Universidad Carlos III de Madrid

TESIS DOCTORAL

Development of a hybrid robotic system based on an adaptive and associative assistance for rehabilitation of reaching movement after stroke

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A mis padres,
y a mi Anto

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Quisiera comenzar agradeciendo a todas las personas que participaron en los experimentos que dieron lugar a los resultados presentados en esta tesis. En especial a los pacientes con daño cerebral, por su buena predisposición y colaboración para realizar todos los experimentos.

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Abstract

Stroke causes irreversible neurological damage. Depending on the location and the size of this brain injury, different body functions could result affected. One of the most common consequences is motor impairments. The level of motor impairment affectation varies between post-stroke subjects, but often, it hampers the execution of most activities of daily living. Consequently, the quality of life of the stroke population is severely decreased.

The rehabilitation of the upper-limb motor functions has gained special attention in the scientific community due the poor reported prognosis of post-stroke patients for recovering normal upper-extremity function after standard rehabilitation therapy. Driven by the advance of technology and the design of new rehabilitation methods, the use of robot devices, functional electrical stimulation and brain-computer interfaces as a neuromodulation system is proposed as a novel and promising rehabilitation tools. Although the uses of these technologies present potential benefits with respect to standard rehabilitation methods, there still are some milestones to be addressed for the consolidation of these methods and techniques in clinical settings.

Mentioned evidences reflect the motivation for this dissertation. This thesis presents the development and validation of a hybrid robotic system based on an adaptive and associative assistance for rehabilitation of reaching movements in post-stroke subjects. The hybrid concept refers the combined use of robotic devices with functional electrical stimulation. Adaptive feature states a tailored assistance according to the users' motor residual capabilities, while the associative term denotes a precise pairing between the users' motor intent and the peripheral hybrid assistance. The development of the hybrid platform comprised the following tasks:

1. The identification of the current challenges for hybrid robotic system, considering twofold perspectives: technological and clinical. The hybrid systems submitted in literature were critically reviewed for such purpose. These identified features will lead the subsequent development and method framed in this work.

2. The development and validation of a hybrid robotic system, combining a mechanical exoskeleton with functional electrical stimulation to assist the execution of functional reaching movements. Several subsystems are integrated within the hybrid platform,

which interact each other to cooperatively complement the rehabilitation task. Complementary, the implementation of a controller based on functional electrical stimulation to dynamically adjust the level of assistance is addressed. The controller is conceived to tackle one of the main limitations when using electrical stimulation, i.e. the highly non-linear and time-varying muscle response. An experimental procedure was conducted with healthy and post-stroke patients to corroborate the technical feasibility and the usability evaluation of the system.

3. The implementation of an associative strategy within the hybrid platform. Three different strategies based on electroencephalography and electromyography signals were analytically compared. The main idea is to provide a precise temporal association between the hybrid assistance delivered at the periphery (arm muscles) and the users' own intention to move and to configure a feasible clinical setup to be use in real rehabilitation scenarios.

4. Carry out a comprehensive pilot clinical intervention considering a small cohort of patient with post-stroke patients to evaluate the different proposed concepts and assess the feasibility of using the hybrid system in rehabilitation settings.

In summary, the works here presented prove the feasibility of using the hybrid robotic system as a rehabilitative tool with post-stroke subjects. Moreover, it is demonstrated the adaptive controller is able to adjust the level of assistance to achieve successful tracking movement with the affected arm. Remarkably, the accurate association in time between motor cortex activation, represented through the motor-related cortical potential measured with electroencephalography, and the supplied hybrid assistance during the execution of functional (multi-degree of freedom) reaching movement facilitate distributed cortical plasticity. These results encourage the validation of the overall hybrid concept in a large clinical trial including an increased number of patients with a control group, in order to achieve more robust clinical results and confirm the presented herein.

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Nomenclature

AD	Anterior Deltoid
ADL	Activities of Daily Living
ANN	Artificial Neural Network
ANOVA	Analysis of Variance
ARAT	Action Research Arm Test
BAT	Bilateral Arm Training
BB	Biceps Brachii
BCI	Brain-Computer Interface
CNS	Central Nervous System
DALY	Disability-Adjusted Life Year
DOF	Degree of Freedom
ECR	Extensor Carpi Radialis
EDC	Extensor Digitorum Communis
EEG	Electroencephalography
EMG	Electromyography
ERD	Event-Related Desynchronization
FDS	Flexor Digitorum Superficialis
FEL	Feedback Error Learning
FES	Functional Electrical Stimulation
FMA	Fugl-Meyer Assessment
GBD	Global Burden of Diseases
HANDS	Hybrid Assistive Neuromuscular Dynamic Stimulation
HLC	High Level Controller
ILC	Iterative Learning Control
LD	Lateral Detoid
LTD	Long-Term Depression
LTP	Long-Term Potentiation
MAS	Modified Ashworth Scale
MCID	Minimal Clinically Important Difference
MEP	Motor Evoked Potential
MMT	Manual Muscle Test
MRCP	Motor-Related Cortical Potential
PAS	Paired Associative Stimulation

PID	Proportional-Integral-Derivative
PR	Power Ratio
PW	Pulse Width
QUEST	Quebec User Evaluation of Satisfaction with Assistive Technology 2.0
RMSE	Root Mean Square Error
rMT	Resting Motor Threshold
ROM	Range of Movement
SAIL	Stimulation Assistance through Iterative Learning
SAM	Self-Assessment Manikin
SMART	Sensorimotor Active Rehabilitation Training
SMR	Sensory Motor Rhythms
TB	Triceps Brachii
TMS	Transcranial Magnetic Stimulation
TP	True positive
WHO	World Health Organization

Objectives and description of the work

Stroke results in an irreversible damage to the brain's tissues. Motor impairment constitutes one of the most common consequence arising after this brain lesion. The level of motor affectation varies between post-stroke subjects, but often, it hampers the execution of most activities of daily living. Consequently, the dependence and the quality of life of the stroke survivors are severely affected.

The rehabilitation of the motor functions is one of the cornerstones topics in post-stroke management. Rehabilitation therapies seek to recover the affected motor functions in order to achieve dexterity and successfully execute activities of daily living. The main underlying process explaining this recovery is the adaptive characteristic of the central nervous system, called plasticity. The primary goal of rehabilitation therapies is to exploit the neural plasticity to maximize the functional outcomes. However, when exploring the reported outcomes, e.g. in upper-extremity motor functions, studies evidenced poor results. Certainly, it was reported that 50-70% of stroke survivors with initial severe or mild paresis of the upper-extremity continued to experience limited function and disuse of their hemiplegic upper limb post-stroke.

This makes the development and validation of alternative rehabilitative methods aimed at recovering (upper-limb) motor impairment a topic of great importance. During the last decades, a number of novel interventions for rehabilitation of upper-extremity for post-stroke subjects have been explored. Among them, the use of robotic devices, functional electrical stimulation and neuromodulation systems has emerged as promising paths. The use of these novel technologies presents an unprecedented alternative for maximizing motor recovery by building on their capability for providing repetitive and intense task-specific training, thus improving motor control and facilitating plasticity.

Objectives

Considering, on the one hand, that upper-extremity motor impairment arisen after stroke affects the execution of most activities of daily living and, on the other hand, the potential rehabilitative benefits of novel therapies (robot and functional electrical stimulation), the present doctoral thesis proposes the combined use of a robotic device, functional electrical stimulation and electroencephalography-based brain-computer interfaces during the execution of reaching movements with the aims of facilitating neural plasticity and promoting recovery of the upper-extremity motor functions.

The main objective of this doctoral dissertation is **to develop and validate a novel hybrid robotic system for rehabilitation of reaching movement in stroke population**. The proposed system combines the advantages of the robotic technology, the functional electrical stimulation techniques and the electroencephalography-based brain-computer interfaces to assist the execution of unconstrained functional reaching movement. This development is conducted to address the challenges identified from an in-depth analysis of the relevant literature.

One of the identified challenges is to provide an optimum level of assistance. An adaptive assistance is implemented to adjust the current intensity according to the user's motor residual capability in order to achieve a successful tracking reaching movement with the affected arm.

As it will be highlighted later on, brain plasticity plays a crucial role for recovery of motor functions after stroke. One possible and widely adopted strategy for promoting plasticity relies on the use of neuromodulation systems. In this work, a brain-computer interface is proposed to precisely pair, associate and synchronize the user's own intention to move with the applied hybrid peripheral assistance, thus ensuring causality. It is demonstrated that neural plasticity could be facilitated uniquely when the precise and causal association between motor-related cortical process and the assistance occurs.

Explicitly, the following objectives are framed within this doctoral thesis:

- To identify main challenges of the current hybrid robotic concept focused on rehabilitation of upper-limb motor function.
- To develop and implement a prototype of a hybrid robotic system (robot mechanical system with functional electrical stimulation technique) to assist the execution of reaching movement.
- To implement and validate an adaptive control strategy to adjust the level of assistance according to the user's motor residual capabilities during the execution of the reaching task.
- To implement and integrate a neuromodulation system within the hybrid platform with the aim of tightly and causally coupling the user's own intention to move with the hybrid peripheral assistance.
- To demonstrate that the precise temporal association between the motor cortex activation identified by motor-related cortical activity and the hybrid assistance could elicit neural plasticity.

- To provide a validation of the overall hybrid concept through a clinical intervention with post-stroke subjects, together with a detailed interpretation of the results.

Methods and structure of the work

The methodology followed to achieve the aforementioned objectives relies on a thorough study of the different aspects related to the motor recovery in the stroke population. This study comprised the motor pathological and functional characteristics of the affected upper-extremity, the principal mechanisms underlying motor recovery after a brain injury and the clinical implications of this brain disorder. The methodology followed in this dissertation is fully in line with the organization of the thesis. Thus, the work has been split into three clear parts. One chapter introduces the rationale of the dissertation. The subsequent four chapters present a series of studies and the contributions. Finally, the last chapter summarizes the main conclusions, the scientific results and dissemination, as well as the future research emerging from this thesis. Accordingly, each chapter (please, see details in the next paragraphs) contributes to the successful accomplishment of the related objectives above presented.

Chapter 1 describes the rationale for the dissertation. It provides a detailed review and account of the different aspects related to the stroke disorder. First, it provides a brief overview about the pathophysiology of stroke and explains how stroke is currently classified. The social burden in terms of mortality, prevalence, cost and disabilities arisen post-stroke were extracted from literature and are briefly summarized here. The common affected body functions are listed and, epidemiological aspects of upper-limb motor impairment are presented. The review in this chapter highlights the importance of novel rehabilitation therapies for improvement current rehabilitation outcomes. Three novel therapies are critically presented, summarizing their main advantages and disadvantages, giving rise to the hybrid concept, i.e. combined use of robotic devices and functional electrical stimulation, proposed and implemented throughout the thesis.

Chapter 2 presents the state of the art on hybrid robotic system with a focus on the rehabilitation of the upper-extremity motor functions. Two perspectives are addressed here: the technical and the clinical one. As a results of this analysis, the main design requirements of the hybrid systems were identified, which in turn guided the developments and studies presented in this dissertation.

Chapter 3 presents the design and development of a fully integrated hybrid robotic system for rehabilitation of functional reaching movements in post-stroke subjects. The hybrid platform is composed of several networked subsystems to jointly enable the novel rehabilitation task. This platform constitutes a comprehensive self-contained tool aimed at promoting the recovery of reaching movements. Complementary, the implementation of an adaptive controller is presented. This controller strategy adjusts the level of assistance according to the user's motor residual capabilities. A detailed explanation about its operation and the assumptions are provided. The technical validation of the platform was conducted in a pilot study with healthy subjects (n = 12). The usability assessment involved a small sample of stroke patients (n = 4) with a reduced number of session (two experimental sessions).

Chapter 4 introduces the associative concept. Here, the use of a neuromodulation system is presented with the main aim of facilitating neural plasticity. This system is integrated into the hybrid platform to tightly and causally couple the user's motor planning process with the peripheral hybrid assistance. Three different associative strategies are critically compared, taking as the primary outcome indicator the plastic effects resulting from the intervention. An experimental protocol is presented with the aim of validating the associative concept. Results from experimentation with healthy volunteers (n = 21) demonstrate the feasibility of associative concept for enhancing the excitability of corticospinal projections to target arm muscles (anterior deltoids, triceps brachii and biceps brachii).

In Chapter 5 the potential rehabilitative effects of the hybrid robotic system are investigated. The system combined both the adaptive and associative assistance developed and tested individually in previous chapters. To this aim, a pilot clinical intervention was conducted. The primary objective was to verify the feasibility of using the hybrid robotic system in clinic rehabilitation and the inspection of its potential effects for recovery the upper-extremity motor functions. Five post-stroke subjects were recruited to participate in an interventional protocol consisting in 12 sessions along 4 consecutive weeks.

Chapter 6 summarizes and concludes the results of this doctoral work. It highlights the scientific results and dissemination derived from the studies conducted in this thesis in the following research fields: biomedical and neural engineering, rehabilitation robotics, functional electrical stimulation and neurorehabilitation. Eventually, it proposes emerging future research activities, out of the outcomes obtained in this thesis.

Framework of the thesis

This work has been carried out with the financial support of the Itaipu Binacional (Paraguay), and it was carried out at the Neural Rehabilitation Group (NRG), Cajal Institute, Spanish National Research Council (CSIC). The first studies presented in this dissertation were performed in the framework of two funded research projects: HYPER (Hybrid Neuroprosthetic and Neurorobotic Devices for Functional Compensation and Rehabilitation of Motor Disorders, grant CSD2009-00067 CONSOLIDER INGENIO 2010) and BRAIN2MOTION (Exoskeletal - neuroprosthesis hybrid robotic system for the upper limb controlled by a multimodal brain-neural interface, grant DPI2011-27022-C02-02). While the last experiments were conducted in framework of the ASSOCIATE project (A comprehensive and wearable robotics based approach to the rehabilitation and assistance to people with stroke and spinal cord injury, grant DPI2014-58431-C4-1-R). Within these research projects, cutting-edge research was conducted in the fields of biomedical and neural engineering, clinic rehabilitation, neurorehabilitation and neuroscience amongst others.

Finally, it is worth mentioning that the close and helpful collaboration with the Centro de Referencia Estatal de Atención Al Daño Cerebral (CEADAC) and with the Instituto de Neurociencias y Ciencias del Movimiento (INCIMOV) constituted an essential asset for the successful progress of the work and studies presented in this thesis.

Chapter 1

Introduction of stroke and rehabilitation of the upper limb motor function

Abstract

This chapter introduces the background and rationale for the development and studies framed in this dissertation. An overview about of stroke is presented. The most relevant consequences post-stroke are identified, including physiological, functional, social and economic aspects, globally and in Spain. From the rehabilitation perspective, the importance of the upper-extremity motor and functional recovery is emphasized. The main rehabilitation premises and the concept of neural plasticity for maximizing recovery outcomes are also presented. Three novel rehabilitation methods for rehabilitation of arm motor function are reviewed: robotic devices, functional electrical stimulation and brain-computer interfaces. Published evidence shows two important aspects. First, novel approaches are needed to increase the potential of robotic and functional electrical stimulation interventions for rehabilitation of upper-limb motor function in stroke survivors. Second, brain-computer interfaces can be exploited to supply assistance in causal association motor cortical processes to improve current therapies by means of the promoted neural plasticity.

1.1 Stroke

The central nervous system (CNS) is a very complex system, yet fascinating at the same time. It can be considered as a bilateral and symmetrical structure composed of two main parts: the brain and the spinal cord. The brain comprise seven structures: the medulla oblongata, pons, cerebellum, midbrain, diencephalon, corpus callosum and the cerebral hemispheres (see Figure 1.1a). The two hemispheres of the human brain can be further divided into four different regions: the frontal lobe, the parietal lobe, the occipital lobe and the temporal lobe see Figure 1.1b). Each brain lobe is responsible for controlling specific set of functions. In this regard, the frontal lobe is mainly related with short-term memory, the planning of motor action and with the control of the movement; the parietal lobe with the somatic sensation, representation of body image and its relation with the extra-personal space; the occipital lobe is mainly responsible for vision; and lastly, the temporal lobe is associated with the hearing, learning, memory and emotion (Kandel et al. 2000).

As all human cognitive functions occur primary in the brain, it can be seen as the central processing organ of the CNS, responsible for controlling multiple complex functions. In adult humans, the brain weights around 1.3 kg (Kandel et al. 2000), representing in average the 2% of the body weight. Although its small size (when compared with the proportion of the human body), it is estimated that the brain spends around 20% of the oxygen and, hence, calories consumed by the body. It was also mentioned that this metabolic activity of the brain is remarkably constant over time, despite of the mental and motor activities are widely varying (Raichle & Gusnard 2002). The brain, as all other organs of the human body, has an extremely dependence of the energy to develop its functions and operate normally. The energy production in the brain relies on metabolism of exogenous compounds with a high-energy content, primarily the oxidation of glucose (Mohr et al. 2011). As the storage of substrates for energy metabolism in the brain is minimal, the functional and structural integrity of the brain depends on a continuous supply of blood by delivering oxygen and glucose (Mohr et al. 2011).

When the blood supply to the brain is disrupted, the brain stops receiving nutrients and oxygen. This event is known as a stroke. A stroke, also considered a brain attack, is caused by a sudden interruption in the blood supply to the brain. The most widely used and accepted definition of stroke was given by the World Health Organization (WHO), which is stated as follow:

"*rapidly developed signs of focal (or global) disturbance of cerebral function lasting longer than 24 hours (unless interrupted by death), with no apparent nonvascular cause*".

Stroke is considered a cerebrovascular disease. After the disruption of the bloodstream, the cells of the brain start to die leading to a damage of the brain areas. Approximately two million brain cells die every minute during a stroke (Gund et al. 2013). The neurons' death results in an irreversible neurological damage that can even cause the death of the living

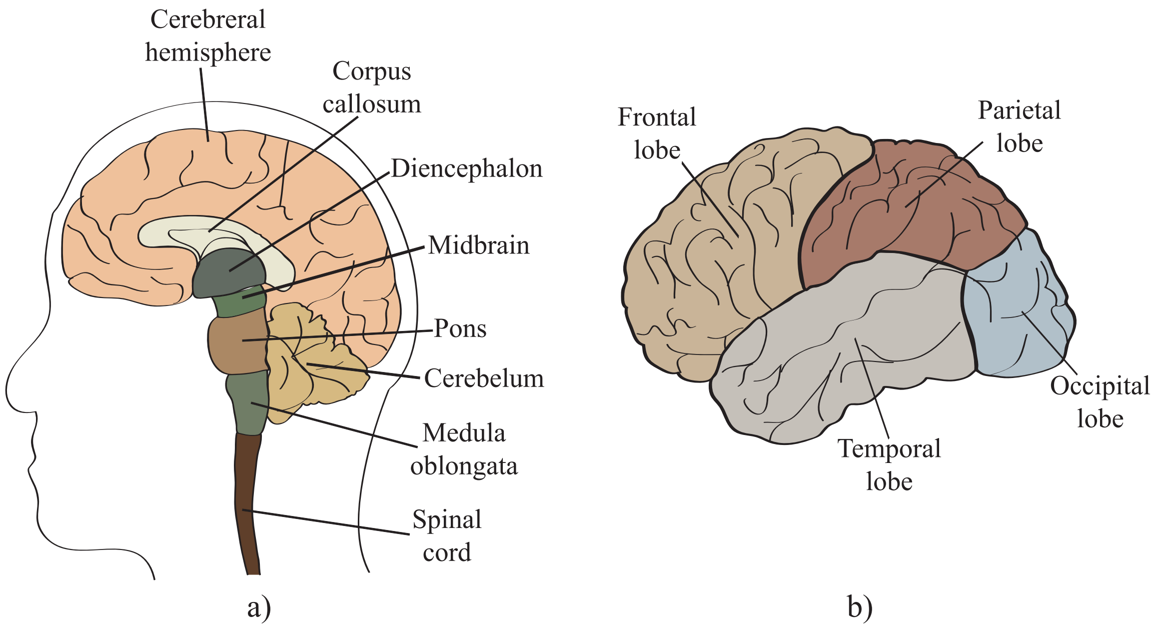

FIGURE 1.1: a) Main components of the central nervous system. b) The four lobes of the cerebral cortex.

being. One or more brain areas can be affected after stroke resulting in the lost or the decrease of functions controlled by that specific area (Muir 2009).

Although stroke always occurs in the brain, there are two different types: ischemic and hemorrhagic. The distinction between these subtypes is very important and urgent for its clinical management, since different procedures are applied on each case (Donnan et al. 2008). A summary of each subtype is given below, with a brief explanation of the principal pathophysiology differences between them.

1.1.1 Ischemic Stroke

Ischemic stroke represents the most common type accounting for about the 70% of reported stroke events (Adams et al. 2007). This type of stroke occurs when the blood vessels inside or close to the brain are occluded causing a disruption of the blood flow in certain brain areas. A representative illustration of the attributed mechanisms underlying the ischemic stroke is depicted in Figure 1.2a. This occlusion leads two zones of injury in the brain referred to as the core and the penumbra ischemic zones (Williams et al. 2010). In the core zone, a little amount of blood flows resulting in an insufficient resource of oxygen and glucose, and in a quickly depletion of stores. As consequence, the brain cells within this area start dying. In the penumbra zone, the blood is still able to flow through collateral arteries linking with branches of the occluded vessels. This is not a time-stable process, but rather it can be considered as a time-limited process (Williams et al. 2010). In case that reperfusion is not reestablished within hours, the cells inside the penumbra zone will die because bloodstream is not enough to deliver oxygen and glucose in the long-term (Donnan et al. 2008).

Different underlying mechanisms can influence the development of an ischemic stroke. The Trial of Organo in Acute Stroke is the most widely classification method used to differentiate these mechanisms (Adams et al. 1993). According to this classification, the ischemic stroke can be divided into large-artery atherosclerosis (also referred as atherothrombotic), cardioembolic, small-vessel occlusion, other determined cause, and undetermined cause. Generally, it has been reported that atherothrombotic, cardioembolic, small-vessel occlusion account for around 75% of all ischemic strokes, while no clear causes can be identified in around 20% of incidents and about 5% of cases result from uncommon causes (Brainin et al. 2014).

The mechanisms involving the large-artery atherosclerosis include intracranial thrombosis (formation of blood clot) as well as intra- and extra-cranial artery to artery embolization (embolus within the bloodstream) that occurring with rupture of a carotid plaque (Williams et al. 2010). Artherosclerotic disease was often evidenced in most of affected people with this stroke mechanism. Cardioembolism occurs as result of emboli that arise from within the heart. The small vessel occlusion, also referred to as lacunar stroke, can occurs by small vessel occlusion secondary to atherosclerosis and by small vessel disease with deposits of eosinophilic cells within the vessel walls (Adams et al. 1993). Patients affected are mostly related with long-standing hypertension, diabetes and/or smokers. Others stroke mechanisms can be attributed to hypercoagulable states, arterial dissections and by the uses of illegal drugs. While undetermined mechanisms of stroke is observed in those patients in which the aetiological factors cannot be identified (Adams et al. 1993).

1.1.2 Hemorrhagic stroke

Hemorrhagic stroke has a low incidence rate when compared to ischemic, representing around 10% to 20% of all stroke events (Ikram et al. 2012). It occurs when a blood vessel within the brain eventually ruptures, spilling blood into the brain (see Figure 1.2b for a representative illustration). Intracerebral hemorrhage is the most frequently cause of this type of stroke, occurring regularly in deep brain structures (Brainin et al. 2014). Less commonly, a hemorrhagic stroke may occur from amyloid angiopathy, which is most common in lobar region and in older persons. Additionally, the rupture of the arteriovenous malformation or aneurysm are associated to hemorrhagic stroke (Williams et al. 2010).

The hypertensive small-vessel disease is identified as the main mechanism underlying the hemorrhagic stroke (Brainin et al. 2014). It has been reported that two-thirds of patients with primary cerebral hemorrhage have either pre-existing or newly diagnosed hypertension (Donnan et al. 2008). Although the occurrence of hemorrhagic stroke is less frequent, it presents bigger death rates when comparing with ischemic stroke (Brainin et al. 2014).

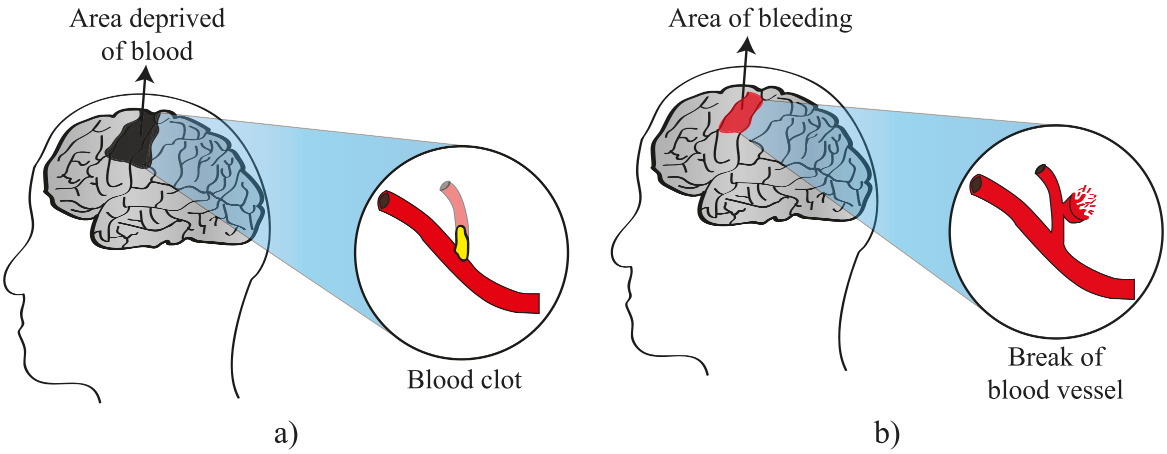

FIGURE 1.2: Types of stroke. a) Ischemic stroke; b) Hemorrhagic stroke.

1.2 Social impact of stroke: the burden

The impact of a disease in a society is commonly referred to as the disease burden. The disease burden is the impact of a specific health problem and can be measured through different factors. The most common and widely reported factors for stroke are: mortality, the incidence and prevalence rates, the disability-adjusted life-year (DALYs), the social cost, and the disabilities arisen after the disease.

When referring to the burden of a disease, the mortality is one of the most valuable and widely used metrics. Specifically, identifying the cause-specific mortality could be a crucial source for the definition and planning of health policies in specific geographic areas. In this regard, the Global Burden of Diseases (GBD) study presented in 2012 has identified the most common cause of death in up to 187 countries from 1980 to 2010 (see Figure 1.3a) (Lozano et al. 2012). In this study, stroke was ranked as the second most common cause of death after ischemic heart disease. It was highlighted that stroke caused about 11.1% of death around the world, approximately 5.9 million. When compared to the reported deaths 20 years earlier, this number represents an increase of 26%. Together, ischemic heart disease and stroke produced a quarter of the global total deaths, representing 12.9 million deaths.

In addition to mortality, some studies have quantified the burden of stroke using its incidence, prevalence and DALY lost (Feigin et al. 2009, Murray et al. 2012, Feigin et al. 2014). In global terms (without any kind of distinction), it was reported that in 2010 the absolute number of people with first stroke was 16.9 million, while there were 33 million of stroke survivors. These numbers represent a significant difference of the score registered in 1990, corresponding to an increase of 68% and 84% respectively. The DALYs is a metric used in GBD studies, which it is based on two components: years of life lost because of death and years lived with disability. An explanation about the methodology and procedures for the calculation of DALYs in GBD 2010 can be found in (Murray et al. 2012). Similar patterns was reported for the DALYs metric, resulting in 102 million of DALYs lost, corresponding to an increase of 12% with respect to the registered score in 1990. When analyzing the registered data in

Spain, a similar increasing trend can be elucidated. As depicted in Figure 1.3b, the global incidence and prevalence in 2010 presented an increase of 26.9% and 88.5% respectively with respect to the record in 1990 (Feigin et al. 2014). Similar trend was found when focusing uniquely in the reported data in Spain. More specifically, Vega et al. reported a stroke incidence of 141 cases per 100000 inhabitants in woman and 148 in men (Vega et al. 2009). However, the mortality in 2010 was reduced 15.9% with respect to the data registered in 1990. This reduction in mortality can be attributed to the improvement in medicine and to the improvements in the social welfare system.

It is worth also mentioning that although the mean age of people with stroke is increasing, there is a substantial number of stroke occurrence in people younger than 65 years (Feigin et al. 2014). It was reported than more than 83000 children and youths aged 20 years and younger are affected by stroke annually, suggesting that stroke should not be considered as a disease of old age.

Another important social burden is the economic cost of the disease, which is an important parameter for social health and research policies. Worldwide, stroke consumes about 2-4% of total health-care costs, and in industrialized countries stroke accounts for more than 4% of direct health-care costs (Donnan et al. 2008). Olesen et al. provided a quantitative evaluation of brain disorder in terms of cost within Europe (Olesen et al. 2012). In this study, the authors estimated that stroke suppose a total annual cost of 64.1 billion € using prices of 2010. In a different study, Alvarez-Sabín et al. reported an estimation of the real cost of stroke in Spain (Alvarez-Sabín et al. 2017). They reported that the cost of patients admitted to stroke units in Spain is 27711 € per patient/years. It has been also reported that the cost of hemorrhagic stroke was slightly higher than ischemic (30332 € vs. 23234 € per patient/year), attributed to the presence of hypertension and the severity of stroke.

Reported results disclose that the global burden of stroke in terms of the mortality, number of people affected every year, stroke survivors, and DALYs lost are great and present an increasing trend over years. Based on these facts, it was estimated that by 2030, there will be almost 12 million of deaths due stroke, 70 million of stroke survivors and more than 200 million DALYs lost (Feigin et al. 2014). As these numbers influence directly the health cost, also the cost of stroke will be increased considerably. Consequently, stroke is considered currently a serious health problem globally (World Health Organization 2003, Bonita et al. 2004).

1.3 Motor impairment

The effects due to stroke are extremely heterogeneous between individuals. These effects are determined by the site and size of the brain lesion (Brewer et al. 2013). Several sequelae can arise after a stroke (see Table 1.1), namely, deficit in language, vision and cognitive capabilities; alterations in body functions as ingestion, defecation, urinary and sexual and the inability for controlling (in)voluntary movements (Langhorne et al. 2009). Between all

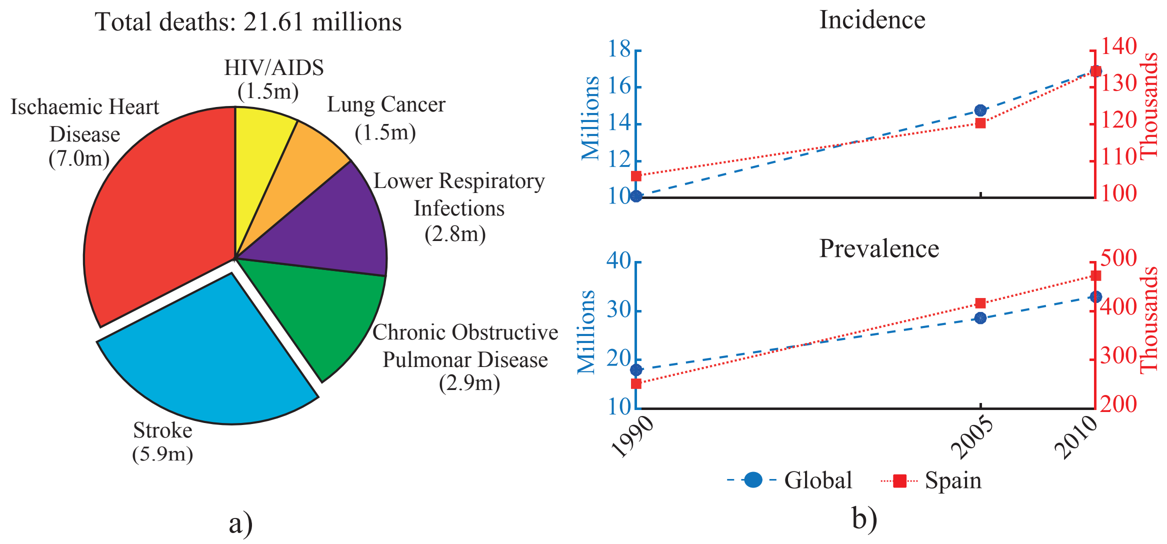

FIGURE 1.3: Burden of stroke. a) Six most common cause of death around the world in 2010; b) Registered incidence and prevalence globally (blue) and in Spain (red) from 1990 to 2010. Graphics generated from the data published in (Lozano et al. 2012, Feigin et al. 2014).

these impairments, motor impairment represents the most common and widely recognized effect after stroke. Motor impairment can be considered as a loss or limitation of function in muscle control of movement or a limitation in mobility (Langhorne et al. 2009).

Motor impairment typically arises after an ischemic or hemorrhagic stroke in which a damage has occurred in the motor cortex, premotor cortex, motor tracts, or associated pathways in the cerebrum or cerebellum (Langhorne et al. 2011). Due to damage in these brain areas, a hemiparesis of the contralateral part of the body is developed hindering the control of movement of the face, arm, and leg of one side of the body. It has been reported that more than 80% of stroke patients experience this condition acutely and more than 40% chronically to varying degrees (Hatem et al. 2016). Furthermore, Lawrence et al. quantified the prevalence of acute impairments in the first-ever stroke population (Lawrence et al. 2001). In this study, the authors reported a prevalence of 77.4% and 72.4% for upper and lower limbs motor deficit respectively.

In relation to the upper limb, it was mentioned that hemiparesis of the contralateral upper extremity is manifested as muscle weakness or contracture, impairment to perform control of movements or a deficit in coordination, changes in muscle tone and joint laxity (Hatem et al. 2016). These motor impairments lead to disabilities that hinder the successful execution of activities such as reaching, picking up objects and holding it with the hand.

It is worth mentioning that these motor impairments are commonly associated with other neurological disorders that aggravate the disability conditions of the people affected with stroke. One of these disorders is the alteration in somatic sensations of the upper extremities (Hatem et al. 2016). Although sensory impairment is recorded less frequently than motor impairment, the reported percentage of stroke survivors with sensory dysfunction vary widely from 11% to 85% (Sullivan & Hedman 2008). Alteration in the somatosensory capability can

Table 1.1: Common impairment and most relevant activities affected in stroke patients

Common impairments after stroke.	Most relevant activities affected.
Reduced ability to control of (in)voluntary movements.	Use of the arm and hand.
Difficulty in mobility and stability of joints	Walking.
Reduced muscle power/tone	Maintaining body position.
Altered proprioception and touch.	Reading, writing and calculation; Solving problems.
Difficulty in ingestion, defecation, urinary and sexual.	Execution of activities of daily living (dressing, toileting, eating, etc.).
Cognitive decline.	Mobility.
Dyphonia/dysarthria/dyphasia.	Communication and speaking.
Reduced energy and motivation, change in personality.	Recreation and leisure.

Data compiled from (Brewer et al. 2013, Langhorne et al. 2011)

result in an impaired detection of sensory information, in disturbed motor tasks performance requiring somatosensory information and in diminished upper extremity rehabilitation outcomes (Hunter & Crome 2002). Both, altered sensation and motor impairment contribute significantly to the loss of function in the upper extremities, and their correct integration for the successful execution of motor tasks is essential.

In addition, a reduced level of movement could eventually lead to changes in muscle, connective and neural tissues, and therefore, inducing secondary complications (Pollock et al. 2014). Some of these secondary problems are: shortening of muscles (contracture); disordered muscle contraction (spasticity); decreased or lost connectivity of the unused neural pathways; and pain.

Although the attention was mainly focused in motor impairment, stroke is also associated with other non-motor impairments that combined with the motor disabilities have an important impact on the quality of life of stroke survivors (Langhorne et al. 2009, Hunter & Crome 2002). Such impairments cause a great functional disability, affecting the independency of stroke survivors and limiting their participation in society (Pollock et al. 2014). Therefore, impairments, and particularly motor impairments, increase the burden of stroke in society.

1.4 Rehabilitation of motor impairment after stroke

In the ancient cultures, motor impairment and other disabilities were addressed following mythological or religious basis, e.g. impaired people was considered to be possessed by spirits or disability was often seen as a punishment for the past misbehaviours (World Health Organization 2010). The notorious advance in science over the last century boosted the consolidation of biological and medical basis for what we know now as the discipline of medical rehabilitation

According to the WHO, rehabilitation is defined as:
"a set of measures that assist individuals, who experience or are likely to experience disability, to achieve and maintain optimum functioning in interaction with their environments".

Rehabilitation is mainly aimed at maximizing people's ability to live, work and learn to their best potential. Evidence suggests that rehabilitation can reduce the functional difficulties associated with disabilities, impairments, ageing and improve quality of life (World Health Organization 2011). In summary, rehabilitation aid in achieving and maintaining optimal functioning in interaction with the environment through achieving the following outcomes:

- prevention of the loss of function;
- slowing the rate of loss of function;
- improvement or restoration of function;
- compensation for lost function;
- maintenance of current function.

The rehabilitation of motor functions is one of the cornerstones of stroke management (Brainin et al. 2014). In previous sections, it was mentioned that the trends in stroke occurrence and the number of stroke survivors are expected to increase over the years, consequently, it is also foreseen an increased quantity of people who benefit from rehabilitation. Thus, rehabilitation therapies will become primordial for stroke survivors and the society. Rehabilitation of motor functions, and of any disability in general, involves a well-known and defined cyclical process consisting of the following steps (Steiner et al. 2002): (1) identification of the person's problems and needs; (2) connecting the problems to relevant factors of the person and the environment; (3) establishing rehabilitation goals; (4) planning and implementing the measures and; (5) assessing the effects. This cyclical process helps medical and physiotherapist staff to personalize the therapy according to the patient's needs in order to maximize outcomes of the rehabilitation therapy.

For achieving the objective of maximizing rehabilitation outcomes, rehabilitation therapies seek to exploit the most important and studied feature of the CNS: the brain plasticity, to be introduced ad discussed in the following paragraphs.

