting position to the target of interest, thus preventing unwanted deviation of the subjects' arm movement from the ideal straight-line path. B) Gravity Support: It always provided gravity support by not letting the subject's forearm drop. C) Assist-As-Asked Paradigm: When a subject asked for

help to complete a movement, the robot arm provided a guiding force to assist the subject in completing the reaching task; when assistance was turned on, the robot produced a virtual spring, with elastic constant of $k = 400 \text{ N/m}$. The spring was then moved at a constant velocity of 5 cm/s towards the selected target, thus smoothly helping the subject in reaching that target. The maximum amplitude of the guiding force was set at 150 N . The effect was like having a spring attached between the subject's forearm and the target, then pulling from the target end of the spring at a constant velocity. During the experiment sessions, the experimenter was near the subject all the time and the robot arm was equipped with software and hardware safety switches, so that the subject or the experimenter could rapidly turn it off.

6.4.3 Experimental Setup and Procedure

Subjects were required to perform the same reaching task in both PE and VE (Figure 6-1) in ten sessions over a course of a month. In each session, subjects were seated on a chair, either in front of a vertical board when performing in PE, or a screen when performing in VE. The affected forearm, i.e. right, was attached to the forearm splint of the robot arm. Based on a pseudo-randomization, subjects either started the experiment in PE followed by VE, or vice versa, in each session.

The experiment in PE consisted of a reaching task to six buttons/targets placed on two rows, each with three buttons with a diameter of 6 cm (Figure 6-1A). The targets were numbered 1, 2, 3 from left to right on the top row and 4, 5, 6 on the bottom row. These six targets were attached to a hinged wooden board. The board was placed so that the middle and right targets (2, 3, 5 & 6) were positioned in front of the subject, parallel to the coronal plane; the two leftmost buttons (1 & 4) were angled at $\sim 130^\circ$. This arrangement of buttons was preferred to account for the shorter range of motions when reaching for the objects placed contralateral to the moving arm. The top and

bottom rows of targets were spaced 25 cm apart; the left- and the right-side buttons were placed 15 cm and 30 cm away from the middle buttons, respectively. A light-emitting diode was placed on top of each button. The height of the experiment board was adjusted in a way that the middle bottom target (#5) was at the level of the subject's xiphoid process of the sternum. Then, based on the subject's right arm length, the experiment board was moved at a distance from the subject so that 150° of elbow extension was required to reach the middle bottom target (#5). The starting position was set at the 14 cm in front of the xiphoid process of the sternum. This configuration allowed different upper limb muscle group activations when reaching for the 6 targets; it covered flexion, extension and abduction in different directions.

VE mimicked PE: a virtual scene showing the wooden board with six call buttons (Figure 6-1B). VE was created by projecting images at 120 Hz to a projection screen, providing a 3D perspective view of the experimental scene. VE was calibrated to have the same metrics as for PE. The position of the robot arm's end effector was displayed as a hand in VE. Movements of the robot arm and hand were reproduced onto the 3D VE on a one-to-one scale.

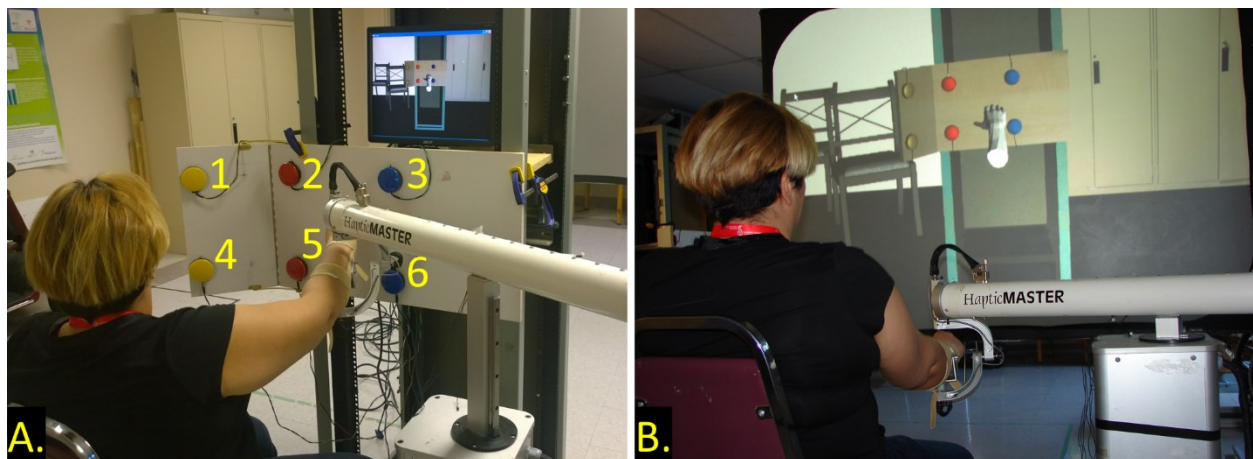


Figure 6-1: A. The Physical Environment and B. The Virtual Environment

In either environment, subjects were instructed to move at a comfortable speed while doing their best to reach and press the target buttons without using any compensatory trunk movements; the experimenter was monitoring every trial and if an excessive compensatory movement was observed, that trial was repeated. If a subject could not reach the target, s/he asked for the robot's assistance by saying the word "force" and the experimenter turned the guiding force on so that the robot would assist in completing the rest of the reaching movement. To allow subjects to try their best in performing the task before asking for the robot assistance, we did not limit their number of reaching attempts or time in any of the trials. During the robot assistance, the subject was still encouraged to continue his/her effort. In PE, one of the light-emitting diodes above the targets was pseudo-randomly turned on to indicate the reach target. In VE, the target button was visually highlighted. In PE, the movement end was indicated in the recording when the target button of interest was physically touched by the subject. In VE, as there was no physical target button present, the robot arm stopped the subject when the target of interest was reached in the virtual space and a "click" sound was played, similar to that of a physical button. When the subject completed a trial, either with or without help of the robot arm, the percentage of the movement distance that was completed without the robot's assistance was displayed as feedback on a monitor placed above the experiment board in PE and displayed on the screen in VE. The robot arm then actively moved the subject's arm back to the starting position. During each session, there were 5 reaching trials to each button, for a total of 30 trials in each environment, summing up to 60 trials per session. There was a short break (less than 5 min) when switching between the two environments. If a subject asked for a break between trials, it was given. Any occurrence of adverse events, such as increased pain, motion sickness, dizziness and headaches during engagement with

the system as well as development of new symptoms during the course of experiment, were recorded for reporting.

6.4.4 Outcome Measures and Data Analysis

To analyse the movement, the trajectory data was digitally low-pass filtered using a Butterworth filter with a cut-off frequency of 6 Hz (dual-pass). Then several kinematic metrics from the trajectory data were extracted as the primary outcome measures of interest. The analysis only focused on the portion of movement that was solely performed by the subject, without assistance from the robot. The kinematic metrics were: 1) *movement completion ratio*, defined as the ratio of the straight-line distance completed by the subject over the distance between the starting point and the target; 2) *mean speed* over the path line (i.e. trajectory); 3) *shakiness*, defined as the number of acceleration profile zero crossings over the path line. A lower shakiness value represents a smoother movement in terms of being less jerky. Subjects were only instructed to reach to the targets (the only set goal); thus, when they reached close to their movement limit, they sometimes struggled to go further. This made the last five percent of some reaching movements very different from the other parts of the trajectory. Therefore, the last five percent of the trajectory in terms of distance was excluded from the movement analysis. To have an accompanying clinical measure to the kinematic outcome measures, the Upper Extremity section of Fugl-Meyer Assessment (FMA-UE) was used as the secondary outcome measure (Fugl-Meyer et al. 1975); the FMA-UE was measured at the first session prior to the start of the experiment and after the last session following the completion of the experiment for all the subjects.

As the PE and VE trials were done in the same session, carryover effect analysis was performed on the “movement completion ratio” measure to investigate whether having such an experimental design allows comparison between the two environments. To this aim, the order of environments

in each session was compared with the difference in performance between the two environments over three categories of *less*, *more*, and *equal* performance. Two “movement completion ratio” measurements were considered equal if were within 5% difference. As the subjects reached 100% *plateau* in some of the trials, those plateau trials were separated from the equal category and were added as the fourth category.

