Biosystems & Biorobotics

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Emerging Therapies in Neurorehabilitation II

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Aims & Scope

Biosystems & Biorobotics publishes the latest research developments in three main areas: 1) understanding biological systems from a bioengineering point of view, i.e. the study of biosystems by exploiting engineering methods and tools to unveil their functioning principles and unrivalled performance; 2) design and development of biologically inspired machines and systems to be used for different purposes and in a variety of application contexts. The series welcomes contributions on novel design approaches, methods and tools as well as case studies on specific bioinspired systems; 3) design and developments of nano-, micro-, macrodevices and systems for biomedical applications, i.e. technologies that can improve modern healthcare and welfare by enabling novel solutions for prevention, diagnosis, surgery, prosthetics, rehabilitation and independent living.

On one side, the series focuses on recent methods and technologies which allow multiscale, multi-physics, high-resolution analysis and modeling of biological systems. A special emphasis on this side is given to the use of mechatronic and robotic systems as a tool for basic research in biology. On the other side, the series authoritatively reports on current theoretical and experimental challenges and developments related to the “biomechatronic” design of novel biorobotic machines. A special emphasis on this side is given to human-machine interaction and interfacing, and also to the ethical and social implications of this emerging research area, as key challenges for the acceptability and sustainability of biorobotics technology.

The main target of the series are engineers interested in biology and medicine, and specifically bioengineers and bioroboticists. Volume published in the series comprise monographs, edited volumes, lecture notes, as well as selected conference proceedings and PhD theses. The series also publishes books purposely devoted to support education in bioengineering, biomedical engineering, biomechatronics and biorobotics at graduate and post-graduate levels.

About the Cover

The cover of the book series Biosystems & Biorobotics features a robotic hand prosthesis. This looks like a natural hand and is ready to be implanted on a human amputee to help them recover their physical capabilities. This picture was chosen to represent a variety of concepts and disciplines: from the understanding of biological systems to biomechatronics, bioinspiration and biomimetics; and from the concept of human-robot and human-machine interaction to the use of robots and, more generally, of engineering techniques for biological research and in healthcare. The picture also points to the social impact of bioengineering research and to its potential for improving human health and the quality of life of all individuals, including those with special needs. The picture was taken during the LIFEHAND experimental trials run at Università Campus Bio-Medico of Rome (Italy) in 2008. The LIFEHAND project tested the ability of an amputee patient to control the Cyberhand, a robotic prosthesis developed at Scuola Superiore Sant’Anna in Pisa (Italy), using the tf-LIFE electrodes developed at the Fraunhofer Institute for Biomedical Engineering (IBMT, Germany), which were implanted in the patient’s arm. The implanted tf-LIFE electrodes were shown to enable bidirectional communication (from brain to hand and vice versa) between the brain and the Cyberhand. As a result, the patient was able to control complex movements of the prosthesis, while receiving sensory feedback in the form of direct neurostimulation. For more information please visit http://www.biorobotics.it or contact the Series Editor.

More information about this series at http://www.springer.com/series/10421

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Challenges in Neurorehabilitation and Neural Engineering

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Abstract Great progress has been achieved in the last few years in Neurorehabilitation and Neural Engineering. Thanks to the parallel development of medical research, the chances to survive a neural injury are growing, so it is necessary to develop technologies that can be used both for rehabilitation and to improve daily activities and social life. New robotic and prosthetic devices and technologies such as Functional Electrical Stimulation, Brain-Computer Interfaces and Virtual Reality are slowly becoming part of clinical rehabilitation setting, but they are far from being part of everyday life for the patients. As technology improves, expectations keep rising and new problems emerge: from cost reduction to the diffusion in the medical environment, from the enlargement of the number of patients who may benefit from these technologies to transferring rehabilitation to the patient's home. All these requests lead to great challenges that researchers have to face to enhance their contribution towards the improvement of rehabilitation and life conditions of patients with neural impairment.

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1 What Is Neurorehabilitation and Neural Engineering

Since emerging of technology that allows collection and analysis of great amounts of data, neuroscience has become an information-driven science. Neural engineering (or neuroengineering) has become a rapidly expanding field thanks to the tremendous progress in the creation of tools capable of interacting with the nervous system, working on the collected data.

Neural engineering is an interdisciplinary research area that brings to bear methods from neuroscience and engineering to analyse neurological functions and to design solutions to problems associated with neurological limitations and dysfunctions [1, 16].

The main goal of this field is to provide rehabilitative solutions and enhanced care for patients with nervous system disorders, thus for neurorehabilitation.
The primary goal of neurorehabilitation is the restoration and maximization of functions that have been compromised or lost due to impairments caused by injury or disease of the nervous system, reducing, where possible, these impairments, enabling an individual to perform at his maximum capacity and allowing greater participation in society.

The fact that neurorehabilitation is becoming more and more fundamental is due to medical advances that have been able to extend life expectancy and to save many more lives after neurological injury [63, 64].

It is fundamental to remember the important distinction between "impairment" and "disability". According to the WHO (ICF International Classification of Functioning) report "impairment refers to an individual's biological condition, whereas disability denotes the collective economic, political, cultural and social disadvantages encountered by people with impairments" [4, 72].
This means that the primary goal of neurorehabilitation is to understand the mechanisms of impairment and to act on the condition itself where possible to reduce the patient's disability.