1.4.1 Brain plasticity associated with motor recovery

For several years in the last century, it was believed that *"once development is complete, the sources of growth and regeneration of axons and dendrites are irretrievably lost. In the adult brain the nerve paths are fixed and immutable: everything can die, nothing can be regenerated"* (Cajal 1959). Subsequent scientific contributions shifted this approach giving rise to the current accepted theory that the CNS of an adult human is capable of reorganization and recovery, and it can be selectively promoted (Dimyan & Cohen 2011).

This reorganization process, which is responsible for the recovery of body function post-stroke, is named neural plasticity. Neural plasticity was first described with regard to the function of synapses (Hebb 1949), and later, this principle was extended to the operation of the overall neural networks (Brainin et al. 2014). Although several definition exist for plasticity, here, the definition given by Murphy & Corbett is transcribed: *"Changes in the strength of synaptic connections in response to either an environmental stimulus or an alteration in synaptic activity in a network"* (Murphy & Corbett 2009). Reported evidence showed that this reorganization (neural plasticity) after stroke can occur in cortical regions immediately adjacent to the infarct or remote from the infarct, both in the same and in the opposite hemisphere (Krakauer 2005, Dimyan & Cohen 2011).

Although the rehabilitation of motor impairment after stroke is particularly heterogeneous, the neurological recovery after stroke follows a nonlinear logarithmic pattern as shown in Figure 1.4. The recovery of body functions is believed to occur through a combination of spontaneous recovery and learning-dependent processes (Langhorne et al. 2011). True neurological recovery takes place during the first 4 to 10 weeks post-stroke, and it is driven by the spontaneous recovery and non-learning-dependent processes. It is hypothesized that several mechanisms are involved in this stage, such as: salvation of the penumbra; physiological and neuroanatomical reorganization (spontaneous neuroplasticity); alleviation of diaschisis and; reperfusion enhanced by post-stroke angiogenesis (Krakauer 2005, Buma et al. 2013). In the past, it was believed that the recovery effects of upper extremity due to spontaneous recovery post-stroke was an inherent behaviour and, nothing could be done to influence it (Hatem et al. 2016). Some studies evidenced that task-specific training as soon as possible can assist the natural pattern of functional recovery to maximize outcomes (Langhorne et al. 2011, Krakauer 2006).

After this period, improvements in terms of body functions are believed to be mainly driven by adaptation or compensatory motor strategies (Buma et al. 2013, Krakauer 2005). At this point, the recovery curve slow down and it attains a plateau at approximately 6 months post-stroke. Yet, it was pointed out that the recovery plateau post-stroke may just reflect an asymptotic learning rather than a true biological limit (Krakauer 2005, 2006). Furthermore, the poor insensitivity of the clinical scales to detect improvements can also contribute to this limitation (Dobkin 2004). Some studies carried out with chronic stroke patients (> 6 months) demonstrated effective results, suggesting the idea that neural reorganization may also take place in the subacute and chronic phase after stroke (Langhorne et al. 2009, Krakauer 2006, Hatem et al. 2016). The mechanisms underlying the neural plasticity at this stage that could result in functional recovery are not well understood yet, but it can be explained by long-term potentiation (LTP) and depression (LTD) of existing synapses, strengthening of alternative networks, synaptic remodeling, and axonal sprouting amount others (Brainin et al. 2014, Dimyan & Cohen 2011). Despite well adaptive plasticity is necessary for recovery of motor functions, in many cases the reorganization can also led into a maladaptive plasticity (Dimyan & Cohen 2011, Buma et al. 2013). In this regard, it is accepted that well-adaptive

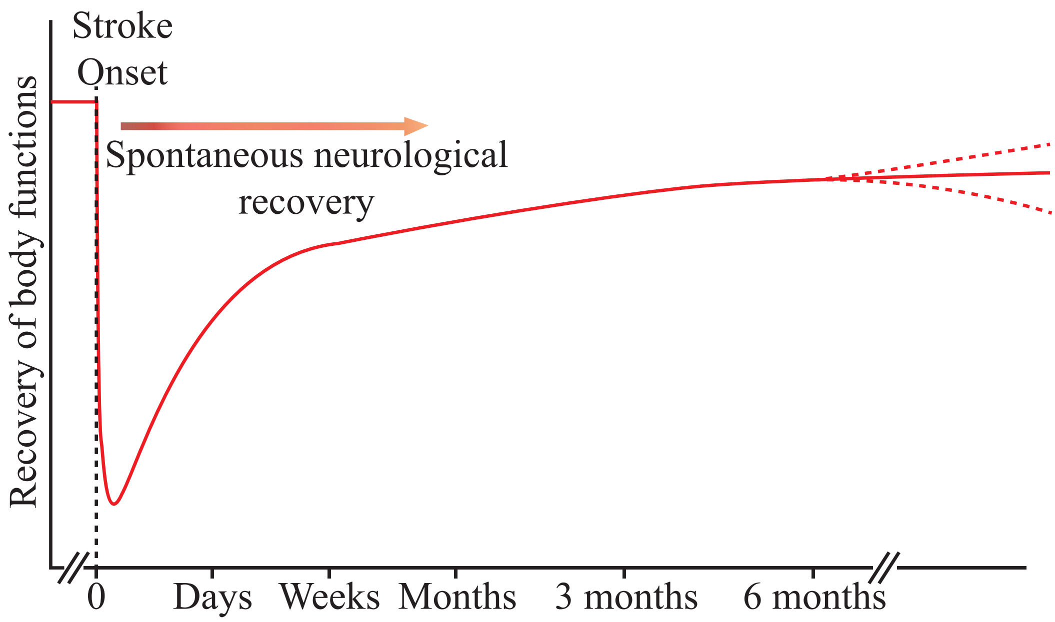

Figure 1.4: Modelled pattern describing the recovery of functions after stroke. Presented curve follows a nonlinear logarithmic pattern, in which the greater degree of recovery takes place after the first three months of stroke onset. Figure adapted from (Langhorne et al. 2011).

brain organization is linked with motor learning, and the learning-related plasticity facilitate recovery after stroke (Krakauer 2005).

1.4.2 Recovering upper-extremity motor function after stroke

Several published studies support the idea that rehabilitation techniques based on motor learning paradigms seeks to facilitate recovery of impaired movement in patients with stroke, more specifically, motor learning is required for lasting brain reorganization (Langhorne et al. 2011, Krakauer 2006). In this scope, a series of principles that maximize the rehabilitation outcome have been widely diffused. Highly patient motivation and engagement, high intensity training and task-specific training seem to be associated with good rehabilitation results (Langhorne et al. 2011).

Currently, the rehabilitation procedure for recovery of upper-extremity motor functions after stroke involves both physical and occupational therapies (Schaechter 2004). The intensity of these therapies varies noticeable across subjects, ranging from a short period of training per day early after stroke onset to considerably larger periods. These therapies involve wide-ranging approaches, most commonly based on task-specific and task-oriented training. Such approaches are mainly supported by the idea of acquiring dexterity in performing selected movements or functional tasks. However, the poor outcomes obtained after training have led to suggest they as inappropriate and insufficient (Hunter & Crome 2002, Schaechter 2004). Additionally, they are claimed to be demanding on time and human resources.

These facts are verified by the several studies. For instance, Hendrick et al. reported that when an initial paralysis of the upper extremity occurred as consequence of stroke, complete motor recovery occurs in 5 to 20% of the patients (Hendricks et al. 2002). In line with this evidence, it has been also reported that 50-70% stroke survivors with initial severe or mild upper extremity paresis will continue to experience loss of function and disuse in the hemiplegic upper limb 2-4 years post-stroke (Hunter & Crome 2002). In a different study, Kwakkel et al. informed that 62% of patients presenting a paralysis of the upper extremity at stroke onset failed to achieve some dexterity at 6 months, indicating a poor prognosis for functional outcome in these group of patients (Kwakkel et al. 2003).

Based on these facts and considering that the upper extremity disability contributes in loss of independence and decrease the quality of life of stroke survivors (Samsa & Matchar 2004), the scientific community is aimed at developing novel methods and technologies to boost the current rehabilitation outcome, paying special attention to those therapies that enhance neural plasticity. In the next section, some of these therapies are briefly presented.

1.5 Novel therapies for rehabilitation of the upper extremity motor function

This section brings an overview of the technologies currently available for rehabilitation of upper limb motor function after stroke. The development of therapies covered in this section were driven mainly by the advancement of technology. As explained in previous sections, it is assumed that neural plasticity of the CNS remains after stroke. Novel therapies seek to exploit this neurological phenomenon and optimize both, the rehabilitation outcome and the user experience, during the therapy session.

1.5.1 Robotics devices

Originally, robots were conceived to be used in industrial environments with the aim of replacing humans. Over the years and with the consolidation of technology, the use of robots were widen to other areas covering different disciplines. One of the most interesting scenarios consist of using robots as assistive and/or rehabilitation tools (Pons 2008). On the one hand, robots can substitute the loss of certain motor function in disabled people, resulting in assistive devices. On the other hand, robots can assist the execution of rehabilitation therapies in order to promote recovery of motor functions (rehabilitation devices). Although both approaches are of great interest, only rehabilitation robots will be discussed in this section and along this work. Until the last decade therapeutic robotics was considered to be in its infancy (Krebs et al. 2008), its use for rehabilitation applications just emerged over the last decade.

Several devices have been proposed over the last years for rehabilitation of upper limb motor functions, some examples are shown in Figure 1.5 (see (Maciejasz et al. 2014, Lo & Xie 2012) for further details). End-effector robots were the earliest considered for rehabilitation of the upper limb. This type of robotic devices support the user's upper limb extremity through a single contact point (commonly the hand or the forearm), so that, the generated forces are transmitted by this interface to the user's arm. This type of robot is simpler, however as the joints of the end-effector robot do not correspond with joints of the human arm, it presents some limitations. Amongst them, we can highlight the difficulties for determining the human arm position, the unfeasibility of applying specific torque to certain upper limb joints, the impossibility of isolate movements at a unique upper limb joint and, the most important, the movements are commonly constrained to one plane. Subsequently, the research approach has shifted towards the use of more sophisticated robotic devices such as exoskeletons (Pons 2010). An upper limb exoskeleton is designed to operate side-by-side with the user's arm, since its mechanical structure is designed with the aim to mirror the anatomical structure of the upper limb. This means that each joint of the exoskeleton directly controls a specific joint of the human arm. Exoskeletons present several advantages for the rehabilitation of upper limb motor functions, namely, more complex movements can be trained, the human arm position can be more easily estimated, the movement of upper limb joint can be isolated and the generated torque can be applied to each joint separately.

Alternatively, rehabilitation upper limb robots can be categorized according to the type of assistance they deliver, leading to passive and active devices. Passive robotic devices cannot actively assist the movement execution, so they are limited to delivering gravity compensation and/or resistive forces (i.e. brakes). The main advantages of this type of devices are the lower cost and smaller size since they do not include actuators. Yet, its use in rehabilitation settings is limited for those users with motor remnant capacity. Instead, active devices possess at least one actuator and, thus, they are able to provide assistance during upper extremity movements. In addition, the capacity of providing active assistance can also be used to exert resistance to the movement. The target population for this type of devices is very broad, spanning the spectrum from users without motor residual capabilities up to those with good motor control. Their principal drawback is the higher cost. In brief, the more complex a robotic system is the more difficult its application in rehabilitation at the clinical setting (Riener et al. 2005). This means that robotic devices with many degrees of freedom (DOFs) and a large range of motion (ROM) are more difficult and time-consuming to apply in daily therapy at the clinical setting. Being the motor recovery an heterogeneous process, the selection of the robotic device must be based on the specific conditions and needs of the user.

As above discussed, motor recovery is associated to motor learning principles. In turn, motor learning depends of the amount of practice, the intensity of the training exercises and the user's motivation (Krakauer 2006, Huang & Krakauer 2009). One of the most important advantages of rehabilitation robotics is its capability of delivering, through automated management, higher dosage (number of movements) and intensity (number of movement per unit of time -minutes or hours-) of therapy comparing with conventional therapy (Huang & Krakauer 2009). Traditional post-stroke rehabilitation therapy involves long sessions of training requiring a significant amount of human effort, rendering it impractical, and in many cases unfeasible, for many physicians and patients (Huang et al. 2016). A direct implication of robotics-supported automated processes is their potential to provide more therapy with less supervision. These observations suggest a possible change of paradigm, where robotic devices could be useful in maximizing the rehabilitation cost-effectiveness (Reinkensmeyer & Boninger 2012).

Taking advantage of the embedded sensors available in robotic devices, a more precise and objective measurement, in terms of kinematics and dynamics,, of the initial motor impairment and its evolution along the treatment can be achieved. In addition, these objective measurements can be used to feed specific biomechanical model in order to accurately analyze joint force and other parameters. These user-specific parameters could provide relevant information for the personalization of the rehabilitation strategy (Huang & Krakauer 2009). With the aim to increase patient's motivation and engagement during therapy, robotic devices can be combined with different types of visual feedback interfaces, such as games or virtual reality environments. These would allow the implementation of challenging scenarios that can be used to set specific objectives throughout the rehabilitation process (Harwin et al. 2006).

The possibility of implementing different control algorithms to modify the behaviour of the robotic device during therapy cater for the implementation of different therapies (Marchal-Crespo & Reinkensmeyer 2009). The development and implementation of control algorithms play an important role in rehabilitation since they define the user-machine interaction behaviour. Reported evidence in literature indicates that particular behavioural implementations do not influence learning, while others promote learning (Reinkensmeyer & Boninger 2012, Huang & Krakauer 2009, Harwin et al. 2006). For instance, the robot's behaviour can be tailored according to the need of the users in order to attain more effective rehabilitation results.

In spite of the aforementioned potential of robotic devices for rehabilitation of the upper limb motor function, its rehabilitation effectiveness compared with traditional therapy is still controversial (Huang et al. 2016, Langhorne et al. 2009, Kwakkel et al. 2008). In this regard, two systematic reviews and meta-analyses, including 246 (Prange et al. 2006) and 218 (Kwakkel et al. 2008) subjects with stroke, have found a significant improvement in the upper-limb motor function after a robotic therapy measured with the Fugl-Meyer scale, in muscle activation pattern, and in speed of executed movement. Also, authors reported that these improvements have a long-term effect of several months to several years, as measured at follow-up. However, both studies reported that these motor function improvements could not be generalized to improvement of outcomes of activities of daily living (ADL). In line with these findings, Langhorne et al. reported similar results, in which robotic devices showed improvements in the arm function, but not in the hand functions (Langhorne et al. 2009). To sum it all up, high intensity repetitive movements constitute an important contribution to the effectiveness of a robotic therapy, and second, robotic therapy had no advantages at low intensity utilization, but it also did not hinder or halt recovery.

In order to increase the benefits of robotics therapy, there are several important aspects to be addressed. Assuming that too much assistance may not promote recovery and given the fact that merely repeating a movement is not enough to learn (Krakauer 2006, Reinkensmeyer et al. 2012), the development of control algorithms to provide the assistance, only when needed, to complete the task constitute a common goal of robotic therapies. This cooperative strategy (human-robot) can promote the active participation of patients, and therefore boost current rehabilitation outcomes. Training more naturalistic movements may also influence positively rehabilitation (Reinkensmeyer & Boninger 2012). Thus, the development of more sophisticated robotic devices that allow users to carry out 3D movements involving several arm joints are necessary. Lastly, the combination of robotic devices with other technologies following a top-down approach (consisting in defining the rehabilitation therapies based on the state of the brain), would exploit endogenous sources of learning and facilitate plasticity (Belda-Lois et al. 2011).

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1.5.2 Functional electrical stimulation

Functional electrical stimulation (FES) uses short electrical pulses to generate muscle contraction. When these artificially induced electrical pulses are intense enough, action potentials in motor-neuron attached to a specific muscle are elicited causing that muscle to contract (Popovic et al. 2002). A representative illustration of this concept is shown in Figure 1.6. Electrical stimulation of muscular tissue has been known since the first observations of Luigi Galvani in 1790, who observed motion after applying electrical wires to paralyzed leg muscles from frogs. Later in 1831, Michael Faraday showed that electrical currents applied to nerves could create active movement (Doucet et al. 2012, IJzerman et al. 2009). The use of FES was first applied over the common peroneal nerve for correction of foot drop during walking in persons with hemiplegia (Liberson et al. 1961). Ever since, it has been widely investigated as a means for rehabilitation and compensation of lower and upper extremities motor disorders (Peckham & Knutson 2005, Popovic et al. 2002).

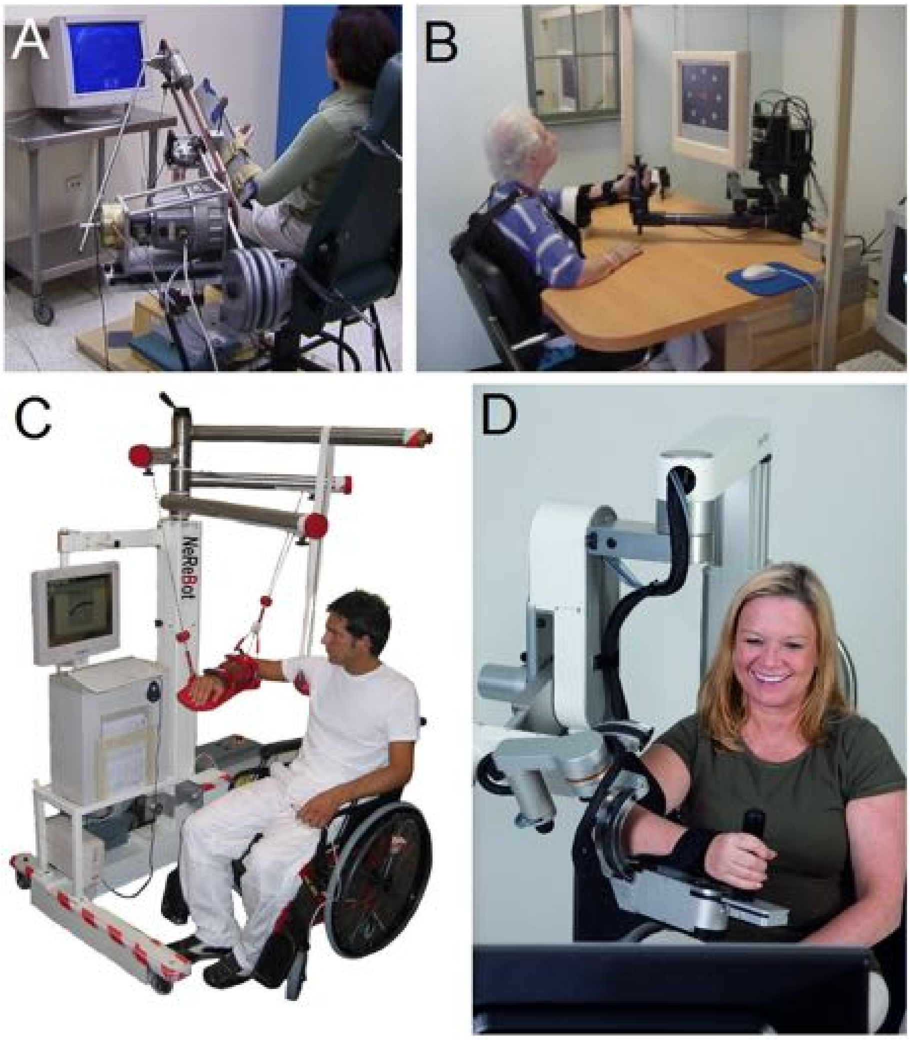


FIGURE 1.5: Examples of end-effectors robotic devices and upper-limb exoskeletons for upper-extremity rehabilitation. Figure reproduced from (Maciejasz et al. 2014).

When using FES, the force generated in a muscle is a function of the total charge transferred to it. The charge is characterized by the stimulus frequency as well as the amplitude and width of the electrical pulse. The amplitude and pulse width regulate the number of muscle fibers that are activated, while the temporal summation of muscle fibers is determined by the frequency at which the pulses are delivered (Sheffler & Chae 2007). Thus, the muscle contraction can be controlled by adjusting these FES parameters.

Electrical stimulation can be supplied using either transcutaneous (over the skin surface), percutaneous (placed within the muscle) or cuff electrodes (wrapper around the nerve that innervates the muscle) (Popović 2014). Transcutaneous, or simply surface stimulation, is performed with self-adhesive electrodes placed on the subject's skin, above the motor-neuron. Although with invasive electrodes (percutaneous and cuff electrodes) a better muscular selectivity is achieved, surface FES systems can be applied at a very early stage of the rehabilitation, allowing early benefit for the patient (Popovic et al. 2001). For such reason, surface stimulation is the most widely used stimulation strategy for rehabilitation of motor function.

The use of FES for rehabilitation of motor functions has been widely explored. However, for its correct use as a rehabilitation or assistive tool, there are some aspects that must be taken into account. Popovic et al. stated that there are three requirements to be fulfilled to use FES for rehabilitation of motor functions (Popovic et al. 2001):

- the muscles that are intended for FES need to be accessible for electrode placement;
- there should not be a major degree of motor-neuron or nerve-root damage of the stimulated muscle;
- the voluntary function of the more proximal limb muscles must remain intact if the FES control of distal muscles relies on voluntary control of proximal muscles.

Several positive effects due to use of FES in stroke persons have been described in the literature. The most obvious benefit is the replacement or assistance of the affected motor functions after stroke, such as gripping and reaching functional movements. Additionally, other numerous physical benefits can be attributed to FES, such as, improvements in upper limb motor impairment, enhancements of dexterity for executing functional upper limb tasks, strengthening of muscles, enhancement in circulation and blood flow, reduction of pain, tissue healing, retardation of muscle atrophy, and reduction of spasticity of the upper limb joints ((Popovic et al. 2005, Thrasher et al. 2009, Eraifej et al. 2017, Maffiuletti et al. 2011). More specifically, it has been demonstrated that FES-based therapy resulted in better functional recovery of the upper limb extremity functions, like grasping and reaching, in stroke survivors when compared with traditional task-oriented training (Thrasher et al. 2009, Alon et al. 2007). Complementary to these physical positive effects, it has also been reported that the use of FES promotes cortical plasticity by enhancing the cortical excitability of the descending motor tracts projected to the upper extremity muscles trained with FES (Kimberley et al. 2004, Barsi et al. 2008, Popović 2014, Thompson & Stein 2004).

This evidence support the use of FES for rehabilitation of upper limb motor function. However, drawbacks such as the non-physiological muscle recruitment hinder its extensive use in clinical settings. The most commonly mentioned issue is the fast and abrupt occurrence of muscle fatigue. Muscle fatigue can be explained by the alteration of two physiological mechanisms responsible for the generation of muscle contractions (Bickel et al. 2011, Maffiuletti 2010, Sheffler & Chae 2007, Gregory & Bickel 2005). First, the recruitment of the muscle fibers by FES follows an inverse order with respect to the natural recruitment process. FES recruits the fast-twitch fibers before the slow-twitch fibers as opposed tom what happens during physiological recruitment. The fast-twitch fibers are innervated by axons with a larger diameter than the slow-twitch fibers. As a result, fast-twitch fibers respond to FES at lower stimulation levels than slow-twitch fibers. Since fast-twitch fibers fatigue more quickly than slow-twitch fibers, the non-physiological order of recruitment of FES techniques contributes to the increased rate of muscle fatigue. The second mechanism is associated with the synchronous recruitment of motor units. Synchronous recruitment means that FES stimulates all motor units at the same time, instead of alternating through the motor unit pool as it

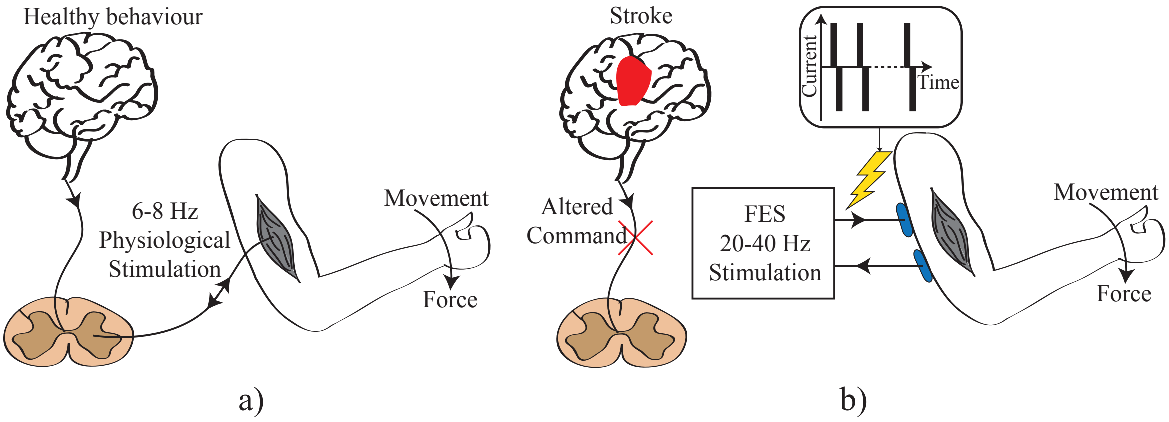


FIGURE 1.6: Movement generation in healthy subjects and motor impaired stroke survivors through functional electrical stimulation (FES). a) Scheme of the intact neurological tract producing tetanic contraction to generate movement; b) Use of FES to generate movement.

is done in physiological neural activation conditions. For this reason, FES requires a much higher stimulation frequency (20-40 Hz) to achieve tetanic contractions when compared with the asynchronous recruitment done by the nervous system (6-8 Hz) (see Figure 1.6). This higher stimulation frequency is the main cause of the increased rate of muscle fatigue (Lynch & Popovic 2008, Sheffler & Chae 2007, Maffiuletti 2010). There are also other factors linked to the altered recruitment of muscles fibers due FES. Specifically, the complexity for generating effective and consistent joint forces difficult the execution of precise and coordinated movements. Moreover, the high complexity and extremely non-linear and time-varying response of the musculoskeletal system to FES preclude the accurate and reliable control of movements.

The clinical application of FES systems is complicated and the scientific community is currently working to overcome these limitations to consolidate the use of FES as a tool for clinical rehabilitation of motor function. Among these efforts, it is worth highlighting the development of more robust and reliable stimulator devices, the use of multi-channel stimulation, the implementation of closed-loop control strategies to adjust the current intensity supplied and to achieve a precise control of movements (Zhang et al. 2007, Lynch & Popovic 2008, Popović 2014). Alternatively, the use of FES under different paradigms is currently being considered to improve the effectiveness of the rehabilitation therapy. There is significant evidence that the activation of paralyzed muscles causally timed to the patient's intent to move, may contribute to larger therapeutic effects than those typically achieved by standard therapies (Daly & Wolpaw 2008, Ethier et al. 2015, Ethier & Miller 2015).

1.5.3 Brain-computer interface

The cortical electrophysiological activity can be acquired through different techniques (see signal acquisition in Figure 1.7). The electroencephalography (EEG) signals are the most common and widely used. The EEG signals represent the electrical activity of the brain recorded from electrodes placed on the scalp. The main advantages of using EEG signals result from being EEG a non-invasive technique, which is commercially available, easy to set-up and, under certain circumstances, robust to possible external interferences. Altogether, EEG is a suitable technique and tool for clinical environments (Chaudhary et al. 2016).

EEG-based brain computer interface (BCI) systems are emerging to provide a communication channel between the human and an external device using brain activity (Wolpaw et al. 2002). The general concept and overview of a BCI system is shown in Figure 1.7. This system opens a door for innovative applications in several fields, with higher relevance in clinical and assistive applications. Initially, BCI systems were conceived in clinical applications to provide an alternative communication (blue dashed rectangle in Figure 1.7 means to patients with lost ability to interact with the environment in any possible natural way (Daly & Wolpaw 2008, Shih et al. 2012). During the last decade, this approach shifted towards using BCI systems in rehabilitation applications (red dashed rectangle in Figure 1.7, in which the main goal is to restore the impaired motor functions of a patient's limb (Daly & Wolpaw 2008, Chaudhary et al. 2016). In this scenario (motor restoration), the EEG signals provide a relevant feature to the communication channel between the human and the assistive device: having real-time access to movement-related cortical processes allows fast estimations of users' intentions, which may in turn lead to achieving causality and more natural interactions. Such natural interfaces are highly desired in man-machine interaction for rehabilitation purposes for some relevant reasons:

- Biological reasons. Human-robot interface systems seek to take advantage of the natural control mechanisms fully optimized in humans.
- Practical reasons. Delays are introduced when natural cognitive processes are encoded into an imposed sequence of tasks. In addition, a training phase is needed to teach the user to generate these non-natural commands or to map a cognitive process into a new set of outputs. Both factors, the delays and the mapping, can also induce fatigue, both at a musculoskeletal level and at a mental level. These limitations may be circumvented if the natural outputs of a cognitive process are used instead.
- Rehabilitation. Interacting directly with cognitive processes of movement is a means to excite them and assess the evolution of the rehabilitation therapy.

The use of EEG-based BCI systems to promote recovery of lost motor function has gained attention during the past few years. Certainly, a large number of interventions to promote motor neuro-rehabilitation have been proposed (Daly & Wolpaw 2008, Chaudhary et al. 2016). Several studies proposed BCI systems to perform motor imagery and provide visual feedback (Pichiorri et al. 2011, 2015), BCIs in combination with physical therapy (Broetz et al. 2010), BCIs triggering a robotic-based therapy (Ramos-Murguialday et al. 2013, Ang et al. 2014, Ono et al. 2014) or BCIs triggering FES (Marquez-Chin et al. 2016, Mukaino et al. 2014).

From this background, two BCI-based strategies in the rehabilitation field can be put forward. The first one is based on the neuro-feedback, which hypothesizes that training the patients

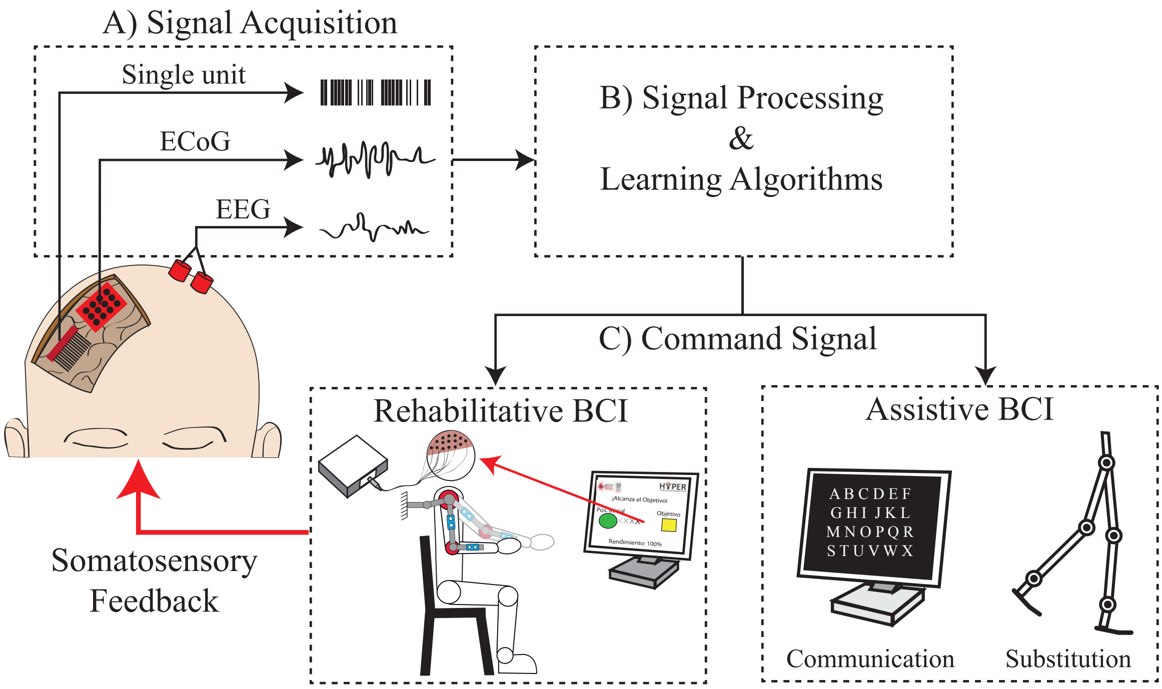


FIGURE 1.7: General overview of a Brain-Computer Interface (BCI) system. A) Electrophysiological signal from the brain acquired using invasively (Single unit and ECoG) or superficially (EEG) techniques. B) Acquired signal are processes to extract useful cortical feature. C) Command generated from pre-processing and learning algorithm to operate assistive devices to help patients with communication or movement, or to operate rehabilitative devices to help recover neural function. ECoG: electrocorticography; EEG: electroencephalography.

to produce more normal brain activation patterns will be accompanied by improved motor function. The second strategy focuses on using brain activity to drive a device providing proprioceptive feedback. This sensory feedback is expected to induce plasticity leading to restoration of the normal motor control. This second strategy relies on the idea that brain activity can guide activity-dependent central nervous system plasticity in the same way as the standard repetitive movement practice carried out by therapists or robots influences it (Várkuti et al. 2013).

The potential relevance of the second BCI-based strategy for changes in motor behavior is exemplified particularly well in the context of stroke rehabilitation. Assuming that the connection between peripheral muscles and the sensorimotor cortex has been disrupted due to a brain damage, such as stroke, a concurrent and coherent activation of sensory feedback loops and primary motor cortex may reinforce previously silent cortical connections by Hebbian learning (repeatedly coincident activation of pre-synaptic and postsynaptic cells reinforces synaptic strength, tending to become associated), and thus support functional recovery (Mrachacz-Kersting et al. 2012, Niazi et al. 2012, Xu et al. 2014).

1.6 Conclusions of the chapter

This chapter presented the motivation for the development and the studies framed within this thesis. This introductory chapter supported the fact that stroke currently represent a serious and major health-care problem globally. Certainly, it constitutes an important economic and societal burden. Brain injury caused by stroke can severely affect several body and/or cognitive functions, and specifically, motor impairments are the most common and disabling consequence that decreases the quality of life of stroke survivors. In this context, the recovery of upper-limb motor function constitutes a prime landmark addressed by current rehabilitation therapies.

With the aim of boosting the current rehabilitation outcome and under the assumption that high intensity and task-oriented training providing a coherence assistance with respect to motor-cortical processes are important principles to promote neural plasticity, the use of robotic devices, FES and BCI technology were proposed. Robotic and FES technologies hold a considerable potential to drive upper-extremity rehabilitation interventions. Yet, when considering the individual use of these alternative rehabilitation methods for recovery the upper-limb motor function, they present limitations that hamper their consolidation in clinical rehabilitation settings.

Based on this analysis, the combined use of assistive technologies (robot and FES) for rehabilitation of reaching movement in stroke patients is explored in this thesis. This combines action (mechanical and electrical assistance) is referred to as hybrid robotic systems. As it will be shown in the following chapters (Chapter 2 and Chapter 3), the hybrid approach holds a great rehabilitation potential since it exploits the main advantages of each technology resulting a more adequate and beneficial therapeutic methodology. In addition, the use of BCI technology to accurately identify motor-related cortical patterns is a key aspect for the interventions proposed in this dissertation. Indeed, it will be shown how important the precise association (causality, synchronization) between the onset of voluntary movements and the hybrid assistance is for promoting neural plasticity (see Chapter 4).

Chapter 2

State of the art of hybrid robotics system for rehabilitation motor functions of the upper-extremities[1]

Abstract

Over recent years, the combined use of functional electrical stimulation and robotic devices, usually referred to as hybrid robotic rehabilitation systems, has emerged as a promising approach for healing lower and upper limb motor disorders. This chapter presents a critical review of the state of the art of current hybrid robotic solutions for upper-limb rehabilitation after stroke. To this purpose, studies have been selected through a search using web databases: IEEE-Xplore, Scopus and PubMed. A total of 7 different hybrid robotic systems were identified. Selected systems are critically compared with respect to their technological components, features and control strategies implemented. Additionally, technological and clinical evidence on the effectiveness of these hybrid robotic therapies are widely presented and discussed. Eventually, the current technological challenges are identified. These challenges provide a valuable information that informed developments in subsequent chapters of this thesis.

[1]This chapter is partly based on:
Resquín F, Cuesta Gómez A, Gonzalez-Vargas J, Brunetti F, Torricelli D, Molina Rueda F, Cano de la Rueda R, Miangolarra J. C and Pons J. L. Hybrid robotic systems for upper limb rehabilitation after stroke: A review. Med Eng Phys. 2016 Nov;38(11):1279-88.

2.1 Introduction

Evidence presented in the previous chapter indicated the need for better ways to improve current rehabilitation interventions aimed at recovering arm motor function after stroke. With this aim, the use of FES and robotic devices has been introduced over the last decade as potential rehabilitative tools to improve the current rehabilitation outcomes. However, the independent use of these technologies still present limitations that hinder their broad use in clinical settings (see previous chapter for detailed information).

Alternatively, the combined use of FES and robots has been proposed as a solution to overcome their individual limitations and increase the robustness, safety and effectiveness of upper-limb rehabilitation interventions. This combined approach has been referred to as Hybrid Robotic Rehabilitation Systems. According to del-Ama et al. hybrid systems can be defined as *"those systems that rehabilitate or compensate motor functions through the combined action of muscle activation with FES and mechanical/electromechanical forces supplied to joints"*(del Ama et al. 2012).

In this chapter, the state-of-the-art (SoA) of current hybrid robotic approaches focused on the upper extremity is presented. Special attention is paid to their rehabilitation targets, to the control/intervention strategies, and to their potential benefits for rehabilitation of the upper-limb motor function. To this aim, the key contributions in literature are identified and analyzed from a technological (e.g. type of devices, multimodal actuation, usability) and a clinical perspective. Eventually, the main challenges for the consolidation of this rehabilitation approach are discussed.