Along with the kinematic metrics, a custom questionnaire was developed to assess how the stroke subjects perceived and experienced the reaching task in both environments using a modified version of the Intrinsic Motivation Inventory (modified-IMI) (McAuley et al. 1989) combined with a modified Short Feedback Questionnaire (modified-SFQ) (Kizony et al. 2005). The modified-IMI consisted of ten questions divided into five items: Interest/Enjoyment, Perceived Competence, Effort/Importance, Pressure/Tension, and Value/Usefulness. The modified-SFQ consisted of two questions about Repeating the experiment and Comfort of the experiment. There were three additional questions about which environment they preferred, which one was easier for them and whether they felt fatigued.

6.5 Results

The results are presented for both environments to provide an illustration of their differences. During the course of the experiment, none of the subjects reported any adverse events such as increased pain or development of new symptoms. Training sessions varied between 30 and 40 minutes. Over the 10 sessions of training, we observed evident changes in movement completion ratio of all the subjects; the subjects became more independent in completing the reaching task and did not require much help from the robot when compared to the first session. In all the subjects, multiple reaching attempts during a single trial before asking for the robot assistance were observed. Figure 6-2 shows the forearm trajectories of one of the subjects in both environments

during the first and last session; the progression/improvement can be well seen in the figure in which the black lines represent the subject's self-movement trajectories without any robotic assistance and the green (lighter) lines represent the portion of movement completed with the robot's assistance. The shaky trajectories of the robot assistance show that the subject continued interaction with the robot during the robot assistance.

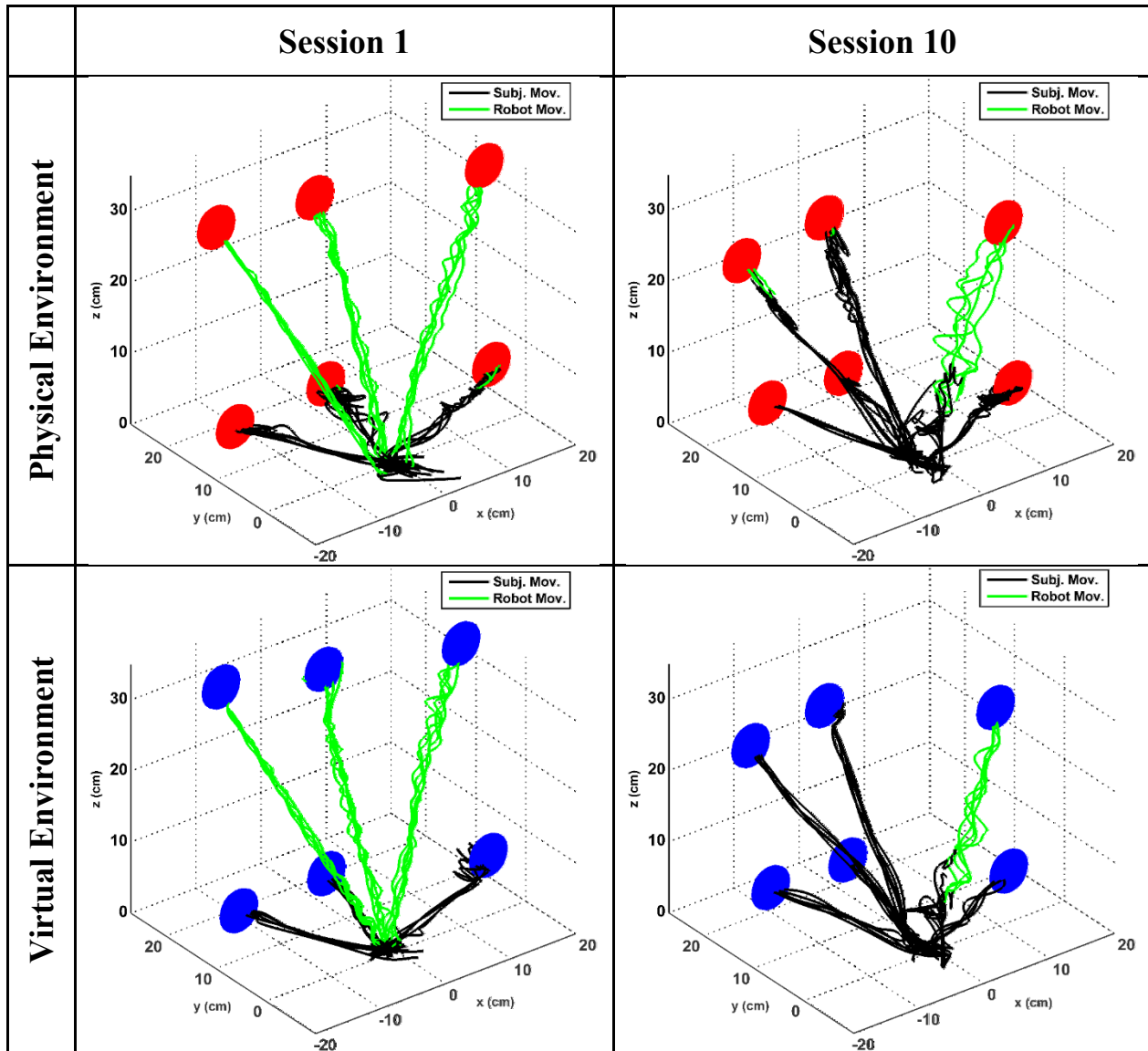


Figure 6-2: Typical trajectories for session 1 and session 10 in both environments. Black lines represent the trajectory performed by the subject (no robot assistance). After 10 sessions of practice, the improvements in reaching without robot assistance are quite evident. No noteworthy difference can be seen between the two environments in terms of reaching trajectories.

To illustrate each subject's improvement in reaching performance following the 10 sessions of practice, we showed each subject's self-movement in the first session versus the last session in

reaching the six targets of interest in both environments in Figure 6-3. Clear improvements in each subject's reaching in both environments can be observed in this figure.

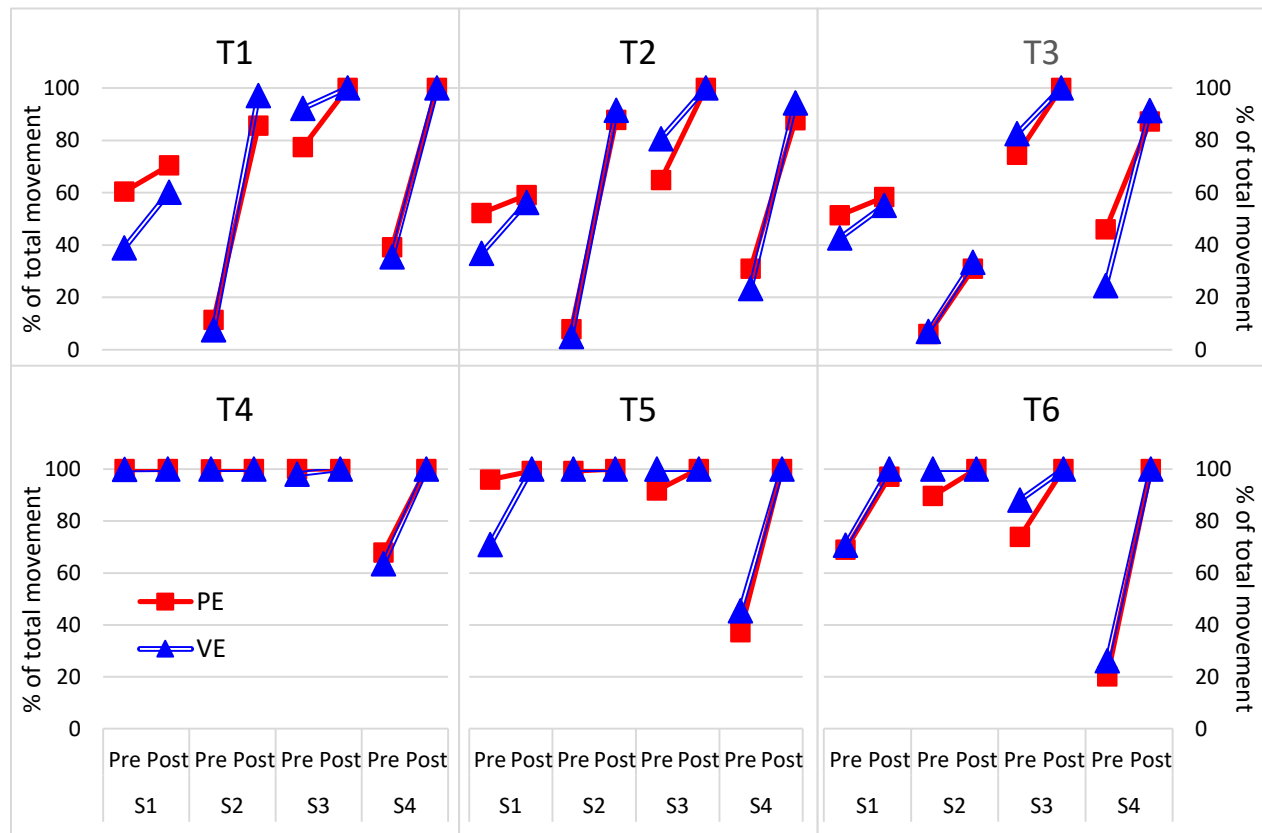


Figure 6-3: Changes in subjects' self-movement in reaching between session 1 (Pre) and session 10 (Post).