The great progress that has been made in the last years in neural engineering is not only on understanding neural mechanisms, detecting and processing the signals, but also on restoring functions of the neural system and creating an interface with external devices [26].
This progress continues parallel to technological advancements in electronics and mechanics, computer science and information and communication technologies. For some applications the drive surely comes from industry and gaming field.

For many years rehabilitation has been dominated by orthopaedic problems, especially during the two world wars. Recently the greater chance of surviving after neurological injury has shifted the emphasis toward rehabilitation of patients with neurological disorders, stroke, traumatic injuries of brain and spinal cord.
According to the World Heart Federation every year, 15 million people worldwide suffer a stroke. Nearly 6 million die and another 5 million are left permanently disabled.

The World Health Organization reports that every year between 250,000 and 500,000 people around the world suffer a Spinal Cord Injury [18].
Overall, over a billion people, about a 15 % of the world's population, have some form of disability, with rates increasing due to population ageing [17].
This has lead over the last years to an increasing interest in understanding the mechanisms of function recovery. This interest is fundamental also because of the enormous variety of impairments that may affect the recovery of functionality, thus life in society.

2 Neurorehabilitation and the Neural System

For many years it was believed that in the adult the nervous system is almost fixed. This was found not to be true, so that now brain plasticity is recognized as a fundamental property of the nervous system.
According to *Oxford Dictionaries* [33], we can define plasticity as the quality of being easily shaped or moulded. Applying this definition to the neural field, we have that plasticity, in this case brain plasticity, is the capacity for continuous alteration of the neural pathways and synapses of the living brain and nervous system in response to experience or injury that involves the formation of new pathways and synapses and the elimination or modification of existing ones [32].
This means that the brain is constructed to change. In fact "Plasticity is defined as the brain's capacity to be shaped by experience, its capacity to learn and remember and ability to reorganise and recover after injury" [23].
This is why moderate spontaneous functional recovery can be found in patients following neural injuries and what rehabilitation tries to work on, as without plasticity there wouldn't be recovery but only a deficit compensation.
In fact a lesion has also effects on areas that are functionally connected with the lesion site. Brain damage is always a damage to the entire network, so that recovery happens mostly in remote regions.
The complete mechanisms of plasticity are not completely understood [22], but it is known that the brain is able to reorganize the neural pathways, both for learning new skills and recovering from injury.
This is true also for the spinal cord, where there is an activity-dependent plasticity.
As new learning changes the spinal cord, compensatory plasticity in brain and spinal cord preserves the old behaviours. Each behaviour repeatedly induces plasticity to preserve its key features despite the plasticity induced by other behaviours.
If an old behaviour is impaired, a new behaviour that targets beneficial plasticity to an important site may improve the old behaviour.
This capacity of compensatory plasticity preserves fundamental functionality like locomotion.

Therapy in neurorehabilitation should be directed to take advantage of the plasticity of the CNS by a functional training.

Training and exercise have effects on cellular and molecular function involved in plasticity.
For example one of the established training techniques following Spinal Cord Injury (SCI) is treadmill based gait training, that has been successfully translated from animal studies to clinic and that has been found to improve connectivity of spared corticospinal pathways [13].

2.1 Why Develop New Technologies for Neurorehabilitation?

The main approaches of neural engineering used to rehabilitate impaired motor function are:

1. Restoration: retain existing structures, both anatomical and neural, and control them for re-establishing a motor function.
2. Replacement: substitution of the impaired motor apparatus with an artificial one controlled by residual structures.
3. Neuromodulation: retraining of the central nervous system to induce plasticity [19, 27].

There are different motivations for developing new technologies for rehabilitation [61]:

- Improved technology may allow more therapy with less supervision, reducing also the costs.
- Thanks to the increasing possibility to measure and quantify functional recovery, therapy could be quantified more accurately and new diagnostic possibilities can arise.
- This new technology has the potential to permit new types of therapy, for example continuous therapy with wearable devices.
- Some kinds of technologies could allow to move rehabilitation to the patient's home.
- Better devices could substitute lost functions (e.g. amputated limbs) so that the user is less restricted in his daily life.

Nowadays a great variety of new technologies is increasingly taking part of the clinical practice, improving the potential of therapists and clinicians to diagnose and rehabilitate. Wearable robotics, virtual reality, brain-machine interfaces and neural prosthetics are playing a leading role in this innovating process [57], and follow the footprints of other devices like Cochlear Implants and Visual Prosthetics.

2.2 Limits of Neurorehabilitation

Following neurorehabilitation many patients with acquired brain injuries observe modest benefits and when progress is made the acquired gains may fail to be maintained outside the medical setting. One of the biggest problems is that rehabilitation strategies are quickly abandoned when active therapy has ceased, thus it is necessary to bring therapy in everyday life to create a major bond between rehabilitation and life after treatment [68] and therefore increase the amount of therapy a patient can receive.

This is particularly true when talking about upper limb rehabilitation, as the latter is often abandoned early because of the adoption of compensatory strategies and the fact that most daily activities can be performed with the intact limb [44]. Also, because of the fact that the one-handed task is more difficult, family members will end up doing certain activities for the patient, causing lack of training in everyday life.

Another problem is given by the high costs of maintaining the therapy at home and the fact that often the patient is abandoned at home with the equipment [25], without the necessary support to continue his rehabilitation.

New technologies, like mobile apps, gamification [21] and portable devices, can become a permanent and seamlessly transparent rehabilitation therapy after the treatment is finished and the patient is sent home. These are technologies that will enable people to treat themselves with very low professional intervention, and may motivate them to keep improving their situation long after the formal treatment. Also, they will become cheaper over time, allowing more and more people to use them.