2.2 Methods

A literature search was conducted on the following web sources: the Institute of Electrical and Electronics Engineering (IEEE Xplore database), PubMed and Scopus databases. The search was carried out without a time limit. In order to reject those studies focused on the lower limb, the term *'upper limb'* followed by the logical conjunction *'and'* were combined with the following keywords: *'Hybrid Exoskeleton', 'Functional electrical stimulation', 'Robots' and 'Exoskeleton'.*

Selected studies were individually reviewed and the following inclusion criteria were applied:

- all papers must fit into the definition of the hybrid robotic system, i.e. present a combined use of robotic devices (passive or active actuation) and FES;
- the technology must be focused on upper limb rehabilitation;
- studies should consider at least one of the following outcome measures: kinematic data, electromyography (EMG) signals, force measure, clinical scales and functional evaluation in stroke patients, and;

Table 2.1: Identified hybrid system for grasping function.

System	Application	Robotic Device	FES Device	Drawback
NESS HandMaster (Alon et al. 2003, Ring & Rosenthal 2005)	Finger flexion/extension	Forearm-Hand plastic orthosis. Passive Device	5 channels (EDC, EPB, FDS, FPL and thenar). Open loop. Button triggered.	Passive robotic device. Preprogrammed FES parameters. Limited functional response to FES during grasping. Non-associative assistance.
HANDS (Fujiwara et al. 2009)	Fingers extension	Wrist hand splint. Passive Device	1 channel (EDC). Closed loop. EMG-based. EMG-triggered.	Passive robotic device. Limited to user with normal EMG activity. Limited functional response to FES during grasping.
Wrist Training (Hu et al. 2010, 2011, 2015).	Wrist flexion/extension.	Two parallels bars. Active Device. Controlled by voluntary EMG.	2 channels (FDS and EDC). Closed loop. EMG-based. EMG triggered.	Limited to user with normal EMG activity. Limited functional response to FES during grasping. No fingers assistance.

Meaning of abbreviation and acronyms: HANDS: Hybrid assistive neuromuscular dynamic stimulation; EMG: Electromyography; EDC: Extensor digitorum communis; EPB: Extensor pollicis brevis; FDS: Flexor digitorum superficialis; FPL: Flexor pollicis longus.

- the article should be written in English.

Studies in which robotic therapy and FES were used separately, or in which the techniques were not used as a therapy, were excluded. Also, hybrid robotic systems assessed in pathologies different from stroke were not considered.

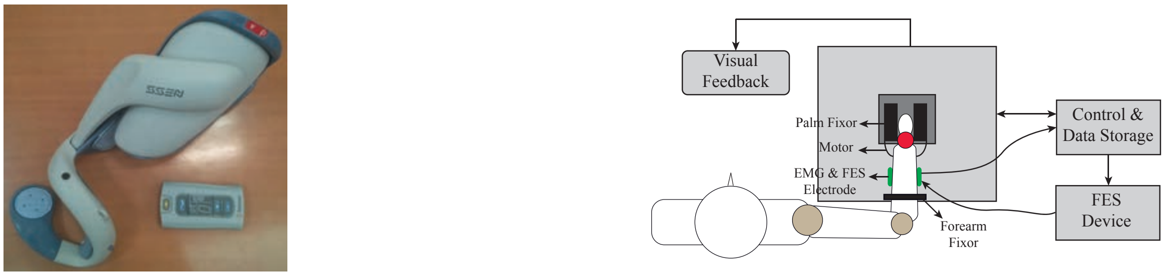
2.3 Results

A total of 13 articles were found and retained for analysis, which correspond to 7 different hybrid robotic systems. Upper-limb functional movements can be divided into two main functions: grasping and reaching. Since these two motor functions involve different joints (distal vs proximal), each requiring specific rehabilitation strategies, the selected studies were classified into two different groups: systems that focus only on grasping (n = 3) and systems that focus only in reaching (n = 4).

2.3.1 Technical overview of hybrid systems

2.3.1.1 Hybrid robotic rehabilitation systems for grasping

Table 2.1 shows a summary of the hybrid robotic rehabilitation systems that have been used for rehabilitation of grasping motor function. The NESS hand Master system represents the first reported hybrid robotic system for assisting grasping (Alon et al. 2003). It consists of a five-channel electrical stimulator embedded in a passive wrist orthosis (see Figure 2.1a). The system assists the hand opening and closing by means of electrodes placed over the extensor muscles, extensor digitorum communis (EDC), extensor pollicis brevis, flexor muscles, flexor digitorum superficialis (FDS), flexor pollicis longus and the thenar muscles group for thumb movement. The electrical pulses are conducted through an open-loop strategy with constant preset stimulation values (pulse amplitude, pulse width and frequency). The passive orthosis does not contribute to joint movements, but supports the wrist joint to facilitate grasping



a) b) c)

FIGURE 2.1: Hybrid robotic systems for grasping rehabilitation. a) Newest version of the NESS HandMaster device (Alon et al. 2003, Ring & Rosenthal 2005). b) Hybrid assistive neuromuscular dynamic stimulation (HANDS) (adapted from (Fujiwara et al. 2009)). c) Experimental setup for wrist flexion/extension training (adapted from (Hu et al. 2010)).

and to smoothen the muscle response to the FES. This orthosis is wired to a control unit used to configure manually the FES parameters and to trigger the electrical assistance by pressing a button.

A similar solution, referred to as hybrid assistive neuromuscular dynamic stimulation (HANDS), was analyzed (Fujiwara et al. 2009). In this study, the authors integrate a wrist hand splint with a single channel electrical stimulation for assisting fingers extension. In this case, stimulation was given solely to the EDC muscle, whereas the splint contributed to inhibition of flexors over activated muscles, and therefore the applied electrical stimulation enhanced agonist muscles recruitment. Although this system relies on a single stimulation channel, its main advantage is that the stimulation intensity could be set using a pulse width modulation technique proportional to the recorded volitional electromyography (EMG) from the targeted muscle (Muraoka et al. 2013, Hara et al. 2006). Figure 2.2a depicts the controller rule implemented in this system, where D_{min} corresponds to the minimum pulse width duration that facilitates voluntary contraction, and D_{max} is the threshold pulse duration equivalent to the highest endurable intensity during maximum voluntary contraction. The voluntary EMG signal was calculated by taking the raw EMG signal after 20 ms of the electrical stimulus, thus both artifact and M-wave were discarded.

Hu et al. presented a FES-robot system for wrist flexion/extension rehabilitation (Hu et al. 2010, 2011, 2015), in which both assistive parts are driven by voluntary EMG signals detected from flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles. The robotic system is based on an actuated end-effector device, composed of two small parallel bars delimited in the horizontal plane (see Figure 2.1a). Stroke patients seated with their affected arm mounted on the system to track a cursor displayed on the screen by moving their wrist at different angular velocities. The total support was given by the contribution of the robot (A_{robot}) and FES (A_{fes}) assistance. The controlled assistance, shown in Figure 2.2b, followed a proportional relation between the EMG amplitude, the maximum torque value during isometric contraction (T_{imv} for robot assistance) or maximum stimulation pulse width (W_{max} for FES assistance), and the constant assistance factor (G), used to adjust the support level (ranged from 0 to 1). Although the assistance factor allows setting different actuation levels

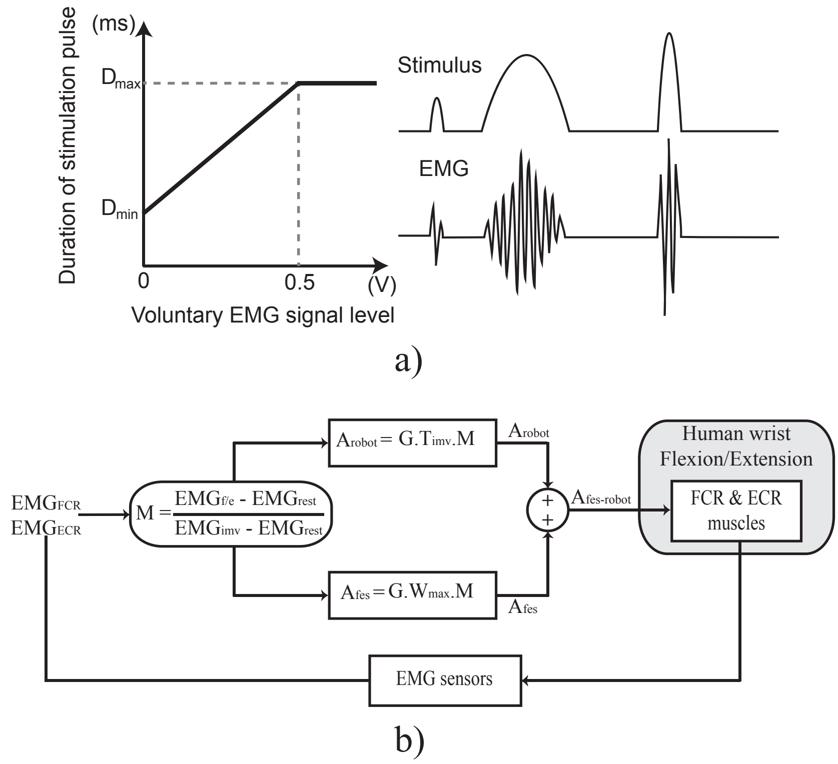


FIGURE 2.2: Implemented robot and FES control algorithm for grasping movement. a) EMG-based FES control strategy for hand opening and closing (Fujiwara et al. 2009). D_{min} and D_{max} define the minimum and maximum stimulation pulse width. b) Cooperative control strategy by Hu et al. for wrist flexion/extension (Hu et al. 2010, 2011, 2015). A_{robot}, A_{fes} represent the torque and FES assistance respectively; G and K are the constants gains used to adjust the magnitude of the assistance torque and FES; T_{imv} is the maximal value of the torque during isometric maximum extension (T_{imve}) and flexion (T_{imvf}); $W_{max,FCR/ECR}$ is the maximum stimulation impulse width applied on the FCR or ECR muscles; $EMG_{flex/ext}$ is the EMG of agonist muscle; EMG_{rest} is the average of EMG level of the muscle; EMG_{imv} is the maximal EMG amplitude of the muscle.

individually to each system (FES and robot), it was demonstrated that better performance (less tracking error) was obtained when FES and robot provided equal contribution (50% FES and 50% robot) (Hu et al. 2011).

2.3.1.2 Hybrid robotic rehabilitation systems for reaching

Four main hybrid systems for the rehabilitation and assistance of reaching functions were identified (Table 2.2). All of them, in contrast with grasping devices, focus their action on proximal joints, i.e. shoulder and elbow.

Barker et al. combined a robotic system, the so-called Sensorimotor Active Rehabilitation Training (SMART), with FES (Barker et al. 2008). The SMART robot consists of a manipulator mounted on a linear track that allows elbow frontal flexion/extension movements (see Figure 2.3a). This mechanical system reduces the difficulty of carrying arm extension movements by limiting the allowed degree of freedoms and minimizing the resistance to the movement. The movement assistance was triggered by voluntary EMG activation and was

TABLE 2.2: Identified hybrid system for reaching function.

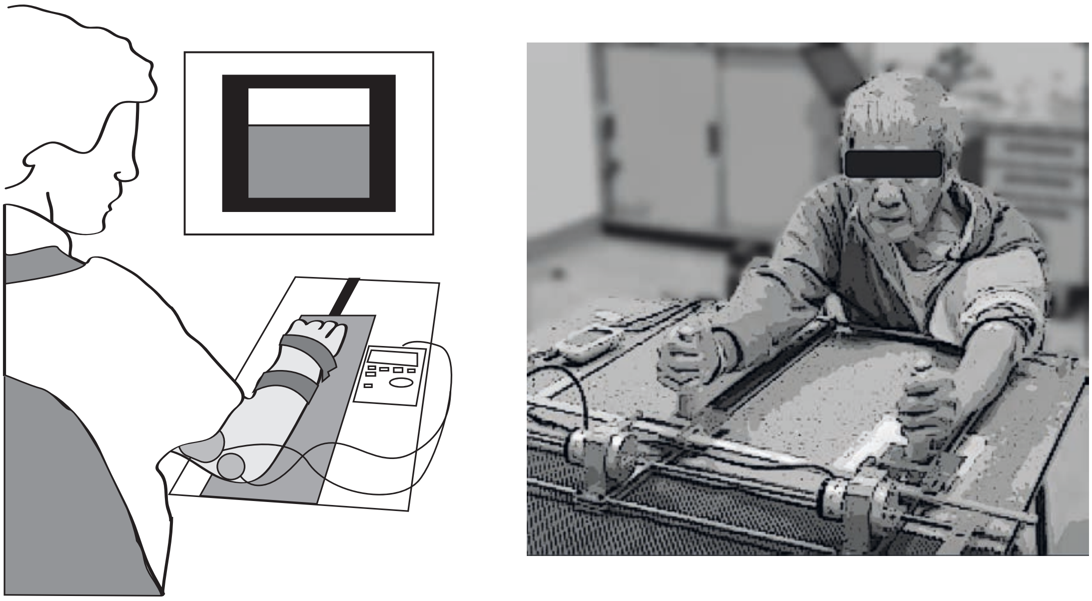
System	Application	Robotic Device	FES Device	Drawback
SMART + FES (Barker et al. 2008).	Elbow extension in horizontal plane.	Horizontal guide platform. Passive device, variable mechanical load.	1 channel (TR). Open loop. EMG triggered.	Constrained movement. Passive robotic device. Preprogrammed FES parameters.
BAT system (Wu et al. 2011).	Elbow extension in horizontal plane.	Horizontal guide platform. Passive device.	1 channel (TR). Open loop. Triggered by error position.	Constrained movement. Passive robotic device. Preprogrammed FES parameters.
Planar end-effector device + FES (Hughes et al. 2009, Freeman et al. 2009*c*,*b*).	Elbow extension in horizontal plane.	5-link planar Arm manipulator. Actuated device. Impedance controller.	1 channel (TR). Closed loop: FB+FF. Button triggered.	Constrained movement. Non-associative assistance.
SAIL system (Meadmore et al. 2012, Freeman et al. 2011).	Shoulder flexion and elbow extension in 3D.	ArmeoSpring® exoskeleton. Passive device.	2 channels (AD and TR). Closed loop: FB+FF. Button triggered.	Limited FES-Robot interaction. Non-associative assistance.

Meaning of abbreviation and acronyms: SMART: Sensorimotor active rehabilitation training; BAT: Bilateral arm training; SAIL: Stimulation assistance through iterative learning; FES: Functional electrical stimulation; TR: Triceps muscle; BI: Biceps muscle; AD: Anterior deltoid muscle; FB: Feedback controller; FF: Feedforward controller; BMI: Brain-machine interface.

driven by FES applied to the triceps muscle. A predefined stimulation pattern was used, consisting of one second of ascending ramp, 5 to 10 seconds of constant stimulation and one second of descending ramp.

Wu et al. implemented the bilateral arm training (BAT) approach (Wu et al. 2011), shown in Figure 2.3b. It was designed to emphasize frontal symmetrical bilateral movements to coordinate the use of both arms during repetitive movement. Two passive manipulators, placed over linear tracks in the horizontal plane, were combined with FES. Similarly to the SMART device, the parallels bars supported the arm's weight and constrained the workspace. Additionally, the manipulator position was used to trigger the FES, as an on/off event: the FES was turned on when the affected arm was falling behind the unaffected arm during the extension movement. The electrical stimulation was applied to triceps muscle with preprogrammed stimulation parameters.

Hughes et al. presented an actuated planar end-effector device combined with FES applied to the triceps muscle (Hughes et al. 2009, Freeman et al. 2009*c*,*b*). In this case, the hand of the patients was strapped to the end of a five-link robotic arm. Subjects had to follow elliptical shaped trajectories at a constant velocity. These trajectories were projected on a Plexiglas disc located over the user's forearm and hand (Figure 2.3c). To ensure safe interaction between the robot and human subjects, a second-order dynamic equation was also used to implement an impedance control (Freeman et al. 2009*b*). The FES assistance was used to facilitate elbow extension movements, using a closed-loop control scheme composed of a linearized feedback controller and a learning feed-forward loop (Freeman et al. 2009*c*). To this aim, a full FES-based human arm model was developed, see (Freeman et al. 2009*c*,*a*) for further information. This detailed model was used to implement the linearized controller in a simple proportional-integral-derivative (PID) arrangement. The learning feed-forward loop was used to adjust the stimulation level to produce an improved performance on successive attempts. To this end, the authors implemented the linear iterative learning control algorithm (ILC). This algorithm facilitated precise tracking over the reference trajectory by adapting the required FES assistance accordingly. This combined control strategy is shown in Figure 2.4a. By implementing this control architecture, the authors tried to fully exploit



a) b)

c) d)

FIGURE 2.3: Hybrid robotic rehabilitation system for reaching movements. a) SMART device combined with FES (figure adapted from (Barker et al. 2008)). b) BAT training based on two parallel bar and FES (figure adapted from (Wu et al. 2011)). c) Planar end-effector work- station combined with FES (Freeman et al. 2009*c*,*b*). d) Unconstrained 3D workstation based on ArmeoSpring® exoskeleton (Meadmore et al. 2012).

the association between the users' motor capabilities and the level of assistance required to help them achieve such movement.

The studies mentioned so far did not consider unconstrained scenarios, i.e. including higher degrees of freedom or complex functional tasks. The 3-dimension rehabilitation system referred to as SAIL (Stimulation Assistance through Iterative Learning) falls in this category (Freeman et al. 2011, Meadmore et al. 2012). The system, shown in Figure 2.3d, combined the passive upper limb exoskeleton ArmeoSpring® with a two-channel FES system. The ArmeSpring® was used to ensure safety and facilitate the execution of reaching movements by suppressing the effect of gravitational forces. The FES system was applied to the anterior deltoid and triceps muscles to assist the arm extension in the 3D space. Subjects were asked

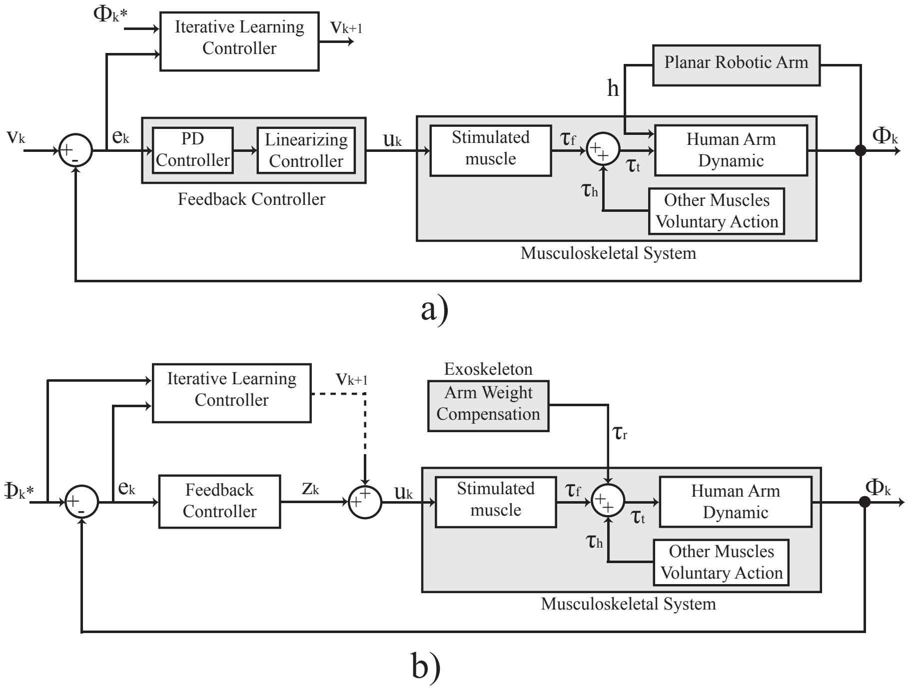


FIGURE 2.4: FES control strategies implemented in hybrid robotic therapies for reaching movements. a) Control scheme representation implemented in the planar end-effector workstation (Hughes et al. 2009). Φ_k^* is the reference trajectory and Φ_k is the measured joint angle at time k; V_{k+1} represents the feedforward update signal for application on next trial; e_k is the error at time; μ_k is the actuation signal; τ_f, τ_h, τ_t are the torque generated due to stimulated muscle, contribution of others muscles and the sum of both respectively; h is the torque provided by the planar robotic device. b) Block diagram of control strategy for 3D rehabilitation system (Meadmore et al. 2012). Φ_k^* is the reference trajectory and Φ_k is the measured joint angles at time k; V_{k+1} represents the feedforward update signal for application on next trial; e_k is the error at time; z_k is the actuation signal for the feedback controller; μ_k is the total $(V_k + z_k)$ the actuation signal; τ_f, τ_h, τ_t are the torque generated due to stimulated muscles, contribution of others muscles and the sum of both respectively; τ_r is the torque provided by the exoskeleton to support the arm against gravity.

to perform reaching exercises that consisted in following a reference target displayed on a screen. The target travelled along a fixed trajectory at various speeds. Authors implemented a similar control scheme for the previously mentioned planar task. The system was assumed to be a two single-input, single-output (SISO) configuration and, under this scenario, the control and movement of the forearm and upper arm were considered independently Freeman et al. (2012). This simplification allowed the implementation of the control scheme shown in Figure 2.4b, a PID feedback controller with a feedforward loop consisting of a phase-lead ILC algorithm. The ILC modifies the control input using the tracking error information from previous trials in order to improve performance.

Further development of the control architecture was made for the same rehabilitation scenario. This time, an input-output linearizing controller with ILC and a Newton-method based ILC controller were developed (Freeman 2015, 2014). However, due to the limited time available during clinical trials, and considering the time-demanding procedure required for musculoskeletal model identification, these strategies were only evaluated on healthy subjects.

TABLE 2.3: Clinical assessment of the reviewed hybrid robotic systems.

System	Patients	Control Group	Outcome Scales
NESS HandMaster (Alon et al. 2003, Ring & Rosenthal 2005).	77 chronic strokes (Alon et al. 2003). 22 sub-acute strokes (Ring & Rosenthal 2005).	None (Alon et al. 2003). Group1: NESS users; Group 2; Conventional therapy (Ring & Rosenthal 2005).	Clinical: JT, B&B, NHPT, MAS, PPI (Alon et al. 2003). Clinical: PROM, MAS, B&B, JT (Ring & Rosenthal 2005).
HANDS (Fujiwara et al. 2009).	20 chronic stroke.	None.	Clinical: UEUS, SIAS, MAS. Pressure force during handwriting. Neurophysiological: CI, H-Reflex, and MEP.
Wrist Training (Hu et al. 2010, 2011, 2015).	5 chronic Stroke (Hu et al. 2010). 5 chronic Stroke (Hu et al. 2011). 26 chronic stroke (Hu et al. 2015).	None (Hu et al. 2010). None (Hu et al. 2011). Group1: EMG-driven Hybrid system; Group2: EMG-driven of robotic device (Hu et al. 2015)	Clinical: FMA, MAS, ARAT. Neurophysiological: CI.
SMART + FES (Barker et al. 2008).	33 chronic stroke.	Group1: EMG-driven Hybrid system; Group 2: robot alone. Group 3: no intervention.	Clinical: motor assessment scale, MAS. Isometric force. ROM.
BAT system (Wu et al. 2011).	23 chronic stroke.	Group 1: Hybrid system. Group 2: Robot alone.	Clinical: FMA, MAL.
Planar end-effector device + FES (Hughes et al. 2009, Freeman et al. 2009*c*,*b*).	5 chronic stroke.	None.	Clinical: FMA, ARAT. Task performance. Isometric force.
SAIL system (Meadmore et al. 2012, Freeman et al. 2011).	5 chronic stroke.	None.	Clinical: FMA ARAT. Task performance.

Meaning of abbreviation and acronyms: FES: Functional electrical stimulation; HANDS: Hybrid assistive neuromuscular dynamic stimulation; SMART: Sensorimotor active rehabilitation training; BAT: Bilateral arm training; SAIL: Stimulation assistance through iterative learning; JT: Jebsen-Taylor; B&B: Block & block; NHPT: Nine-holes peg test; PPI: Perceived pain intensity; ROM: Range of movement; UEUS: Upper extremity utility score; SIAS: Stroke impairment assessment set; FMA: Fugl-Meyer assessment; MAS: Modified Ashworth score; ARAT: Action research arm test; FIM: Functional independence measure; MAL: Motor activity log; CI: Co-contraction index; MEP: Motor evoked potential.

2.3.2 Clinical evaluation

In this section, a brief overview of the clinical evaluation of the reviewed hybrid robotic systems is presented. Table 2.3 summarizes of the most relevant clinical features considered in these studies.

2.3.2.1 Clinical outcomes of hybrid system for grasping rehabilitation

The NESS HandMaster was evaluated in two separate studies. Articles reported trials with a large sample of chronic (n = 77) (Alon et al. 2003) and sub-acute (n = 22) (Ring & Rosenthal 2005) stroke patients.

Alon et al. evaluated the NESS HandMaster with 77 chronic stroke patients (Alon et al. 2003). They reported a significant improvement in the Jebsen-Taylor, Box & Block and Nine-Peg Test scores. Also, the results showed a significant reduction in the perceived pain intensity after therapy, whilst the modified Ashworth scale (MAS) at the shoulder, elbow, wrist and fingers was not significantly reduced.

Ring et al. defined two types of sub-acute stroke patients for the evaluation of the NESS HandMaster (Ring & Rosenthal 2005). Type I consisted in those patients with no active voluntary motion at the fingers and wrist (n = 10). Type II comprised patients with partial active voluntary range of motion (n = 12). Patients were also assigned to the control group (conventional therapy) and the experimental group (NESS Hand Master users). Considering the MAS, a significant improvement was found on type I experimental group for shoulder and fingers (p = 0.05 and p = 0.04), and in the type II experimental group for the shoulder

($p = 0.03$), wrist ($p = 0.04$), fingers ($p = 0.01$), and thumb ($p = 0.04$). The evaluated range of motion of the arm joints showed a greater improvement in proximal upper limb in the type I group. However, the difference did not reach a level of statistical significance. The type II group showed greater level of improvements, with significant level for shoulder flexion ($p = 0.03$), wrist extension ($p = 0.02$) and wrist flexion ($p = 0.04$). The functional tests (Box & Block and the Jebsen-Taylor) presented significant improvement in both types of the treated group.

In the case of the HANDS system, its effects were evaluated in 20 chronic stroke patients (Fujiwara et al. 2009). Results revealed significant improvements ($p < 0.01$) in two of the four evaluation points (drinking with a glass and turning over a page) of the upper extremity utility score (UEUS). The finger test as well as the knee-mouth test of the stroke impairment assessment test (SIAS) also improved significantly ($p < 0.001$ and $p = 0.02$). The MAS were reduced significantly at the elbow wrist and finger extensors ($p < 0.001$), and the pen pressure capability increased significantly ($p = 0.008$). The H-Reflex showed significant changes of reciprocal inhibition at all three intervals after intervention (0, 20 and 100 ms), while the co-contraction index measured with EMG and the motor evoked potential elicited by transcranial magnetic stimulation improved, but not significantly. The clinical outcome measures and computer-aided ratings were assessed in 15 of the 20 patients three months after the end of the intervention. The evaluation showed a significant effect in comparison with the pretreatment assessment in the "drinking with a glass" task and the "turning over a page" task in the UEUS, the SIAS finger score, the MAS (elbow, wrist, finger) score, the pen pressure, and the grip strength ($p < 0.05$). When comparing the post-treatment values with those at the 3-month follow up, a significant difference was found in the "drinking with a glass" task and the grip strength ($p < 0.05$).

With their wrist training system, Hu et al. carried out a single-blinded randomized controlled trial with 26 chronic stroke patients to evaluate the effectiveness of the wrist training platform (Hu et al. 2015). Recruited patients were divided into two different groups, so that fifteen of them received EMG-driven robot therapy (control group), and the rest ($n = 11$) EMG-driven FES robot rehabilitation (experimental group). The clinical evaluations showed significant improvements in the Fugl-Meyer assessment (FMA) shoulder/elbow, a significant decrease in the MAS elbow/wrist for both groups after the training and sustained results after 3 months ($p < 0.05$). The experimental group achieved higher scores (better outcomes) in the post and 3-month follow-up evaluation. The FMA wrist/hand and the action research arm test (ARAT) significantly improved only in the experimental group ($p < 0.05$) and this increase compared with the baseline remained till 3 months later. The EDC and FCR pair co-contraction index (CI) was significantly decreased for the experimental group ($p < 0.05$); and after session 10, most CI values of experimental group were significantly lower than those of the control group ($p < 0.05$). These findings show the potential of the hybrid approach to conduct both clinical and neurophysiological improvements.

2.3.2.2 Clinical outcomes of hybrid system for reaching rehabilitation

With the SMART plus FES system, Barker et al. carried out a single blinded randomized clinical trial with 33 chronic stroke subjects (Barker et al. 2008). The subjects were allocated in one of three groups: SMART Arm with stimulation triggered by volitional EMG activation (SMART plus FES), SMART Arm alone (SMART), and home program without alternative treatment (control). The authors reported that both SMART and SMART plus FES groups achieved a significant improvement in all outcome measures after 4 weeks (post training) and at 12 weeks (2-month follow-up), while the control group showed no change. The difference in the amount of improvement exhibited by the SMART and SMART plus FES groups was not statistically significant. These findings are opposite to those found during the wrist training (Hu et al. 2015), where major improvements were reported in the FES plus robot group. The authors justified the results by indicating that the repetitive nature of the therapy was principally responsible for the observed changes in the evaluations.

The BAT system was assessed with 23 chronic stroke patients in (Wu et al. 2011). The patients were divided into two groups: training with BAT and FES (experimental), and BAT without FES (control). The results revealed no differences in the inter- and intra-groups for the FMA and the MAS. The ARAT presented significant improvements after training in both groups and at one-month follow-up the improvement was only significantly in the experimental group.

Hughes et al. (Hughes et al. 2009) presented a preliminary evaluation of a planar end-effector device combined with FES, with five chronic stroke patients. The results indicated improvements in the tracking ability of patients when performing unassisted reaching task (without FES). They also report an improvement in the generated force under isometric conditions measured with the end-effector robot. Clinical assessment showed a reduction in upper limb impairment using the FMA score ($p \leq 0.05$), while the ARAT did no show significant changes.

A preliminary clinical evaluation of the SAIL system was performed with five chronic stroke subjects (Meadmore et al. 2012). The execution of unassisted reaching task (without FES) showed that the tracking accuracy improved over the course of the intervention for both shoulder and elbow. The clinical scales revealed significant improvements in the FMA ($p = 0.001$), while no changes were found for the ARAT. These results were consistent with the ones obtained when training the reaching with the planar end-effector device and FES (Hughes et al. 2009). The authors reported that with the SAIL system the FMA scores obtained were greater (mean difference of 9.3 vs. 2.5) (Meadmore et al. 2012). Authors suggested that one possible reason for the difference in results is that the SAIL intervention trained two muscles in 3D space, whereas the planar end-effector device and FES trained only triceps in 2D space.

2.4 Discussion

The hybrid robotic systems reviewed in this chapter represent the state of the art of the combined use of robotic and FES devices for upper limb rehabilitation after stroke. In this chapter, the key technological features of this recent emerging rehabilitation method (hybrid concept) and its clinical potentials were presented. In what remains of this chapter, the main challenges of the hybrid concept are identified and presented. Three challenges are considered: technological features, clinical deployment and usability of the system, which informed the studies presented in the following chapters of this thesis.

2.4.1 Improving technical aspects: hybrid approach challenges

Hybrid robotic systems combine two technologies (FES and robotic devices) into one platform, complementing each other to build on the performance of each individual approach. For this purpose, it is necessary to establish what is the role of each technology within each platform and how it will improve the overall rehabilitation results.

The most used hybrid robotic systems combined end-effector robotic devices with FES. End-effector robots have been mostly used to support the arm's weight and to delimit the workspace while the FES was used to drive the movement of the arm during the task execution. The main advantage of this approach is the simplicity of the setup (usually 1 DOF) that facilitated the implementation of the control algorithms. However, two main drawbacks arise when considering these devices. First, the amount of assistance during movement is limited since the mechanical forces are not applied directly to specific joints and the movement is mainly driven by FES. Second, the range of motion of this type of robotic devices is limited. Therefore, only a limited set of rehabilitation exercises can be carried out, with a negative impact in task generalization, which is an important factor for promoting motor recovery after stroke (Krakauer 2005).

Among the reviewed studies, only the SAIL system presented by Meadmore et al. (Meadmore et al. 2012) considered the use of a passive exoskeleton in combination with FES for assisting movement in a 3D space. Passive exoskeletons have the advantage over end-effector robotic devices of fully supporting the whole arm against gravity at the joint level. Also, they can provide a larger range of motion in the 3D space. This allows more flexibility to apply FES and focuses it only on driving the arm movements, this way reducing the stimulation intensity and the muscle fatigue onset. However, this setup is limited by mechanical constraints and requires a robust and reliable FES system to drive the movements successfully.

A full hybrid robotic system (from the actuation perspective) is the one that provides support by combining an exoskeleton with active actuators and FES. Several systems following this approach have been reported for lower limb and gait rehabilitation (del Ama et al. 2012). Despite the broad diffusion of powered upper limb exoskeletons in recent years (Maciejasz et al. 2014), the combination of these devices with FES has not been reported for the upper limb rehabilitation. This combination could improve the performance of current hybrid robotic systems significantly since the arm movement does not only depend on the FES assistance. For example, the inability to drive limbs with FES and the reported low rate of the system performance in (Westerveld et al. 2014), could be significantly improved if additional mechanical assistance is provided at the joint level. Furthermore, this combination could allow the development of novel interventions, such as targeting specific muscles groups with FES, while supporting the rest of the arm movement with the exoskeleton. However, the main challenge for full hybrid robotic systems is the development of optimal shared control strategies between the FES, the exoskeleton while taking into account the patients' remnant motor capacity to promote and potentiate the effects of therapy.

A robust FES controller plays a crucial role in the successful deployment of hybrid robotic systems. The performance of FES systems depends on the implemented control strategy, the number of stimulation channels and the correct electrode placement (Lynch & Popovic 2008, Popović 2014). The control strategy should be able to compensate the non-linear and time-varying response of the musculoskeletal system due to the non-physiological motor unit recruitment (Maffiuletti 2010). In addition, the controller parameter must be individualized to each user in order to address the inter-subject variability to FES response.

Therefore, simple FES control strategies (e.g. open-loop and linear feedback controllers, i.e. PID) are often inadequate for controlling the execution of motor tasks, as they cannot properly manage the high muscle response variability (Lynch & Popovic 2008, Freeman et al. 2012). Also, when using a model-based feedback controller, the modeling of the musculoskeletal system is a major concern. Indeed, this type of controllers requires a detailed mathematical description of the musculoskeletal system to work properly. The fitting of the model and the personalization of the model's parameters result in a complex and time-consuming task requiring additional sessions (Freeman et al. 2009*a*, Zhang et al. 2007). Furthermore, the non-modeled dynamics and the simplification assumed to build the model reduce the robustness of the controller performance. For instance, Westerveld et. al used a model predictive control algorithm based on a second order model with a success rate of less than 20% for opening the hand (Westerveld et al. 2014), suggesting that this type of control strategy results inappropriate to drive complex functional task such as the grasping.

Alternatively, the learning feedforward loop reported in (Hughes et al. 2009, Meadmore et al. 2012, 2014, Kutlu et al. 2015) represents an interesting approach, since it exploits the repetitive nature of robot-aided rehabilitation to learn from the errors of previous attempts. This learning capability provides a way to compensate for the physiological changes of patients (e.g. muscle response variation due to muscle fatigue or spasticity). However, it still required to model the musculoskeletal response to FES for a proper operation. Although this strategy is more convenient for driving movement assisted with FES, the controller performance is influenced by the non-modeled dynamics, the linearization of the model and the restrictions imposed when deducing the individualized model. Furthermore, the complexity of the inferred model increases considerably when considering movements in 3D space, such as reaching, and movements involving multiple degrees of freedom, such as grasping.

On the other hand, control strategies based on neurophysiological signals, like EMG, are in many cases restricted. Certainly, the disorders to the central nervous system caused after Stroke (e.g. spasticity) could affect significantly the quality of the EMG signals, which limits the applicability of the EMG-based controllers. Moreover, when considering this approach, the controller robustness is influenced by the implementation of complex blanking algorithms to separate the useful physiological signal from artifact generated by the electrical stimuli.

A good control of grasping motion is necessary for promoting the patients' motivation and engagement during therapy, otherwise the inability to perform the tasks could lead to frustration. For grasping tasks, the number of stimulation channels influences the precise control of the hand and fingers movements considerably. Due to the high density of muscles at the forearm, the use of few stimulation channels typically results in a reduced motor functional response and this problem is more noticeable when surface electrodes are used (Popović 2014). It has been demonstrated that the use of multi-pad electrodes (e.g. a matrix of electrodes) improved the precision of controlled movement significantly (Malesevic et al. 2012).

2.4.2 Rehabilitation Outcomes

Published systematic reviews reported that after robot-based therapy, stroke patients presented a reduction in motor impairment but did not improve in functional abilities (Kwakkel et al. 2008, Prange et al. 2006). It has been suggested that upper limb rehabilitation is location specific (Johnson 2006, Meadmore et al. 2014). Thus, reaching rehabilitation will only improve motor impairment in the proximal joints (shoulder and elbow) while grasping training will have impact only in the wrist and fingers. In line with this evidence, hybrid robotic systems for reaching (Hughes et al. 2009, Meadmore et al. 2012) showed improvements in the motor impairments (measured by FMA) but not in functional improvements (measured by ARAT scale). This evidence suggests that the whole upper limb must be considered in rehabilitation to achieve a better reduction in motor impairment and functional changes.

Under a clinical perspective, performing a direct comparison between studies is challenging due to the lack of standard evaluation metrics or procedures across studies. This issue was pointed out by Huang and Krakauer in (Huang & Krakauer 2009) for post-stroke rehabilitation therapies. Also, the relatively small number of studies and their methodology, as well as the small number of subject that were tested, makes it difficult to reach a generalization. Only four studies considered the inclusion of a control group for the evaluation of the hybrid robotic systems (Ring & Rosenthal 2005, Hu et al. 2015, Wu et al. 2011, Barker et al. 2008), and these control groups were different in all cases. The inclusion of a control group for demonstrating the effectiveness of a hybrid rehabilitation system is important. However, it is difficult to be implemented in practice due to the high number of patients that will be required during the experimentation. In fact, since two therapies are being implemented jointly (robot and FES), at least three groups of patients would be necessary to check whether the hybrid robotic system results in significant improvements with respect to robotic and FES separately.