This improvement in reaching was achieved in most cases in less than 10 sessions and reached a plateau; this plateau was dependent on the subject and the target (Figure 6-4) but not the environment. We defined the plateau session as the session in which a subject's self-movement graph reached its highest peak with no apparent decline in improvement (no more than 5% change in average decline of the following sessions). There were negligible and inconclusive differences between PE and VE in terms of the plateau session number and the amount of final self-movement completion. Subjects 1 and 4 never reached a plateau in targets 1, 2 & 3 and 3, respectively, while completing 60% and 90% of the whole movement in those targets, respectively. For Subject 2,

while the plateau was reached in the third session in target 3, it was stopped at 35% of the whole movement for the rest of sessions and the subject could not improve his independent reaching movement towards that target. Target 4 (bottom left) was the easiest target for the subjects to attain 100% of movement completion ratio. It was followed by target 5 and then 6 (bottom middle and right, respectively). The upper targets were harder for the subjects to improve their reaching performance during the study sessions.

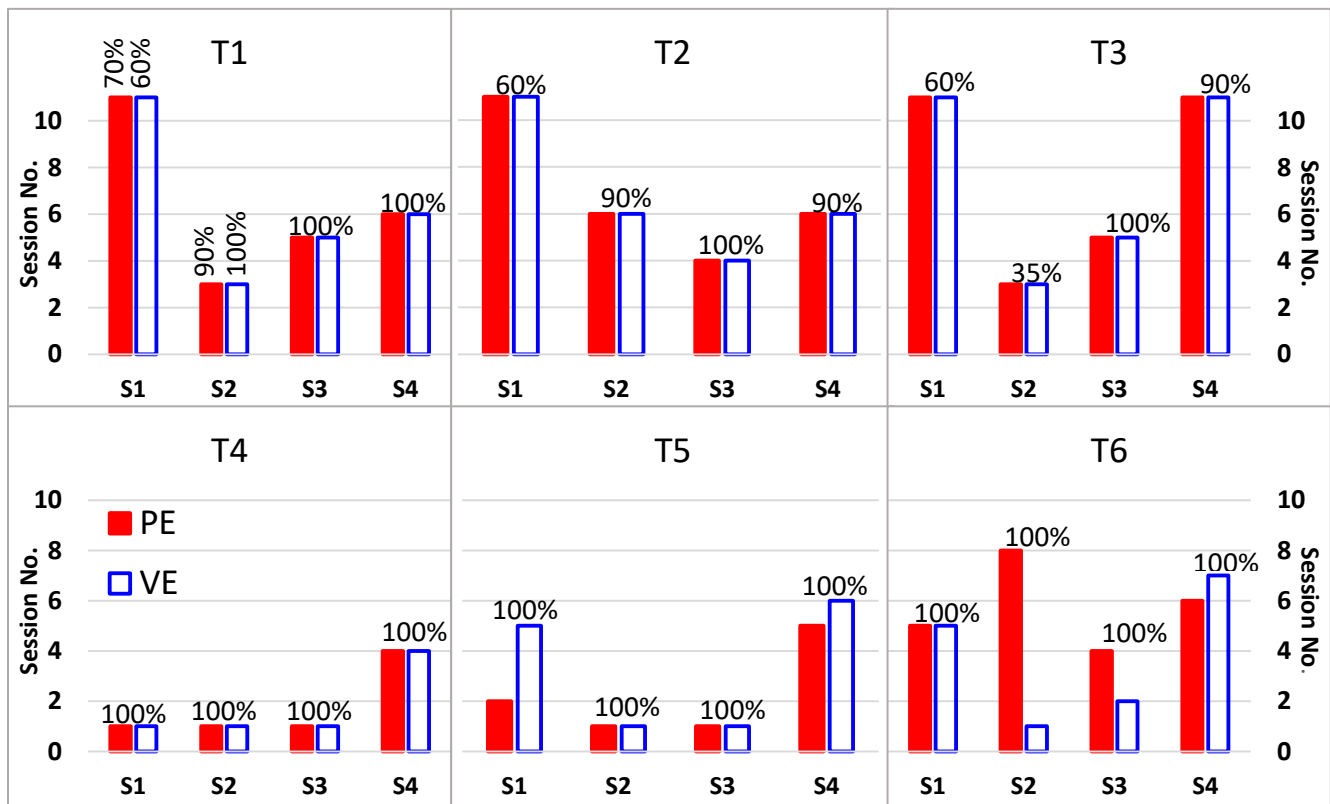


Figure 6-4: The session number that each subject reached their self-movement plateau during the 10 sessions of reaching practice. Values more than 10 sessions indicate that the plateau was not reached (S1 in T1, T2 and T3 and S4 in T3). The amount of subject's self-movement following plateau is also indicated as a percentage on top of each bar (rounded to the nearest tens place). In the cases that the plateau was not reached, the subject's self-movement at the last session is also indicated on top of the bar.

Changes in the average shakiness measure between the sessions that the subjects reached a plateau and the sessions after the plateau are illustrated in Figure 6-5. There has been a reduction in the average shakiness measure after reaching the plateau in all the subjects except for Subject 1 (and Subject 4 at targets 1 & 2 in PE). We did not find any noticeable differences between the two environments (PE and VE) in terms of changes in shakiness measure.