Also techniques in telerehabilitation will have to ensure that machine-mediated therapies fit to the patient at a particular stage of recovery [25].

Obviously a match between the patient's and the rehabilitation team's goals is required, both in the medical setting and in home therapy. The prescription of the intervention has to be not only on the basis of knowledge of neurorehabilitation because often what a patient needs is not what he/she wants.

Greater progress may be achieved if the clinician is able to assist the patient in achieving his goals or making progress that can motivate him/her to further commitment. This means also that the primary aim of the treatment should be directed to improve movement disorders and not the clinical signs.

3 Major Challenges to Face

There are several technologies and application areas of neurorehabilitation and neural engineering, so there are different specific challenges that have to be faced in the next years to allow widespread outside of the research field.

3.1 Robotic Rehabilitation

In rehabilitation, the goal of the different exercises is to perform specific movements to provoke motor plasticity and improve motor recovery, minimizing functional deficits.
Recovery of the motor function can occur through neural reorganization finding alternative paths to activating the muscles for a task, or using alternative muscles in compensatory strategies [53, 55].
As commonly stated, traditional physical therapy is hard work, both for the patient and the therapist (often more than one is needed, especially for gait rehabilitation), which may lead to injuries. Moreover the duration of the therapy session is often limited by the therapist's endurance.

This is where robots come into hand.
The rapid growth in this field can be attributed to:

- the emergence of hardware for haptics and advanced robotics, that permit to operate in a safe environment for the patient and the therapist.
- the drop of computing costs and the emergence of software for real-time control.

Robotic rehabilitation aims to reduce the workload and the physical effort of the therapist, allowing more intensive and repetitive motions, and to assess quantitatively the motor recovery by measuring different variables, like force and movement patterns.
One of the main problems of robot-based neurorehabilitation is to get the new treatment accepted, remembering the fact that acceptance is a necessary but not sufficient condition for the technology adoption.
Surely the fact that rehabilitation robots can be used both for gaining information and for intervention could influence the adoption of this technology, but it is necessary to validate the ability of this information to measure underlying phenomena and to give a realistic quantitative measurement of the recovery process.
Rehabilitation robots are used for intervention on:

- Lower limbs, where the training has to be repetitive and task-specific. The stimulus has also to be appropriately intense, as in locomotion the load is essential for appropriate leg muscle activation.
- Upper limbs, where movement targets are acquired from a variety of sensory channels including vision and touch. This information is used to update internal models to encode also the sensory consequences of the interactions.

Tables 1 and 2 present a synthesis of some of the studies that have investigated the use of robot therapy, highlighting the prescription of the intervention and the Functional Scales used to measure the outcomes. It must be considered that although there are a number of smaller pilot studies, there are only few larger clinical trials evidencing the use of robot therapy [43].

Table 1 Clinical studies about rehabilitation using robot therapy for the upper limb

Device	Disability	Functional scale	Prescription
MIT-MANUS (Volpe, 2000) [69]	2 weeks after single stroke	MPS, MSS, FIM	Regular therapy + five 1-h session a week (25 total)
MIT-MANUS (Fasoli, 2003) [20]	Single, unilateral stroke within the past 1–5 years	AS, FMA of upper extremity function, MSS, Medical research council MPS	4–5 h weekly for 4 weeks
MIT-MANUS (Krebs, 1999) [37]	Hemiparesis	FMA for upper extremity function, MPS for shoulder and elbow, MSS for shoulder and elbow, MSS for wrist and fingers	Conventional therapy + 4–5 h per week of robot-aided therapy
IMotion2 (MacClellan, 2005) [49]	Stroke, more than 6 months after stroke, shoulder and elbow deficits	Upper-limb MSS, Wolf motor function test, MPS, FMA for upper extremity function	18 sessions over 3 weeks, two sessions a day at 1-h each, 3 days a week
MIME—Stäubli PUMA-260 (Lum, 1999) [45]	Stroke, 1–45 months post-stroke	FMA, strength improvements in joint actions	24 1-h sessions over 2 months
MIME—PUMA-560 (Lum, 2002) [46]	Stroke, more than 6 months after cerebrovascular accident, chronic hemiparesis	FMA, FIM, biomechanic measures of strength and reaching kinematics	24 1-h sessions over 2 months at least 6 months post first stroke
MIME—PUMA-560 (Lum, 2006) [47]	Stroke, subacute	FMA for upper extremity function, MSS, FIM, MPS, mAS	15 1-h treatment sessions over 4 weeks
GENTLE/s [10]	Stroke, residual arm disfunction	FMA, MAS, mAS	30 min of intervention three times per week
ARM Guide (Reinkensmeyer, 1999–2000) [58–60]	Stroke, at least 6 months after brain injury	CMSA, Rancho functional test of the upper extremity	24 1-h therapy sessions over 2 months

(continued)

Table 1 (continued)

Device	Disability	Functional scale	Prescription
Robot-assisted arm trainer (Hesse, 2003) [29]	Stroke, more than 6 months after stroke, chronic hemiparesis	mAS score for spasticity, arm section of the Rivermead motor assessment score	15 min net treatment with arm-trainer every workday for 3 weeks (15 sessions) + 45 min of individual physiotherapy and occupational therapy
Armeo spring (Colomer 2013) [9]	Stroke, chronic hemiparesis	mAS, motricity index, FMA, MAS, manual function test, Wolf motor function test	3 one-h sessions per week for a total of 36 sessions