However, the significant improvements achieved in most of the reported studies support the hypothesis of the relative benefits of using combined robotic devices with FES for upper limb rehabilitation after stroke.

2.4.3 Improving the human-machine interaction: associating peripheral assistance with user's motor intent

Associating the peripheral assistance onset with the user's movement intention in a causal and synchronized manner has been shown to be an important factor for eliciting neural plasticity and, therefore, to facilitate neuromuscular recovery (Ethier et al. 2015, Mrachacz-Kersting et al. 2012). Recent studies have demonstrated that the application of peripheral assistance precisely synchronized with the user's motor intent induce long-term potentiation in the corticospinal pathway in healthy volunteers (Mrachacz-Kersting et al. 2012, Xu et al. 2014) and stroke patients (Mrachacz-Kersting et al. 2015).

In this regard, only a few of the reviewed hybrid systems have addressed the associative paradigm (applying peripheral assistance in coherence with user's own intention to move) by using voluntary EMG activation to trigger the system assistance (Fujiwara et al. 2009, Hu et al. 2015, Barker et al. 2008). However, the optimal stimulus timing may be degraded by the intrinsic delay between cortical and peripheral activity (Ethier et al. 2015). Also, the quality of the EMG could be affected as a result of the level of impairment, which has a direct impact on the timing and reliability of the intention detection systems.

EEG-based BCI could be used as an alternative to the EMG intention detection for hybrid robotic systems. The advantage of these interfaces is that the synchronization between motor intent and motor execution can be realized without much delay. However, these interfaces have shown low reliability, mainly due noise and artifacts in the acquired signals (Ethier & Miller 2015). Nevertheless, this is an interesting avenue that could be considered to improve the rehabilitation outcomes of hybrid robotic systems.

2.5 Conclusions of the chapter

This chapter presented an overview of studies in which the combined use of robotic devices with FES was reported for rehabilitation of upper-limb motor function in stroke survivors. These systems represent the state of the art of hybrid robotic system for rehabilitation upper-limb motor functions. Hybrid robotic systems are an emerging approach aimed at combining two different but complementary assistive methods. The main goal under this hybrid perspective is to enhance current rehabilitation capabilities of each individual technique and provide a more robust rehabilitation intervention.

Still many challenges remain to be addressed. From the technological perspective, the inclusion of exoskeleton devices would enable a more natural movement in an unconstrained environment, with the capability of implementing more complex and sophisticated rehabilitation paradigms. In this context, the implementation of adaptive FES-based controllers addressing the non-linear and time-varying musculoskeletal response to FES is necessary. It is worth mentioning that long calibration time or additional sessions to calibrate the controller parameters must be avoided for usability. In spite of evidence that optimal association between the hybrid assistance and the user's own intention to move would promote plasticity, none of the systems hereby reviewed succeeded in demonstrating that plasticity was elicited as a result of the intervention. From the clinical perspective, the development of unconstrained systems capable to train complex functional movements is preferred. It has been shown that training functional movements results in improvements of motor impairment and in functional abilities. This is the starting point and requirements for the developments to be introduced in next chapters.

Chapter 3

Implementation of a FES-based adaptive assistance in a hybrid robotic system for rehabilitation of reaching movement after stroke[1]

Abstract

This chapter presents the integration of a hybrid robotic system for rehabilitation of reaching movement after stroke. Also, a concise evaluation, from the technical and clinical perspectives, of the usability of the hybrid robotic system in the clinical setting is conducted. The hybrid system comprises four components. The hybrid assistance is given by a passive exoskeleton to support the arm weight against gravity and a functional electrical stimulation device to assist the execution of the reaching task. A feedback error learning (FEL) controller has been implemented to adjust the intensity of the electrical stimuli delivered to target muscles according to the performance of the users. This control strategy is based on a proportional-integral-derivative feedback controller and an artificial neural network as the feedforward controller. Two experiments have been carried out. First, the technical viability and the performance of the FEL controller were evaluated in healthy subjects (n = 12). Second, a small cohort of patients with a brain injury (n = 4) participated in two experimental sessions to evaluate the system performance. The overall satisfaction and emotional response of the users after using the system were assessed. In the experiment with healthy subjects, a significant reduction of the tracking error was found during the execution of reaching movements. In the experiments with patients, a decreasing trend of the error trajectory was found together

[1]This chapter is partly based on:
- F. Resquín, J. Gonzalez-Vargas, J. Ibáñez, F. Brunetti, J.L. Pons. Feedback error learning controller for functional electrical stimulation assistance in a hybrid robotic system for reaching rehabilitation. Eur J Transl Myol. 2016;26(3).
- F. Resquín, J. Gonzalez-Vargas, J. Ibáñez, F. Brunetti, I. Dimbwadyo, L. Carrasco, S. Alves, C. Gonzalez-Alted, A. Gomez-Blanco and J.L. Pons. Adaptive hybrid robotic system for rehabilitation of reaching movement after a brain injury: a usability study. J Neuroeng Rehabil. 2017 Dec 12;14(1):104.

with an increasing trend in the task performance as the movement was repeated. Brain injury patients enthusiastically accepted the system as a rehabilitation tool. The results presented in this chapter demonstrate the technical feasibility of using the hybrid robotic system for rehabilitation of reaching. Patients reported a great satisfaction and acceptance of the hybrid robotic system.

3.1 Introduction

The previous chapter highlighted the potential rehabilitative benefits of using hybrid robotic systems for rehabilitation of upper extremity motor functions. Only a few studies in the literature included stroke patients as testing subjects. In order to maximize the treatment's outcomes and achieve functional improvement it is necessary to train movements which involve multiple degrees of freedom (> 1 DOF) as well as functional movements Freeman et al. (2012), Meadmore et al. (2014). In this scenario, the implementation of a robust and reliable FES controller is required. As discussed in the previous chapter, the appropriate design and implementation of FES controllers play a key role to achieve stable and robust motion control in hybrid robotic systems. The control strategy must be able to drive all the necessary joints to realize the desired movement, and to compensate any disturbance, e.g. muscle fatigue onset as well as the strong nonlinear and time-varying response of the musculoskeletal system to FES (Maffiuletti 2010, Lynch & Popovic 2008).

Meadmore et al. presented an interesting hybrid robotic system for rehabilitation of reaching movement in 3D space (Meadmore et al. 2012). A model-based iterative learning controller (ILC) was implemented to adjust the FES intensity based on the tracking error of the previously executed movement (Freeman et al. 2011, Meadmore et al. 2012). This iterative adjustment allows compensating for disturbances caused by FES. Although this approach addresses some of the issues related to motion control with FES, to work properly, it requires a detailed mathematical description of the musculoskeletal system. In this context, non-modeled dynamics and the linearization of the model can reduce the robustness and performance. Furthermore, the identification of the model's parameters is complex and time consuming, which limits its usability in clinical settings (Lynch & Popovic 2008, Zhang et al. 2007).

The Feedback Error Learning (FEL) scheme proposed by Kawato (Kawato 1990) can be considered as an alternative to ILC. This scheme was developed to describe how the central nervous system builds an internal model of the body to improve the motor control. Under this scheme, the motor control command of a feedback controller is used to train a feedforward controller to learn implicitly the inverse dynamics of the plant (i.e. the arm) on-line. In addition, this on-line learning procedure also allows the controller to adapt and compensate for disturbances. In contrast with the ILC, the main advantage of this strategy is that the controller does not require an explicit model of the plant to work correctly and that it can directly learn its non-linear characteristics. Therefore, using the FEL control strategy to control a hybrid robotic system can simplify the setup of the system considerably, which makes easier to deploy it in clinical settings as well as to personalize its response according to each patient's musculoskeletal characteristics and remnant movement capabilities. The FEL has been used previously to control the wrist (Kurosawa et al. 2005) and the lower limb (Koike et al. 2011) motion with FES in healthy subjects. But, this control strategy has neither been implemented in a hybrid robotic system nor tested with stroke patients.

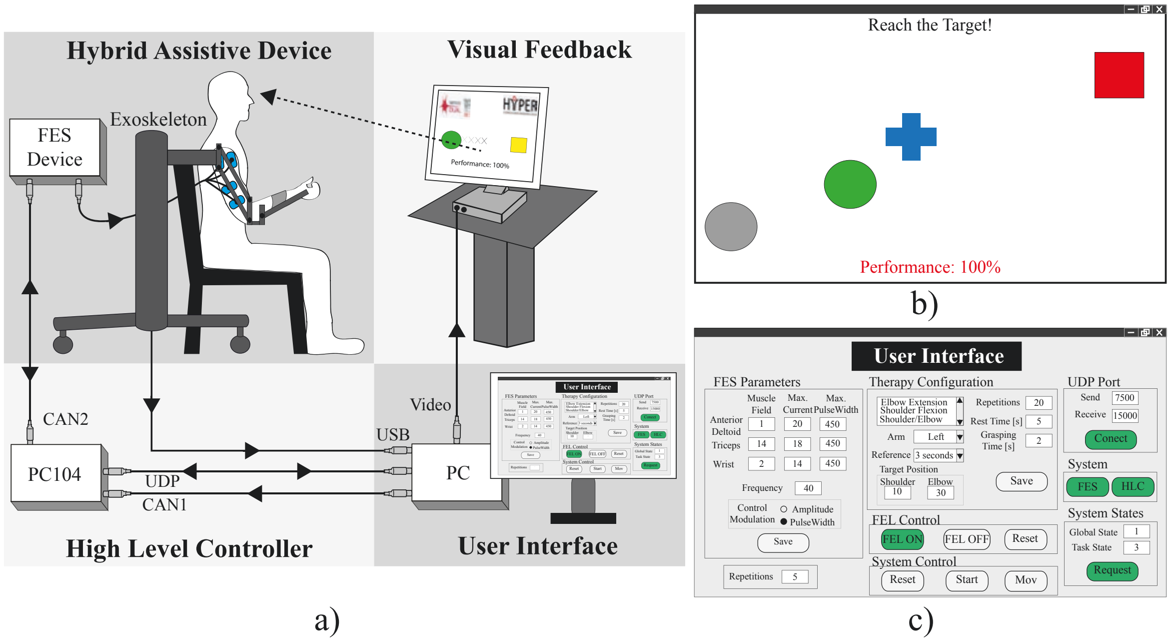


FIGURE 3.1: a) General overview of the presented hybrid robotic platform for reaching rehabilitation. b) Visual feedback provided to the users. The green ball represents the actual arm position, the blue cross is the reference trajectory, the initial and final position are represented by the gray ball and red square respectively. c) Interface for system configuration.

In this chapter, a fully integrated hybrid robotic system based on an FEL scheme for rehabilitation of reaching movement in stroke patients is presented. The FEL algorithm adjusts the FES intensity to precisely track reference trajectories during reaching movements. In order to evaluate the system, a two-step experimentation was carried out. The first part consists of demonstrating the technical robustness and viability and the learning capability of the FEL controller to drive coordinated shoulder-elbow joint movements in healthy individuals. The second part consists of testing the usability of the platform with stroke patients in a more realistic rehabilitation scenario. For this purpose, the patients' performance and overall satisfaction and emotional response after using the system was assessed.

3.2 Hybrid rehabilitation platform for reaching rehabilitation

In this section, the hybrid robotic system for rehabilitation of reaching in patients post-stroke is introduced. The system focuses on assisting users to move their paretic arm towards specific distal directions in unconstrained space. During the execution of this task, the FEL controller adjusts the intensities of the electrical stimuli delivered to target muscles in order to assist the subjects in accurately tracking the reference trajectories.

Figure 3.1a shows the general overview of the hybrid platform. This rehabilitation platform comprises four main components: the hybrid assistive device (upper limb exoskeleton plus FES device); the high-level controller (HLC); the visual feedback and the user interface.

The hybrid assistance is provided by an upper limb exoskeleton, ArmeoSpring® (Hocoma, Switzerland) and an IntFES stimulator (Technalia, Spain). The Armeo is a passive exoskeleton aimed at supporting the arm weight against gravity. In addition, the exoskeleton limits the workspace, constraining the movements to a controlled area. Since stroke patients typically suffer from an over-activity of flexor muscles of the arm and a loss in activity of the triceps brachii (TB), anterior deltoids (AD) and finger extensor muscles (Lum et al. 2004, Krakauer 2005, Meadmore et al. 2012), the FES is delivered through biphasic electrical pulses at the TR and the AD muscles.

The HLC is implemented in a PC104 architecture running under the xPC Target® operating system (The MathWorks Inc.) for real-time operation. This component estimates the arm joint position, generates the reference trajectory (from the initial position to the target) and executes the control algorithm to set the FES intensity delivered at target muscles.

Figure 3.1b shows the visual feedback interface, which is integrated into the platform to guide and encourage the user to accomplish the rehabilitation task. In order to present users an intuitive and easy to understand visualization paradigm, the arm movement was represented in the front screen using geometric blocks indicating the current arm position, the initial and the target position. Thus, a green circle represents the user's arm movement, and the x- and y-axis indicate the movements of the elbow and shoulder joints, respectively. The blue cross represents the reference trajectory that users should follow. This cross moves from an initial position (grey circle) to the final position (red square).

At the end of each trial, the performance of the task is calculated and shown to the user, who is in turn instructed to maximize this result throughout the session. The performance is estimated from the difference between the generated signal reference and the current position of the controlled joints (see Section 3.4.2.2 for further details). This score is also used to change the color of the ball during the task execution. This way, the system provides an augmented feedback, which allows users to monitor their performance during the movement. The ball turns green if the performance is excellent (80% or more), yellow if it is good (between 60 and 80%), orange if it is moderate (between 40 and 60%) and red when it is poor (40% or less).

Lastly, a user interface (Figure 3.1c) is integrated into the architecture allowing the easy configuration of the therapy parameters, i.e. trained right/left arm, FES parameters, tracking reference velocity and range of movements. Both interfaces (visual feedback and user configuration) were coded and implemented using custom made Matlab methods.

3.3 FES-based controller design

The controller strategy used to adjust the intensity of the delivered current intensity during the execution of the trained task is presented, as well as the assumed assumptions for its proper operation.

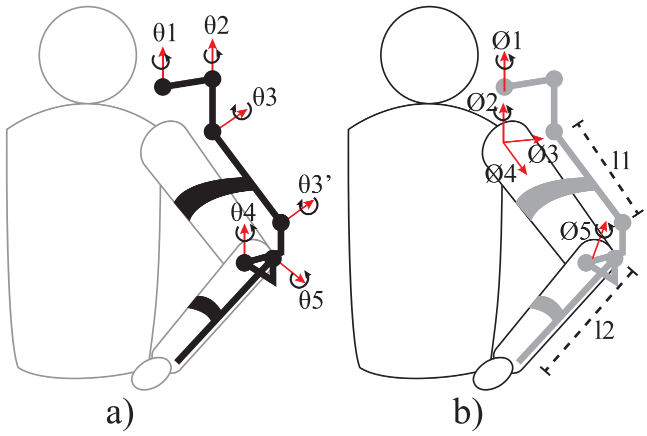


FIGURE 3.2: Kinematic representation of the rotation axes. a) Exoskeleton $\theta = \theta_1, \theta_2, \theta_3, \theta_4, \theta_5$. b) Human arm $\phi = \phi_1, \phi_2, \phi_3, \phi_4, \phi_5$.

3.3.1 Human arm position

Figure 3.2a depicts the rotation axes of angular position transducers embedded in the exoskeleton. With these transducers, the angular position of the human arm joints can be inferred considering the following assumptions: *i*) there is a fixed parallel arrangement between the arm and the exoskeleton segments l1 and l2 (Figure 3.2b); *ii*) the stimulation of the AD muscle produces a moment on an axis that is fixed with respect to the shoulder (axis ϕ_2), and the stimulation of the TB produces a moment on the axis that is orthogonal to both the forearm and the upper arm (axis ϕ_5). Hence, the vector $\phi = [\phi_1, \phi_2, \phi_3, \phi_4, \phi_5]$, representing the human arm position, is defined by implementing the same objective transformation fully described in (Cai et al. 2011, Freeman 2015).

3.3.2 Feedback error learning implementation

The main goal of the FES-based controller is to adjust the intensity of the electrical stimuli provided on specific muscles to achieve a precise control of motion. To this aim, the FEL algorithm modulates the pulse width (PW) of the electrical pulse delivered at the AD and TB muscles between 50 and 450 μs. The frequency of the stimulation was set at 40 Hz with constant pulse amplitude. The amplitude was adjusted according to the motor response and comfort of each user.

Two FEL controllers were implemented (one for each joint, shoulder and elbow) within the hybrid robotic system. Each controller consisted of a PID feedback loop combined with an artificial neural network (ANN) arranged as feedforward loop (Figure 3.3). The ANN provides a way for the controller to learn a non-linear inverse model of the arm. Thus, it is assumed that the learned dynamics covers both the musculoskeletal responses to the FES and the effects of the shoulder-elbow inter-joint biomechanical coupling. As opposed to other solutions (e.g. ILC (Meadmore et al. 2012)), there is no need to take into account this coupling explicitly thus facilitating the implementation of the controller. This learning process in the ANN occurs by using the output of the PID controller as the correction factor. While the inverse dynamics has not been learned, the PID controller is the main contributor of the control action with a small influence from the ANN. As the movement is repeated and the inverse dynamics is learned, the contributions to the control action are gradually inverted. Eventually, the ANN drives the execution of the reaching task while the PID controller compensates only for unknown or unlearned dynamics of the system (e.g. unexpected muscle responses to FES) (Kurosawa et al. 2005).

A PID controller with an additional inner loop that prevents the integral term to windup was implemented. This additional loop was introduced because only positive output values generate muscle activations (FES actuation) while negative values are ineffective. However, negative values are required for the FEL to learn, which could lead to windup the integral term. Thus, the modified PID controller is given by Equation 3.1:

$$u(t) = k\, e(t) + k_d \frac{de(t)}{dt} + \int (k_i\, e(t) + k_t\, e_s(t)) \tag{3.1}$$

where $e(t)$ represents the error trajectory; $e_s(t)$ is the difference between the PID output and the output of the saturator; and k, k_d, k_i and k_t are the constant parameters for the proportional, derivative, integral and the anti-windup terms. To guarantee the correct performance of the PID controller, these parameters were adjusted using the Ziegler and Nichols method of the averaged movement responses in healthy subjects.

The feedforward loop relies on a three-layer ANN, as shown in Figure 3.3b (nine inputs, nine hidden nodes and one output node). A sigmoid function was used to activate neurons in the hidden layer while a linear function was used to activate the output neuron. The inputs to the ANN are the desired angular position, velocity and acceleration profiles, from time n to $n+2$, which result in 9 inputs. These profiles were calculated beforehand (see next section) and normalized in the range of -1 to 1. The learning process was active along the execution of each movement using the gradient descent algorithm (Marsland 2015). The ANN size and topology were chosen based on previous studies (Watanabe & Fukushima 2011, Kurosawa et al. 2005). In this regard, the ANN size was set as the minimum number of nodes ensuring a proper performance of the system.

3.3.3 Reference generator

Studies in the field of motor control showed that arm movements tend to follow a homogeneous pattern across subjects (Huang & Krakauer 2009). This pattern is based on a straight path of the hand with smooth and bell-shaped velocity profile. Therefore, to generate such tracking reference, the minimum jerk trajectory method described by Flash and Hogan was implemented (Flash & Hogan 1985). This reference has been successfully used in previous rehabilitation robotic devices (Huang & Krakauer 2009).

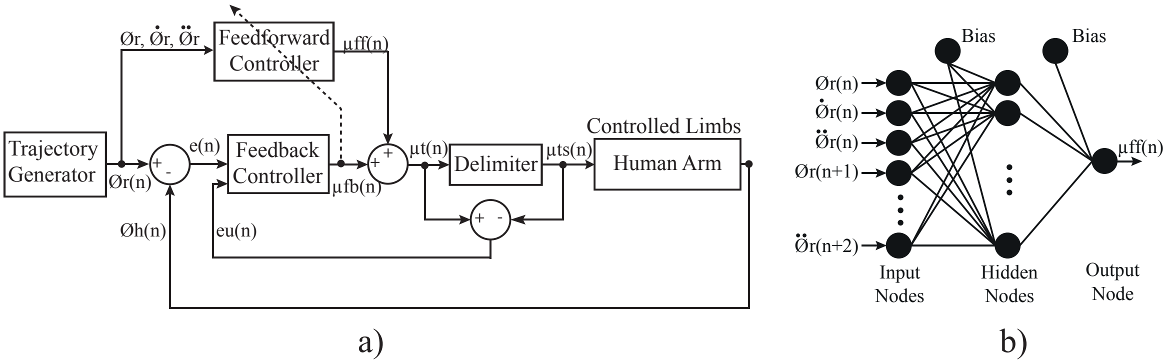


FIGURE 3.3: a) Block diagram of the FES-based Feedback Error Learning (FEL) controller. b) Artificial Neural Network used as feedforward loop. $\phi_r, \dot{\phi}_r, \ddot{\phi}_r$) represent the desired angular position, velocity and acceleration respectively; ϕ_h is the measured position of the human arm; $e(n)$ is the error position; μ_{ff}, μ_{fb} are the control signal generated for the feedback and feedforward controllers respectively; μt is the total assistance; μ_{ts} is the assistance at the output of the saturator; e_u is the difference between $_{ts}$ and $_t$.

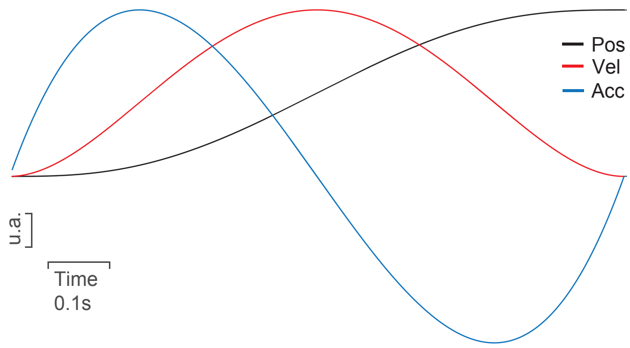


FIGURE 3.4: Position, velocity and acceleration profiles of the minimum jerk trajectory function (Flash & Hogan 1985).

Equation 3.2 shows the analytical expression used to derive the position reference required at the input of the FEL control algorithm:

$$\phi_{r,i} = \phi_i^s + (\phi_i^f - \phi_i^s)\,(10\,(t/d)^3 - 15\,(t/d)^4 + 6\,(t/d)^5) \tag{3.2}$$

ϕ_i^s is and ϕ_i^f represent the initial and target angles of the i-joint respectively, d is the movement total duration and t is the current time with $0 \leq \text{t} \leq \text{d}$. The velocity and acceleration profiles can be inferred by the first and second time derivatives of Equation 3.2. The position, velocity and acceleration profiles defined by the minimum jerk function are depicted in Figure 3.4.

3.4 Methods

3.4.1 Participants and evaluation protocol

All participants received oral and written information about the details of the experiment, and signed a consent form to participate and publish the data collected from the experimentation. All experimental protocols followed the Declaration of Helsinki and were approved by the Clinical Ethics Committee of the Centro Superior de Estudios Universitarios La Salle, Universidad Autnoma de Madrid (CSEULS-PI-106/2016).

The hybrid platform was assessed with two different experiments. Only healthy subjects participated in the first experiment. This experiment was conceived to test the technical viability of the proposed hybrid rehabilitation system and to verify the learning capability (arm dynamics model) of the FEL controller to successfully drive the arm following the desired shoulder-elbow coordinated trajectory with FES. The second experiment was designed to test the usability of the proposed hybrid robotic system in a realistic rehabilitation scenario with brain injury patients. Therefore, two sessions with a greater number of arm movements than experiment 1 were conducted.

Considering that the muscular response to FES depends on several factors, such as the placement of the electrodes over the skin and changes in human motor physiology (Popović 2014). And to avoid bias between inter-subjects and inter-session data, all experiments were carried out without previous knowledge of the musculoskeletal system. Thus, the weights of the ANN were initialized to small random values close to zero at the start of all sessions.

3.4.1.1 Experiment 1

For the first experiment, 12 healthy subjects (7 males, 1 left-handed and aged 27.1 $\pm$ 2.78 years old) were recruited. Each participant took part in a single evaluation session. Before starting the experiment, the exoskeleton was adjusted to the arm's dimensions of the subject. The gravity support level was regulated in such a way that the arm was kept about their thigh in the horizontal plane. Surface electrodes (Pals platinum - rectangle 5$\times$5 cm) were attached to the AD and TB muscles. The maximum pulse amplitude was determined by increasing gradually the current of the stimulator until a motor response was observed with a comfortable stimulation level as perceived by the participant. During this procedure, the PW of the stimulation signal was fixed at 450 μs. To define the maximum range of movement and determine the target position, the maximum electrical stimulation intensity to both muscles was simultaneously applied and the resulting movement was recorded. After analyzing the recording data, the target position was defined as the maximum angle achieved at each joint (shoulder and elbow). These maximum angles were used in the minimum jerk function (Equation 3.2) to generate user-specific reference trajectories.

Table 3.1: Description of patients recruited for the experimentation with the hybrid system.

Patient	Gender	Age (years)	Diagnosis	Affected side	Time (months)	BI	FIM	ULMI
P1	Male	52	IS	Left	13	98	85	25
P2	Female	37	HS	Left	15	91	84	25
P3	Female	30	TBI	Left	12	95	90	23.5
P4	Male	21	IS	Left	12	61	66	25

Meaning of acronyms: IS: Ischemic stroke; Hemorrhagic stroke; TBI: Traumatic brain injury; FIM: functional independence measure; BI: Barthel index; ULMI: upper limb part of motricity index; Time: time since injury.

After this initial procedure, the participants performed twelve reaching movements driven by the FEL controller. During the execution of these movements, participants were asked to let the FES move their arm and to avoid activating any muscle voluntarily. For this test, the visual feedback interface was disconnected,therefore the participants did not receive any information about the movements. In all trials, a period of three seconds was used to drive the arm from the starting position to the target. Between movements, the participants had a resting period of approximately 10 seconds to reduce the effects of muscle fatigue.

3.4.1.2 Experiment 2

For this experimentation stage, patients with brain injury who met the following inclusion criteria were recruited: patients older than 18 years old, with more than 6 months from the brain injury, with hemorrhagic, ischemic stroke or traumatic brain damage, with cognitive capabilities to follow instructions, with response to electrical stimulation in affected upper limb muscles. Subjects with any implanted metal in the affected upper limb, with a history of epilepsy episodes and/or pregnancy were excluded from the experiment. Three chronic stroke and one traumatic brain injury subjects (age 35 $\pm$ 13.09, full details are provided in Table 3.1) were recruited. None of the patients had prior experience with rehabilitation therapies based on FES or robots.

The functional examination of patients was based on three scales: the functional independence measure (FIM) (ranged from 18 to 126) (Hamilton et al. 1994), the Barthel index (ranged from 0 to 100) (Mahoney & Barthel 1965), and the upper limb part of Motricity Index (ranged from 0 to 25) (Demeurisse et al. 1980). Patients participated in one evaluation and two experimental sessions. The evaluation session was aimed to assess patients' conditions, verify their response to FES and explain to them the system operation. The experimental sessions were carried out a week later with a separation of 48 hours between them. In these sessions, patients had to perform a tracking task with their affected arm following a reference presented on a screen in front of them. After each movement, patients were instructed to place their arms back in the initial position and rest for approximately 10 seconds before starting a new movement. Similarly to experiment 1, the stimulation was delivered at the AD and the TB and the same initial procedure was followed to define the FES maximum intensity and the range of movement.

The first day, the session consisted in 5 assisted runs of 8 movements each, plus one additional run of 3 unassisted (without FES) movements. In the second session, participants carried out 8 assisted runs (8 movements) and one unassisted run (3 movements). Thus, a total of 40 and 56 assisted movements were performed on the first and second sessions, respectively. At the start of each session, the feedforward model was reset.

On the pre-session (a week before the experimental sessions) patient P4 presented good response with no discomfort to FES. Nevertheless, on the first experimental session, he reported discomfort on the arm when FES was applied. This discomfort could be associated to an increase in hypersensitivity during those days. As a consequence, the system could not be used with this subject and he was excluded from the experimental sessions.

3.4.2 Data analysis

3.4.2.1 Experiment 1

The efficacy of the system to assist in the execution of the reaching movement was assessed using the root mean squared error (RMSE) between reference and actual trajectories for each joint. The assistance supplied by the controller was quantified relative to the maximum electrical stimulation. This metric was computed by dividing the norm of the controller output (PW) by the norm of the maximum stimulation that could be supplied (450 μs). Complementary, the FEL capability for learning the inverse dynamics of the controlled limb was assessed using the power ratio (PR), according to (Equation 3.3)

$$PR_{ff} = \frac{\sum_{k=1}^{N} P_{ff}}{\sum_{k=1}^{N} P_{fb} + \sum_{k=1}^{N} P_{ff}} \times 100 \tag{3.3}$$

In this equation, the P_{ff} and P_{fb} are the square value of stimulation intensity (output power) of the ANN and the PID controller, respectively. The PR_{ff} represents the proportion of the ANN output relative to the total controller actuation command. This value should be close to 100% when the ANN has learnt the inverse dynamics of the controlled limbs.

The inter-joint coordination between the shoulder and elbow joints throughout the execution of reaching was assessed using the index of the temporal coordination (TC-index) introduced in (Cirstea et al. 2003). This parameter was proposed to evaluate the temporal coordination between adjacent joints involved in reaching. In brief, to suppress tremor-like oscillation in the angular velocity a recurrent exponential smoothing algorithm to the joint velocity was applied: $V_{i+1} = aV_i + (1-a)v_i$, where v_i is the angular velocity, V_i is the smoothed value of velocity, and a is a smoothness coefficient. The *'a'* parameter was set to 0.75 based on previous evidence (Cirstea et al. 2003). Subsequently, a temporal angle (T angle) was calculated as the angle between the downward vertical and a line from the origin (placed at the initial position) to successive data points along the velocity-angle plot (ordinate is the angular velocity; abscissa is the angular displacement). Finally, the TC-index was defined as the difference between the elbow and shoulder T angles at each time throughout the reaching movement. Here, the root mean squared of the TC-index difference between the reference and the actual arm trajectories was computed to evaluate the capability of the FEL controller to improve the inter-joint coordination.

The mean values of the RMSE, FES intensity, PR_{ff} and the TC-index were calculated across subjects to observe the evolution of these values along the twelve trials. Additionally, the RMSE and the PR_{ff} at each joint (shoulder and elbow), and the TC-index score of all users (n = 12) on trials one, four, eight and twelve were compared independently using the Friedman's ANOVA test. Only these trials were selected in order to gain statistical power and considering the symmetry distribution of these trials with respect to the number of repetitions performed. A post hoc analysis of these metrics was conducted by applying a Bonferroni correction for significance level (fixed at $p < 0.0083$) and using the Wilcoxon signed-rank tests.

3.4.2.2 Experiment 2

For the experimentation with brain injury subjects, the RMSE was averaged for each run and user. The trend of these errors was calculated applying the best-fitting linear regression across the RMSE data of all subjects. A total of 4 linear curves were generated for each combination of subjects, session and muscle. Similarly, the PR_{ff} of the FEL controller was averaged for each user and session over the executed run to visualize its evolution along the sessions.

The index of the task performance displayed on the user's screen during the execution of the task is also analyzed. The following steps were followed to calculate this metric (see Equation 3.4). First, the Euclidian distance between the reference trajectory and the actual joint angles during FES application was calculated. Then, the actual Euclidian distance was divided by the maximum distance (reference trajectory versus initial position). This result was subtracted from 1 and multiplied by 100, where a performance of 100 corresponded to perfect tracking.

$$Performance = \left(1 - \frac{\sum_{i=1}^{T} \sqrt{(\phi_{r2,i} - \phi_{2,i})^2 + (\phi_{r5,i} - \phi_{5,i})^2}}{\sum_{i=1}^{T} \sqrt{(\phi_{r2,i} - \phi_{2,1})^2 + (\phi_{r5,i} - \phi_{5,1})^2}}\right) \times 100 \tag{3.4}$$

In this equation, T is the duration of the movement, $\phi_{r,i}$ is the reference trajectory and ϕ_i represents the shoulder and elbow joint angles, respectively. The trend of the performance was estimated by applying the best-fitting linear regression across the data of all subjects. Two linear curves were generated, each corresponding to one of the two sessions.

In order to analyze the importance of the system's adaptive assistance to accomplishing accurate reaching movements and to improve the inter-joint coordination, the execution of the unassisted run (3 trials without FES) was compared with the last 3 trials of the final assisted run (with FES). The task's performance and the TC-index were used to compare both conditions. Differences were assessed using the Friedman's test. Additionally, the post hoc analysis with Wilcoxon signed-rank tests was conducted with Bonferroni correction, resulting in a significance level of $p < 0.0083$.

The satisfaction of the patients after participating in the experimental sessions was assessed using the Quebec User Evaluation of Satisfaction with Assistive Technology 2.0 (QUEST). QUEST is an evaluation specifically designed to measure satisfaction with a broad range of assistive technology devices in a structured and standardized way (Demers et al. 2002). The scoring method rated from 1 (not satisfied at all) to 5 (very satisfied). Complementarily, the users' affective experience with the hybrid system throughout the sessions was evaluated using the Self-Assessment Manikin (SAM). This scale is a non-verbal pictorial assessment technique that directly measures the pleasure, arousal and dominance associated with a person's affective reaction to a wide variety of stimuli (Morris 1995). All patients were asked to fill both satisfaction surveys after completing the last session.

3.5 Results

3.5.1 Experiment 1

Figure 3.5 shows a representative example of the FEL operation with one healthy volunteer. The tracking accuracy for shoulder (left column) and elbow (right column) during the 1^{st} and 12^{th} movements are depicted in Figure 3.5a. In this case, the achieved RMSE in the first trial (blue line) was 6.32° for the shoulder and 9.35° for the elbow. In trial 12 (red line), the tracking accuracy was significantly improved since the RMSE was reduced to 1.9° for the shoulder and 1.77° for the elbow. Figure 3.5b depicts the corresponding actuation signals of the FEL controller along the same trials. It can be observed that in the first trial (first row), the total assistance (u_t) is mostly overlapping with the contribution of the feedback loop (u_{fb}), resulting in a PR_{ff} of 9% and 15% for the feedforward controller (u_{ff}) for shoulder and elbow respectively. The contribution of each controller is swapped on trial 12 (second row of Figure 3.5b). At this point, the feedforward contribution increased, with a PR_{ff} of 97 and 99% for each joint, while the feedback controller was only compensating for disturbances.

Figure 3.6a shows the mean of the normalized RMSE score with respect to the first trial across subjects over the 12 reaching trials and their corresponding standard error (shaded areas). A final score of 0.47 and 0.41 for each joint respectively was achieved at the last trial (12th movement), indicating an error reduction of more than 50% with respect to the first trial. When analyzing tracking accuracy for the first, fourth, eighth and twelfth trials (values shown in Table 3.2), the Friedman's ANOVA test revealed that the RMSE along these trials differed significantly in both joints, with $\chi^2(3) = 14.7, p = 0.002$ and $\chi^2(3) = 21.5, p < 0.001$ for shoulder and elbow respectively. The post hoc analysis (results on Table 3.3) revealed

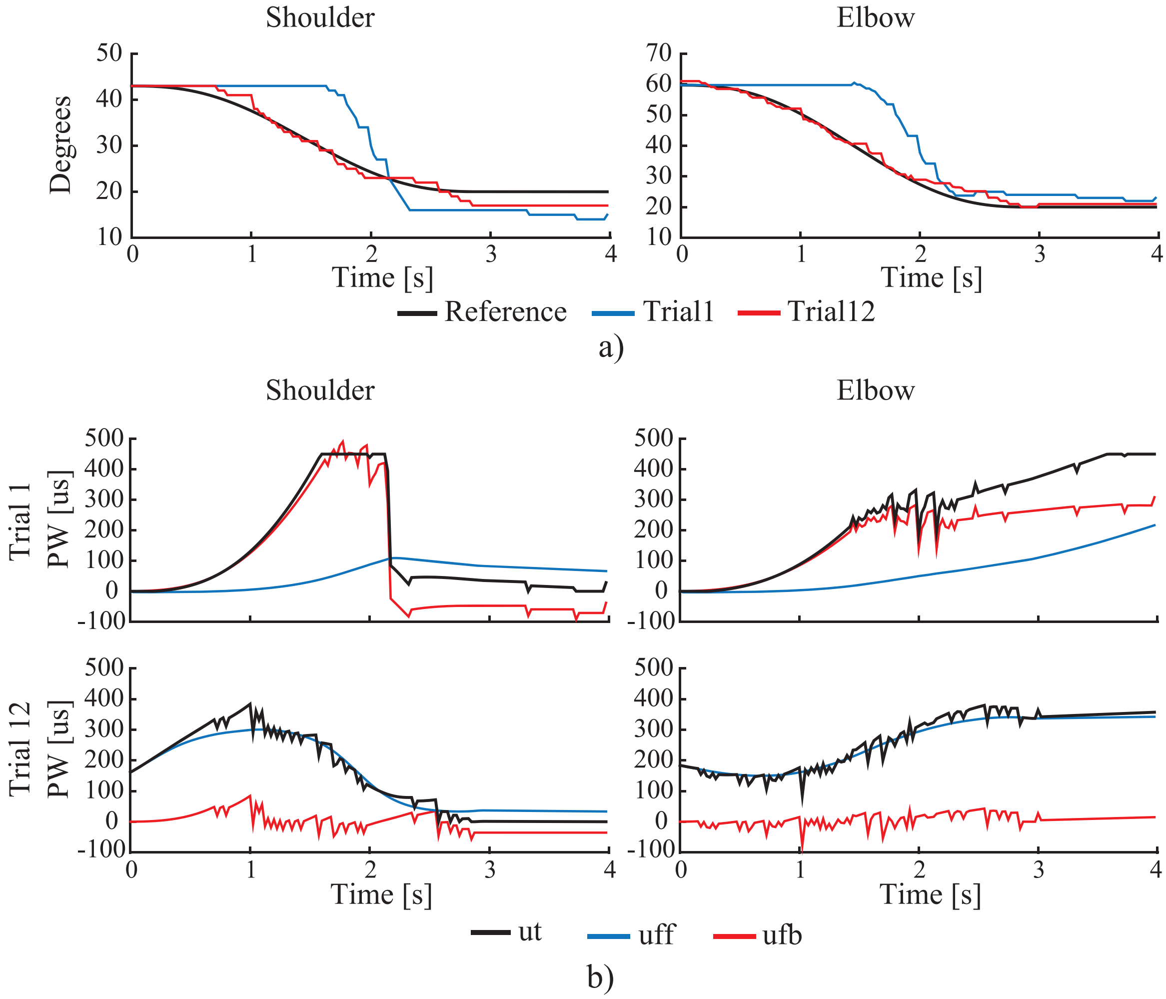


FIGURE 3.5: A representative example of the FEL controller performance in one healthy subject. a) The tracking accuracy during trial 1 (red) and trial 12 (blue) for shoulder (left) and elbow (right) joints. b) The output signal of the feedback error learning controller during the first and twelfth movement execution; u_{fb} (in red) is the control signal given by the feedback controller; u_{ff} (in blue) represents the control action of the feedforward controller; u_t (in black) corresponds to the output of the FEL controller ($u_{ff} + u_{fb}$).

that for both joints, the RMSE value for trial four, eight and twelve were significantly reduced when compared to trial one. The differences between trials four, eight and twelve were not significant in any joints.