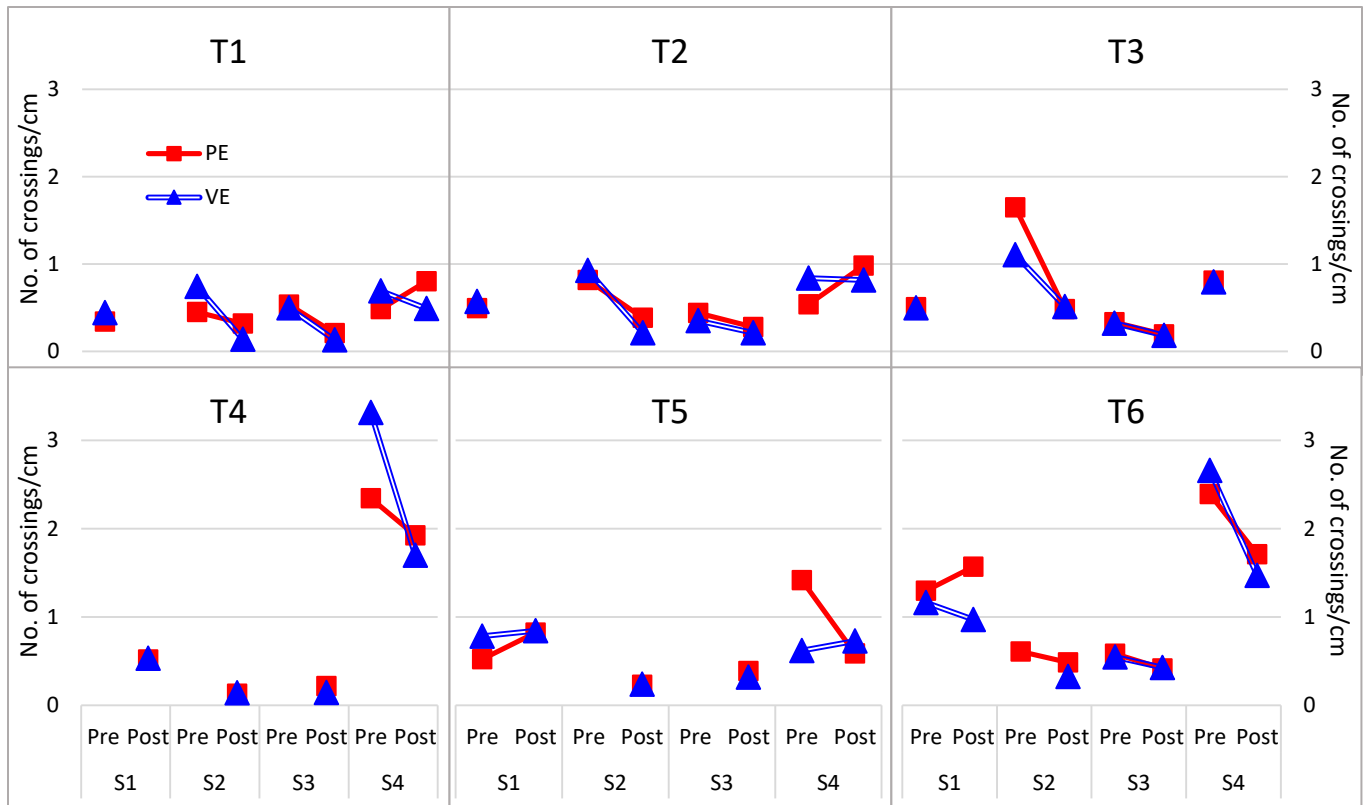


Figure 6-5: Changes in the Shakiness measure between the plateau session (marked as *Pre*) and the last session (marked as *Post*). At those that plateau was not reached only the shakiness measure of the last (10th) session is shown on *Pre* value. At those that plateau was reached right at the first session, the shakiness measure of the last (10th) session is shown on *Post* value.

In terms of Mean Speed outcome measure, the visual inspection of all the subjects' data did not reveal any trend across the ten sessions of practice. However, some differences/trends in the mean speed between the targets were noticed. Figure 6-6 shows the average and standard deviation of

the mean speed over the ten sessions of the study in reaching each target for each subject. No noticeable differences between the two environments can be seen in this figure. The common trend among all the subjects was in the lower targets (i.e. targets 4, 5 and 6) in which all the subjects, in either environment, demonstrated the highest speed when reaching for target 4, followed by targets 5 and then 6.

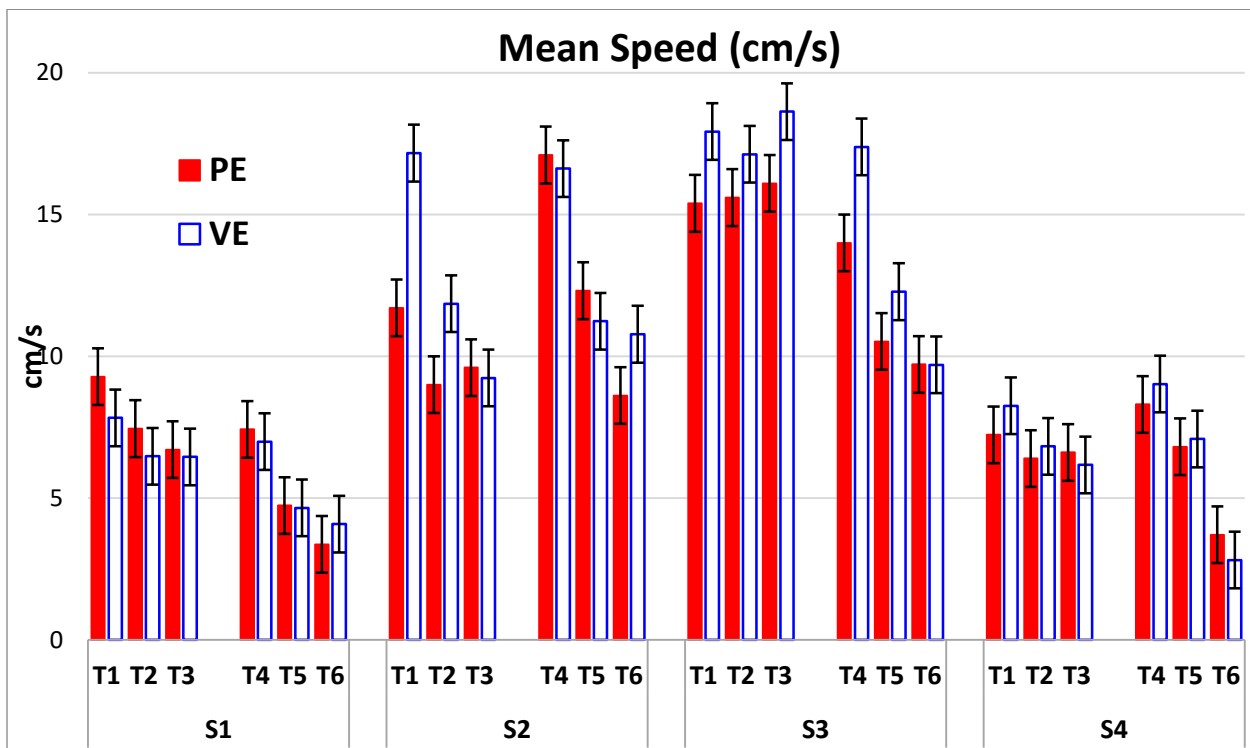


Figure 6-6: Difference in Mean Speed between targets for each subject in both environments. Each bar shows the average of the mean speed outcome measure for a specific target through all the sessions and the error bar shows its standard deviation. S1 to S4 indicate subject IDs. T1 to T6 indicate target numbers. PE and VE represent Physical and Virtual environments.

The results of carryover effect analysis are displayed in Table 6-2. The “PE-VE” represents that PE trials were performed first by the subjects followed by VE, while the “VE-PE” shows the reverse order. The differences between the “movement completion ratio” of PE and VE (VE was subtracted from PE) was categorized into 4 sections of “PE<VE” (less), “PE>VE” (more), “PE=VE” (equal within 5% difference) and “PLATEAU” (in both PE and VE, the “movement

completion ratio” has reached 95%-100%). The “No. of Trials” in the “PE-VE” order shows that if there was a carryover effect, we would have seen a higher number of trials in “PE<VE” category; however, this is not the case and all the three categories have similar number of trials. On the other hand, in the “VE-PE” order, presence of carryover effect should have caused higher number of trials in “PE>VE” category which is not the case. In addition, the mean difference and its standard deviation do not show much difference between the categories based on the environment order. Figure 6-7 shows one of the subject’s “movement completion ratio” (self-movement) over the 10 sessions with the order of the environments being displayed. Similar to the carryover effect analysis in Table 6-2, no evident carryover effect can be observed in Figure 6-7.

Table 6-2: Carryover Effect Analysis on All the Trials of All the Subjects. “PE-VE” and “VE-PE” represent the environment order.

Movement Completion Ratio Difference Categories	No. of Trials		Mean Difference (%)		Standard Deviation (%)	
	PE-VE	VE-PE	PE-VE	VE-PE	PE-VE	VE-PE
PE<VE	23	22	-11.5	-17.1	5.4	10.4
PE>VE	27	12	15.7	12.2	11.0	7.6
PE=VE	24	15	0.4	-0.4	3.1	3.0
PLATEAU	64	53	-0.3	0.1	1.2	1.2