Abbreviations ADL Activities of daily living, *AS* Ashworth scale, *mAS* Modified ashworth scale, *BI* Barthel index, *BBS* Berg balance scale, *CMSA* Chedoke-McMaster scale, *FAI* Frenchay activities index, *FMA* Fugl-Meyer assessment, *FAC* - Functional ambulation category, *FIM* Functional independence measure, *MAS* Motor assessment scale, *MPS* Motor power score, *MSS* Motor status scale, *MI* Motricity index

Table 2 Clinical studies about rehabilitation using robot therapy for gait

Device	Disability	Functional scale	Prescription
Lokomat (Hidler, 2009) [30]	Stroke, less than 6 months	BBS, FAC, NIH stroke scale, MAS, Rivermead mobility index, FAI, SF-36 health survey	45 min sessions, 3 days per week, for 8–10 weeks, for a maximum total of 24 sessions
Lokomat (Hornby, 2008) [31]	Stroke, chronicity	Emory functional ambulation profile, BBS, FAI, Medical outcomes questionnaire (SF-36), mAS	12 30-min sessions
Lokomat (Husemann, 2007) [35]	Stroke, subacute	Massachussetts general hospital FAC, 10m time walking test, mAS, MI, German version of the BI	30 min of conventional physiotherapy + 30 min of robotic training daily
Lokomat (Mayr, 2007) [51]	Stroke, 0.5–10 months, inability to walk unaided	EU-walking scale, Rivermead motor assessment scale, MI, Medical research council scale of strength, AS of tone	group A: 3 weeks of Lokomat training, 3 weeks of conventional physical therapy, 3 weeks of Lokomat training. Group B: 3 weeks of conventional physical therapy, 3 weeks of Lokomat training, 3 weeks of conventional physical therapy. Treatment applied 5 times a week, for up to 30 min.
Gait trainer (Pohl, 2007) [56]	Stroke, subacute	ADL, BI, FAC, Rivermead mobility index, MI	20 min locomotor training + 25 min physiotherapy

(continued)

Table 2 (continued)

Device	Disability	Functional scale	Prescription
Gait trainer (Werner, 2002) [70]	Stroke, subacute	FAC, Rivermead motor assessment, mAS	A: 2 weeks of gait trainer therapy, every workday, with a net walking time of 15–20 min. B: 2 weeks of treadmill therapy with partial body weight support, every workday, with a net walking time of 15–20 min. Group A: pattern ABA. Group B: pattern BAB
Electromechanical gait trainer (Tong, 2006) [66]	Stroke, subacute	Elderly mobility scale, BBS, FAC, MI, FIM, BI	5 sessions per week for 4 weeks, 20 min of gait training as part of 1.5 h of rehabilitation session

Abbreviations ADL Activities of daily living, *AS* Ashworth scale, *mAS* Modified ashworth scale, *BI* Barthel index, *BBS* Berg balance scale, *CMSA* Chedoke-McMaster scale, *FAI* Frenchay activities index, *FMA* Fugl-Meyer assessment, *FAC* Functional ambulation category, *FIM* Functional independence measure, *MAS* Motor assessment scale, *MPS* Motor power score, *MSS* Motor status scale, *MI* Motricity index.

These main fields of application influence the problems and challenges to be faced, even if there are some in common.

Although the field of rehabilitation robotics is strongly emerging and an increasing number of systems has entered the market over the last years or is in development and in trial in research institutes, a widespread use of these systems especially for personal use in home care and home rehabilitation has not occurred yet.

There are multiple reasons that limit the spread of those systems.

Especially the integration of robotic technology, like actuating systems and sensor systems, into rehabilitation devices strongly increases the costs of such devices.

Therefore less hospitals or even private users can afford such devices and insurance companies do not cover the costs.

Surely a key challenge is how to enhance the therapist's skills with the robot technology, considering the robot as a tool. This means to use the robot to have the possibility to carry out longer and more intensive rehabilitation sessions without overloading the therapist, allowing the latter to focus more on the patient and its movements.

The usability of new systems can be limited, also due to the increased complexity of the devices. A specialized training is needed for the therapists to be able to use them and the setup time may also be too stressful for the patient. This can result in a limited acceptance from both the medical personnel and the patients.

This influences also the engineering evolution of this technology, as there is a need for more integrated solutions that ideally have similar protocols and interfaces, reducing the learning curve by the medical staff.

A further limit to overcome for the robots for upper limb rehabilitation is the division between reach and grasp investigating the integration in single devices, as the recovery of hand motor function is crucial to perform activities of daily living [52].

All kinds of rehabilitation robots have to be designed to assist "as needed", because if the movement strategy is invariant, the neural control circuit becomes non-responsive. Ideally, the robot has to exert no interference unless the patient is unable to perform a task.

The goal must be to reduce the dependence on the robotic mechanisms to encourage relearning, using also strategies involving other kinds of technology (Sect. 3.2).

Despite the great possibilities offered by this type of technology rates of adoption in rehabilitation are very low.

This could be changed by getting robotic technologies past the feasibility study stage and analysing the economic sustainability, as cost is one of the big issues.

Current systems are often bulky while the mobile systems still lack long duration power supply solutions.

Last but not least clinical studies show little evidence for a superior effectiveness of robot-based neurorehabilitation in locomotor training [11]. It seems though that the best results can be achieved when the robot is applied in conjunction with conventional therapy [15].