The FES intensity, expressed as a percentage of the maximum stimulation, applied at shoulder and elbow over the twelve trials is shown in the Figure 3.6b. Here, the total assistance is given by the contribution of the feedforward (dark gray area) and feedback (light gray area) loops that are measured using the PR score. In both joints, the PR_{ff} is increased as the movement is repeated (dark gray area), while the output of the feedback loop (PR_{fb}) is decreased (light gray area). The statistical test found that the PR_{ff} at trials one, four, eight and twelve (values shown in Table 3.2) differed significantly in both joints, with $\chi^2(3) = 29.5, p < 0.01$ for shoulder and $\chi^2(3) = 32.7, p < 0.001$ for elbow. The post hoc multiple comparison showed that in both joints, the contribution of the feedforward controller (PR_{ff}) at trials four, eight and twelve increased significantly when compared with

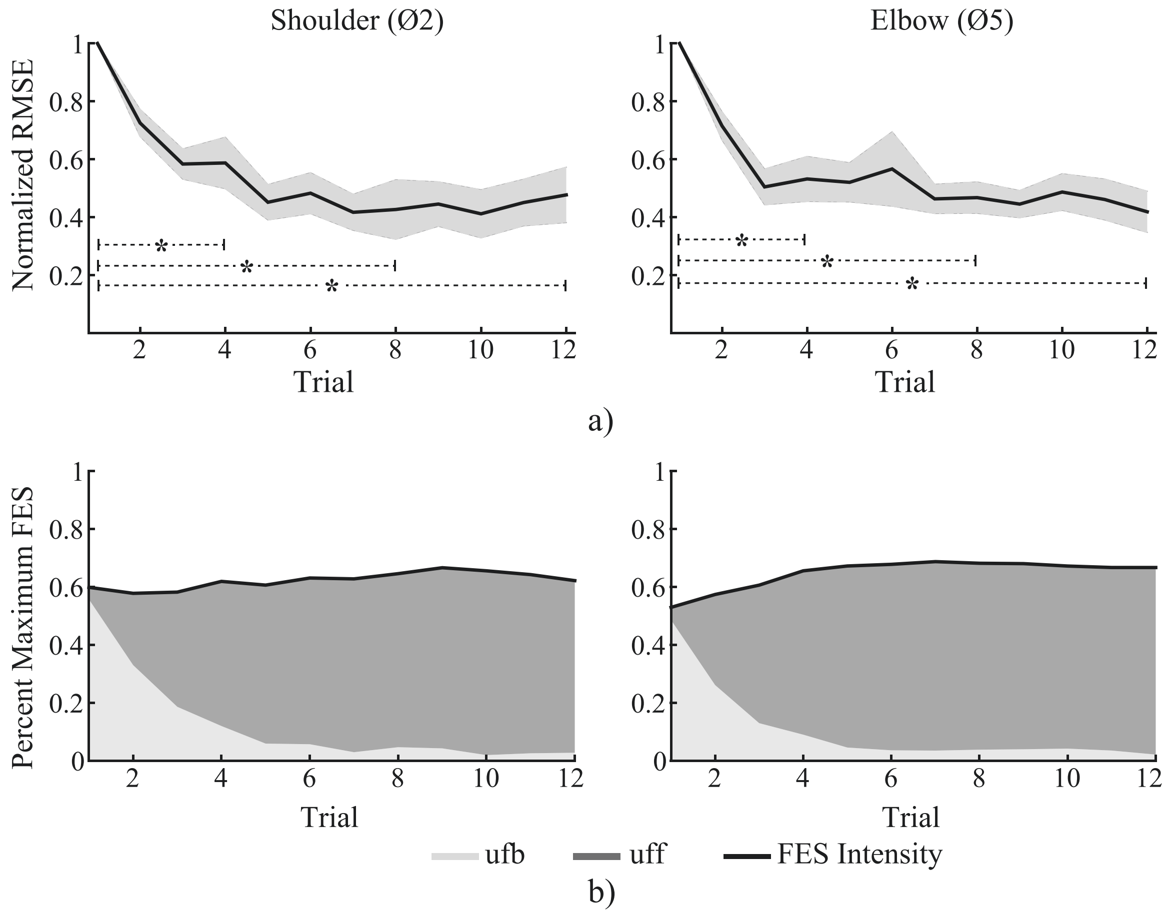


FIGURE 3.6: a) Mean values of the normalized root mean squared error (RMSE, black line) and its standard error (gray shaded areas) across healthy subjects, corresponding to the shoulder (left) and elbow (right) joints. Dotted lines denote significance difference between trials. b) Mean values of provided FES intensity, represented as a percentage of the maximum stimulation intensity, across subjects. Light gray and dark gray areas depict the contribution of the feedforward (u_{fb}) and feedback (u_{ff}) loop to the total FES intensity, measured with the power ratio (PR).

TABLE 3.2: Mean and standard deviation values across healthy subjects.

	RMSE [°]		Power Ratio [%]		Normalized RMS
	Shoulder	Elbow	Shoulder	Elbow	TC-index
Trial 1	5.9 ± 2.3	12.1 ± 3.9	6.9 ± 7.9	8.22 ± 4.7	1
Trial 4	3.5 ± 2.7	6.5 ± 4	80.7 ± 17.1	86.3 ± 14.2	0.93 ± 0.31
Trial 8	2.9 ± 3.7	5.3 ± 1.7	92.8 ± 13.9	94.5 ± 10.4	0.83 ± 0.46
Trial 12	3.2 ± 3.6	4.9 ± 3.1	95.6 ± 7.3	96.9 ± 5.3	0.70 ± 0.38

Meaning of acronyms: RMSE: root mean squared error; RMS: root mean square; TC-index: temporal coordination index.

the value at the first trial and the twelfth trial with respect to the fourth (results of post hoc analysis are shown in Table 3.3). At the elbow joint, the PR_{ff} value for trial eight was also significantly higher than the fourth trial, but not at the shoulder joint. No significant differences were observed between trials eight and twelve in any joints.

The evolution of the normalized RMS of TC-index between the reference and the arm trajectories both for the shoulder and elbow joints along trials is presented in Figure 3.7. It can

TABLE 3.3: Results of the Wilcoxon post hoc test.

	RMSE			Power Ratio				
	$1^{st} vs. 4^{th}$ trial	$1^{st} vs. 8^{th}$ trial	$1^{st} vs. 12^{th}$ trial	$1^{st} vs. 4^{th}$ trial	$1^{st} vs. 8^{th}$ trial	$1^{st} vs. 12^{th}$ trial	$4^{th} vs. 8^{th}$ trial	$4^{th} vs. 12^{th}$ trial
Shoulder	p = 0.002 r = -0.62	p = 0.005 r = -0.57	p = 0.003 r = -0.6	p < 0.001 r = -0.71	p < 0.001 r = -0.71	p < 0.001 r = -0.71	p > 0.008	p = 0.002 r = -0.62
Elbow	p = 0.001 r = -0.67	p < 0.001 r = -0.71	p < 0.001 r = -0.71	p < 0.001 r = -0.71	p < 0.001 r = -0.71	p < 0.001 r = -0.71	p = 0.05 r = -0.57	p < 0.001 r = -0.71

Bonferroni correction for multiple comparison established the level of significant at p < 0.0083. p: level of significance; r: effect size; RMSE: root mean squared error; PR: power ratio.

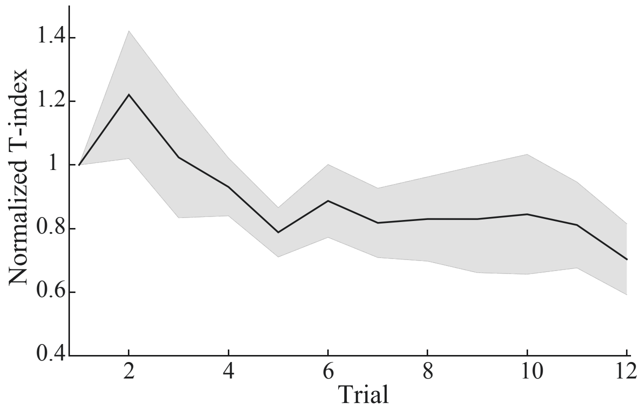


FIGURE 3.7: Evolution of the root mean square error of the temporal coordination (TC) index between the generated reference and arm trajectories. Shaded area represents standard error.

be observed that the inter-joint coordination index is reduced across the trials. Although the statistical test did not find significant differences between trials one, four, eight and twelve ($\chi^2(3) = 6.7, p = 0.08$), the final score of the TC-index (0.7 ± 0.4) shows an improvement 30% with respect to the first trial (see Table 3.2).

3.5.2 Experiment 2

3.5.2.1 Performance results

The evolution of the RMSE as function of the executed run for each subject, joint and session in depicted in Figure 3.8a. The estimated linear fitting curves at the shoulder resulted in slopes of -0.38 for session one, and -0.1 for session two. These results represent an average RMSE reduction from 4° to 2.9°. The fitting for the elbow presented a slope of -1.07 and -0.2 for each session respectively, which corresponds to a decrease in the RMSE value from 7.3° to 4.5°. Figure 3.8b shows the evolution of the PR_{ff} over the run for each participant, muscle and session (blue, red and green curves). Additionally, the corresponding average values across subjects and the corresponding standard deviation are represented (black lines). At the shoulder joint, the PR_{ff} presented an average value across subjects of $58.3 \pm 33.1\%$ and $44.8 \pm 26.2\%$ on the first run for session one and two respectively. This value has increased to $89.5 \pm 13.4\%$ and $89.1 \pm 10.1\%$ on the second run for each session respectively. No important differences were observed on the remaining runs. For the elbow joint, the PR_{ff} value at the elbow presented an increasing trend with an average value across subjects of

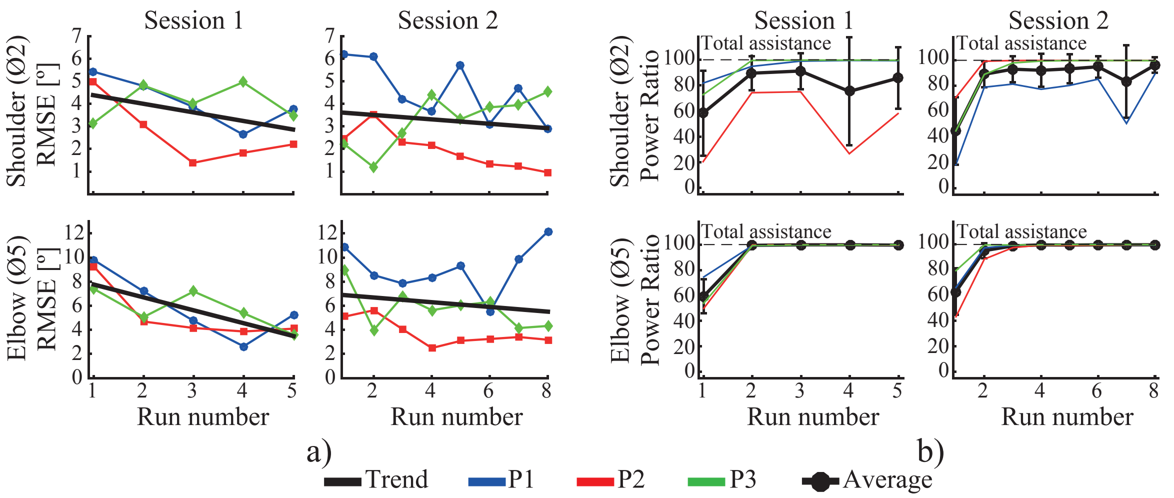


FIGURE 3.8: a) Evolution of the root mean square error (RMSE) averaged for each run. The first column represents the RMSE for session one divided in shoulder (top) and elbow (bottom), while the second column depicts the error for session two. The black lines represent the calculated linear regression for each combination of subject, muscle and session. b) Evolution of the PR_{ff} for each subject. The black line represents averaged PR_{ff} across subjects and its corresponding standard error. The first column represents the PR_{ff} for session one divided in shoulder (top) and elbow (bottom), while the second column depicts the value corresponding for session 2.

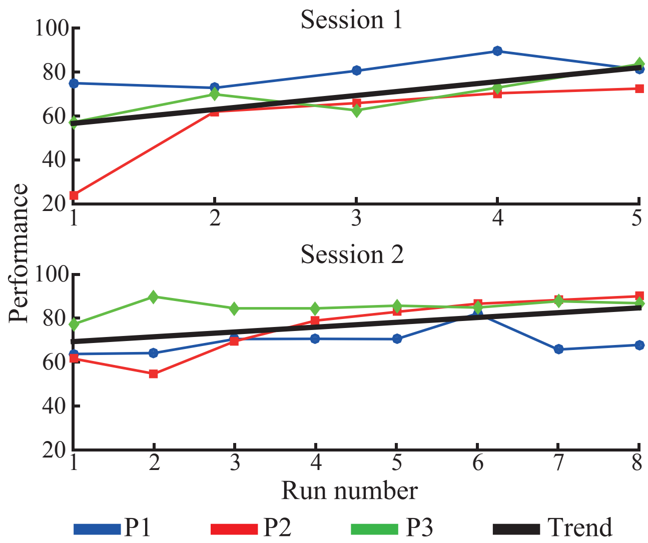


FIGURE 3.9: Averaged tracking performance for each run corresponding to session one and two. The black lines represent the linear fitting regression across subjects.

59.4 ± 13.2% and 62.9 ± 18.3% on the first run for session one and two respectively. This value was increased to 99.4 ± 0.3% and 95.2 ± 6.9% on the second run for each session, and it achieved a final value of 99.6 ± 0.2% and 99.8 ± 0.1% on the last executed run of each session respectively.

Figure 3.9 depicts the corresponding averaged tracking performance for each run during session one and two. The black lines represent the trend of these values for each session. In both cases (session 1 and 2), the linear curves present positive slopes (0.06 for session one

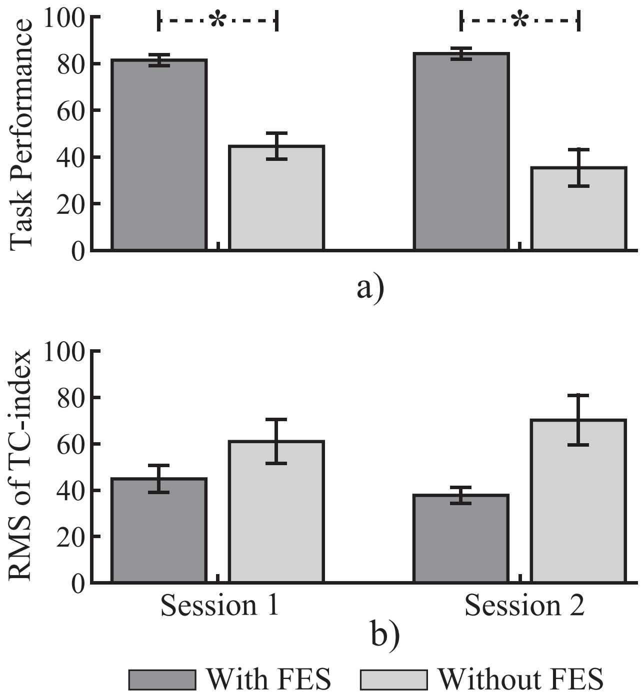


FIGURE 3.10: a) Mean task's performance across subjects considering the last assisted and the unassisted runs. The error bars represent the standard error; b) Mean root mean squared (RMS) of the temporal coordination index (TC-index) differences between the generated reference and the arm trajectories across subjects considering the last assisted and the unassisted runs. The error bars represent the standard error. Asterisks indicate significant differences.

and 0.02 for session two) indicating an increase in performance from 56% to 82%, and from 69% to 84% for each session, respectively.

Figure 3.10a shows the quantitative comparison of the task's performance when the movement was carried out with and without FES. This picture illustrates the average values of the task's performance across all users, where the error bars represent the standard error. The Friedman's ANOVA reveals a significant difference between conditions ($\chi^2(3) = 22.2, p < 0.001$). The post host confirm that in both sessions, the task's performance was significantly better when participants carried out the reaching task with FES assistance (session one: 81.4 ± 9% and session two: 84.2 ± 9%) than when participant performed the task without FES (sessions one 44.4 ± 18.9% and two 35.3 ± 25.8%), with p = 0.008, r = -0.63 for the first and p = 0.004, r = -0.68 for the second session respectively. No significant difference was found in the score between neither the unassisted task nor the assisted task on different sessions, meaning that both conditions (assisted and unassisted) did not change between sessions. The RMS values of the TC-index between reference and the arm trajectories (shoulder and elbow) for the assisted and the unassisted runs across subjects are depicted in Figure 3.10b. Although the execution of reaching movement without FES presented worst inter-joint coordination (higher RMS of the TC-index difference between the reference and the arm trajectory) in both sessions, the statistical test did not find significant differences between these values and the achieved with FES.

TABLE 3.4: Satisfaction score of all brain injury patients.

Quest. How satisfied are you with the system features?	P1	P2	P3	Mean
1. The dimensions (size, height, length, width) of your assistive device?	5	5	5	**5**
2. The weight of your assistive device?	5	5	5	**5**
3. The easy in adjusting (fixing, fastening) the parts of your assistive device?	5	5	5	**5**
4. How safe and secure your assistive device is?	5	5	5	**5**
5. How easy it is to use your assistive device?	5	5	5	**5**
6. How comfortable your assistive device is?	4	5	5	**4.67**
7. How effective your assistive device is (the degree to which your device meets your needs)?	5	5	5	**5**
SAM assessment				
1. Pleasure	9	9	9	**9**
2. Arousal	5	6	5	**5.33**
3. Dominance	9	9	7	**8.33**

Meaning of acronyms and scales. QUEST: Quebec User Evaluation of Satisfaction with Assistive Technology 2.0; SAM: Self-Assessment Manikin. QUEST scale: 5 (very satisfied), 4 (satisfied), 3 (more or less satisfied), 2 (not very satisfied) and 1 (not satisfied at all). SAM depicts the pleasure, arousal and dominance dimension with a graphic character arrayed along a continuous nine-point scale.

3.5.2.2 Satisfaction assessment

Table 3.4 shows the results of the satisfactions scales. In the QUEST questionnaire, the system obtained a high evaluation score in all the items. This assessment reveals an overall average score of 34.67 over the 35 points. The SAM survey scored an overall average value of 9 in pleasure, 8.33 in dominance, while the arousal item was set slightly over the middle of the scale with a value of 5.33.

3.6 Discussion

This chapter presented the analysis of the technical viability of the FEL controller and evaluated the usability of a hybrid robotic system for the rehabilitation of reaching movements in healthy subjects and patients with upper limb motor impairment due to a brain injury. The proposed hybrid platform integrates several subsystems in a self-contained tool. The system provided adaptive assistance by means of the implementation of the FEL controller. To the best of our knowledge, this is the first time that the FEL algorithm has been integrated in a hybrid robotic system to assist in two simultaneous muscles during the execution of a functional task such as reaching. It is also the first time that FEL has been tested with brain injury patients using a hybrid robotic system for upper limb rehabilitation.

3.6.1 Technical viability and system performance

Experiment 1 was aimed at showing that the hybrid robotic system is capable to assist the execution of reaching movements by activating the shoulder and elbow simultaneously using only FES. Healthy subjects were asked to refrain from activating their muscles voluntarily and let the FES move their arm. In this experiment, the capacity of the FEL controller to learn from tracking errors in order to adjust the control action according to the individual responses to FES was demonstrated. The significant reduction of the RMSE at both joints (Figure 3.6a, lines in black) confirms an improvement of the tracking accuracy as the movement is repeated. The shaded areas in dark gray depicted in Figure 3.6b denote the significant increase of the PR_{ff} measures in the controlled joints, showing the learning process of the controller. Furthermore, as no significance was found for RMSE after the fourth trial and in the PR_{ff} after the eighth trial with the healthy participants, it can be suggested that the FEL only requires a few movement examples to attain a stable and appropriate assistance.

Similar behavior was demonstrated in Experiment 2 with brain injury participants. In this experiment, brain injury patients were asked to realize the movement actively while the FES provided the activation needed for the patient to complete the task. The negative slopes of the linear fitting curves derived from the RMSE values over the two sessions (Figure 3.8a) show a trend towards a reduction of the error as the tracking task was repeated. This improvement was translated into an enhancement of the performance score fed back to the users (Figure 3.9). In general, an improvement in the performance from 62.5% to 83% (averaged from both sessions) was achieved. The PR_{ff} values after the second run also presented important higher score than the first run in both joints. The score obtained during the execution of the task with and without FES assistance revealed the difficulty of patients to carry out the required reaching movement without FES (see Figure 3.10). The average task's performance of the users during the execution of the assisted reaching task (82.8%, averaged from both sessions) was twice of the value obtained without assistance. Therefore, the results confirmed that the hybrid assistance improved significantly the task's performance by adapting the delivered FES intensity according to the patients' needs and capabilities, helping them to complete the tracking movements.

When looking at the effect of the FEL controller to the inter-joint coordination during the execution of reaching movement, from experiment 1 can be observed an improvement of the shoulder-elbow coordination throughout the trials execution (see Figure 3.7). However, this improvement did not result into a significant improvement when compared with the first trial. Similarly, experiment 2 showed that assisted movement resulted in better inter-joint coordination than the movement performed without assistance (without FES). These results suggest the capability of the FEL controller to learn the shoulder-elbow inter-joint biomechanical coupling.

Freeman et al. presented the use of ILC to continuously adapt the FES intensity during reaching movements in a similar hybrid robotic system (Freeman et al. 2011). This algorithm was tested with healthy subjects performing ten repetitions of a given task. The RMSE reported in their study was, on average for the first six trials, $9.69° \pm 9.22°$ and $12.54° \pm 9.87°$ for shoulder and elbow angles, respectively. In comparison, the approach presented here achieves an overall tracking error of $3.2° \pm 3.6°$ for the shoulder and $4.9° \pm 3.1°$ for the elbow after 12 trials in the experiment with healthy subjects (n = 12). These improvements could be attributed to the FEL capability of learning a more precise inverse dynamics model of the non-linear musculoskeletal characteristics of the arm (Kurosawa et al. 2005, Watanabe & Fukushima 2011). Therefore, the proposed FEL system represents a robust and reliable strategy to tackle the subject's individual differences and the necessity of a complex model describing the arm dynamics for 3D movement (Meadmore et al. 2012, Freeman et al. 2011).

Model-based controllers typically require the definition of multiple parameters before their use, resulting in time-consuming tasks and requiring one or more additional sessions prior to the intervention (Hughes et al. 2009, Meadmore et al. 2012, Kutlu et al. 2015). Moreover, due to the physiological changes occurring over the days, a re-calibration procedure is often required to maintain the performance within acceptable levels (Kutlu et al. 2015). Unlike model-based systems, the FEL strategy needs neither a user-specific model nor a previous model. The algorithm is always learning and adapting in real time. With the approach proposed here, there is no need to adjust any parameters within one session, between sessions or between patients, which provides great robustness to the rehabilitation, especially if it is to be used by clinical (non-technical) operators.

3.6.2 User satisfaction

The users' perception when dealing with FES or robotic technologies for upper extremity rehabilitation is scarcely reported in the literature. Nevertheless, if a system is not found useful and motivational, it will be used less frequently and adherence will be an issue (Hughes et al. 2011). In this regard, QUEST user's satisfaction scale reported great satisfaction with our system in all items, since most scores reached a value of 5 over 5. The SAM scale results related to pleasure and arousal showed scores of 9 and 5.33 ± 0.58 respectively, suggesting that patients were satisfied with the use of the system. The result of dominance shows that patients perceived high level of control (9/10) while using the system. A low score in dominance may be interpreted as a marker of patients' feeling of being controlled or submissive, adopting a passive attitude.

Patients' motivation has been shown to be an important predictor of long-term changes in quality of life and rehabilitation outcomes (Grahn et al. 2000). The QUEST and SAM assessments suggest that patients found the system attractive, and they adopted an active attitude without feeling under pressure or stressed.

3.6.3 Limitations

Due to the complexity of the shoulder movement during the execution of reaching movements in unconstrained space (Jarrassé et al. 2014), bigger variability in the PR_{ff} metric is observed at this joint when compared with the elbow. This effect is more noticeable with brain injury patients (see Figure 3.8b). This larger variation can be attributed to a more varying response at the shoulder joint to FES. As no mechanical assistance is provided during the movement execution, these differences can be explained by the amount of electrical current required at the shoulder to lift the arm up. Meadmore et al. observed similar limitations (Meadmore et al. 2012). Therefore, the use of mechanical devices with active support could result in a more consistent response at the shoulder joint. Still, and as discussed in previous chapter, the development of an optimally shared control between the FES and the mechanical assistance are needed.

The use of the proposed system could be limited by different conditions of a patient. In the present study, the participant P4 had to be excluded from the experiment due to a change in his perception of FES, possibly due to a hypersensibility experienced throughout the experimental sessions. Therefore, special attention should be paid to refined inclusion criteria. Certainly, the guidance given by Huang et al can be followed, where it was suggested that patients with medium level (suggested by Fugl-Meyer Assessment and Motor Assessment Scale score) of motor skills are preferred when considering robot-based rehabilitation therapies (Huang et al. 2016). Alternatively, active exoskeletons could be considered to reduce the intensity of FES. With such a system, the exoskeleton assistance can be reduced progressively to increase the FES stimulation and promote voluntary movement.

The results reported in this study are based on a reduced number of patients and sessions. As the potential rehabilitation benefits of the present hybrid robotic system is out of the scope of this study, it is necessary to conduct a larger clinical study involving more patients and sessions.

3.7 Conclusions of the chapter

In this chapter, a fully-integrated hybrid robotic system for rehabilitation of reaching movement was presented. The system relies on several subsystems that cooperatively assist during the rehabilitation exercise. The system caters for a rehabilitation scenario where unconstrained functional movements in 3D space are promoted.

An easy to deploy FES-based adaptive assistance was implemented in order to adapt the assist intensity according to user's motor residual capability. This adaptive controller is based on the feedback error learning algorithm. It was demonstrated that the FEL is capable to learn the inverse dynamics model of the arm, and consequently, smoothly adjusting the level of assistance over the trials. Interestingly, this adaptive strategy does not require additional sessions neither a tedious and exhaustive procedure to be configured.

Experimentations performed with healthy participants and patients with brain injury demonstrate the suitability of FEL scheme to assist the execution of reaching movements in 3D space. Patients' reports on the intervention reveal a great satisfaction and acceptance of the hybrid robotic system. These results support the idea that complementing rehabilitation with the hybrid system hereby proposed might be useful to increase the dosage of therapy and to augment patient's engagement and motivation during the rehabilitation process. In the next chapter, a BCI system is combined with the hybrid robotic system to provide causal and timed assistance to elicit plasticity.

Chapter 4

Eliciting neural plasticity by the timed association of the user's motor intent with the peripheral hybrid assistance[1]

Abstract

This chapter presents the implementation of an associative approach combining the hybrid assistance delivered by the system presented in Chapter 3 with users' motor intent. The adaptive hybrid assistance is triggered when the users' own intention to move is detected to assist the execution of functional reaching movements. The first objective framed in this chapter is to verify whether the precise temporal pairing between the peripheral stimulation and the user's motor intent during the execution of a functional reaching movement can induce an enhancement in excitability of the descending motor corticospinal tract projected to the arm muscles (plasticity) in healthy subjects. The second objective is to compare the intervention effects when three different techniques (EMG, BCI offline and BCI online) are used to detect the user's intent to move and associated it with the externally applied hybrid peripheral assistance. Twenty-one healthy subjects (11 males and 10 females, age: 29.3±3.98 *years) participated in the experimentation. Results revealed positive intervention's effects in all implemented strategies (BCI offline, BCI online and EMG). However, stronger and more consistent intervention's effects were achieved with the BCI offline intervention. Thus, this strategy reported a significant increase in excitability of the corticospinal projection (larger MEP size) after the intervention in the assisted (AD, TB) and unassisted (BB) target muscles*

[1]This chapter is partly based on:
- F. Resquín, O. Herrero, J. Ibáñez, J. Gonzalez-Vargas, F. Brunetti, J. L. Pons. Electroencephalography-guided Upper-Limb Hybrid Robotic Platform to Modulate Cortical Excitability. IEEE International Conference on Systems, Man and Cybernetics, 2017 (Accepted).
- F. Resquín, J. Ibáñez, O. Herrero, J. Gonzalez-Vargas, F. Brunetti, and J.L. Pons. "User's Motor Intent Guided Upper-Limb Hybrid Robotic Platform to Efficiently Modulate Cortical Excitability: A comparison of three strategies". (To be submitted)

of the arm. Because of the efficacy of this intervention (BCI offline), it represents an efficient neuromodulation strategy for inducing plastic changes into the motor cortex.

4.1 Introduction

In Chapter 2, the main challenges of the hybrid robotic system for rehabilitation of the upper-extremity motor functions were identified. Based on these requirements, in Chapter 3 a hybrid robotic system providing adaptive assistance, according to the user motor residual capability, during the execution of unconstrained reaching movement was presented. It was demonstrated that, the system can assist accurately tracking movements by supplying FES assistance at the AD and TB muscles simultaneously. Moreover, brain injury patients rated the system positively, presenting a great acceptability for using the system as a rehabilitation tool. However, there is evidence showing the relevance of exploiting the natural plasticity of the sensorimotor system to maximize rehabilitation potential of therapies (Di Pino et al. 2014, Dimyan & Cohen 2011). Certainly, intrinsic physiological and anatomical neural plasticity are important processes that underlie substantial gain of motor function after stroke (Ward 2005, Dimyan & Cohen 2011, Schaechter 2004).

At the cortical level, different mechanisms are responsible for facilitating these plastic changes (Ward 2005, Nudo 2006). One of those, is referred to as activity-dependent neural plasticity, which is commonly linked to the long-term potentiation (LTP) phenomenon (Ziemann 2004, Sanes & Donoghue 2000). The LTP consists of persistent strengthening of the synaptic connection associated to the Hebbian theory, which states that synapses that experience correlated activation of two converging inputs are strengthened whereas those weakened by uncorrelated activity are lost (Hebb 1949). It has been shown that this physiological phenomenon can be induced through associative protocols by the precise causal and temporal pairing of a peripheral and cortical stimulus (Carson & Kennedy 2013, Stefan et al. 2000, Thabit et al. 2010, Ziemann et al. 2008).

The paired associative stimulation (PAS) is a widely diffused associative protocol, consisting of a low frequency peripheral stimulation, applied over the peripheral nerve of the wrist (Stefan et al. 2000) or over the peroneal nerve in the leg (Mrachacz-Kersting et al. 2007, Mrachacz-Kersting & Stevenson 2017), timed and paired with a transcranial magnetic stimulation (TMS) delivered to the contralateral primary motor cortex. In these studies, the motor evoked potential (MEP) on target muscles elicited by TMS was used to quantify the effects of the PAS protocol. The MEP response gives a valuable and quantifiable information about the excitability of the cortical projection to the target muscles (plasticity) (Rotenberg et al. 2014, Rossini et al. 2015). It was shown that PAS can induce plastic changes measured as an increase in the amplitude of the MEPs, and its effect was persistent (duration > 30 minutes). Although PAS constitutes a great potential for inducing plastic changes in a short time ($\sim$30' minutes), it presents some limitations. The principal one relies on its functional implication, since the exogenous cortical stimulus activates several brain areas at the same time rather than following a sequence of neural activation as happens during voluntary movements.

In the rehabilitation field, a neuromodulation BCI can be defined as a system conceived for inducing neuroplasticity (Daly & Wolpaw 2008, Soekadar et al. 2015). In this regard and similar to PAS, there are several studies showing that timed-association between user's intent to move (cortical activation) and peripheral afferent feedback yields to a well-adaptive plasticity (Ethier et al. 2015). In this context, Mrachacz-Kersting et al. obtained similar results to those obtained in the PAS, when substituting the exogenous TMS stimulus given in PAS by a natural endogenous activation of the motor cortex occurring when imagining or performing a movement and registered through EEG (Mrachacz-Kersting et al. 2012). This cortical activation is called motor-related cortical potential (MRCP), and it consists of a low-frequency potential generated in association with the planning and execution of a cued or self-paced voluntary movement (Jankelowitz & Colebatch 2002, Jochumsen et al. 2013). It is characterized by a negative deflection of the EEG signal up to 2 seconds before a movement is executed, with the peak of maximal negativity occurring shortly after the onset of the movement (Shibasaki & Hallett 2006, Shakeel et al. 2015).

In the study presented by Mrachacz-Kersting et al., it was demonstrated that a peripheral electrical stimulus over the peroneal nerve timed with the negative peak of the MRCP results in an increased excitability of the cortical projections to the tibialis anterior muscle (plasticity) when assessed with TMS in healthy subjects (Mrachacz-Kersting et al. 2012). Remarkably, they have also confirmed that this elicited plasticity is correlated with motor functional improvements of the lower limb in stroke patients (Mrachacz-Kersting et al. 2015). In this line, Xu et al. substituted the peripheral electrical stimulus with a robotic device providing mechanical support to execute the same ankle dorsi-flexion task in healthy subjects, and obtained similar results (Xu et al. 2014). Despite these promising results, in these studies the number of muscles involved in the tasks (dorsi-flexion) was limited (single muscle for one degree of freedom) and were based on analytical tasks instead of functional ones.

Later on, other studies followed the same approach to corroborate cortical plastic changes, when executing grasping movements assisted by FES (McGie et al. 2015) and a robotic device (Kraus et al. 2016). In these studies, a EEG-based BCI using sensory motor rhythms (SMR) was implemented to link the user's motor intent with the afferent feedback. Although the functional implication of this task (grasping) is high (from the rehabilitation perspective), both studies failed to demonstrate a significant increase in excitability of the cortical projections to the hand muscles when measured with TMS. One possible explanation can be attributed to the low capability of the BCI system to provide timed association (cortical activation with the proprioceptive afferent feedback). These pieces of evidences prove the importance timing in the delivery of proprioceptive feedback to achieve neural facilitation.

It is worth noting that there still are some gaps to address towards the consolidation of the associative concept (user's intent to move plus peripheral assistance) in clinical interventions. First, it has not been demonstrated yet that interventions following the associative approach cause an increase in excitability of the cortical projections to the upper-limb muscles. Second, the impact of the associative concept in a functional task, involving a multi-degree of freedom task and several muscles, has not been yet addressed.

In this chapter, the associative approach is implemented by combining the hybrid assistance delivered by the system presented in Chapter 3 with the user's intent to move. Thus, the adaptive hybrid assistance is triggered when the user's motor intent is detected to assist the execution of functional reaching movements. The objectives of this chapter are two-folded. First, we want to verify that timed peripheral stimulation with the user's motor intent during the execution of a functional reaching movement can induce a distributed enhancement in excitability of the descending motor corticospinal tracts projected to the arm muscles (plasticity) in healthy subjects. Secondly, we aim at comparing the intervention's effects when three different techniques (EMG, BCI offline and BCI online) are used to detect the user's intent to move and associated it with the externally applied hybrid peripheral assistance.

4.2 Method

4.2.1 Subjects

Twenty-one healthy subjects (11 males and 10 females, age: 29.3 $\pm$ 3.98 years) participated in the experimentation. None of the subjects presented any history of neither sensory-motor disorder nor physiological deficit. All participants signed a consent form to participate and publish the data collected from the experimentation.

4.2.2 Materials and Instrumentation

4.2.2.1 EEG and EMG acquisition during intervention

EEG signals were recorded from 28 positions (AFz, F3-F4, FC3-FC4, C5-C6, CP3-CP4, P3-P4, and Oz according to the international 10-20 system) using active Ag/AgCl electrodes (Acticap, Brain Products GmbH, Germany). The reference was set to the voltage of the earlobe contralateral to the arm moved and Oz was used as ground. Additionally, electromyography (EMG) signals were recorded from two bipolar electrodes placed at AD and TB muscles, with ground and reference separated from the EEG signals and placed over the radius at the wrist. EEG and EMG signals were amplified using the gUSBamp (g.Tec GmbH, Austria) and were sampled at 256 Hz.