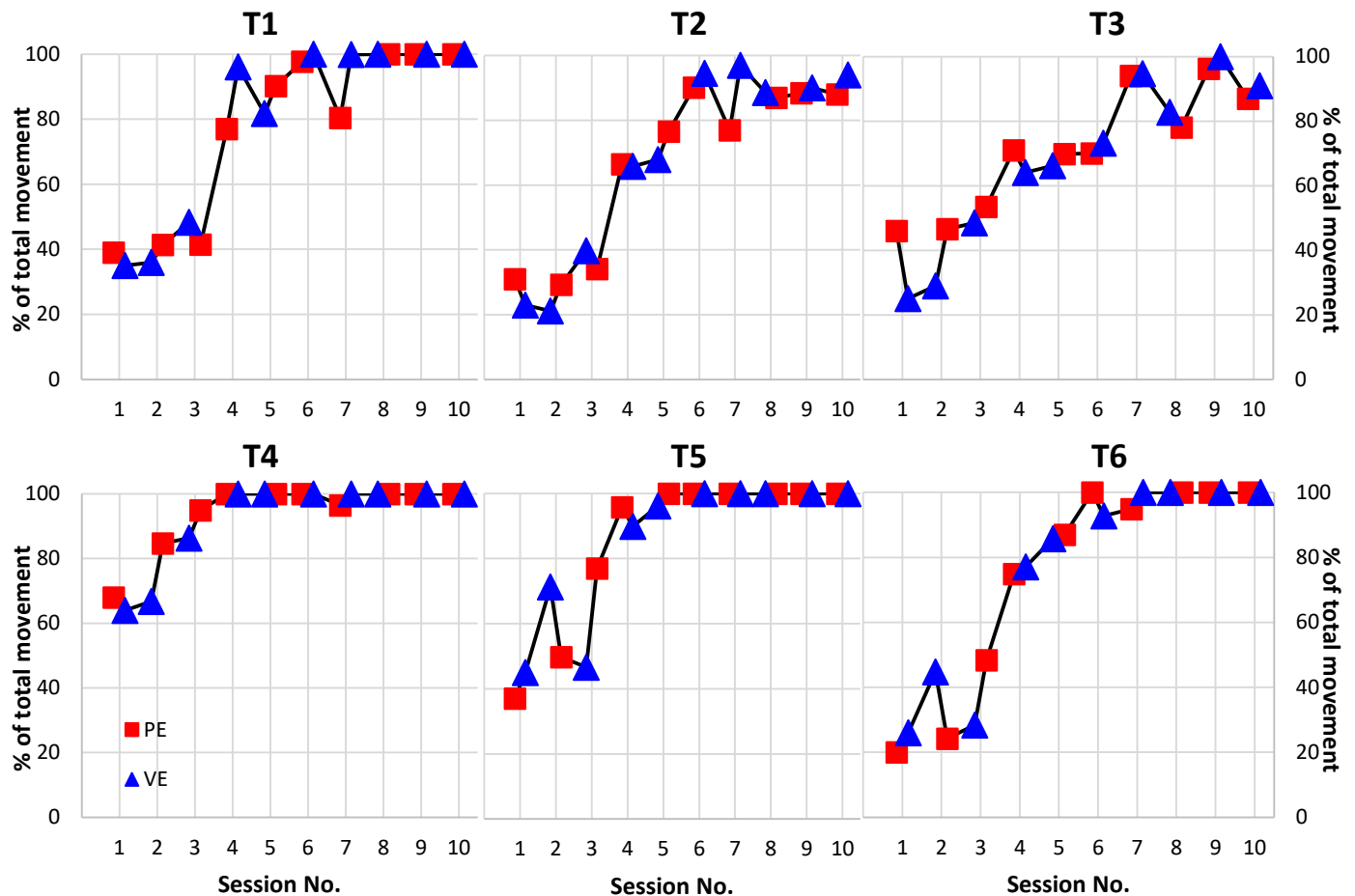


Figure 6-7: The order of environments across the ten sessions of training is shown for one of the subjects. No evident carryover effect can be observed.

The changes in FMA-UE scores prior to the start and following the end of the study are shown in Figure 6-8. All subjects showed improvement in their FMA-UE score following the completion of the study. These improvements were between 3 and 5 points. At the sixth session, S3 reported (with a lot of emotion) that while she had not been able to push the elevator button in the last 20 years following her stroke, she has become able to do it; we checked this with her on the last session and she said she has become very comfortable in doing it. She mentioned that this has been the most effective therapy she has taken and she wanted to know if there was a way she could continue the robot-assisted therapy sessions. Another subject, S4, showed a lot of excitement when

he became able to reach the targets during the sessions. S4 also reported that prior to this study, he had instances of burning his affected hand when opening the oven door, but now he has more control of using his affected hand when handling the oven door and have not had any burning incidence. These statements were self-reported by these two subjects.

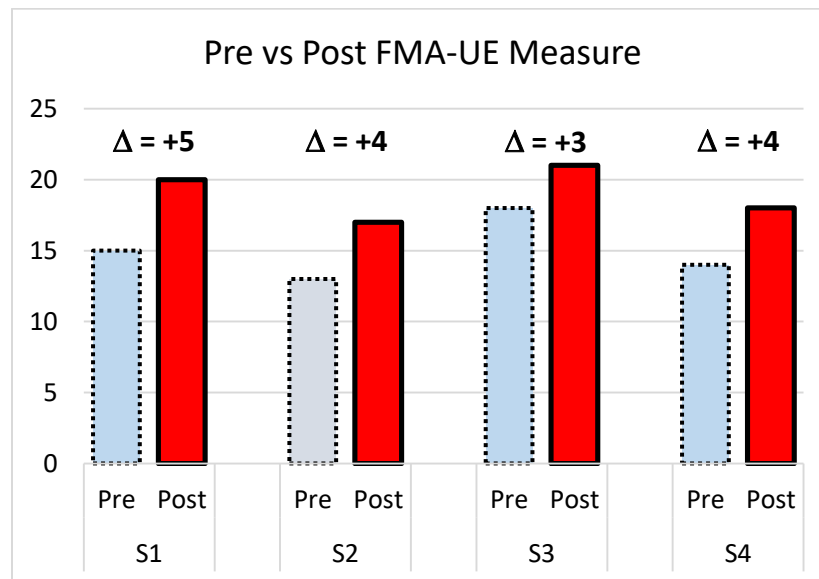


Figure 6-8: Changes in the FMA-UE scores of all the subjects before the start (Pre) and after the completion (Post) of the study. S1 to S4 are participant IDs.

The responses to the custom questionnaire is summarized in Figure 6-9. We did not find any noticeable difference between the two environments in terms of subjective experience. All the subjects expressed positive feedback in terms of enjoyment and interest and were comfortable in either environment. All of them were positive about repeating the task in either environment; two of them felt more toward PE and one felt more toward VE. They were all satisfied with their perceived performance/competence in both environments. All of them put “a lot of effort” in PE while two mentioned putting lesser effort in VE compared to PE. They felt some pressure in doing the tasks in both environments except one subject who felt being under a lot of pressure to do the task in PE. Two of them felt that the activity was very useful for their affected arm in either PE or VE, one felt that the activity in VE is very useful but somewhat useful in PE, and the other one

reported the opposite. The total IMI scores (out of 35) in PE vs. VE for participants 1 to 4 were 27 vs 23, 25 vs 24, 29 vs 28 and 32 vs 30, respectively. In terms of environment preference, two subjects chose PE and two chose VE. In terms of the environment being easier for the reaching task, one of them chose both environments as equal, two chose VE and one chose PE. Finally, all the subjects reported feeling some fatigue; two in PE and two in VE.

Receiving feedback on their movement was very important to the subjects. They were all asking how much of self-movement they achieved the session before for each target and were trying to improve their reaching performance based on that score.