3.2 Virtual Rehabilitation

Virtual Reality is defined as "The computer-generated simulation of a three-dimensional image or environment that can be interacted with in a seemingly real or physical way by a person using special electronic equipment, such as a helmet with a screen inside or gloves fitted with sensors" [33].
The recent advances in this field, mostly driven by the entertainment industry, have led to an increasing availability of devices that can be used for rehabilitation purposes [28]. The availability of low cost HD displays and the possibility to use also everyday systems like smartphones as virtual reality devices has led to a reduction of hardware prices.
Virtual Reality allows a great influence on therapy when coupled with other methods: combined with rehabilitation robotics it allows to influence the feedback received by the patient through perturbation. Virtual systems can distort reality, thus trying to enhance improvements taking advantage of error augmentation and tricking the nervous system with altered sensory feedback [25].
One of the great advantages of Virtual Rehabilitation is interactivity and motivation [6]. This is especially true in game-based therapeutic approaches. The real-time multi-sensory feedback can be used for correction and the control over the different scenarios allows to achieve things impossible in the real world for the patient. Another great advantage is the real-time data collection and storage. Remote data access is fundamental for another field in which Virtual Reality can be useful, which is Virtual Telerehabilitation. Telerehabilitation may be beneficial for the reduction of healthcare costs. Since the goal is to bring the rehabilitation home with the patient, there is the need for mobile, networked treatments for long-term training, monitoring and online communication with the therapist. Despite the enormous potential in this field, there are great challenges to face for the widespread adoption of Virtual rehabilitation. The therapist's attitude fearing substitution is a great gap to overcome. Also the interfaces present problems, as they were not designed as medical equipment: this often leads to the difficulty of sterilization for repeated use by different patients. Even if costs have dropped significantly in the last years, the prices are still prohibitive for health clinics, also because here are almost no commercial systems available. This is also related to the fact that there is a great lack of cost-benefit analysis. The long-term consequences are not known and there are only few medical studies, so that the lack of outcome data for improvements does not satisfy the critics of the medical environment. Also compatibility between the different systems is a great issue.

Telerehabilitation has also additional challenges, due to the inadequate communication infrastructure that may limit videoconferencing with the patients in case of difficulty. Another aspect is the safety of the patient, as they may risk to re-injure themselves. Thus control softwares need to be integrated to make sure the patient is not exercising at higher level than prescribed or for longer than necessary [6]. While with telerehabilitation there is the risk of losing specificity and customizability of the treatment, it can be very useful if there is also remote control by the therapist, so that the medical staff can better structure the therapy, both for in-hospital and at-home sessions.

3.3 Brain-Computer Interfaces

The Brain-Computer Interface, called BCI, is a technology that allows communication and/or control for real-time interaction between the human brain and external devices [50]. A BCI recognizes the intent of the user through the signals of the brain. The user's intent is then translated into a desired output that does not depend on the normal pathways of peripheral nerves and muscles. It is fundamental to provide real-time feedback to the user, so that he/she can make fine adjustments to optimize the output.

There are many issues that preclude translation of experimental BCIs into clinical applications meaning that much experimentation has to be done before getting to BCI as a safe and efficient rehabilitation tool.
One of the major issues of this field is surely the kind of signals of brain-activity that have to be recorded. Obviously, the closer the sensor is placed to the neuron, the better are quality and spatial definition of the acquisition. There are different degrees of invasiveness that also influence the challenges that have to be faced.

1. Non-invasive
   Electroencephalographic (EEG) signals are recorded from the scalp. The main problem is that EEG has limited frequency range, low spatial resolution and a great susceptibility to interferences and artefacts (Electromyographic and Electrooculographic signals).
   These facts limit the number of possible applications, as the transfer rate may not be sufficient to eventually control arm or leg prostheses with multiple degrees of freedom.
   On the other hand, this kind of BCI can allow severely and partially paralyzed patients to reacquire basic forms of communication and motor control.
2. Invasive
   If one of the goals in the future is to restore movements using artificial prostheses with multiple degrees of freedom, it becomes clear that it will be necessary to use invasive approaches, as they permit recording of high-resolution signals from the brain [40].
   Electrocorticographic (ECoG) signals are recorded from surgically implanted sensors. These sensors are placed on the surface of the cortex. Thanks to the elimination of the influence of the skull and the dura this kind of sensors is closer to the brain, resulting in a greater signal amplitude, wider frequency range and better resolution.
   Then there are intracortical methods for recording brain signals. They record the brain activity signals from electrodes implanted directly in the brain.
   However both these invasive recording methods require surgery, causing issues such as the risk of tissue damage, bleeding and brain infection. Another problem is linked to the long-term recording stability, which at the moment can not be completely achieved, so that significant improvements are required to get to a fully-applicable system for chronic clinical application in humans.

To get to the possibility of using BCIs based on invasive recording methods in clinical applications, it is necessary to invest research efforts on improving some key features:

- Stable, long-term recording from multiple brain areas.
  This problem includes different other issues:
  - Biocompatibility: The materials have to be biocompatible so that the brain won't reject the electrodes.
  - Tissue damage: There is the risk of lesions induced by the placement or by the relative motion of the electrode in the brain.
  - Inflammatory reaction: Initial implant of the electrode is believed to damage the surrounding structures, causing the microglia to be activated. In the acute response there is a secretion of inflammatory cytokines, some of which are neurotoxic at high concentrations. In the chronic response there is an encapsulation of the electrode by the astrocytes, which create a layer forming a barrier around the electrode.
  - The electronic circuits implanted in the brain have to be compact and with low power consumption.