4.2.2.2 Hybrid robotic system

The hybrid robotic system presented in the previous chapter is used to assist the execution of unconstrained reaching 3D movements. Similar configuration is set for this experiment, the electrical stimuli are simultaneously delivered at 40 Hz over the AD and TR muscles, and the PW of the electrical stimuli is modulated to adjust the current intensity (see Chapter 3 for

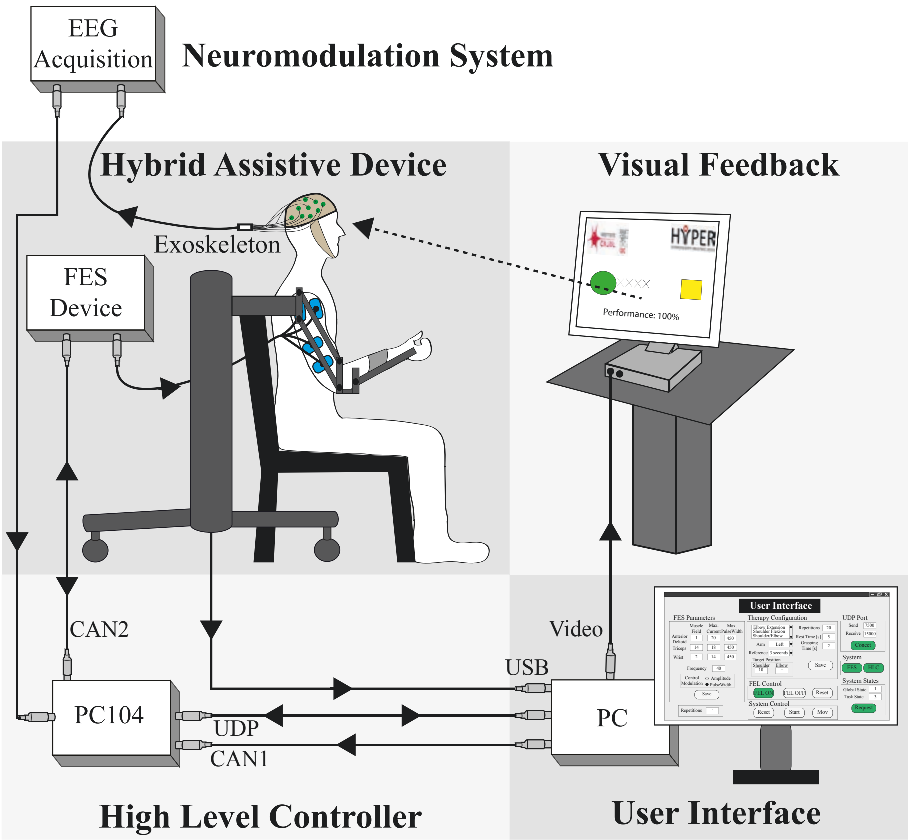


FIGURE 4.1: General overview of the integrated hybrid robotic and the neuromodulation system for rehabilitation of reaching movement.

details). The block diagram of the full system (hybrid system plus neuromodulation system) is illustrated in Figure 4.1.

4.2.2.3 TMS for eliciting motor evoked potentials

A Magstim 200 TMS system (Magstim Company, U.K.) with a figure-of-eight coil was used to elicit MEP responses. The MEP responses were recorded from the EMG signal using bipolar electrodes, with ground and reference placed over the radius at the wrist. The EMG signal was sampled at 2400 Hz and amplified using the gUSBamp. Custom-made software was developed for acquisition and visualization of MEP amplitude using Simulink® (Mathworks Inc.).

4.2.3 Experimental Procedure

The experimental protocol is schematically shown in Figure 4.2a. It consists of three stages: pre-assessment, intervention and post-assessment. Two pre-assessment measures (Pre0 and Pre1) were carried out in order to set the baseline MEPs. Next, subjects participated in the experimental intervention. Finally, the effects of the intervention were evaluated immediately (Post) and 30 minutes (Post30) after the intervention.

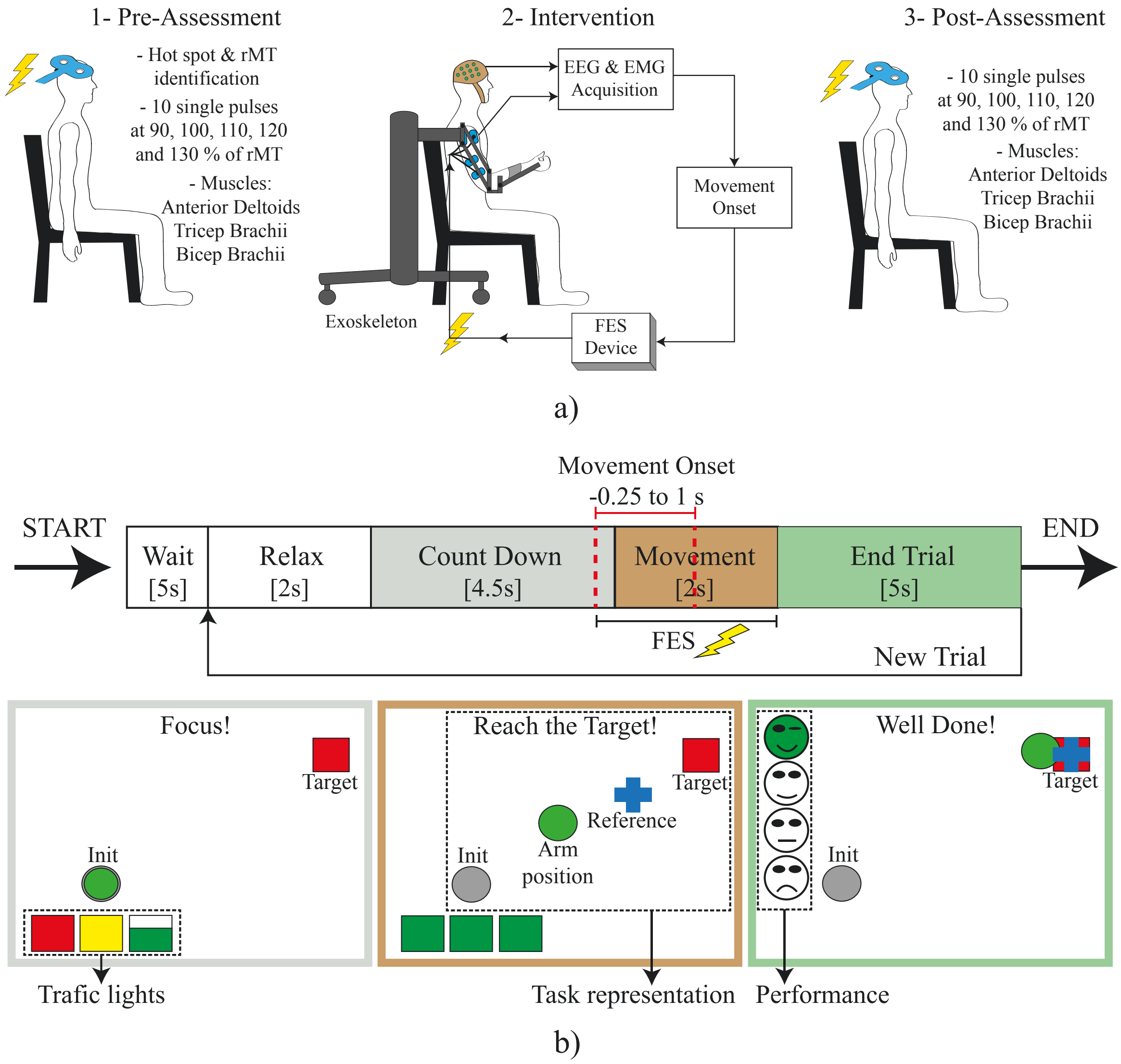


FIGURE 4.2: a) Experimental protocol used for experimentations; b) Implemented state machine to present the visual cue and guide users during the intervention.

4.2.3.1 Pre0-, Pre1-, Post- and Post30-assessment

The brain response to single-pulse TMS delivered over the motor cortex was measured from the AD and TB and bicep brachii (BB) muscles (target muscles). The TMS pulses were applied contralateral to the arm moved during the experiment. In 20 of the participants the TMS stimuli were delivered on the right cerebral hemisphere in order to induce MEPs on the left arm. While in a single subject, the TMS pulses were applied in the opposite cerebral hemisphere (left) to record MEPs of target muscles in the right arm.

Before the first pre-assessment measure (Pre0), skin preparation was performed (rubbing with cotton and alcohol) and EMG electrodes (rectangular 22.225×34.925 mm, NeuroPlus™) were placed over the target muscles (AD, TB and BB). Once these electrodes were placed, they were fixed until the end of the experiment. All participants seated in a chair (without armrest) and were instructed to keep their arm extended (in direction to the ground) and relaxed. The TMS coil was held tangentially to the skull forming an approximate angle of 45° between the handle and the sagittal plane. Next, the hot spot of stimulation was determined. This site was identified as the area in which the most consistent MEPs on the AD and TB muscles were simultaneously elicited. This position was marked on the patient's head with a permanent marker to ensure that the stimuli were consistently delivered over the same area of the motor cortex across all assessment stages (Pre0, Pre1, Post and Post30). Subsequently, the subject-specific resting motor threshold (rMT) was estimated using the reduced relative frequency method (Groppa et al. 2012).

After this initial procedure, two assessment measures were performed (Pre0 and Pre1), separated approximately 10 minutes between them. During all the assessment stages, ten MEPs were elicited at five different TMS intensities: 90%, 100%, 110%, 120%, and 130% of the rMT. These ten MEPs were divided in two blocks of five stimuli each to avoid the possibility of biasing the measurements by misplacing the coil. The intensity of the TMS stimuli were randomized across subjects and delivered every 6.5 seconds.

4.2.3.2 Intervention

Before starting the intervention, the subjects were equipped with the hybrid assistive system. First, the exoskeleton was adjusted according to the subjects' arm lengths. The level of mechanical support was regulated such that the arm was kept about the subjects' thighs in the horizontal plane. Surface electrodes (Pals platinum - rectangle 5×5 cm) for FES were attached to the AD and TB muscles by the previously located EMG electrodes.

As the hybrid robotic system comprises an adaptive controller adjusting the FES intensity during the task execution according to the user performance (see Chapter 3 for detailed information), the maximum and minimum FES intensity thresholds was determined for each subject. The lower threshold was established as the minimum amplitude in which the user perceived the stimulus and a visible muscle contraction was apparent. Thus, it was set slightly below to the motor threshold (MT). This threshold was set since only strong enough externally applied peripheral electrical stimulation (close to the MT) arriving at the primary motor cortex from the somatosensory cortex elicits cortical plasticity (Stefan et al. 2000, Chipchase et al. 2011). While the maximum FES intensity was defined as the maximum current that subjects considered comfortable. After the calibration of the FES parameters, the subject-specific range of movement of the assisted limb was established. This range represents the distance to be covered by the subject in each movement performed.

The last step before starting with the intervention consisted of instrumenting the participants with the EEG and EMG acquisition system, which operates using the configuration explained in Section 4.2.2.1. In order for the subjects not to be aware of the experimental intervention (strategy used to detect movement onset), this preparation procedure was applied to all of them.

The intervention consisted in two stages: the calibration and the experimental movements. The calibration stage was based on the execution of 30 movements without FES assistance divided into two blocks of 15 movements each. All subjects were asked to follow the instructions presented on the screen, which cued to perform reaching movements. To this end, the visual feedback presented in Section 3.2 was modified. In this setup, a cue-based interface was developed to guide the user through the intervention while providing information on the arm position (shoulder and elbow) and the task performance level.

A state machine, as shown in Figure 4.2b (upper row), was implemented to manage the intervention events. This state machine relies on five main states: 'Wait', 'Relax', 'CountDown', 'Movement' and 'EndTrial'. During the 'CountDown' state, three different rectangles are displayed on the interface (gray screen layout in Figure 4.2b). These rectangles are incrementally filled up following a traffic light paradigm (red, yellow and green colors) lasting 1.5 seconds each. Thus, a period of 4.5 seconds is used for movement preparation. Subjects were instructed to remain as relaxed as possible during this period. When the last rectangle is entirely filled (green color), all rectangles are turned in green, indicating the movement state. At this moment, the reference trajectory (the blue cross shown in the brown screen layout of Figure 4.2b) starts moving towards the target position (red square at top left), and subjects were asked to perform the reaching movement following this reference. Simultaneously, the arm position is fed back to the users (the green circle), where the x- and y-axis indicate the movements of the elbow and shoulder joints, respectively. In all reaching movement carried out in this study, a period of one second was allowed to reach the target from the initial position. After the movement was executed, the system also reported information on the quality of the movement by using different face colors according to the measured performance ('EndTrial' state, light green rectangle of Figure 4.2b). The green face indicated a good performance ($\geq$ 90%), yellow a moderate performance ($\geq$ 75%), orange a bad performance ($\geq$ 50%) and red a poor performance ($\geq$ 50%) (see Chapter 3 for further details).

Finally, the last part of the intervention consisted of the experimental stage, in which participants performed the same cue-based reaching movements with the hybrid robotic assistance being triggered by the detection of the subjects' motor intent (following the procedure explained in Section 4.2.4). The same instructions were given to all participants and the same procedure was followed in order to blind them in terms of the control or experimental group to which they were assigned. All reaching movements were executed with the contralateral arm to the cerebral hemisphere in which the TMS pulses were elicited.

4.2.4 Implemented strategies to define the assistance onset

In order to assess the optimal way (in terms of its capacity to induce plasticity) to associate the hybrid assistance to the user's movement intent, three different strategies to determine the movement onset were implemented. Each subject was assigned to one of these experimental interventions by considering the following criteria. After finishing the calibration stage, the movement-related cortical patterns (MRCP and SMR) were obtained from the EEG signals.

For all subjects, these patterns were carefully inspected and the BCI online detector (see following Section 4.2.4.2) was trained. From these training data, the performance of the classifier was evaluated considering its accuracy for correctly estimating the user's movement intent. Those users who presented consistent motor cortical patterns and resulted in a reliable performance of the BCI online detector (detection accuracy > 40%) were assigned to the BCI online experimental group, whereas those subjects with poor detection accuracy were randomly allocated to the BCI offline and EMG group.

4.2.4.1 BCI offline

Eight subjects (5 males and 3 females, one left-handed, age: 30.4 $\pm$ 4.3) were part of this experimental group. This strategy uses the negative peak of the MRCP to determine the instant of time in which the hybrid assistance was delivered to assist the execution of the functional reaching movement. The MRCP considered with this method represents a physiological generated brain activation and it contains information on movement planning and execution (Shakeel et al. 2015, Jankelowitz & Colebatch 2002, Shibasaki & Hallett 2006). Indeed, the negative peak is linked to the onset of the movement execution. Thus, the recorded EEG signals during the 30 calibration movements were used to identify the time occurrence of the negative peak (in average) of the MRCP with respect to the beginning of the 'Movement' state. This time was subsequently used during the experimental stage of the intervention to consistently deliver the assistance, thus, the assistance onset was fixed during the experimental stage of the intervention. This strategy is called BCI offline since the movement onset (time point for when to deliver the assistance) was determined offline.

The offline processing consisted of dividing the recorded EEG signals into epochs of 5 seconds for each individual trial, corresponding to 3 seconds before to 2 seconds after the beginning of the 'Movement' state indicated by the visual cue. The mean and maximum values of the EEG signal for each epoch were calculated and visually inspected. The epochs with notorious higher mean or maximum values were individually removed. After removing the epochs affected with artifacts, the EEG signals were band-pass filtered (Butterworth, 1st order, $0.05 \leq f \leq 5$ Hz), and subsequently a common-average reference spatial filter was applied to enhance the MRCP feature in each epoch. Finally, the mean MRCP of each channel over the epochs were calculated to obtain the averaged MRCP. The negative peak of this averaged MRCP minus 25 ms was used to set the time point when the hybrid assistance must be delivered. Based on evidence from previous studies (Stefan et al. 2000, Mrachacz-Kersting et al. 2015), the 25 ms represent the estimated delay for the afferent peripheral stimulus applied at the upper extremity to reach the motor cortex.

All participants carried out 60 timed and causally associated reaching movement divided in three blocks of 20 movements each. Due to a muscular lesion in the left arm, one subject performed the intervention with the right arm, so TMS stimulation was delivered at the right cerebral hemisphere.

4.2.4.2 BCI online

Five subjects (3 males and 2 females, all right-handed, age: 26.8 ± 4.7) took part of this experimental group. Unlike to the BCI offline approach, this strategy (named BCI online) was used to tightly control the time-onset of the assistance in each trial during the experimental stage of the intervention. The main advantage of this strategy is that it promotes the active movement planning and engagement of the users (Ibáñez et al. 2017, Xu et al. 2014). For this purpose, a EEG-based BCI was implemented using custom-made Simulink model (The Mathworks Inc., Natick MA, USA) in a dedicated computer. The classifier was used to detect user's movement intent and trigger the assistance of the hybrid robotic system (Ibáñez et al. 2014, 2017). This classifier combines information from two cortical processes, the event-related desynchronization (ERD) and MRCP, to boost the performance of the detector.

In brief, the EEG signals recorded from 30 movements at the calibration stage of the intervention were used to extract the best features and to train the online classifier. The recorded EMG signals have been used to identify the time occurrence of the 30 voluntary movements. To this end, the EMG signals from AD and TB muscles were band-pass filtered (Butterworth, 1st order, $25 \leq f \leq 127$ Hz) and then rectified. For each participant, the muscle showing best signal to noise ratio was selected as the input of a single threshold detector, in which a threshold of 10% of the maximum EMG amplitude during the voluntary movements for each subject was used. Finally, the detected onsets were visually inspected to ensure that artifact and involuntary or residual movements were correctly discarded.

For the ERD detection, a band-pass filter (Butterworth, 2nd order, $6 \leq f \leq 30$ Hz) and a small Laplacian filter were first applied. The power values of each EEG channel were estimated using the Welch's method in segments of 1.5 s and frequencies ranged from 7 to 30 Hz (Hamming windows of 1 second, 50% overlapping). The values obtained from -3 to -0.5 seconds with respect to the time onset of the voluntary movement execution were labeled as resting examples. While the estimation at the movement onset ($t = 0$) were labeled as movement samples. The Bhattacharyya distance was used to select the 10 best features (channel/frequency pairs) to build a Bayesian classifier.

For the detection of the MRCP pattern, a band-pass filter (Butterworth, 1st order, $0.05 \leq f \leq 5$ Hz) was first applied to extract the low-frequency components of the EEG signals. A common-average reference spatial filter was applied and subsequently a modified version of the large laplacian filter using as reference the average information from eight peripheral channels in the EEG electrode layout was used to minimize the weight of individual reference channels. After a visual inspection of the averaged MCRP, one or more channels were individually selected to generate a virtual one by subtracting the average recordings of channels F3, Fz, F4, C3, C4, P3, Pz, and P4 to them. The average MRCP from -1.375 to 0.125 s of the selected channels was obtained using the training data. This pattern was then used to design a matched filter. During the online function, the matched filter was applied to the virtual channel of the validation dataset.

Finally, the outputs from the ERD- and MRCP-based detectors were combined using a logistic regression classifier. This classifier was trained by taking the output estimation of both detectors (ERD and MRCP). The time interval from -3 to -0.5 seconds with respect to the movement onset was considered as resting stage, while the time interval from -0.125 to 0.25 seconds was labeled as movement stage. A threshold was applied to the estimations to decide every 5 samples (19.53 ms) if a movement intention were detected. This threshold was optimally obtained using the calibration dataset and following the criterion of maximizing the true positive (TP) rate, i.e. the percentage of trials with correct motor intention detection and with no incorrect detections.

Considering that rehabilitation systems must be robust enough to avoid unexpected responses, e.g. delivering peripheral electrical pulses long before the intention to move occurs, a contingency method to prevent subjects from receiving electrical stimuli wrongly (long before the movement intention or once movement has accomplished) was implemented. Thus, BCI system was only enabled during the time interval from -250 ms to 1 s with respect to the beginning of the 'Movement' state. This time interval is indicated with the vertical dotted lines in the Figure 4.2b. The subjects were advised that the electrical stimuli appeared whenever motor-related processes were observed within this time window and they were instructed to report trials (movement executions) in which the FES was received too soon or too late with respect to their expectation.

All subjects performed sets of 20 movements with their left arm until at least 50 good pairings (also called association: electrical stimuli arriving on time with the user's intent to move), or 110 movements were achieved.

4.2.4.3 EMG

In eight subjects (3 males and 5 females, two left-handed, age: 30.1 $\pm$ 2.8) the EMG signal was used to determine the assist onset, in contrast to previous strategies in which the FES assistance was set based on the EEG signals. Here, the peripheral electrical stimuli over the target muscles were triggered when muscle activation was identified. To this aim, an online detector based on a single threshold was implemented using a custom-made Simulink model (The Mathworks Inc., Natick MA, USA) in a dedicated computer.

In this detector, a band-pass filter (Butterworth, 1st order, $25 \leq f \leq 127$ Hz) was first applied, and the resulting signal was rectified. The rectified signal was smoothed to obtain the envelope using a moving average filter with a windows length of 30 samples and 50% of overlapping. The detector identified muscle activation when the envelope of the EMG signal was higher than a predefined threshold. The detector's threshold was set to the mean value plus seven standard deviations of the envelope signal. These values (mean and standard deviation) were dynamically updated for each trial, taking the envelope signal during the first two and half seconds of the 'Count Down' state (when users were instructed to be relaxed). Similarly to the BCI online group, the users' movement onset was estimated only within the same time interval from -250 ms to 1 s with respect to the beginning of the 'Movement' state. All subjects performed 60 trials divided in 3 blocks of 20 movements each with their left arm.

4.2.4.4 Control experiments

Two control experiments were designed for experimentation. In the first study, five subjects (3 males and 2 females, all right-handed, age: 30.2 ± 4.9) participated in one additional session to verify the effects of the reaching movement alone (without FES assistance and BCI). This control experiment was conceived to verify whether the voluntary execution of the same motor task (reaching movement with the exoskeleton) without FES assistance produces changes in the excitability of the cortical projection to the target muscles of the arm. Five subjects (5 males and 3 females, all right-handed, age: 28 ± 3.5) took part in the second control experiment. In this case, the control experiment was proposed to confirm the importance of delivering the assistance timed with the user's intent to move. This second control experiment consisted in triggering the FES assistance at the beginning of the 'Movement' state. The same number of movement repetitions as in the BCI offline and the EMG experimental intervention were performed in both control experiments, i.e. 60 reaching movements divided in 3 blocks of 20 movements each.

4.2.5 Outcomes Measures

The primary outcome measure was the corticospinal descending motor excitability of the target muscles (AD, TB and BB muscles) measured using the peak-to-peak value of the recorded MEP response to single-pulse TMS during the Pre0-, Pre1-, Post- and Post30-assessment. The amplitude of the ten elicited MEP was averaged for each subject, and calculated for different TMS intensities (90, 100, 110 120 and 130%) and assessment intervals (Pre0, Pre1, Post and Post30) using custom-made software developed in Matlab. The average responses of each individual at each TMS intensity and assessment interval were normalized as a function of the maximum MEP amplitude at the Pre0 assessment stage. This normalization was conducted in order to combine all users' response and evaluate the effects of the intervention.

In addition, the EMG background activity before the TMS stimulus was quantified by calculating its root mean square (RMS) value along a window interval of 30 ms. This metric was used to verify that all subjects were in a basal condition without any voluntary muscle contraction prior to the TMS stimuli. In addition, this metric was used to check that the basal condition prior the TMS pulse did not differ between the assessment stages (Pre0, Pre1, Post and Post30).

Complementary to the analysis of the MEP amplitude, the average negative time occurrence of the MRCP pattern used to define the stimulation onset in the BCI offline group is informed. In the BCI online group, the performance of the BCI detector is reported. For this purpose, the accuracy of the detector to estimate correctly the user's intent to move is quantified by the true positive (TP) rate, which is defined as the percentage of trials with movement detection in the time interval from -0.25 to 1 second (BCI enable interval, vertical red lines depicted in Figure 4.2b) with respect to the beginning of the movement stage (cue). Thus, to calculate the TR rate, those movements with a good pairing (association) and those in which the stimulus arrived soon or late (from -0.25 to 1 seconds) according to the user's perception are considered. Finally, the accuracy of the muscle activation onset detection and the average detection time with respect to the cue is computed for the EMG group.

4.2.6 Statistical Analysis

The participant ages as well as the values of rMT and FES thresholds were compared to assess whether the experimental conditions established between groups differed. A one-way ANOVA with factor 'Group' (1: BCI offline, 2: BCI online; 3: EMG; 4: Control I; 5: Control II) was conducted to explore whether there were any differences in the participant's age and the rMT between groups (experimental and control groups). Three-way mixed ANOVA with factors Group (1: BCI offline, 2: BCI online; 3: EMG; 4: Control I; 5: Control II), 'Muscle' (1: AD and 2: TB) and 'FES Level' (1: minimum and 2: maximum) was considered to evaluate differences in the FES threshold established between groups.

A three-way repeated-measures ANOVA with factors 'Time' (1: Pre0; 2: Pre1; 3: Post; and 4: Post30), 'Muscle' (1: AD; 2: TB; 3: BB) and 'Intensity' (1: 90%; 2: 100%; 3: 110%; 4: 120%; and 5: 130%) was used to investigate both, the basal condition prior to the TMS stimulus through the EMG background and the intervention's effect throughout the 'Time' to change the excitability of the descending cortico-muscular pathway given by the MEP amplitude response. The statistical analysis was performed separately for each experimental and control group (EMG, BCI offline, BCI online, Control I and Control II). Statistical significance was assumed for $p \leq 0.05$. Whenever the ANOVA revealed a significance difference, a post hoc test with Bonferroni correction was carried out to find out the specificity of the effect due the intervention.

4.3 Results

Table 4.1 shows the average participants' age for the experimental and control groups. Additionally, the average rMT and the FES thresholds (minimum and maximum for each muscle) across groups are presented. The one-way ANOVA reveals no differences between participant's ages across groups neither between the established rMT ($p > 0.05$ in both cases). The three-way mixed ANOVA used to identify differences in applied FES thresholds between groups did not find any differences when considering the factor 'Group' nor between its interaction with other factors ($p > 0.05$ in all cases). These results indicate that similar experimental conditions were established between groups (experimental and control groups).

Table 4.1: Average values of the experimental condition for each group.

	Age [years]	rMT [%]	FES threshold AD Min [mA]	FES threshold AD Max [mA]	FES threshold TB Min [mA]	FES threshold TB Max [mA]
BCI offline	30.4 ± 4.3	63.4 ± 11.1	9.8 ± 2.2	14 ± 2.6	8.6 ± 2.1	11.6 ± 2.6
BCI online	26.8 ± 4.7	60.6 ± 25.7	9.8 ± 2.4	13.6 ± 2.4	7.8 ± 0.8	12 ± 4.5
EMG	30.1 ± 2.8	70 ± 9.5	9.4 ± 1.3	13.3 ± 2	8.8 ± 1.2	11.3 ± 1.8
Control I	30.2 ± 4.9	65.4 ± 11.9	-	-	-	-
Control II	28 ± 3.5	65.6 ± 8.1	10.8 ± 1.3	13.8 ± 2.5	10 ± 1.6	12.4 ± 1.1

Meaning of acronyms. rMT: resting motor threshold; FES: functional electrical stimulation; AD: anterior deltoids; TB triceps brachii; Min: minimum value; Max: maximum value.

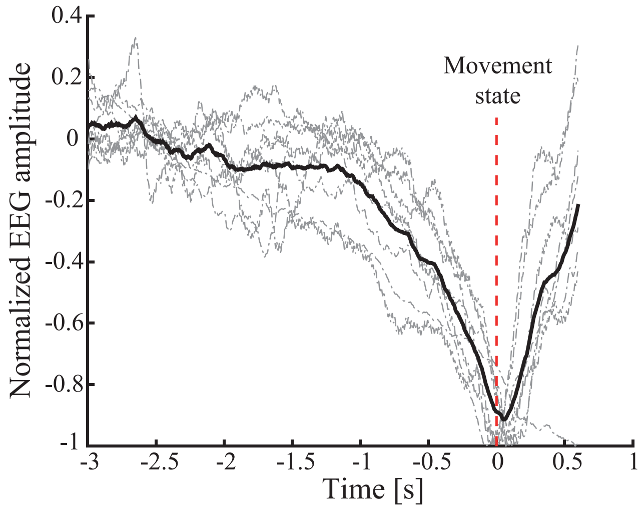


Figure 4.3: Normalized amplitudes of the average MRCP of all subjects (dotted lines in gray) and average MRCP across subjects (continuous black line). The vertical red line indicates the beginning of the movement state (cue).

In all interventions (experimental and control), the statistical test confirmed similar baseline condition prior to the TMS stimulus, measured through the EMG background, across all assessment stages (Pre0, Pre1, Post and Post30), with $p > 0.05$ for the 'Time' factor and its respective interactions.

4.3.1 BCI offline

Figure 4.3 illustrates the MRCP signals of the subjects who took part of the BCI offline experimentation. Across all subjects, the average negative peak of the MRCP occurred at 48.34 ± 129.5 ms with respect to the beginning of the 'Movement' state. Thus, the FES assistance was delivered in average at 23.34 ms after the cue.

The first column of Figure 4.4 shows the averaged DA (first row), TB (second row) and BB (third row) MEP peak-to-peak value for all subjects plotted as a function of the rMT for each intervention session. The MEP amplitudes for each individual muscle are expressed as a fraction of the respective maximum MEP size at the Pre0-assessment. When analyzing the effect of the intervention through the MEP peak-to-peak value, the three-way repeated ANOVA

TABLE 4.2: Performance of the cue-based BCI system used in the experimentation of the BCI online group.

Participants	Total Number of Movements	Number of Associations	BCI accuracy [TP %]
P1	110	52	62.72
P2	100	41	81
P3	70	51	80
P4	80	51	95
P5	100	48	68
Mean ± SD	**92 ± 16.4**	**48.6 ± 4.5**	**77.3 ± 12.6**

Meaning of acronyms. TP: true possitive.

revealed a significant difference in the factor 'Time', indicating that the MEP amplitude significantly changed between the assessment intervals ($\chi^2(3) = 16.37, p = 0.001$). The analysis also revealed a significant difference when considering the interaction of 'Time×Intensity' ($\chi^2(12) = 24.2, p = 0.02$). Additionally, the 'Time×Muscle×Intensity' term resulted in a significant difference ($\chi^2(24) = 38.84, p = 0.028$).

The post hoc test of the factor 'Time' revealed that the measure MEP amplitude at the Post-assessment was significantly increased with respect to the Pre0 and Pre1 stages (with $p = 0.028$ and $p = 0.016$ respectively). Similarly, the MEP amplitude at the Post30-evaluation was significantly larger when compared with the amplitude at Pre1 ($p = 0.036$). Other comparison did not presented differences (Pre0 vs Pre1 and Post vs Post30). The analysis performed to identify the specificity of the intervention's effects when considering the 'Time×Intensity' interaction showed that, at 110% and 130% of the stimulation intensity, the MEPs amplitude for the Post- and Post30-assessment were significantly increased when compared to the amplitude at both pre-evaluations (Pre0 and Pre1), with $p < 0.05$ in all cases. Moreover, at 120% of the stimulation intensity a significant difference was found between the Pre0 and Pre1 assessment with respect to the Post evaluation ($p < 0.05$).

When pooling the three-terms interaction, it was found that the MEP amplitude at the DA muscle at 110% and 130% intensity during the post intervention significantly increased with respect to the Pre0- and Pre1-assessments ($p < 0.05$). Furthermore, MEPs at the 130% intensity were significantly larger 30 minutes after the end of the intervention when compared to both pre-assessment (Pre0 and Pre1), with $p < 0.01$ in both cases. Remarkably, the post hoc test showed that the recorded MEP size at 110% intensity 30' minutes after the intervention (Post30) of the BB muscle (unassisted) was significantly increased with respect to both the pre-assessment stages ($p < 0.05$). Moreover, the MEP size measured after the experimentation (Post) was significantly larger than the Pre0- and Pre1-evaluation at 120% of the TMS intensity ($p < 0.05$).

4.3.2 BCI online

The performance of the BCI system is presented on Table 4.2. Participants carried out on average a total of 92 ± 16 movements. The overall TP score of the BCI system was 77.3 ±

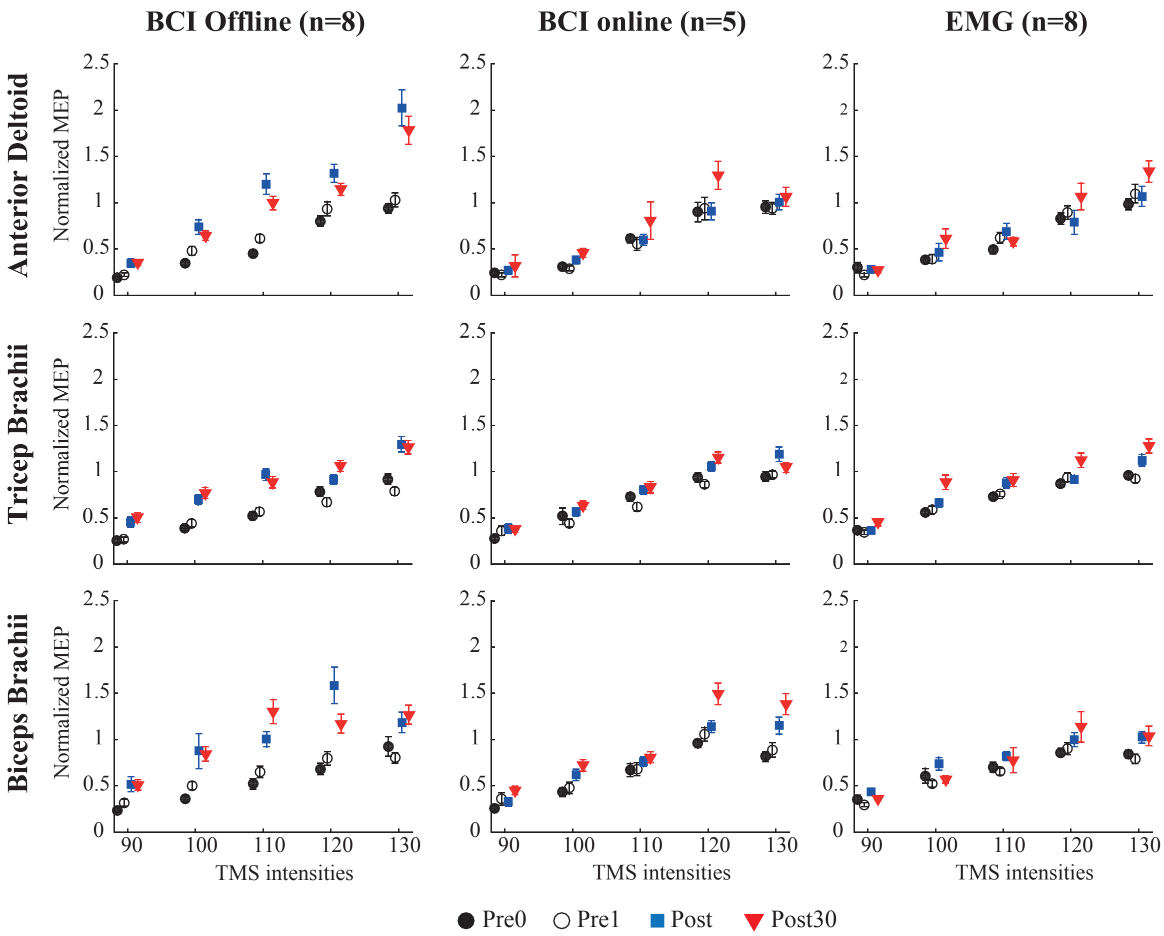


FIGURE 4.4: Measured input-output response of the MEP peak-to-peak value across the Pre0-, Pre-, Post- and Post30-assessment intervals for the three target muscles, Anterior Deltoid (first row), Triceps Brachii (second row) and biceps Brachii (third row), and each experimental intervention BCI offline (first column) BCI online (second column) and EMG (third column).

12.6% across all subjects, which is consistent with the reported BCI accuracy in literature (Ibáñez et al. 2014, Xu et al. 2014, Jiang et al. 2015).s

The input-output curve representing the average normalized MEP amplitude for the target muscles as a function of the TMS intensities is depicted in the second column of Figure 4.4 (central part). The statistical analysis of the intervention effects revealed that the MEP amplitude significantly differ at the assessment points ('Time' factor), with $\chi^2(3) = 9.44, p = 0.024$. However, there was found no statistically difference when considering the interaction of 'Time' with any of the other factors ($p > 0.05$). The post host test did not reveal significant difference between the assessment time intervals ($p > 0.05$) since the Bonferroni correction was applied for multi-comparison.

4.3.3 EMG

The muscle activation detector achieved an accuracy of 100%. Figure 4.5 shows the time with respect to the cue (beginning of 'Movement' state) in which the muscle activation was

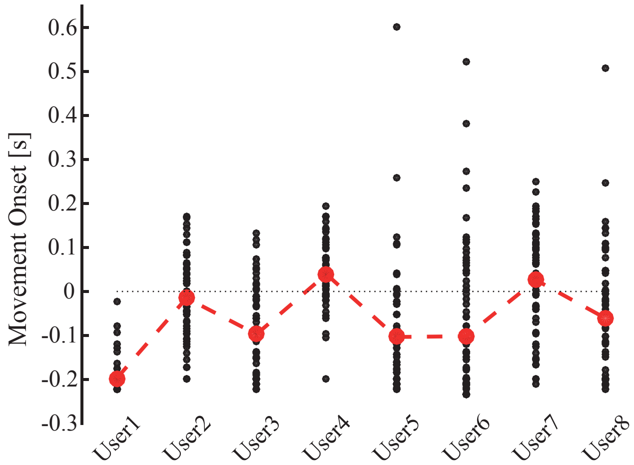


FIGURE 4.5: EMG movement onset detection time with respect to the cue event. Black circles represent individual detection (for each trial) while the red circles denote the average detection time.

detected for each subject (black circles) and the average detection time for each subject (red circles). On average, the onset of muscle activation occurred at -0.064 $\pm$ 0.079 seconds with respect to the cue event.