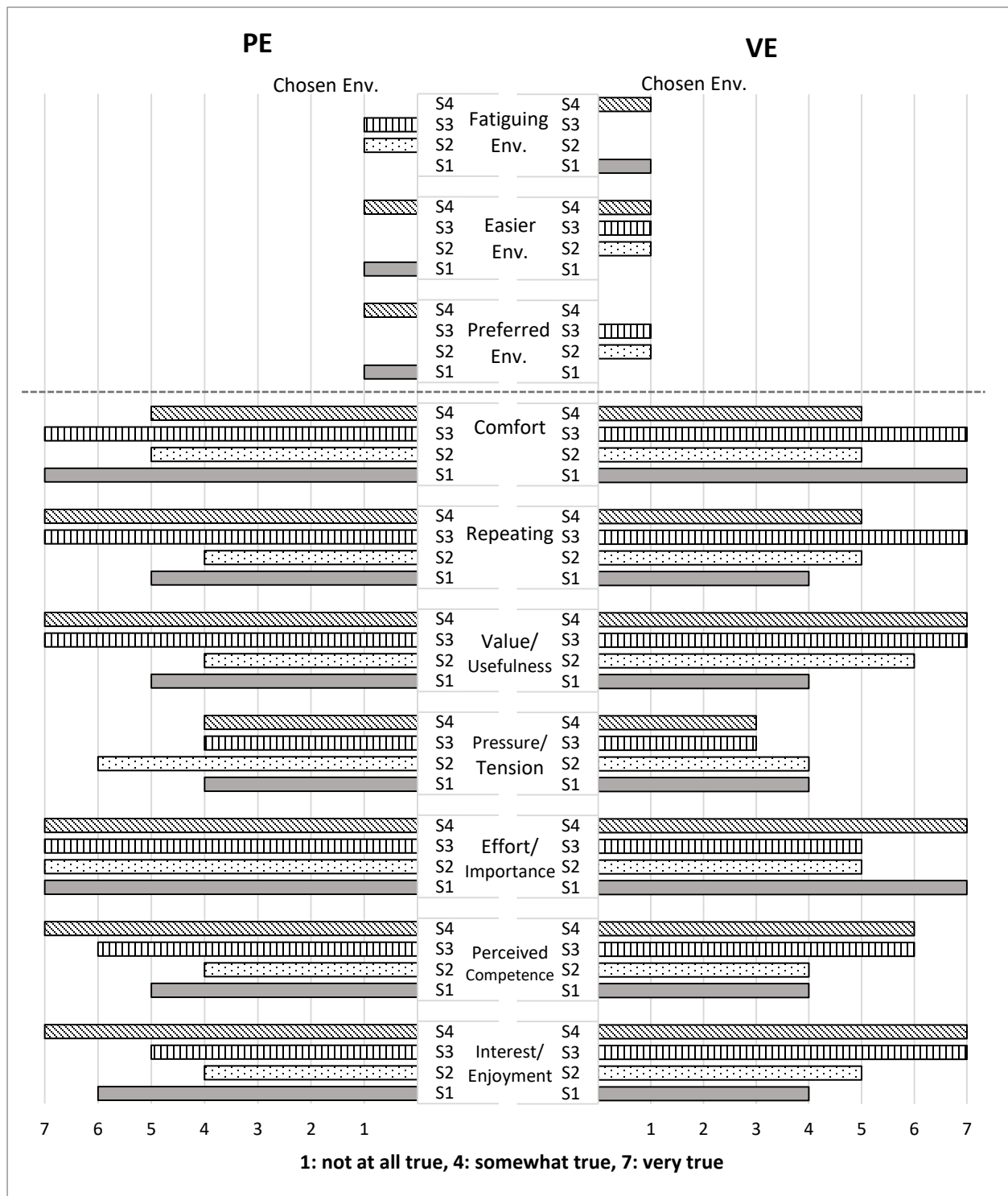


Figure 6-9: The responses to the custom questionnaire, consisting of modified-IMI, modified-SFQ and questions about the choice of environment (Env.). The modified-IMI and modified-SFQ used a 7-point Likert scale while the choice of environment were dichotomous questions. S1 to S4 are subject IDs.

6.6 Discussion

This study illustrates the potential benefits of the designed RT protocol in retraining of the arm function of MTS chronic stroke subjects. All the subjects increased their shoulder and elbow active range of motion by improving their arm reaching performance between the first and last session. None of the subjects reported any adverse events. We consider two possible factors involved in achieving such results. First, in developing this RT protocol specific to MTS chronic stroke patients, we only focused on arm reaching training of these individuals as opposed to training a functional task involving both arm and hand, due to the severity of their UL impairment. This is a purposeful design based on the results obtained by the Krebs group (Krebs et al. 2008). We therefore focused on reducing the arm impairment in this subpopulation before proceeding to any functional task training. However, our protocol is not a pure impairment-oriented training but a goal directed simple training which was attainable by the subjects. Such a simple goal-oriented task allowed the subjects to become focused on the task, i.e. reaching, and be very attentive and aware of their performance results (i.e. the feedback).

Second, we used the Assist-As-Asked paradigm in the RT protocol, rather than the well-known Assist-As-Needed (AAN) paradigm. In an AAN paradigm, the subject's movement is continuously monitored by the robot and the amount of assistance required to achieve a given task is estimated based on the subject's performance and is then provided by the robot. In terms of retraining the UL of stroke patients using RT, the AAN paradigm has been used with different robotic devices (Basteris et al. 2014). In robotic gait therapy, the AAN paradigm is shown to be more effective than a continuous assistance paradigm for elements such as balance and rhythmic patterns of movement with limited degrees of freedom (Srivastava et al. 2015). While in the AAN paradigm the subject still tries to perform the movement, this paradigm might not let the subject perform at

his/her full potential and leads to submaximal or lower efforts by the subjects. Subjects may simply wait to let the robot move their arm. To overcome this drawback, a strategy involving reducing the amount of assistance had been suggested and implemented (Reinkensmeyer et al. 2012). On the other hand, our Assist-As-Asked paradigm lets subjects try their best during the reaching task and reach their peak performance before asking for assistance. In the current study, we observed that all the subjects had trials in which multiple reaching attempts (during a single trial) were done before asking for the robot assistance. In addition, all the subjects were quite responsive to the feedback about their movement; they were all asking how much of self-movement they achieved the session before for each target and were trying to improve their reaching performance based on that score. That being said, it can be argued that a lazy stroke subject or a one with a lack of motivation could still not try his/her best and rely too much on the robot assistance in the Assist-As-Asked paradigm. The same problem can appear in an AAN paradigm for the same type of subject. Developing a modified version of the Assist-As-Asked paradigm that ensures subjects reach their peak performance before asking for assistance should be pursued in future studies; such an evaluation can be done by monitoring the amount of subject's effort during each trial (e.g. measuring the subject's maximum voluntary force by the robot at the beginning of each session and setting a percentage of that as the minimum force threshold to be applied by the subject, setting a minimum number of attempts, or setting a minimum amount of time) prior to providing robot assistance. Further study is required to compare the effectiveness of the Assist-As-Asked paradigm with other RT paradigms.

The improvements in reaching were achieved in most cases in fewer than 10 sessions of practice and reached their plateau which was subject and target dependent. For two of the subjects that did not reach plateau in the top row targets, i.e. subjects 1 and 4, increasing the number of sessions

might have helped them to improve their reaching performance in those targets. For Subject 2, the plateau was stopped at 35% of movement completion ratio when reaching target 3, which required the most amount of shoulder abduction, shoulder flexion and elbow extension among the targets; for such a case, changing the target location to a more reachable position based on his ability might have helped him. This was seen in the bottom row targets where reaching target 4 was the easiest for the subjects to complete followed by targets 5 and 6. This might be due to the location of the targets which required less shoulder abduction, shoulder flexion and elbow extension. In other words, the protocol and number of therapy sessions should not be fixed for all the subjects, but should be adjusted based on their performance.

In a majority of cases where subjects reached a plateau in their movement completion ratio (11 out of 14 plateau cases in PE and 11 out of 13 in VE), the shakiness decreased following the movement completion plateau. Due to a lack of neuroimaging studies, the underlying neurological mechanism responsible for these improvements in the kinematic measures are not known (Buma et al. 2016). However, the theory of sub-movements blending during motor recovery in stroke has shown that during post-stroke recovery, the criterion for refinement of movement patterns is not constrained to improving smoothness measures such as shakiness, but more toward gaining back the function; following the regain of the function, the shakiness decreases (Rohrer et al. 2002). In other words, shakiness exhibits a non-monotonic behaviour during motor recovery. Therefore, the lesson that can be learned is that the decision to stop the training of a movement should not only be based on the movement completion plateau but also on tunings of other parameters of movement such as shakiness. Tracking these changes is possible in RT (Bosecker et al. 2010).

While improvements in kinematic measures were evident and measurable, the FMA-UE only changed 3 to 5 units of score, which was below the minimal detectable change (MDC) of 5.2 (Lin

et al. 2009) and/or minimal clinically important difference (MCID) of 7 (Sivan et al. 2011). A recent study, however, has shown that the MCID can be accepted at 4 (Lundquist and Maribo 2016). As we only focused on training the arm, not the wrist and hand, we did not expect a major improvement in FMA-UE. Further, the tests in FMA-UE do not differentiate between the two aspects of movement: strength and motor control (Kitago et al. 2015). Therefore, it might not be a clear representative of the improvements by the subjects achieved with the RT. Presence of a control group would have allowed attributing the FMA-UE changes to the Assist-As-Asked protocol.