  Management of the response after implant of the electrodes is critical for long-term stability as it can help to preserve neurons near the implant.
- Developing efficient algorithms: With an increasing number of "channels" to be read or stimulated, also the complexity of the analysis increases [24]. This is especially true if the goal is to restore lost functions. In this case it is necessary to read, process and generate many signals at the same time.
- Learning how to incorporate prosthetic devices into body representation using brain plasticity. It seems that long-term utilisation of an actuator directly controlled by the brain activity might lead to cortical and subcortical remapping, assimilating the actuator in the same maps that represent the body [7, 39].

Besides this, also advances in miniaturization and biosensors are expected to facilitate a non-invasive kind of monitoring of neuronal signals.

3.4 FES—Functional Electrical Stimulation

Functional Electrical Stimulation (FES) is a rehabilitation technique that uses electrical current to stimulate peripheral nerves. FES enables muscles to perform activities even though they might be weak or paralyzed because of neurological disease or injury.
This means that the stimulated peripheral motor nerves innervating the muscle tissue have to be intact to permit improvement or restoration of the overall muscle activity through this technique.

FES devices use different stimulation strategies:

- Surface electrodes which are placed on the skin over the targeted motor points of the muscles to be stimulated. They are noninvasive, inexpensive and easy to apply, but they are not able to isolate deep muscles, can irritate the skin and cause pain.
- Percutaneous electrodes which are placed close to the motor point of muscles. The electrodes are passed through the skin, but are only considered for short-term FES interventions. They provide high selectivity and a repeatable response.
- Implantable electrodes are placed around muscle nerves or over muscles. They are characterized by high selectivity, but they also present mechanisms of failure that include insufficient strength, poor recruitment properties, problems with stimulus threshold and poor repeatability. Other problems are linked to biological factors caused by the surgical installation which include encapsulation, infection and rejection of the electrode. Due to the long term implant, there are also electrochemical degradations and mechanical failures.

FES can be used to generate a body function that the patient is unable to perform alone, thus as a permanent orthotic system.
It can also be used for providing short-term therapy to restore voluntary function, this means to help the neuromuscular system relearn the execution of impaired functions. The main fields of application are after stroke and spinal cord injury:

- Lower limbs: Drop foot and gait
- Upper limb: Grasping and reaching
- Bladder and bowel control.

Speaking of FES as a therapeutic system (FET—Functional Electrical Therapy), it can be used to compliment other movement therapies to augment the rehabilitation potential, thus applying it with different types of ergometers for arm and leg cycling or also stepping. This kind of therapy, although very promising, is not widespread due to the lack of studies and the experience required to apply it.
Another problem is linked to the pain due to the electrical stimulation. This pain and tissue damage is inversely related to the electrode's size, because of the high charge and current density [48].
Coupling this stimulation with other technologies could improve daily life for patients. For example, combining FES with robotics would permit to achieve precise movements involving multiple degrees of freedom. Also the development of neuroprostheses based on a combination between FES muscle stimulations and the analysis of muscle synergies may be feasible in the future, as well as the combination with BCI. The combination with BCI technology shows a lot of promise for the future, but development is still required for extracting accurately brain activity in the planning state before the patient initializes his motor commands to get the necessary information to trigger the electrical stimulus to be sent to the effector muscles.

3.5 Prosthetics

Great advances have also been achieved in the field of prosthetics, even if the progress has not been as remarkable with upper-limb prostheses as it has been for artificial legs [54].
Thanks to the integration with Electromyographic (EMG) signals, which reflect the neural information from the neurons, it is possible to activate prosthetics' functions. It has been proposed that a hybrid BCI (h-BCI) could improve the accuracy of implementation of the subject's voluntary intentions by the prosthesis. A shared-control model of operation, on which the h-BCI would be based on, would be achieved by combining high-order brain-derived signals of the subject's voluntary intentions, and low-level artificial "reflex-like" circuits, for improving the precision of the generation of the prosthesis' movements [40].
The fact is that the loss of motor functions, especially the action of grasping, creates a life-long dependency on caregivers. This dependency also leads to a decrease of quality of life [2], so it is a primary goal to restore the functionality at least partially to permit the patient to regain some independence.
The field of prosthetics could draw many benefits from the integration with the BCI, although mainly from more invasive processes.
In fact one of the major issues related to this field is the absence or reduced chance of feedback from the prosthetic devices.
Virtual Reality could be used to provide feedback, mostly during the learning and training process.
Tactile and proprioceptive peripheral signals contribute to the normal use of the limbs and to the perception that they belong to the body. To get this sensory information back from the subject's brain in case of a prosthesis, it will have to be equipped with various sensors that can provide this kind of information [41, 42, 62], continuously informing the brain about the effector's function [36].
Some studies carried on on monkeys suggest that cortical microstimulation might be a useful way to get long-term feedback from prosthetic limbs controlled by a BCI to the brain.

Another problem is surely the integration of new technologies into devices that are suitable for real-life and long-term use. When transferring new technologies from research prototypes into commercial devices it is important to remember that the environment in which they will be used is not as fixed as the research field, which could mean that the power supply needed might not be the same for a certain amount of time and that there could be different kinds of errors that would not be expected.

The neuroprosthetic developments in the next years should include fully implantable recording systems that transmit multiple streams of electrical signals wirelessly to a BCI, that decodes spatial and temporal characteristics of movements and intermittent periods of immobility [40].