The third column of Figure 4.4 illustrates the group averaged peak-to-peak MEP value for all TMS intensities. When examining the changes in the MEP amplitude due to the intervention, the statistical test revealed that the MEP size differs significantly across the assessment intervals ($\chi^2(3) = 9.05, p = 0.029$), but no significance was found when considering the interaction 'Time' and the other factors ($p > 0.05$). Due to the Bonferroni correction, the post host test failed to find out significant difference between the assessment time interval ($p > 0.05$).

4.3.4 Control Experiments

Contrasting the results obtained in the experimental groups, for both control experiments (I and II), the MEP peak-to-peak value did not presented any significant difference across the assessment intervals ('Time'), with $\chi^2(3) = 0.482, p = 0.7$ for Control I and $x^2(3) = 2.75, p = 0.076$ for Control II. Similarly, no effects were detected when considering the interaction of 'Time' with the other factors ($p > 0.05$).

4.4 Discussion

In this chapter, an associative intervention was presented, in which the previously presented hybrid robotic system for rehabilitation of reaching was causally timed to the user's motor intent with the aim to promote neural plasticity. Remarkably, this is the first time that such an associative intervention shows distributed (more than one muscle) enhancement of the descending motor corticospinal projection (larger MEP size) to the assisted (AD, TB) and unassisted (BB) muscles of the arm.

4.4.1 A comparison of the interventions' effects: BCI offline, BCI online and EMG

When comparing the effects of the different strategies to associate the user's motor intent to the hybrid peripheral assistance, the EMG and BCI online strategies resulted in similar results, i.e. an increase in MEP size throughout the assessment time intervals, while more consistent and robust effects were achieved with the BCI offline strategy (see Figure 4.4). Although the EMG and BCI online intervention presented an increase in MEP amplitude immediately after and at 30' minutes follow up, significant effects were only revealed when considering the ANOVA factor 'Time' individually. In contrast, the results of the BCI offline strategy revealed more reliable and specific effects due the intervention. Indeed, specific effects were revealed for the Post- and Post30-assessment with respect to both pre-evaluation. Furthermore, principal effects were observed for 110%, 120% and 130% of the TMS intensity in target muscles (AD, TB and BB).

Associative paradigms, as the one hereby introduced, are a good example to show that plastic changes can be elicited in the central nervous system (Stefan et al. 2000, Kujirai et al. 2006, Thabit et al. 2010, Mrachacz-Kersting et al. 2012). Several studies in the literature showed evidence that the pivotal principle underlying this plastic change (LTP-like effects), is the consistent, precise and causal synchronicity between the artificially induced afferent volley reaching at the motor cortex and the movement-specific cortical activation (as the negative peak of the MRCP) (Mrachacz-Kersting et al. 2012, Xu et al. 2014, Niazi et al. 2012, Mrachacz-Kersting et al. 2015). This timing has been demonstrated to be critical for inducing LTP-like effects (Mrachacz-Kersting et al. 2012). Consequently, the less reliable intervention's effect obtained with the EMG intervention strategy when compared to the BCI offline one can be attributed to the non-optimal stimulus timing, since there exist an intrinsic delay between the cortical activation of movement and the detection of the EMG activity (Ethier et al. 2015).

The BCI offline strategy represents a practical solution for implementation a EEG-based BCI neuromodulation intervention. Under this approach, once the negative peak of the MRCP is determined, the time to deliver the peripheral stimulus is kept fixed regardless of the mental or engagement condition of the users. From the rehabilitation perspective, the BCI online strategy could be seen as more engaging by subjects and better suited for eliciting Hebbian-based neuroplasticity (Xu et al. 2014, Niazi et al. 2012, Ibáñez et al. 2017). The rationale underlying this strategy is the capability of providing a reliable and timely estimation of the user's movement intent, thus adapting the onset of the stimuli according to the inter-trial variability of the motor-related cortical processes (ERD and MRCP). However, the online detection of motor-related cortical activities, such as MRCP and ERD, is still challenging due to noise and artifacts in the raw EEG (Ethier & Miller 2015, Daly & Wolpaw 2008).

Although the BCI online detector implemented in this chapter presented similar accuracy to the data reported in literature (Xu et al. 2014, Niazi et al. 2012, Ibáñez et al. 2014, Ibáñez et al. 2014), the less reliable intervention's effects of the BCI online intervention compared with BCI offline can be attributed to the intrinsic latencies existing when implementing online detectors. Consequently, further attention must be paid to reduce latencies and so that a tight coupling between the hybrid assistance and the motor-related cortical processes can be achieved.

Results presented in this chapter show that the BCI offline strategy is a robust strategy to use BCI technology as a neuromodulation technique. Our results are in line with recent studies reported in literature (Mrachacz-Kersting et al. 2012, 2015). This method is mainly supported by the fact that the MRCP remains stable within one recording session (Mrachacz-Kersting et al. 2012). It was also demonstrated that there is no significant variation of this cortical process over different recording sessions (Mrachacz-Kersting et al. 2012). All in all, we can conclude that the more effective results achieved with the BCI offline intervention are likely due to the consistent activation of the primary motor cortex via neural information coming from other brain regions (MRCP generation (Lu et al. 2012)) and from the peripherally generated sensory feedback reaching the brain from stimulated target muscles of the arm. This precise and coherent activation is assumed to be responsible for the achieved significant increase of the corticospinal projections of target muscles (stimulated and non-stimulated muscles).

Evidence from literature and the results of the control groups demonstrated that plastic changes cannot be elicited in the absence of these coherent activations (Mrachacz-Kersting et al. 2012, Xu et al. 2014). In fact, performing the reaching task alone did not present any plastic change (control I). It is worth mentioning that the cue and the peak negativity of the MRCP do not necessarily occur at the same time (see Figure 4.3). Although the time occurrence of this peak (as a function of the cue) is repeatable within one subject between days (Mrachacz-Kersting et al. 2012), the variability across subjects is in the order of a few hundred milliseconds. This variability occurs due to the user's capacity to react to a cue. Again, by taking the time occurrence of the peak negativity, it was ensuring that the afferent stimulation arrived during the subjects' own intention to move.

It is well known that plastic changes can be elicited in the nervous system at different levels (e.g. cortical (Stefan et al. 2000) or spinal (Wolpaw 2007) level). Although no measure was performed to check the location of changes presented in this chapter, from evidence presented in literature it can be indicated that the plastic changes occur at supra-spinal (cortical) level (Mrachacz-Kersting et al. 2012, Xu et al. 2014, Niazi et al. 2012).

4.4.2 Comparison with similar studies presented in literature

Former studies consisting in the use of BCI technology as a neuromodulation system to promote upper-limb motor recovery have been based on sensorimotor rhythms, specifically

ERD and event-related synchronization (ERS) cortical processes (Ramos-Murguialday et al. 2013, Pichiorri et al. 2011, 2015, McGie et al. 2015, Kraus et al. 2016). In these studies, the SMR cortical activity was used to detect the subject's movement intent. The principal drawback of these methods is the need for numerous training sessions until subjects are able to control the signal adequately. However, MRCPs are characterized by occurring naturally as a person starts or imagines a movement, and thus, they do not require prior training (Garipelli et al. 2013, Jiang et al. 2015, Xu et al. 2014).

The study presented by McGie et al. compared the effects of the BCI- and EMG-based control of FES during grasping with healthy subjects using changes in MEP size as the primary outcome (McGie et al. 2015). In this study, an ERD-based online detector was used to estimate the movement onset during the BCI intervention. The authors found an increase in MEP size following BCI-FES and, especially, EMG-FES interventions. However, these changes were not significant. In contrast, the MRCP-based intervention hereby introduced clearly illustrates the appropriateness of using the MRCP to promote neural plasticity.

The somatosensory feedback elicited by FES (muscle spindles, mechanoreceptors, proprioceptive information, etc.), the execution of a multi-degree of freedom functional movement (high functional implication) and the voluntary action for executing the reaching task (voluntary effort) constitute the key features of our approach. In a previous BCI study with chronic stroke patients, the importance of the somatosensory feedback was emphasized (Ono et al. 2014). In this study, patients who received somatosensory feedback by an active hand orthosis triggered by brain signals (ERD events) led to functional improvements after therapy, while no changes were observed in the group of patients who only received visual feedback. The contribution of agonist and antagonist muscles and all other afferents involved during the execution of highly functional tasks, such as the reaching, might play an important role in relaying enough information to the cerebral cortex (Mrachacz-Kersting et al. 2015). Similarly, the effect of FES to elicit cortical plasticity during the execution of functional movements was shown to be enhanced when it was combined with volitional effort (Barsi et al. 2008). Therefore, the strong and distributed intervention effects observed with our BCI offline strategy can be attributed to the consistent integration of the voluntary action and the timed peripheral stimulation during the execution of a highly functional task, which results in inputs to the motor cortex with relevant agonist and antagonist information.

4.4.3 Implications for rehabilitation of upper-limb motor function

It is currently well accepted that sensorimotor and functional improvements have neurophysiological correlates resulting from plastic changes within the central nervous system (Beaulieu & Milot 2017, Stinear 2010). Indeed, the presence of MEPs in acute stroke subjects is an important prognosis factor for motor and functional recovery of both lower and upper limbs (Hendricks et al. 2003*a*,*b*, Pizzi et al. 2009, Piron et al. 2005). Noticeably, it was also found that functional recovery in acute stroke patients is directly correlated with the propensity of inducing LTP-like changes in the affected and unaffected motor cortex (Di Lazzaro et al.

2010). Similarly and more recently, Mrachacz-Kersting et. al. demonstrated that an associative BCI approach induced LTP-like effects measured as an increase in MEPs size, and remarkably, these plastic changes resulted in functional improvement of the lower limbs with only three interventional sessions (Mrachacz-Kersting et al. 2015). This evidence and the results presented in this chapter provide strong support for the use of neuromodulation techniques, as the associative BCI concept, to facilitate a well-adaptive plasticity and promote motor recovery after stroke. In line with these facts, it is hypothesized that the hybrid system presented throughout this dissertation could eventually lead to improvements of the upper limb motor function in stroke patients.

4.5 Conclusion of the chapter

The spontaneous brain plasticity (physiological and anatomical) occurring after a stroke represents one of the most important neurological processes underlying the recovery of motor functions. This important fact has changed the scope of current rehabilitation therapies, which explore alternative rehabilitative methods with the goal of exploiting the natural plasticity of the sensorimotor system, and hence, improving motor functional recovery. Pieces of evidence reviewed in this chapter support the potential of using a BCI as a neuromodulation system to elicit well-adaptive plasticity.

In this chapter, the hybrid assistance delivered during reaching was tightly coupled to the user's motor intent with the aim of eliciting neural plasticity (associative intervention). Three different approaches (BCI offline, BCI online and EMG) were implemented to verify the potential effects of the associative intervention. Results with healthy participants revealed positive intervention's effects in all implemented strategies since significant differences in MEPs size measure on target muscles were obtained after the interventions when considering uniquely the factor 'Time' (Pre vs Post and Pre vs Post30). However, stronger and more consistent intervention's effects were achieved with the BCI offline intervention. Remarkably, a distributed effect was achieved with this strategy (BCI offline), an increase in excitability of the corticospinal motor projections to the assisted (DA, TR) and unassisted (BB) muscles. Because of the efficacy of this intervention (BCI offline), it represents an efficient neuromodulation strategy for inducing plastic changes into the motor cortex.

In view of the work presented by Mrachacz-Kersting et al., in which changes in MEP size of the tibialis anterior muscle through three BCI associative interventional sessions were correlated with improvements in gait function (Mrachacz-Kersting et al. 2015), and the results presented in this chapter, a plausible hypothesis would be that the use of the hybrid robotic system based on the adaptive and associative assistance will result in improvement of the upper limb motor function in stroke patients. The study presented in the following chapter is planned to address this hypothesis.

Chapter 5

Clinical evaluation of the hybrid robotic system with the adaptive and associative assistance in post-stroke patients

Abstract

In the previous chapter, we showed that the causal association between motor cortex activation and the hybrid peripheral stimulation resulted in a facilitation of the cortico-muscular pathways. In this chapter, a pilot clinical study with a small cohort of port-stroke subjects is presented with the aim of proving the potential benefits of the hybrid robotic system. The interventional protocol consists of 12 training sessions along four consecutive weeks, in which post-stroke participants carried out reaching movements assisted with the hybrid robotic system. The BCI offline strategy was implemented to associate the user's intent to peripheral assistance. The analysis of the patient's ability for executing unassisted reaching tasks along sessions and the assessment of changes in patients' clinical scales before and after the intervention period were conducted to study the potential impact of the intervention. Complementarily, the user's perceived value of using the system as a rehabilitative tool was evaluated. Moderately affected participant showed an improvement between 40% to 60% in performance when executing unassisted reaching movement. Likewise, the manual muscle and the box and block tests showed important improvement of the affected upper extremity. Severely affected participants did not show improvement in the execution of unassisted reaching movements. Clinical scales revealed a marginal improvement in the muscle manual test. The overall patients' assessment of the therapy reflected their acceptance of the proposed interventional protocol. The results presented in this chapter demonstrate the feasibility of using the hybrid robotic system based on the adaptive and associative assistance for post-stroke rehabilitation.

5.1 Introduction

In preceding chapters, the theoretical basis and technological implementation of a hybrid robotic system for rehabilitation of reaching after stroke have been presented. Based on the requirements (Chapter 2), an adaptive FES-based controller to assist reaching movements was implemented (Chapter 3). Simultaneously, the feasibility of using the hybrid platform with stroke patients in the clinical setting was assessed, resulting in a great acceptability. Subsequently, an associative EEG-informed intervention was proposed with the aim of promoting a well-adaptive neural plasticity (Chapter 4). It was shown that the time precise pairing of motor cortex activation identified through innate voluntary cortical activity and the peripheral hybrid assistance leads to cortical plastic changes. Yet, the combined use of these concepts (adaptability and associativity) within the hybrid platform for rehabilitation of reaching has not been tested with post-stroke patients in a multi-session intervention.

Accordingly, the clinical evaluation of our hybrid robotic system is presented in this chapter. To this purpose, a pilot clinical study was proposed in order to validate the concepts and developments framed in this thesis. According to the classification of clinical trials for rehabilitation robots (Lo 2012, Dobkin 2009), a Category I - 'Pilot Consideration-of-Concept Study' is proposed in this chapter. This involves a small cohort of stroke patients without a control group with the goal of testing the clinical feasibility and the potential benefits of the hybrid platform. Moreover, this small-scale clinical trial seeks to evaluate the user's satisfaction when using the robotic platform during several sessions maintained in the time (12 session in one month). This evaluation will establish the basis and the direction to be pursued for a more specific and larger clinical study, beyond the aims of this thesis.

5.2 Methods

5.2.1 Participants

Five inpatients with stroke (age 47.6 ± 7.3 years; 3 males) admitted at the Centro de Referencia Estatal de Atención al Daño Cerebral (CEADAC) with a lesion in the area of the middle cerebral artery were recruited for this study. Detailed description of the patients' clinical data is presented in Table 5.1. All participants received oral and written information about the details of the experiment, and signed a consent form to participate and publish the data collected from the experimentation. All experimental protocols followed the Declaration of Helsinki and were approved by the Clinical Ethics Committee of the Centro Superior de Estudios Universitarios La Salle, Universidad Autónoma de Madrid.

TABLE 5.1: Clinical data of post-stroke patients participating in this study.

Patient	Gender	Age (years)	Diagnosis	Affected Side	Time since injury (months)
P1	Male	56	HS	Right	5
P2	Male	49	IS	Right	10
P3	Female	47	IS	Right	6
P4	Female	50	IS	Left	9
P5	Male	36	IS	Left	3

Meaning of acronyms. IS: Ischemic Stroke; HS: Hemorrhagic Stroke.

5.2.2 Inclusion and Exclusion criteria

Male and female stroke patients who met the following inclusion criteria were included in the study:

- age between 20 and 75 years old;
- individuals with unilateral stroke resulting in hemiparesis;
- sub-acute or chronic stroke, i.e. interval of at least 3 months (sub-acute) or interval of at least 6 months (chronic) from stroke onset to the time of enrollment;
- cognitive ability to follow instructions, thus, able to actively participate in the training protocol;
- with motor response to FES;
- signed the consent form.

Exclusion criteria for post-stroke participants were:

- non-stroke caused functional deficit of the arm/hand motor function or a history of more than one stroke clinically registered;
- with previous or current history of epilepsy;
- with other neurological disorder, such as Parkinson's disease;
- with implanted metal or electronic devices;
- pregnant women;
- with a severe cognitive dysfunction;
- with visual or hearing impairment;
- affected with a joint contracture or deformities in the affected upper-extremity that limits the movement of this extremity;
- does not tolerate FES;

- with skin lesion that may hinder or prevent the application of FES or the upper-limb exoskeleton;
- ingesting any medical drug that would prevent the application of standard rehabilitation;
- declined to sign the consent form.

5.2.3 Materials

The hybrid robotic system presented in Chapter 3 and Chapter 4 was used to assist the execution of reaching during the intervention sessions (see Section 3.2 and Section 4.2.2.2 for further details). The same EEG and EMG acquisition system with the same configuration, as explained in Section 4.2.2.1, were used to provide timed assistance with respect to the user's motor-related cortical process (associative assistance). Likewise, the same cue-based visual interface (as explained in Section 4.2.3.2) was utilized to guide the user throughout the training sessions and, to provide information regarding the arm position (shoulder and elbow) and the task's performance. Figure 5.1 shows one stroke participant performing the reaching exercise with our hybrid platform. The general scheme of operation, the principal functions and components are also shown.

5.2.4 Study design

The study proposed in this chapter consists of a rehabilitation therapy based on the hybrid robotic system to recover the arm motor function through training of reaching movements. Patients with stroke underwent this experimental therapy in addition to their usual therapeutic routine as prescribed and supplied by clinical experts at CEADAC.

The study protocol was registered retrospectively in the ISRCTN register with study ID ISRCTN12843006[1]. he general structure of this clinical pilot study protocol is shown in Figure 5.2. The study consists in three principal stages: the initial assessment, the invention and the final assessment. These stages are following explained.

5.2.4.1 Initial assessment (Ev1)

The initial assessment consisted in two separated sessions: assessment and MRCP's reliability, which took place in different days. The assessment session was aimed to obtain the baseline motor and functional conditions of the stroke patients participating in this study (see Section 5.2.5.1). While the MRCP's reliability session was conceived to introduce the system operation to the users, to ascertain the suitability of the patients for using the hybrid

[1]Use of neuromodulation system and assistive devices for rehabilitation of upper limb motor function after stroke (ISRCTN12843006); DOI: 10.1186/ISRCTN12843006. Available: https://goo.gl/6MqqXd (last visit: 15/08/2017).

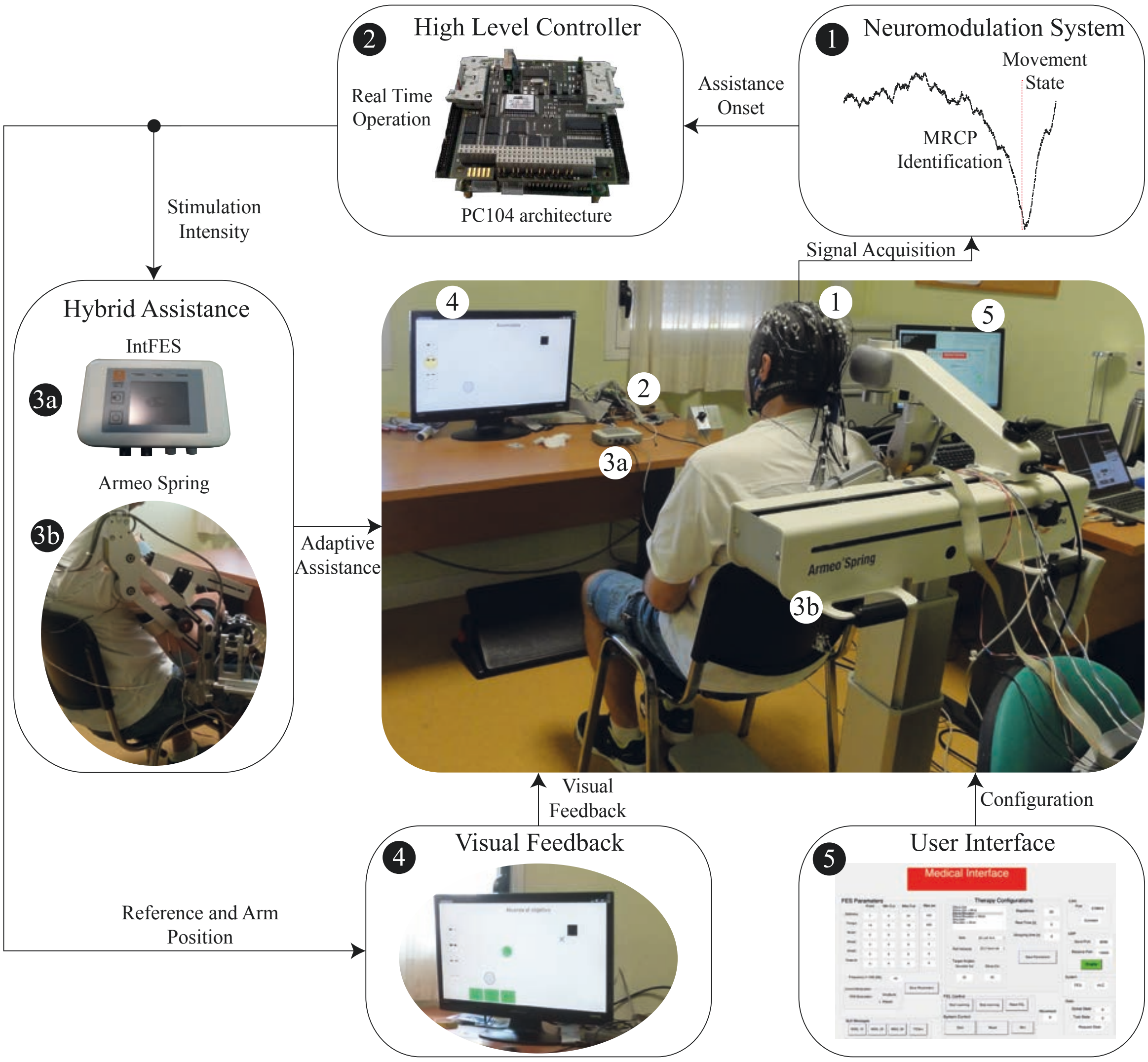


FIGURE 5.1: General overview and components of the hybrid robotic system. 1) Neuromodulation system based on a EEG brain-computer interface to estimate the stimulation onset (negative peak of the movement-related cortical potential). 2) High Level Controller to provide the adaptive assistance. 3) Hybrid Assistance composed of the IntFES stimulator (3a) and the ArmeoSpring (3b). 4) Visual Feedback interface to guide user's during the interventional session. 5) User Interface to configure system's parameters (stimulation threshold, range of movement, movement repetitions).

robotic system and to verify the feasibility in determining the negative peak of the MRCP during the execution of reaching movement with the robotic system. To this end, two tasks were performed during the reliability session. First, the system optimal configuration was found for each subject. These parameters were recorded to facilitate a faster preparation process in subsequent interventional sessions. The following parameters were individually determined: the exoskeleton segments length according to the patient's arm, the gravity support level, the maximum stimulation current (FES intensity) and the maximum range of motion. All these parameters were found by following the same steps introduced in section Section 3.4.1.1 and Section 4.2.3.2 for system adjustment.

Following to this procedure, patients were equipped with the EEG system and were asked to perform 2 blocks of 20 movements each without FES assistance. All subjects were asked to follow the instructions shown in the screen, which cued them to perform reaching movements. The recorded EEG signals were used to verify the feasibility of identifying the MRCP's feature (see Section 4.2.3.2).

5.2.4.2 Interventional sessions (Se1-12)

The intervention stage comprised twelve sessions; this is, three sessions per week through four consecutive weeks (see Figure 5.2). In accordance to the results presented in Chapter 4, the BCI offline strategy was used in this clinical trial. Consequently, the same steps introduced in section Section 4.2.4.1 were applied (see intermediate rectangle in Figure 5.2). In brief, after instrumenting the patients with the EEG system, they were asked to carry out 30 calibration movements without FES assistance (BCI calibration). In case a patient was not able to execute the reaching movement, he/she was instructed to imagine the arm movement since the MRCP was demonstrated to be generated also when a movement is imagined (Niazi et al. 2011, Shakeel et al. 2015, Niazi et al. 2013). The recorded EEG signals during these calibration movements were used to the time at which the negative peak of the MRCP occurred (in average) with respect to the beginning of the 'Movement' state.

During the training step (lower rectangle in Figure 5.2), all participants carried out 60 to 80 reaching movements divided in runs of 20 movements each. During training, the hybrid assistance was delivered at the instant of time when the negative peak of the MRCP occurs minus 25 milliseconds.

At the end of all training sessions, patients were asked to attempt three unassisted movements to observe the evolution of their motor capability (Evaluation). For these unassisted reaching movements, a period of three seconds was used in all sessions to accomplish the task. The target position was defined on the first training session and was kept fixed along all sessions.

5.2.4.3 Final evaluation (Ev2)

The final assessment was conceived to assess the final patients' conditions and their subjective evaluation. This stage is composed of a single assessment session, which was carried out in the subsequent week after the end of the training stage. In this session, the same evaluation procedure as in assessment session prior the intervention (Ev1) was applied (see Section 5.2.4.1).

5.2.5 Outcomes measures

Clinical scales were used as the primary outcome measure. Complementarily, kinematics data were used to evaluate the effects of the intervention. The patients' satisfaction and their perceived value were also assessed.

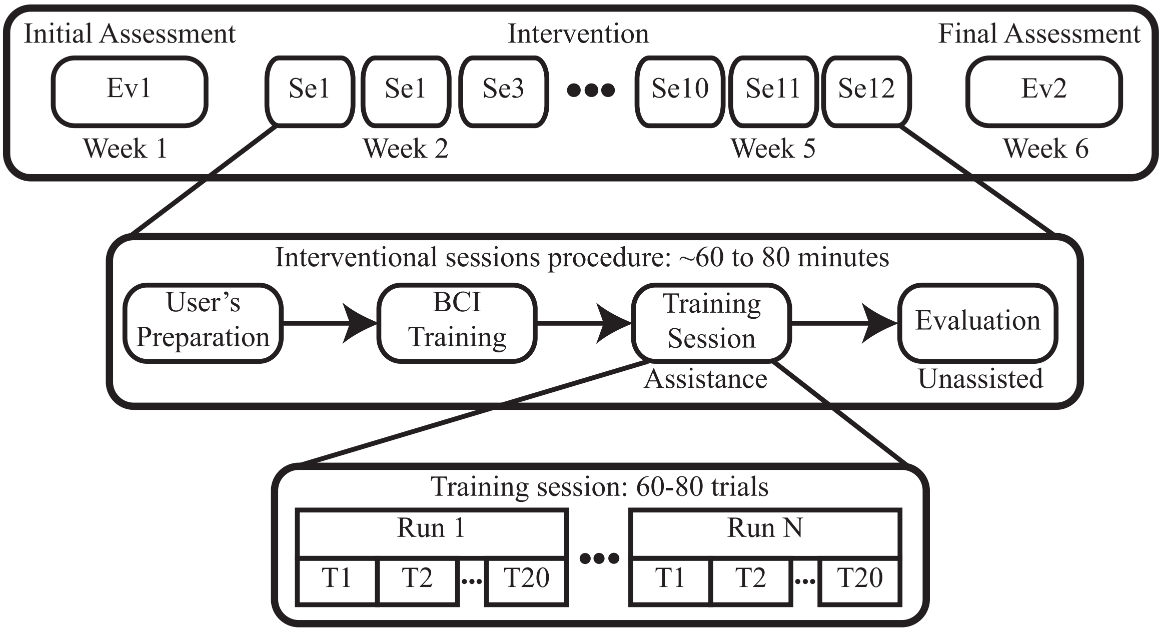


FIGURE 5.2: Description of the pilot study protocol designed to evaluate the hybrid robotic system. Ev: evaluation; Se: session. T: trial.

5.2.5.1 Clinical Scales

Clinical experts performed motor and functional tests in the first (Ev1) and sixth (Ev2) weeks to verify patient's improvements.

The upper-limb muscles weakness was assessed using the manual muscle test (MMT). This test can be effective in differentiating true weakness from imbalance or poor endurance. It is an integral part of the neurologic exam, especially for patients with stroke, brain injury, spinal cord injury, and several other neurological problems (Naqvi & Sherman 2017). This method involves testing key muscles from the upper and lower extremities against the examiner's resistance. The score is given following the Medical Research Council Manual Muscle Testing scale, where the patient's strength is graded from 0 (No muscle activation) to 5 (Muscle activation against examiner's full resistance, full range of motion) (Lamb 1985). In this study, only the muscles involved the flexion/extension movement of the shoulder, elbow and wrist joints were evaluated.

The modified Ashworth scale (MAS) was used to quantify the upper-limb muscle spasticity in recruited stroke participants. The MAS consists of a 6-point scale ranged from 0 to 4, which adds a 1+ scoring category to indicate resistance through less than half of the movement. Lower scores (0) represent normal muscle tone and higher scores (4) represent spasticity or increased resistance to passive movement (Bohannon & Smith 1987). As the hybrid robotic system is focused on rehabilitation of reaching movement involving proximal joints of the upper-extremity, the MAS of lateral deltoids (LD), AD and TB muscles are reported.

The box and block test was considered to measure the unilateral gross manual dexterity of the impaired arm (Mathiowetz et al. 1985). This test consists in transporting wooden blocks from one compartment to another, and the scoring method is the number of blocks transported within a period of 1 minute.

5.2.5.2 Kinematic data

The three unassisted movements (evaluation) attempted at the end of each training session are used to quantify the evolution of the kinematics pattern during the reaching execution. For each session, the RMSE of each joint (shoulder and elbow) and the task's performance is calculated (see Section 3.4.2.2 for further details). A best-fitting linear regression across the RMSE and performance score is applied to examine its trend along sessions.

5.2.5.3 Satisfaction assessment

Similar to the evaluation performed in Chapter 3, the QUEST and SAM tests are considered to evaluate the user's satisfaction, perceived comfort, and acceptability of the hybrid platform after the interventional sessions.

In brief, the QUEST is an instrument specifically designed to measure satisfaction for a broad range of assistive technology devices in a structured and standardized way (Demers et al. 2002). The test includes 12 items, which are related to device characteristics (n = 8) and assistive technology services (n = 4). The scoring method rates from 1 (not satisfied at all) to 5 (very satisfied). Only the items related to the device characteristics were used for this study, due to the lack of external assistive services. Therefore, the maximum possible score was 5 for each item, and 35 for the total scale.

Self-Assessment Manikin (SAM) is a non-verbal pictorial assessment technique that directly measures the pleasure, arousal, and dominance associated with a person's affective reaction to a wide variety of stimuli (Hodes et al. 1985). For pleasure, SAM ranges from a smiling, happy figure to a frowning, unhappy figure; and for arousal, from sleepy with eyes closed to excited with eyes open figure. The dominance dimension represents changes in control with changes in the size of SAM: a large figure indicates maximum control in the situation. The subject can place a mark over a continuous nine-point scale.

5.3 Results

Data presented in this section is based on three stroke participants (P1, P2, and P5), since two participants (P3 and P4) left the experimental training due to external reasons. One participant (P3) developed a neuropathic contracture in muscles of the affected arm after the second week hindering him to carry out reaching movements and receiving electrical stimulation. The other subject (P4) left the study at the third week of the intervention due to personal problems.

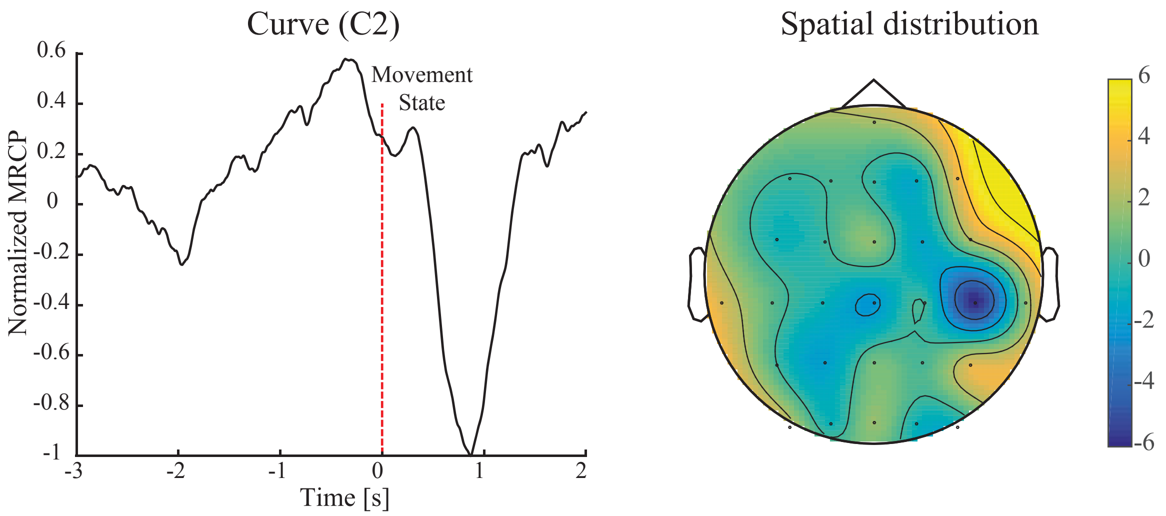


FIGURE 5.3: Motor-related cortical potential (MRCP) of the P1 patient. The MRCP's curve of the most representative EEG channel (C2) is shown in the first column while the spatial distribution of the MRCP is illustrated in the second column. To optimize visualization, baseline was defined within [-3, -2] seconds with respect to the movement state (vertical red line at t = 0).

For a better understanding of the data presented in this section, the three stroke participants who completed the full experimental protocol (P1, P2 and P5) were divided into two groups according to their level of motor impairment (severe and moderate arm motor impairment). Participants scoring 0 or 1 in the MMT test, indicating that they cannot move their arm voluntary at all or have very limited voluntary movements, were classified as severe. Participants scoring higher than 1 in the MMT test were classified as moderate. Consequently, stroke patients P2 and P5 were classified into the severe group, while P1 was allocated to the moderate group.

5.3.1 Patient with moderate arm motor impairment: P1

5.3.1.1 Feasibility of the MRCP

The negative peak of the MRCP was used to establish the instant of time with respect to the visual cue in which the hybrid assistance is delivered. Figure 5.3 shows the average MRCP of participant P1 during the MRCP's reliability session of the initial assessment and its spatial distribution. Fieldtrip's *ft_multiplotER* and *ft_topoplotER* functions in Matlab (The Mathworks Inc., Natick MA, USA) were used to obtain the patterns (Oostenveld et al. 2011). The negative peak of the illustrated MRCP occurs at 0.8672 seconds after the visual cue (movement state). For this individual stroke patient, the averaged negative peak event of the MRCP across all sessions occurred at 0.9512 ± 0.0664 seconds with respect to the visual cue. Thus, for this individual subject, the hybrid assistance was delivered at 0.9296 seconds after the movement state.

TABLE 5.2: Changes in clinical scales between pre- and post-intervention assessments.

Participant	MMT						MAS						B&B	
	Shoulder (Flex/Ext)		Elbow (Flex/Ext)		Wrist (Flex/Ext)		Anterior Deltoid		Lateral Deltoid		Triceps Brachii			
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
P1	2/2	2/2	2/2	2/2	2/2	4/4	0	0	0	0	1	0	7	13
P2	0/1	1/1	1/1	1/0	0/0	0/0	3	3	3	2	3	3	-	-
P5	0/1	1/2	0/0	2/1	0/0	1/0	3	3	3	3	3	3	-	-

Meaning of acronyms. MMT: manual muscle test; MAS: modified Ashworth scale; B&B: Box and Block.

5.3.1.2 Changes in Functional Scales

The first part of Table 5.2 summarizes changes observed in the three examined functional scales (MMT, MAS and Box and Block) for patient P1 after training. In the MMT, the P1 patient achieved a representative increase of 2 points in muscles involved in wrist flexion and extension movements, while no changes were observed in proximal joints (shoulder and elbow) of the impaired arm. The MAS revealed an improvement in the TB muscle (from 1 to 0), attaining the highest possible score (0 indicates a normal muscle tone). It is worth mentioning that both the AD and MD muscles attaining maximum score in the MAS before the intervention. Remarkably, the box and block test revealed an important improvement in hand dexterity, since the patient managed to move five additional wooden blocks after the intervention with respect to the initial assessment (from 7 blocks to 13).

5.3.1.3 Analysis of the kinematics

Figure 5.4a shows the time-averaged trajectory of arm joints (shoulder and elbow) across the three unassisted reaching movements corresponding to the first and last training sessions. In the first session, the P1 patient achieved a RMSE of $5.81° \pm 3.2°$ and $9.11° \pm 0.6°$ for shoulder and elbow respectively. At the last session, the RMSE was reduced to $3.94° \pm 2°$ and $8.48° \pm 3.4°$ for each joint respectively. The estimated linear fitting curves from the RMSE values across the sessions resulted in slopes of -0.11 and -0.32, indicating a decreasing trend of the error trajectory as the session proceeded. Similarly, Figure 5.4b depicts the evolution of the task's performance when executing the unassisted reaching movement along the sessions. The fitting curve (red line) across all values resulted in a slope of 2.02, indicating an improvement from 40% to 63% in task's performance.