We only performed one baseline (pre) measurement of FMA-UE and did not perform multi-baseline evaluations because all the stroke subjects were in their long-term chronic stage and we expected a stable and non-varying baseline in terms of motor impairment level for all of them: the onset of stroke in three of the subjects was more than two and half years (2.7, 6.6 and 20.9 years post-stroke) and in one of them was more than a year and half (1.6 years post-stroke) (Table 6-1). Due to intrinsic nature of the robotic arm to measure kinematic and kinetic data, we quantified the improvements in subjects' reaching in every session. Kinematic measurements are sensitive to small and more specific changes in body parts movements (Alt Murphy and Häger 2015), not dependent on experimenters' observations, recorded by precise and accurate equipment, highly repeatable with high resolution (Bosecker et al. 2010), and represent physically measurable outcomes. That being said, the improvements seen in the kinematic measures of the reaching task are likely influenced by the subjects learning the task over the 10 sessions of practice and therefore cannot be directly contributed to impairment reduction unless accompanied by improvements in clinical measures. In this study, two of the subjects reported increased usage of their arm in daily activities which presents transfer of learning the reaching task to real world applications. However,

we could not perform follow-up measures to study whether there were any maintained long-term effects. In future works, clinical measures, such as FMA-UE, Stroke Impact Scale and Motor Activity Log, should be used as the main outcome measures of interest in evaluating the effectiveness of the Assist-As-Asked protocol; such a study should also include follow-up measures to investigate its long-term effect.

The results of this proof-of-concept study shows that it is feasible to use the Assist-As-Asked protocol in both physical and virtual environments. Regarding the choice of environment, we did not find any noticeable and/or meaningful differences in terms of the movement variables (movement completion, mean speed and shakiness) between the two environments. This can be explained by a study on healthy subjects comparing reaching tasks in a physical versus virtual environment in presence/absence of visual/haptic feedback (Ebrahimi et al. 2016) in which the results showed that the subjects' performance were similar in both environments when the subjects had visuo-haptic feedback in VE. In this study, besides the presence of visual feedback in PE and VE, the robot arm provided haptic feedback at the end-point in VE for the subjects by stopping them when the virtual button was reached. Also, both PE and VE shared the same haptic feedback in terms of forearm attachment to the robot arm. Subjective experience of the subjects in terms of motivation and preference was also similar between the two environments. In other words, the choice of environment was more of a personal preference than having any effect on the outcomes. In summary, in designing an RT platform for MTS chronic stroke survivors, choice of environment, either physical or virtual, does not necessarily influence the outcome of therapy sessions; the choice of environment should be decided based on other factors, such as cost, feasibility, etc.

The current study has several limitations in the study design. The main one is the small number of subjects that are investigated. As there were only four participants in this study, results presented here have to be cautiously interpreted and only used for designing a larger experiment. Another issue was the experimental design in which both PE and VE were performed in the same session (AB design) and whether this would have resulted in carryover effects. This design was very ideal for analysis of the subjective perception of the subjects about the reaching practice in both environments. In terms of kinematics of reaching performance, the carryover effect analysis (Table 6-2) showed that there were no immediate carryover effects (intra-session) on the reaching performance. However, this does not rule out longer carryover effects (inter-session) of one environment over the other. Having used an alternating intervention design, such as ABAC design, in which the PE and VE were not used concurrently, would have been more suitable for this multiple case study. An ideal experimental design to compare the effect of environment on RT would be a between-subject design, which might not be practical considering the high between-subject variability in stroke survivors.

6.7 Conclusion

This proof-of-concept study demonstrated that using the Assist-As-Asked protocol in moderate-to-severe chronic stroke survivors is feasible and may carry potential benefits for the stroke survivors. It was also shown that the Assist-As-Asked protocol can be used with both physical and virtual environments. We conclude that in designing a robot-assisted training platform for moderate-to-severe chronic stroke survivors, choice of environment, either physical or virtual, may not necessarily influence the outcome of therapy sessions.

6.8 Acknowledgments

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Chapter Seven : GENERAL DISCUSSION AND IMPACT

The main aim of this thesis was to examine the use of robotics in the rehabilitation of stroke survivors with moderate-to-severe upper limb motor impairments. Four studies were completed to this aim. The first study examined the effectiveness of robot-assisted therapy based on the current literature, i.e. performing a systematic review and meta-analysis of the literature. The subsequent three research studies examined two aspects of robot-assisted therapy in chronic stroke patients with moderate-to-severe UL impairments; choice of environment and a new RT protocol. The implications and impact of this PhD thesis and the future direction of research are discussed below.

7.1 Effectiveness of RT in Stroke Patients with UL Motor Impairments

In the first study (Chapter Three), the effectiveness of RT in upper limb stroke rehabilitation was analyzed by performing a systematic review and meta-analysis of the literature at the time. The key message of this study was that when the duration/intensity of conventional therapy (CT) was matched with that of the robot-assisted therapy (RT), no difference existed between the intensive CT and RT groups in terms of motor recovery, activities of daily living, strength, and motor control. However, depending on the stage of recovery, extra sessions of RT in addition to regular CT were more beneficial than regular CT alone in motor recovery of the hemiparetic shoulder and elbow of patients with stroke; gains were similar to those that have been observed in intensive CT. The extra therapeutic duration/intensity might be the reason for this result; the high number of repetitive movements generated during RT was probably the key reason for this therapeutic effect. In other words, the use of robotics by itself does not translate into better therapy for people with stroke. Rather, robots deliver highly repetitive therapeutic tasks with minimal supervision of a

therapist and these additional sessions of RT improve motor recovery of the hemiparetic shoulder and elbow of patients with stroke.

In terms of robotic devices discussed in the first study, almost none of them were designed for motor improvements of the distal UL (i.e., hand and wrist) and therefore the therapeutic program in these studies mostly focused on the shoulder and elbow of the participants with stroke. As a result, the improvements in motor recovery, strength and motor control from additional RT were training specific, attributed to the proximal UL. However, as the focus of the RT programs was mainly on recovery of motor rather than functional abilities of the UL, the performance of the RT groups was not different than the CT groups in terms of functional abilities in both matched duration/intensity and additional RT groups.

7.2 Role of Environment in RT of Chronic Stroke Patients with Moderate-to-Severe Motor Impairments

The second study (Chapter Four) looked at the choice of environment, i.e. physical or virtual, in a single session reaching task, comparing three groups: healthy individuals and chronic stroke patients with mild-to-moderate and moderate-to-severe UL motor impairments. The first two groups did not need any robotic help while the last group needed robotic help to complete the reaching tasks. This study showed that there were no differences in terms of the movement variables (speed, straightness, and shakiness) between the two environments for any of the three groups of this study. In the third (Chapter Five) and fourth (Chapter Six) studies, we looked at the role of environment over multiple sessions of training only in chronic stroke patients with moderate-to-severe UL impairments which required the robot assistance for completing the reaching task. Similar results were obtained in which we did not find any noticeable and/or meaningful differences in terms of the movement variables (movement completion, mean speed

and shakiness) between the two environments. As a previous study comparing reaching tasks in real vs virtual environment showed that healthy subjects' performance was similar in both environments when they had visuo-haptic feedback in VE (Ebrahimi et al. 2016), we suggested that this might be the reason behind no difference in performance between VE and PE; both PE and VE shared the same haptic feedback in terms of forearm attachment to the robot arm, and also besides the presence of visual feedback in VE, the robot arm provided haptic feedback at the end point for the users by stopping them when the virtual button was reached. In addition, in our design, the presence of the robot arm may have removed the reliance of stroke subjects on compensatory trunk movements; it may have allowed them to perform the reaching task without risk of sudden fall of the arm by providing when-needed anti-gravity support and guiding force, and let them move their arm in a virtual tunnel to minimize extra deviation of the movement from optimal path. This can even explain the subtle differences seen between PE and VE in the Subramanian study (Subramanian et al. 2013) as there were no common visuo-haptic feedback present in the two environments.

Besides finding no difference in terms of movement variables between the two environments, analysis of subjective experience of the stroke subjects revealed no difference between the two environments as well. There was no overall preference for either environment. Even feeling fatigued or choosing an easier environment was similar between the two environments. This shows that not only was the movement pattern the same in both VE and PE, but also the subjects' experience was similar as well. In other words, the choice of environment was more of a personal preference than any effect based on motor outcomes.