3.5.1 Cognitive Prosthesis

Cortical prostheses seek to restore cognitive functions that have been lost due to diseases or injuries [65]. This kind of prostheses has to deal only with internal brain signals, creating an appropriate output by encoding the input brain signals so that the damaged brain area can be bypassed restoring the cerebral function.
It is necessary to understand what the part of the brain does, then connect it to the rest of the brain in the appropriate way.

Recent studies have concentrated on hippocampal-cortical prosthesis to restore the memory functions.
The Hippocampus is the region of the brain that forms declared memories and damage in these areas can result in permanent loss of the capacity to create new long-term episodic memories.
The idea of this kind of prostheses is to use multielectrode arrays for the extraction of short-term memory applying them upstream from the damage, transmitting the activity to the device that transforms the input into output and then transmits this information downstream from the damage, electrically stimulating the output of the Hippocampus and permitting to send the memory for storage. In this way it would be possible to bypass the damage in the hippocampal areas.
It is necessary to understand the models [5] of transformation between short-term memory and long-term memory to translate them into hardware and to move from studies on animals to the application on the human model.
Also technical issues will have to be overcome, as miniaturization and low power batteries are a must for this kind of implant.
Another problem is related to the same challenges that invasive BCI methods have to face, as this kind of implant requires brain surgery, with high risks of brain damage and rejection of the implant.
In this case also a great ethical issue arises, because of the direct intervention on the brain. Many people fear that this would affect the subject's identity, modifying the personality and changing intelligence, transforming the human being into a machine.

4 Common Issues Limiting the Diffusion of New Technologies in Neurorehabilitation

Even if some great improvements have been achieved in neurorehabilitation technology, this kind of treatment is still uncommon in the clinical environment.

There are different issues that may limit its spread. Some of these issues are common to most fields of neurorehabilitation, while others are significantly linked to specific topics and environments that arise in technologically assisted rehabilitation [12].

4.1 Psychological Issues

There is a great influence of acceptance in the difficulty to spread new technologies in neurorehabilitation.
The aim of some devices, like in robotic rehabilitation, is to require less medical personnel pro patient but at the same time permitting the therapist to completely focus on helping, correcting and motivating the patient. This fact may lead to the fear of being substituted on part of the therapists.
It is fundamental to accept that only integration between the old and the new is possible at the moment. Technology and robots in particular can not substitute completely the therapist's function [8]. So this fear of the medical environment to be substituted is surely unnecessary and counterproductive.
Nevertheless there is another problem of acceptance by caregivers which relates that the constant evolution of technology requires learning new solutions and capabilities, changing the clinical behaviour mastered over years by the therapists [67].

Another great challenge regarding acceptance of this kind of technology is on the part of the patient [14]. It is important to remember that new technologies may be intimidating and overwhelming for some users, especially older people that are not used to modern technologies.
Especially older patients might not appreciate the fact that technology may reduce the personal contact with a caregiver.
Then there is the problem of implants. To be accepted by the patient, the implant has to act in the same way and feel like the part of the subject's body it will substitute or implement (e.g. prosthetical limbs, neural prostheses).

The point is that laboratory experimentation does not require attention to issues like portability, aesthetic design, conformity [52].
A study conducted by Diaz [11] reviewed 43 robotic systems as far as functionality and acceptance. They found that most of them are not marketed, are too bulky and not affordable for most people. Studies have found that robotic therapy can be as good as conventional treatment, but as long as it doesn't have significant improvements, showing clear advantages, it will find little acceptance. Virtual reality, on the other hand, is usually much cheaper and feasible. However, there are not enough studies and clinical trials to support a broad acceptance, even though it has been found that it is a safe procedure [38]. To permit the widespread of this technology, it is necessary to merge aesthetic and engineering design, as social acceptability is a key concern for patients.

4.2 Ethical Issues

New technologies used in neurorehabilitation are not suitable for all neural impairments, nor for every stadium of rehabilitation, nor for all patients.

This limitation is often linked to:

- The characteristics of this kind of technology
  This application of different technologies is recent, so the use is related to present studies, preventing a differentiated and effective utilization of this kind of technology for various types of pathologies.
- The possibility to apply the technology to the different patients
  Some devices can only be used on patients with specific characteristics, thus limiting the possibility to help in some kinds of situations (e.g. in the case of cochlear implants the presence of auditory nerve fibers is essential for the functioning, some devices can only be used in the chronic phase after the neurological damage and not in the acute stage).
- The different factors that may influence directly the condition of the patient.

This leads to some sort of "discrimination" between different patients that may not have the same opportunities of treatment.

Another issue is the absence of an "informed consent" for certain types of neurorehabilitation: with the introduction of new technologies into the clinical practice it will become necessary to inform people about the application of these technologies, about the benefits and of course the risks of the therapy.
This may not be easy if we think about the fact that most people do not know much about these kinds of therapies and that the patient may not be fully aware of all the implications of his/her decision.

Another great challenge is avoiding an economical discrimination between patients. Because of the high costs of this kind of treatment at the moment, not all patients may have access to neurorehabilitation. Surely a goal must be the diffusion of this technology allowing everybody to have access to it. This may be closely linked to at home rehabilitation.
Even if the cost benefit ratio may not always be in favour of the new devices, medical facilities may be still able to recover the cost by spreading the use of these devices. This may be significantly more difficult in the case of devices for continuing the rehabilitation process at the patient's home.
This may create the possibility to continue with at home rehabilitation only for wealthy people.