5.3.2 Patients with severe arm motor impairment: P2 and P5

5.3.2.1 Feasibility of the MRCP

Like in the case of the moderate group, the negative peak of the MRCP was used to establish the instant of time with respect to the visual cue in which the hybrid assistance is delivered for patients in the severe group (P2 and P5). Although these patients cannot move their affected arm or have a very limited capacity for moving it voluntary, it was possible to produce the MRCP when they imagined a reaching movement (Niazi et al. 2011, Heremans

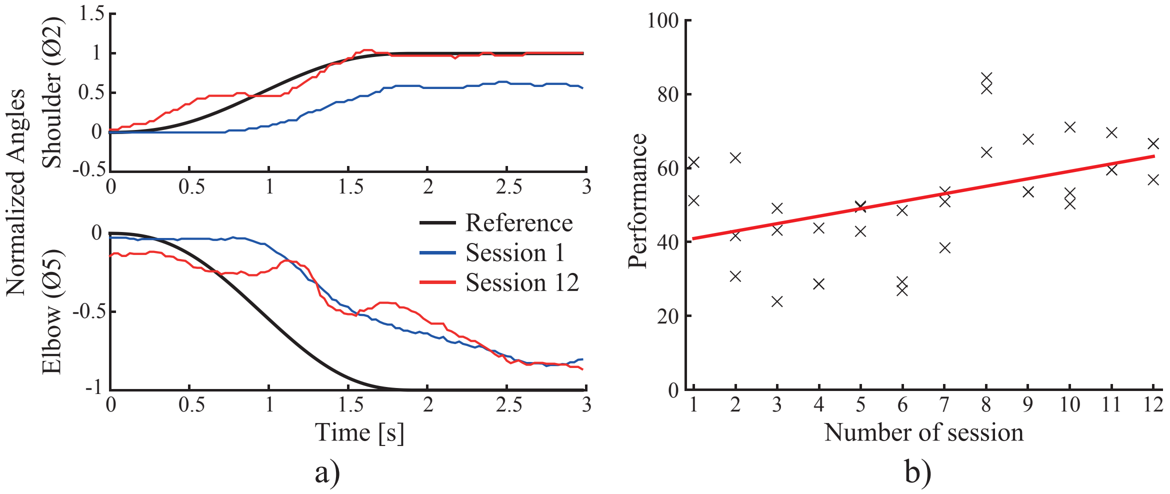


FIGURE 5.4: a) Representative example of the tracking accuracy during the execution of the unassisted movement. Joints trajectories represent the time-averaged response of the first and last interventional sessions. b) Achieved task's performance score during the execution of the unassisted reaching movements along sessions. The solid line represents the best linear fitting indicating the trend of the score. See Section 3.4.2.2 for the task's performance score.

et al. 2009, do Nascimento & Farina 2008). Figure 5.5 shows the MRCP curves from the most reactive EEG electrode and the spatial distributions for both patients during the MRCP's reliability session of the initial assessment. Plots were obtained using the same fieldtrip's functions previously cited (see Section 5.3.1.1). As shown in the figure, the occurrence of the negative peak in the MRCP curve varies between both patients, as well as its spatial distribution. For P2, the negative peak of the MRCP (upper plot in the first column) occurs at 0.09766 seconds after the visual cue (movement state). When analyzing this peak along the intervention sessions, this event occurred in average at 0.0583 ± 0.0435 seconds with respect to the movement state. The negativity peak in the plotted MRCP curve of patients P5 (lower plot in the first column) took place at 0.7344 with respect to the cue. For this subject, the average negative peak across all sessions happened at 0.5918 ± 0.2183. Consequently, the hybrid assistance was delivered in average at 0.0333 and 0.5668 for each patient respectively.

5.3.2.2 Changes in clinical scales

The second part of Table 5.2 shows the changes observed in clinical scales for subjects classified within the severe group. When analyzing the results of the MMT, it is observed that patient P2 achieved an improvement of one point for the shoulder flexion after the intervention, whereas no improvements are observed in the remaining joints. When examining the score in the same clinical scale for patient P5 after the training sessions, an improvement for shoulder flexion and extension (one point each), for elbow flexion and extension (two and one point respectively) and for wrist flexion (one point) can be observed. The MAS scale revealed no changes for both patients in any muscles. None of these patients could perform the box and block test either before or after the intervention.

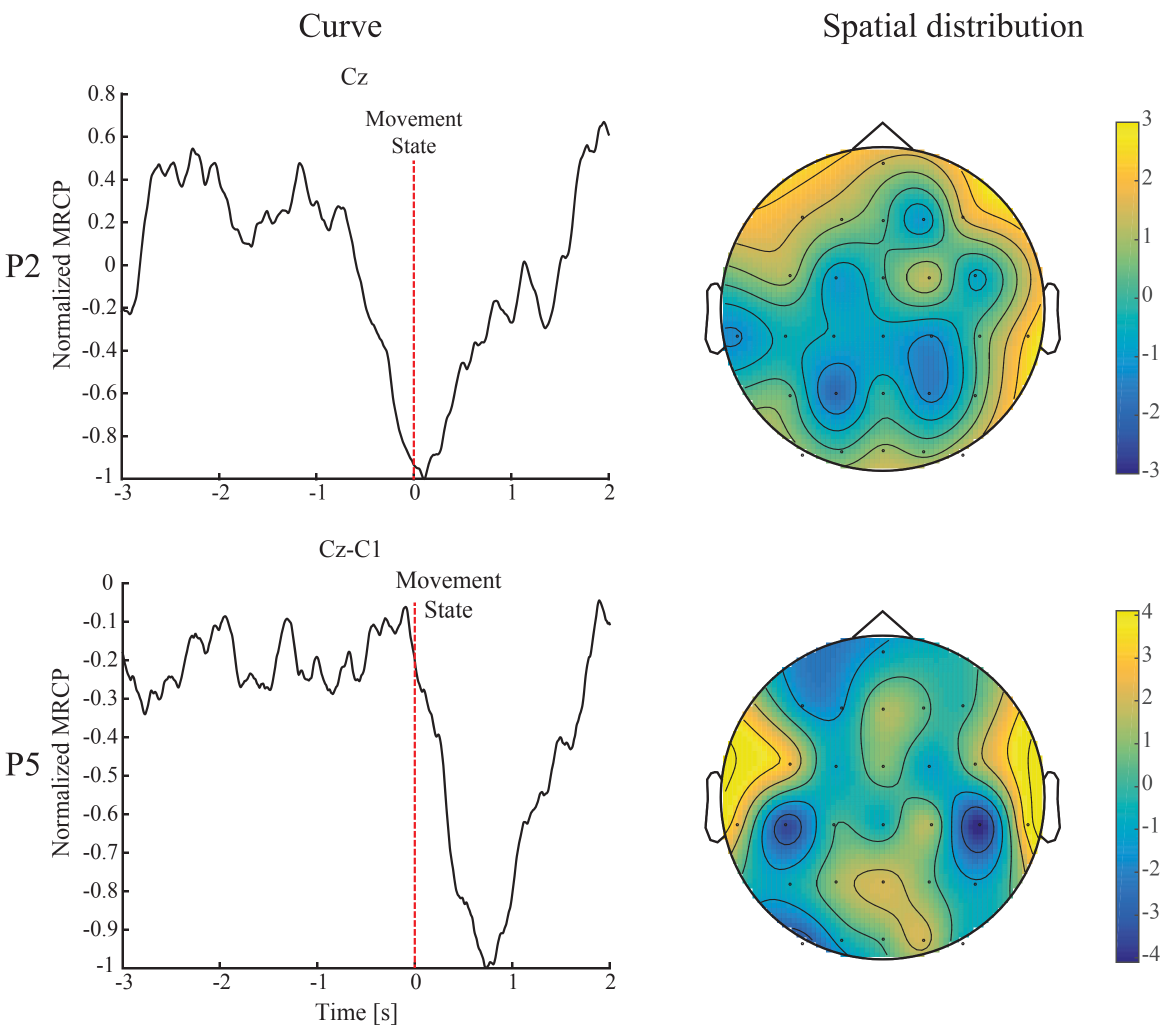


FIGURE 5.5: Motor-related cortical potential (MRCP) of patients P2 and P5. The firs column illustrates de MRCP's curve of the most representative EEG channels, while the second column portrays the spatial distribution of the MRCP. To optimize visualization, baseline was defined within [-3, -2] seconds with respect to the movement state (vertical red line at t = 0).

5.3.2.3 Analysis of the kinematics

A representative example of arm kinematics during the execution of the unassisted reaching task is depicted in Figure 5.6a. The blue and red lines represent the time-averaged trajectory of the shoulder and elbow joints corresponding to the first and last training sessions respectively. As it can be observed (the first column of the figure) patient P2 could neither perform voluntary movement with his affected arm before nor after the intervention. The second column of the same figure shows slight differences in the tracking accuracy between the first and last session corresponding to patient P5. In average, a RMSE value of $11.4° \pm 2.78°$ and $38.5° \pm 3.42°$ was registered at each respective joint (shoulder and elbow) in the first session, while in the last session values of $10.02° \pm 1.3°$ and $36.07° \pm 2.35°$ were achieved. Indeed, the inferred linear fitting curve from the RMSE values for patient P5 across sessions resulted in slopes of -0.47 and -0.0079 for shoulder and elbow respectively, indicating a slight decreasing trend over the sessions. Figure 5.6b shows the task's performance of both patients against

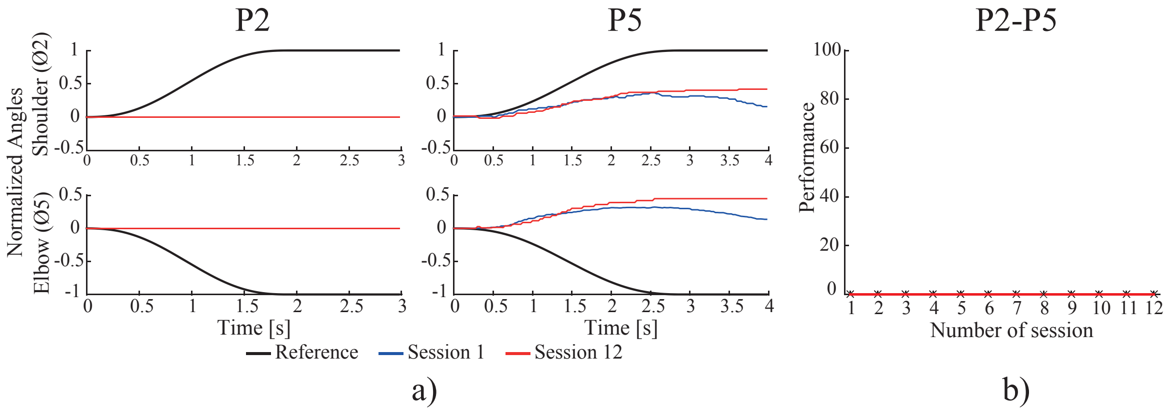


FIGURE 5.6: a) Representative example of the tracking accuracy (P2: first column; P5 second column) during the execution of the unassisted movements. Joints trajectories represent the time-averaged response corresponding to the first and last interventional sessions. b) Achieved task's performance score of both patients (P2 and P5) during the execution of the unassisted reaching movements along sessions.

TABLE 5.3: Satisfaction score of post-stroke patients

Quest. How satisfied are you with the system features?	P1	P2	P5	Mean
1. The dimensions (size, height, length, width) of your assistive device?	5	4	4	**4.33**
2. The weight of your assistive device?	5	3	4	**4**
3. The easy in adjusting (fixing, fastening) the parts of your assistive device?	5	3	5	**4.33**
4. How safe and secure your assistive device is?	5	4	5	**4.67**
5. How easy it is to use your assistive device?	5	4	4	**4.33**
6. How comfortable your assistive device is?	5	4	4	**4.33**
7. How effective your assistive device is (the degree to which your device meets your needs)?	5	4	4	**4.33**
SAM assessment				
1. Pleasure	1	5	3	**3**
2. Arousal	5	5	5	**5**
3. Dominance	5	5	7	**5.67**

QUEST: Quebec User Evaluation of Satisfaction with Assistive Technology 2.0; SAM: Self-Assessment Manikin. QUEST scale: 5 (very satisfied), 4 (satisfied), 3 (more or less satisfied), 2 (not very satisfied) and 1 (not satisfied at all). SAM depicts the pleasure, arousal and dominance dimension with a graphic character arrayed along a continuous nine-point scale.

the training sessions. Due to the lack of voluntary movement by patient P2 and the limited range of movement achieved by patient P5, the score remained at the minimum value (0%) in all sessions.

5.3.3 Usability assessment: users' satisfaction

The users' satisfaction is reported globally, thus, without considering any distinction regarding the severity of participants. Table 3.4 summarizes the evaluation of the users' satisfaction after participating in the clinical pilot trial. It can be noted that in the QUEST questionnaire, the hybrid robotic system obtained a score higher than four in all items (with maximum score of 5). The overall user's satisfaction achieved an average score of 30.33 out of 35 points. It is worth mentioning that the safety feature obtained the higher score (4.66 over 5), while the weight item got the lower score (4 over 5). The SAM survey scored an overall average value of 3 in pleasure, while the dominance and arousal aspects were set over the middle of the scale with a score of 5 and 5.67 respectively (maximum score is give at 9).

5.4 Discussion

The pilot clinical study seeks to evaluate the usability, safety and the potential rehabilitation effects of our hybrid robotic system for training reaching movements. To our knowledge, this is the first time an upper-limb hybrid robotic system based on adaptive and associative assistance have been tested clinically in a training protocol with post-stroke patients. On the one hand, the adaptive assistance adjusted the required level of support online during training. This adjustment strategy provides a tailored level of assistance since the delivered current intensity is personalized to successfully complete the reaching task. On the other hand, the adaptive assistance was causally delivered with respects to movement-related cortical processes (MRCP) with the aim of promoting plasticity (associative concept). Overall, it has been proven the feasibility of implementing this integral concept embedded in an upper-limb robotic platform in clinical trials with post-stroke subjects. Moreover, the clinical scales and the user's satisfaction evaluations suggest the training potential and its acceptability.

One of the most relevant features verified in this study was the reliable identification of the MRCP curve in post-stroke patients with different levels of arm motor impairment. This is a key aspect to promote plasticity since it allows the coherent and consistent association of the assistance to the user's intent (see results from Chapter 4). The MRCP reflects a regulatory mechanism which takes place during planning and execution of a motor task (Jankelowitz & Colebatch 2002, Fang et al. 2007). The early components of the MRCP are associated with preparation for movement execution (planning), while the cognitive effort with the negativity peak of the curve (Daly et al. 2006, Fang et al. 2007). Pieces of evidences presented in literature have shown that post-stroke subjects present MRCP pattern alteration compared to the patterns generated in healthy subjects in terms of spatial and temporal distributions (Fang et al. 2007, Daly et al. 2006, Yilmaz et al. 2013). Thus, the MRCP tends to show a delayed peak hundreds of milliseconds after the actual onset of the movement coupled with abnormal elevated amplitude. These issues in combination with the innate heterogeneity brain lesions may explain the delayed occurrence of the MRCP in P1 and P5 participants. In spite of these shortcomings, the MRCP could be determined even in those patients with a severe motor impairments. It is known that patient's ability to accurately perform a motor task is significantly enhanced when a cue is provided (Heremans et al. 2009, Mrachacz-Kersting et al. 2015). Therefore, the cued approach of the study described in this chapter can be considered appropriate for implementing an associative intervention.

Apart from the analysis of the arm's kinematic data recorded along the sessions and the assessment of clinical scales, no other neurophysiological analysis was considered in this study. Due the small cohort of patients participating in this study, changes in the EEG signal after the intervention period such as the MRCP (cognitive planning and effort feature), the ERD (laterality) or power in motor cortical rhythms during rest could not be explored. In order to examine such changes and given the high intra-patient variability in the EEG information across days, a large sample of patients is required to obtain consistent results (Shenoy et al. 2006, Ibáñez et al. 2017). As it was shown in the previous chapter, changes in cortical excitability derived from non-invasive TMS brain stimulation are better suited to assess neurophysiological changes (neural plasticity). Yet, due to the inherent physiological variability of the corticomotor system, larger sample size is also required in order to increase the statistical power and obtain reliable results (Lewis et al. 2014, Rossini et al. 2015). Considering that the primary objective of this study is to test the clinical feasibility and the potential rehabilitative benefits of the hybrid robotic system considering a small cohort of patients, the verification of neural plastic changes is out of the scope of this study. This important aspect is planned to be addressed in future works.

Changes in arm kinematics were observed in the patient with moderate arm motor impairment (P1), in terms of task's performance and tracking accuracy (measured with the RMSE for each joint along sessions, see Figure 5.4). In the severe group, one patient (P5) achieved marginal improvement in tracking while the other patient (P2) did not show any change. Indeed, the improvement of patient P5 was very slight since it was not reflected in the measure of the task's performance, where both patients were rated with the minimal score (see Figure 5.6). The limited range of the arm movement and the lack of sensitivity of the task's performance scale may be the reasons why the patient P5 was rated with the minimum value.

As to functional changes, similar results are observed. The patient with moderate arm motor showed improvements in all clinical scales (see the first part of Table 5.2). The estimation of the minimal clinically important difference (MCID) of the MMT is not reported in literature. However, on the basis of clinical experience and estimates reported for similar outcome measures in different domains, the MCID was set at 10% of the total range of the scales (Van Der Lee et al. 1999). Consequently, the scores in wrist flexion/extension obtained with patient P1 immediately after the intervention (an improvement in 2 points) can be considered much higher than the MCID. Although the same participant managed to move five additional blocks with respect to the measure before the intervention, this improvement almost attained the minimal detectable change (5.5 blocks) reported for chronic post-stroke survivors (Chen et al. 2009). In the case of patients with severe motor condition (P2 and P5), minimal improvements were detected in the MMT (one point). Evidence presented in literature suggests that to obtain clinically relevant results with this group of subjects (severely affected) longer periods of training with intensive consecutive sessions are required (12 to 16 weeks, 4 to 5 sessions per week) (Popovic et al. 2005, Thrasher et al. 2009). Although the clinical results hereby presented cannot be generalized, these preliminary results are consistent with other robot-based studies in which moderately affected patients were more responsive to robot-aided therapy than severely affected patients (Ferraro et al. 2003, Stein et al. 2004). Similarly, Popovic et al. showed that post-stroke subjects with moderate and severe arm functional conditions responded positively to FES-based therapy (Popovic et al. 2002); but, the group with moderate motor function improved significantly their ability to carry out functional tasks, while the severe affected did not. This differential responsiveness can be explained by the fact that high initial motor function likely promotes positive stroke-rehabilitation outcome in general (Buma et al. 2013, Krakauer 2005, Kwakkel et al. 2003, Di Lazzaro et al. 2010). Therefore, it can be suggested that the selection criteria of post-stroke subject enrolled to robotic and FES therapies constitutes an important factor to exploit the maximum benefits of these novel therapies.

With respect to the satisfaction assessments, the QUEST survey shows a great users' satisfaction. When comparing the score of this questionnaire obtained in this chapter (30.33) with the one obtained in Chapter 3 (34.67), a slightly lower score can be observed. This can be likely explained by the relative lower number of sessions in Chapter 3 (only 2 experimental session). In general, a great acceptance was obtained in all aspects, indicating the feasibility of complementing standard rehabilitation therapies with the use of the hybrid robotic systems.

The principal limitation of this study is the reduced number of enrolled patients and the lack of a control group. However, the feasibility of using the system in real clinical settings is demonstrated. Future comprehensive studies should be conducted to prove the potential clinical benefits of the system to complement standard rehabilitation therapies.

5.5 Conclusion of the chapter

The concepts and the technical developments presented throughout this document have been validated in a real clinical pilot study with a small cohort of post-stroke subjects. This study is, to our knowledge, the first one in which the use of a upper extremity hybrid robotic system based on an adaptive and associative assistance was conducted with stroke patients along several sessions with the aim of verifying it potential rehabilitative effects.

The results presented here suggested the feasibility of implementing the associative concept for rehabilitation of arm motor function clinically. Even though the MRCP curve and its spatial distribution differ between subjects, it could be identified in both moderate and severe arm motor impaired participants. The reported improvements in the clinical scales and in the arm's kinematics, in unassisted reaching tasks, reflect the potential rehabilitative effects of the adaptive and associative concepts for rehabilitation of the arm's motor functions. In line with studies reported in literature, subjects with moderate arm motor impairment may benefit more from the therapy hereby proposed. It is believed that subjects affected with a severe arm motor impairment could experience further improvements by increasing the number of training sessions. In general, recruited stroke patients tolerated the hybrid robotic therapy and no adverse effects were reported. From the acceptability standpoint, all system features showed to be suited for clinical interventions and fulfilled the expectations of users.

Finally, it is worth mentioning that the rehabilitative potential should be taken carefully since this study involves a small cohort of patients and lacks a control group.

Chapter 6

Conclusions and future works

Abstract

This chapter outlines the most relevant contributions presented along this dissertation, as well as the role that these contributions played for the achievement of our objectives. In addition, the scientific publications resulting from this work are listed. Finally, the chapter finishes with a brief outline of the future work emerging from the research line presented in this work.

6.1 Contributions

The work presented in this dissertation was aimed at the design and validation of a hybrid robotic system providing an adaptive and associative assistance for rehabilitation of reaching in post-stroke subjects. In order to reach this objective, we elaborated on the requirements for upper-extremity motor rehabilitation in patients with stroke, the technical and clinical challenges of hybrid robot-based therapies focused on the upper-limbs, the combination and applicability of robot and FES strategies to assist the execution of reaching movement and, the proposal and evaluation of novel algorithms for personalizing the assistance considering time and intensity factors. We consider that all these activities contributed significantly to the field of biomedical and neural engineering, rehabilitation robotics, functional electrical stimulation and neurorehabilitation.

The major contributions of this dissertation are summarized as follows:

- We conducted the first critical review of the state of art of hybrid robotic system for rehabilitation of upper-limb motor function in post-stroke subjects. Both, technical and clinical aspects were considered and the main challenges of this novel rehabilitative method were identified. Some of these challenges were addressed in this dissertation.
- We conducted the design of a fully integrated upper-limb hybrid robotic system for assisting the execution of unconstrained reaching movement. This platform combined several subsystems, representing a comprehensive rehabilitative tool. The platform allows acquiring information from different types of noninvasive sensors (EEG, EMG and transducers embedded in the exoskeleton) to characterize the planning and execution processes of reaching movements (with cortical and kinematic features). The platform was also capable of on-line processing the acquired data and of generating an adequate feedback.
- We led to the implementation and validation of the FEL controller into a hybrid robotic system to dynamically adjust the level of assistance according to the users' motor capabilities. It is the first time that the FEL controller was tested in healthy and post-stroke subjects to drive the execution of a multi-degree of freedom upper-limb movements.
- The development of a cue-based EEG and EMG neuromodulation system to causally associate the hybrid assistance peripherally applied to the user's intent during the execution of functional reaching movements. Three different associative strategies (BCI offline, BCI online and EMG) were critically compared, and the importance of a precise timing association was elucidated.
- We attained the first demonstration that precise temporal association between motor cortex activation and adaptive hybrid assistance during the execution of functional motor tasks of the upper-extremity elicited distributed neural plasticity. Remarkably,

the associative intervention's effect resulted in an improvement of the descending motor corticospinal projection to the assisted and unassisted arm muscles (AD, TB and BB).

- We proved that the hybrid robotic system based on the adaptive and associative assistance constitutes a feasible alternative for rehabilitation of upper-extremity motor functions. The results of the pilot clinical intervention with a small cohort of post-stroke subjects constitute the background of further clinical oriented research in the field of neurorehabilitation.

6.2 Scientific Dissemination

The work described in this dissertation has produced a number of publications in scientific journals, national and international conferences, as well as two book chapters. Furthermore, the outcome of this work has been integrated in other research projects, which have also been properly disseminated. All the publications are mentioned next.

Publications in journals:

1. F. Resquín, J. Ibáñez, O. Herrero, J. Gonzalez-Vargas, F. Brunetti, and J.L. Pons. "User's Motor Intent Guided Upper-Limb Hybrid Robotic Platform to Efficiently Modulate Cortical Excitability: a Comparison of Three Strategies" (To be submitted).

2. F. Resquín, J. Gonzalez-Vargas, J. Ibáñez, F. Brunetti, I. Dimbwadyo, L. Carrasco, S. Alves, C. Gonzalez-Alted, A. Gomez-Blanco and J.L. Pons. Adaptive hybrid robotic system for rehabilitation of reaching movement after a brain injury: a usability study. J Neuroeng Rehabil. 2017 Dec 12;14(1):104.

3. F. Trincado, E. Lopez-Larraz, F. Resquín, A. Ardanza, S. Prez-Nombela, J. L. Pons, L. Montesano, A. Gil-Agudo. A pilot study of the brain-triggered electrical stimulation with visual feedback in patients with incomplete spinal cord injury. Journal of Medical and Biological Engineering. (Accepted: 20/09/2017).

4. F. Resquín, J. Gonzalez-Vargas, J. Ibáñez, F. Brunetti and J.L. Pons. Feedback error learning controller for functional electrical stimulation assistance in a hybrid robotic system for reaching rehabilitation. Eur J Transl Myol. 2016;26(3).

5. F. Resquín, A. Cuesta-Gómez, J. Gonzalez-Vargas, F. Brunetti, D. Torricelli, F. Molina Rueda, R. Cano de la Rueda, J. C. Miangolarra and J. L. Pons. Hybrid robotic systems for upper limb rehabilitation after stroke: A review. Med Eng Phys. 2016 Nov; 38 (11): 1279-88.

6. E. Hortal, D. Planelles, F. Resquín, J.M. Climent, J.M. Azorín and J. L. Pons. Using a brain-machine interface to control a hybrid upper limb exoskeleton during rehabilitation of patients with neurological conditions. J Neuroeng Rehabil. BioMed Central Ltd; 2015 Oct 17;12(1):92.

Books Chapters:

1. Alessandro C, Beckers N, Gebel P, Resquín F, Gonzalez J, Osu R. Motor Control and Learning Theories. In: Pons JL, Raya R, Gonzalez J, editors. Emerging Therapies in Neurorehabilitation II. 2015. p. 225-50.

2. Brunetti F, Resquín F, González V, Ceres R, Freire Bastos T. Interfaces basadas en señales electromiográficas. In: José M. Azorín, Ramón Ceres, Anselmo Frizera TFB, editor. La Interacción de Personas con Discapacidad con el Computador: Experiencias y Posibilidades en Iberoamérica. Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo (CYTED); 2013. p. 83-101.

Selected publications in international and national conferences proceedings directly related to the topics of the dissertation:

1. F. Resquín, O. Herrero, J. Ibáñez, J. Gonzalez-Vargas, F. Brunetti, J. L. Pons. Electroencephalography guided Upper-Limb Hybrid Robotic Platform to Modulate Cortical Excitability. IEEE International Conference on Systems, Man and Cybernetics. Canada, 2017 (Oral presentation)

2. F. Resquín, J. Ibáñez, O. Herrero, J. Gonzalez-Vargas, F. Brunetti, J. L. Pons. Aumento de la excitabilidad cortical inducido mediante una asistencia híbrida guiada por BCI para la rehabilitación del movimiento de alcance. IX Congreso Iberoamericano de tecnologías de Apoyo a la Discapacidad. Bogotá, Colombia, 2017. (Accepted, oral presentation)

3. Resquín F, Gonzalez-Vargas J, Ibáñez J, Dimbwadyo I, Alves S, Torres L, et al. Hybrid Robotic System for Reaching Rehabilitation after Stroke: reporting an usability experimentation. In: Proceedings of the 3rd International Conference on NeuroRehabilitation (ICNR 2016), Segovia, Spain. 2016. P. 679-84. (Oral presentation)

4. Barbouch H, Resquín F, Gonzalez-Vargas J, Khraief-Hadded N, Belghith S, Pons JL. Hybrid Robotic System Simulation for the exploration of novel control strategies. In: Proceedings of the 3rd International Conference on NeuroRehabilitation (ICNR 2016), Segovia, Spain. 2016. (Poster presentation)

5. Martínez-Expósito A, Ibáñez J, Resquín F, Pons JL. Task influence on motor-related cortical signals: Comparison between upper and lower limb coordinated and analytic movements. In: Proceedings of the 3rd International Conference on NeuroRehabilitation (ICNR 2016), Segovia, Spain. 2016. (Poster presentation)

6. Dimbwadyo I, Carrasco L, Resquín F, Gonzalez-Vargas J, Ibáñez J, Alves S, et al. Satisfacción de los usuarios con un sistema robótico hbrido para la rehabilitación del miembro superior. In: LXVIII Reunión Anual Sociedad Española Neurología. Valencia.; 2016. (Poster Presentation)

7. Resquín F, Ibáñez J, Gonzalez-Vargas J, Brunetti F, Dimbwadyo I, Alves S, et al. Combining a hybrid robotic system with a brain-machine interface for the rehabilitation of reaching movements: A case study with a stroke patient. In: 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). Orlando, Florida.: IEEE; 2016. P. 6381-4. (Oral presentation)

8. Resquín F, Gonzalez-Vargas J, Ibáñez J, Brunetti F, Dimbwadyo I, Alves S, et al. Hybrid Robotic System for Reaching Rehabilitation after Stroke. In: XXI Conference of the International Society on Electrophysiology and Kinesiology (ISEK). Chicago; 2016. (Oral presentation)

9. Resquín F, Ibáñez J, Gonzalez-Vargas J, Dimbwadyo I, Carrasco L, Alves S, et al. Sistema robótico híbrido para la rehabilitación del miembro superior. Cognitive Area Networks 8o Simposio CEA de Bioingeniería 2016 Interfaces hombre-máquina Cerebro y periferia un camino ida y vuelta. Madrid; 2016. p. 97-101. (Oral presentation)

10. Resquín F, Hortal E, Planelles D, Brunetti F, Azorín JM, Pons JL. Sistema Robótico Híbrido para la rehabilitación del miembro superior dirigido por comandos volitivos. In: VIII Congreso Iberoamericano de Tecnologías de Apoyo a la Discapacidad. 2015. p. 189-92. (Oral presentation).

11. Úbeda A, Planelles D, Hortal E, Resquín F, Koutsou AD, Azorín JM, et al. A Brain-Machine Interface Architecture to Control an Upper Limb Rehabilitation Exoskeleton. In: Proceedings of the 2nd International Conference on NeuroRehabilitation (ICNR 2014). Springer International Publishing; 2014. P. 795-803. (Biosystems & Biorobotics; vol. 7). (Oral presentation)

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18. Resquín F, Bravo E, Gómez-Soriano J, Brunetti F, Pons JL. Protocol and system for spastic behavior simulation through the generation of cutaneous reflexes. In: Proceedings of the 1st International Conference on NeuroRehabilitation (ICNR 2012). Springer Berlin Heidelberg; 2012. P. 431-5. (Poster presentation).

Part of the research work presented in this dissertation has been awarded as the **"Best Student Contribution"** at the 3rd. International Conference on NeuroRehabilitation (ICNR2016), Segovia, Spain, 2016. **This distinguished award underlines the relevance and quality of the research work presented in this dissertation.** The work leading to this distinguished award is following cited:

"Resquín F, Gonzalez-Vargas J, Ibáñez J, Dimbwadyo I, Alves S, Torres L, Carrasco L, Brunetti F, and Pons J.L. Hybrid Robotic System for Reaching Rehabilitation after Stroke: reporting an usability experimentation. In: Proceedings of the 3rd International Conference on NeuroRehabilitation (ICNR 2016), Segovia, Spain.2016. p. 679-84."

To sum it all up, the work presented in this dissertation has produced four journal publications (plus one contribution under revision and another that will be soon submitted), eighteen contributions to international and national conferences, two book chapters, and the distinguished award for the best student contribution at the ICNR 2016 conference. Additionally, this work was subject to presentations in a number of seminars and briefings in both the Department of Systems Engineering and Automation (UC3M) and the Cajal Institute of the Spanish National Research Council (CSIC).

6.3 Future works

The applied methodology and the presented results in this doctoral thesis represent a reference milestone that encourages several ongoing studies and projects related with the investigation framework presented herein. Some of the topics considered are related to questions that emerged during the analysis or/and interpretation of the results, while others are studies planned as the continuation to those presented in this dissertation. The future studies identified can be organized in three groups associated with different aspects presented along the thesis.

The most immediate works are related to the continuity of the study presented in Chapter 5. These works are proposed with the goal of extending the results obtained therein and provide stronger evidences to support the clinical effectiveness of the hybrid robotic system. To this end, the group of Neural Rehabilitation (CSIC) is currently collaborating closely with the Centro de Referencia Estatal de Atención al Daño Cerebral (CEADAC) and the Instituto de Neurociencias y Ciencias del Movimiento (INCIMOV). As results of this collaboration, the following works are planned to be addressed:

- To confirm that the associative concepts lead to cortical plastic changes in post-stroke subjects. It is expected similar results showed in Chapter 3 with healthy subjects, in which an enhancement of the corticospinal projection of the arm muscles was demonstrated.
- To design and carry out a clinical intervention procedure in which a larger sample of patients can be considered, so that, more reliable clinical results are reachable. In this regard and considering the classification of clinical trial of rehabilitation (Maciejasz et al. 2014, Lo 2012), a category II - 'Development-of-concept study' is planned. This clinical trial is conceived with the aim of verifying the device therapeutic efficacy including a control group following a randomization and blinded outcome assessment.

From the technological perspective, and with the aim of increasing the functionality of the hybrid robotic platform, several research works for further research can be derived. This works can be classified within the bioengineering and the rehabilitation fields. Some of them are listed in the next lines:

- To include mechanical exoskeleton with active actuation, capable providing mechanical assistance during the execution of functional task. The inclusion of exoskeleton with active assistance will allow that patients without FES response could use the system. Moreover, it could improve the performance of the current hybrid robotic systems significantly since the arm movement does not only depend on the FES assistance, specifically in subject severely affected. However, it opens a window for the development of an optimally shared controller for ruling the operation and complementary assistance contribution of the FES and the exoskeleton to the voluntary motor effort exerted by the patients.
- To increase the rehabilitative connotation of the system by extending the application of assistance to the hand and wrist muscles. It is expected that the execution of reaching a grasping task involving the whole upper limb may achieve motor and functional improvement of the whole arm.
- The integration of electrode arrays for improving the muscle recruitment response to FES yielding to a more effective stimulation pattern and to a more beneficial therapeutic response. Particularly, there has been significant interest in using electrode arrays

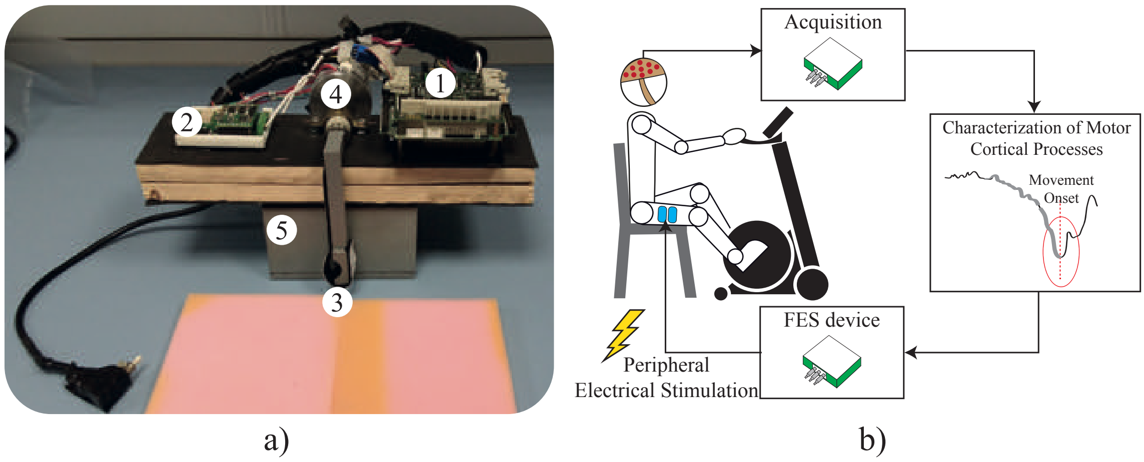

FIGURE 6.1: a) Main components of the analogous platform developed for further studies targeting upper-limb distal muscles. 1: High level controller; 2: Motor Driver; 3: Mechanical support for the index finger; 4: Motor and embedded encoder; 5: Power supply. b) Associative intervention concept framed within the ASSOCIATIVE project for the lower-limb.

to address the electrode location for producing greatest level of appropriate movement and minimizing undesired effects (O'Dwyer et al. 2006, Koutsou et al. 2016). Complementary, Complementary, stimulation of multiple contact point, as the provided with array of electrodes, could be considered to delay the appearance of the adverse effects due to the onset of muscle fatigue (Malesević et al. 2010).

- To implement advanced and entertaining visual paradigm to increase users' engagement. Regarding the great potential of using virtual reality paradigm in the rehabilitation fields (Shin et al. 2016, Yates et al. 2016), the execution of the rehabilitation task here presented could be combined with more attractive and enthusiastic virtual reality environment.

The recording and analysis of the cortical electrophysiological signal in the rehabilitation field result of great interest since it provides valuable information regarding the cortical state. Certainly, to study the basis and the precise characterization of plastic and functional changes due a BCI-based associative facilitation platform open a new research topic related to the neuroscience field. The principal goal is to understand the underlying mechanism, the prime factors influencing the cortical changes occurring as consequence of the associative intervention and its correlation (if it exists) with the (re)learning of the motor control. In this regard, a FPU scholarship project, supported by the Spanish Ministerio de Educación, Cultura y Deporte (MECD), pretends to address mentioned research line. For such purposed, an analogous platform was developed involving distal arm muscles with large motor cortical representation (see Figure 6.1a). This platform represents a simplified approach considering that involved muscles are widely studied and well characterized in literature.

Likewise, the ASSOCIATE project (DPI2014-58431-C4-1-R) is aimed at validating the effectiveness of a novel intervention to promote motor control re-learning in neurological patients by means of an associated use of motor planning at brain level, sensory stimulation at cortical level and afferent feedback provided with a wearable lower extremity exoskeleton. Due the difficulties of implementing associative approach in non-stationary scenarios, this concept was instigated un a similar lower-limb functional tasks, as the cycling (see Figure 6.1b). Similar results than the found in Chapter 4 are expected to be generated in the lower-limbs, as well as a deep interpretation of the mechanisms occasioning these cortical neural changes.

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