One important finding, in both the single-session and multi-session studies, is that the choice of environment, whether physical or virtual, is not a key factor in designing a robot-assisted reaching

protocol for stroke survivors with moderate-to-severe UL impairments. We recommend that, in stroke rehabilitation, the choice of environment should be decided based on considerations such as cost, training activities, feasibility, amount of therapist supervision and space requirements, and not the type of environment itself.

7.3 “Assist-As-Asked” Robot-Assisted Training Protocol

The “Assist-As-Asked” robot-assisted protocol was developed in this research work aiming at improving arm function of chronic stroke subjects with UL motor impairments. In this new scheme, the robot provides assistance only when the subject specifically asks for it. In the third (Chapter Five) and fourth (Chapter Six) studies, we reported the results of training with this new protocol in a case report and a proof-of-concept study, respectively. The subjects were all in the chronic stage of stroke with moderate-to-severe UL motor impairments.

In the case report study (Chapter Five), we reported use of Assist-As-Asked protocol by an individual with a long-term chronic stroke (20+ years) over 10 half-hour sessions. The results showed noticeable improvements in the subject’s reaching performance accompanied by a small increase in FMA-UE score. The improvements were also transferred into real life activities, as reported by the subject. This study demonstrated that even in long-term chronic stroke cases, RT can be used as a promising tool for regaining some UL motor function.

The fourth study (Chapter Six) presented the results of the proof-of-concept study on this new protocol. All the stroke participants increased their shoulder and elbow active range of motion by improving their arm reaching performance between the first and last session. None of the subjects reported any adverse events. We discussed that two possible factors involved in achieving such results. First, in developing this RT protocol specific to moderate-to-severe chronic stroke patients, we only focused on arm reaching training of these individuals as opposed to training a functional

task involving both arm and hand, due to the severity of their UL impairment. This is a purposeful design based on the results obtained by the Krebs group (Krebs et al. 2008). We therefore focused on reducing the arm impairment in this subpopulation before proceeding to any functional task training. However, our protocol was not a pure impairment-oriented training but a goal-directed simple training which was attainable by the subjects. Such a simple goal-oriented task allowed the subjects to become focused on the task, i.e. reaching, and be very attentive and aware of their performance results (i.e. the feedback). Second, we used the Assist-As-Asked RT protocol, rather than the well-known Assist-As-Needed (AAN) protocol. In an AAN protocol, the subject's movement is continuously monitored by the robot and the amount of assistance required to achieve a given task is estimated based on the subject's performance (e.g., in terms of movement velocity or range of motion) and is then provided by the robot (Emken et al. 2007; Huang et al. 2017; Nordin et al. 2014; Wolbrecht et al. 2008). While in the AAN protocol, the subject still tries to perform the movement, this protocol might not let the subject perform at his/her full potential and leads to submaximal or lower efforts by the subject. The subject may simply wait to let the robot move their arm. To overcome this drawback, a strategy involving reducing the amount of assistance had been suggested and implemented (Reinkensmeyer et al. 2012). On the other hand, our Assist-As-Asked protocol allowed subjects to try their best during the reaching task and reach their peak performance before asking for assistance; we observed that all the subjects had trials in which multiple reaching attempts (during a single trial) were done before asking for the robot assistance. In addition, all the subjects were quite responsive to the feedback about their movement; they were all asking how much self-movement they achieved the session before for each target and were trying to improve their reaching performance based on that score.

In this PhD work, we showed that the Assist-As-Asked protocol is a feasible RT protocol for moderate-to-severe stroke patients and improves their reaching performance in couple of practice sessions. Even long-term chronic stroke patients might benefit from this training protocol.

7.4 Future Direction of Research

Stroke does not act like a disease which affects involved people with common symptoms and health problems, but it is different for each person based on which areas of the brain (and to what extent) are damaged due to stroke; therefore, it results in individualized level of disability for each person with stroke. Such a diverse range of disability requires tailored rehabilitation plans and approaches based on each individual's needs. Following discharge from a rehabilitation unit, each stroke survivor in their chronic stage lives with different levels of disability. The focus of this research work was on chronic stroke survivors with moderate-to-severe UL motor impairments. Use of robotics as a viable rehabilitation tool with a new protocol, i.e. "Assist-As-Asked", was investigated in this work. The role of environment, whether physical or virtual, in RT was also examined.

As the number of subjects in this research work was limited, the next step would be to run an RCT study with a higher number of subjects to study the effectiveness of the Assist-As-Asked protocol. The RCT study should use clinical measures (such as FMA-UE, Stroke Impact Scale and Motor Activity Log) as the main outcome measures of interest in evaluating the effectiveness of the Assist-As-Asked protocol instead of kinematic measures; such a study should also include follow-up measures to investigate the long-term effects of the Assist-As-Asked protocol. In addition, further study is required to compare the effectiveness of the Assist-As-Asked protocol with other RT protocols such as assist-as-needed (AAN) protocol. While with the current Assist-As-Asked protocol, we observed that the stroke participants tried their best before asking

for robot's help, as expected, it still can be argued that a lazy stroke subject or a one with a lack of motivation could still not try his/her best and rely too much on the robot assistance in the Assist-As-Asked paradigm. The same problem can appear in an AAN paradigm for the same type of subject. Developing a modified version of the Assist-As-Asked paradigm that ensures subjects reach their peak performance before asking for assistance should be pursued in future studies; such an evaluation can be done by monitoring the amount of subject's effort during each trial (e.g. measuring the subject's maximum voluntary force by the robot at the beginning of each session and setting a percentage of that as the minimum force threshold to be applied by the subject, setting a minimum number of attempts, or setting a minimum amount of time) prior to providing robot assistance.

The robotic device used in this work was an end-effector robotic arm and the training task was an impairment-oriented training of the arm and not a functional task-oriented training. As discussed previously (section 6.3), for the stroke patients with moderate-to-severe UL impairments, at least some basic elements of motor control need to be restored before starting a task-oriented training (Krebs et al. 2008; Platz et al. 2005). However, most ADLs performed with the UL require performance of the arm and hand together. Therefore, while restoring proximal joint movements, i.e. shoulder and elbow, is important, training of the distal joint movements, i.e. wrist and fingers, is as important as the proximal ones in the stroke patients. That being said, there is no need for a training protocol consisting of the two at the same time as the goal in chronic moderate-to-severe stroke patients is restoration of basic motor control elements at first. Therefore, future research should consider hand training either concurrently or separately with arm training.

In a broader perspective, the future research should focus on individual training for chronic stroke patients based on each individual's level of disability and biomarkers. For instance, for

moderate-to-severe levels of motor impairment, robotics can be used while for mild-to-moderate ones, virtual reality (with or without robotics based on the need of the individual) to be used. Based on testing the integrity of corticospinal tract, use of other modalities such as neuromuscular electrical stimulation (NMES) (Knutson et al. 2015) and/or applying repetitive transcranial magnetic stimulation (rTMS) (applying a low-frequency rTMS, i.e. less than 1 Hz, on the contralesional motor cortex to suppress its activity or/and a high-frequency rTMS, i.e. more than 1 Hz, on the ipsilesional motor cortex to increase its excitability) (Hao et al. 2013) in conjunction with robot-assisted therapy and virtual reality should also be considered.

Since stroke patients in chronic stages very often do not have access to any therapy in rehabilitation centres (due to lack of therapeutic resources, financial problems, lack of insurance support, loss of interest due to very low gains, etc.), developing home-based solutions for them is of utmost importance. Therefore, the future research should focus on developing affordable home-based solutions to incorporate training into the daily routine of stroke survivors in chronic stage. Several studies have already focused on use of low-cost virtual reality rehabilitation systems in home settings (Standen et al. 2015; Kairy et al. 2016; Standen et al. 2017) but there is a need for developing affordable home-based robot-assisted therapy systems for stroke patients with moderate-to-severe impairment levels. Future research should focus on development and feasibility and effectiveness assessment of such systems to have more of them available for stroke survivors; home-based RT systems like those presented in (Sivan et al. 2014) and (Zhang et al. 2011) or even a combined clinic-home RT system approach (Kim et al. 2015) are good examples in this direction. With recent advances in home-based telerehabilitation (Chen et al. 2015), i.e. use of telecommunications by therapists to guide, evaluate and support patients remotely, a telerehabilitation home-based RT system would allow the therapist to set the intervention strategy,

plan the system, and monitor patient's progress (and update the intervention plan accordingly) while all being done remotely. Future research on such a system is crucial.

7.5 References

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