4.3 Legal Issues

Today many of the devices developed for neurorehabilitation at the prototypal state. This means that they can be used for research purposes but they are not allowed into medical practice.
Some other devices went through this step and can be used in clinical environments but not always the certification they get permits their use in every state.
This is because of the different rules and laws that decide about this kind of matter. This is a great limit for the diffusion of new technologies as it takes a great amount

of time to modify and adapt a functioning device to fit the rules of a specific country to be used out of the research environment and in the clinical setting.

Another point is the responsibility once this technologies are allowed into the clinical practice. It is important to clarify who is the responsible for technical problems or damages caused to the device or, even worse, by the device to the patient.

4.4 Economical Issues

In the healthcare market introducing a new kind of technology means to have to reorganize care processes and protocols [67].
Some of the barriers may depend on the lack of evidence about the economic implications of the new technologies. This leads to the fact that the short-run perspective, with the current cost of technology as primary driver for decision on adoption, risks to prevail.
In this perspective the effectiveness of new technologies is a necessary but not sufficient condition for their adoption.
The cost benefit ratio is not always in favour of this kind of technology, mostly because, for an optimal rehabilitation, the patient has to get through different devices. This problem is closely linked to technical and engineering evolution: today a device that is able to cover the whole rehabilitation process does not exist and probably won't exist for a long time to come. Every rehabilitation device focuses on a specific type of task, mainly because technology is not yet able to support this specific need.
Economical challenges for the diffusion of this technological devices become closely linked to ethical issues if the drive for study and research comes from the industrial environment or from certain institutions that push towards specific types of technologies. This happens also if technologies derive from a different field of application and use, like the gaming industry, and if this origin limits the diffusion and the use of this devices.
This would mean that technologies get a drive to development only if external institutions and industries have interest in them, which is mostly an economical interest.
However this problem could be also a great resource: research and development of rehabilitation devices can take advantage of already existing technologies investing their precious time into the adaptation of this technologies to the specific purpose of rehabilitation.

Funds have always been a great issue in the world of research. Despite this great limitation of the research environment, many groups are working on similar or even identical topics. A great challenge for the future should certainly be a unification of efforts and a better dissemination of the results.
Cooperation between people with different background or coming from different countries is mandatory, but it is not always easy and feasible mainly because of the high costs and the competition to get public funds.

4.5 Technological Issues

One big issue is that nowadays technology is still not able to meet the needs and requirements of neurorehabilitation and neural engineering in the long term.
This is sometimes related with the fact that technologies developed for other uses are introduced in neurorehabilitation and are not specialized for the needs that arise in this application field.
This is especially true for gaming technology that the gaming industry develops or is going to develop: it can not be taken for granted that this kind of technology will be appropriate for use in rehabilitation. Also robotic technology that is used in robotic assistive devices and training systems is often not specifically developed for this applications but rather for industrial applications. Therefore there is still room for technological improvements to increase the performance of robot based rehabilitation systems.
Other problems include also the ease of use, the level of training for therapists and caregivers to master the technology.
Another limit of many technologies is that they can only be used by patients with preserved residual voluntary movement. The FES systems for grasp restoration are an example of this limit, as they can only be used with preserved shoulder and elbow function.

4.6 Medical Research Issues

Though the advantages of the new technologies have been described by some researches, these studies are far too few and too small to draw strong conclusions.When they exist, clinical trials are of small sample sizes, sparse and lack of consistent methodologies, preventing a wider use of this technology. This is sometimes linked to the fact that it's not always easy to quantify what is happening during rehabilitation, especially if response by the patient is minimal because of his/her impairment, leading also to the difficulty to carry out validation studies.
Results concerning the training protocols required to induce functional improvements (e.g. locomotion) are scarce and the relationship between the improvement and training dosage is still unclear [57].
Furthermore in most fields, advantages compared to traditional rehabilitation methods are not clear.
Another problem is linked to the fact that often the aim of the treatment is directed to the improvement of the clinical signs and not to the improvement of the movement disorder like it should.
According to the World Health Organization, "Rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal

physical, sensory, intellectual, psychological and social functional levels. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination" [34].

This is because every person needs to be put in a context, as functioning and disability are results of the interaction between the health conditions of the person and their environment [71]. In addition to this, even if there are small gains in function, these may not be sufficient for everyday life. This fact also highlights the issue of a kind of validation that is "meaningful" for the subject: this process should be based on real-life activities and not on clinical signs and scales.

Finally, on a larger base, there are limits in the dissemination, defined as the active approach of spreading evidence-based intervention, and the multidisciplinary approach in clinical practice for an appropriate application into therapeutic intervention.

5 Conclusions

As seen in the previous sections, the constant evolution of technology that can be used for rehabilitation in case of neural damages creates hope for always greater goals, but also greater problems and future challenges.

For robotic rehabilitation, it will be necessary to produce adaptable devices with great intelligence to better tailor the therapeutic and assistive intervention to the needs of the patient, also addressing the problem of limited degrees of freedom, as human motion is the sum of complex movements that this kind of technology should be able to reproduce. This technology will have to be able to meet the needs of both the patient and the rehabilitation progress using cost-effective devices with user interfaces that make them intuitive and easy to use.

Cost-effective technologies are also fundamental in Virtual Rehabilitation. This means that the evolution towards high-quality affordable products is necessary to enable the spread of this promising tool in clinical settings and in at-home rehabilitation. This has also to be supported by the development of clinical, methodological and technical standards along with clinical trials for consistent evidence for usability and efficacy [57].

The importance of addressing the needs of the patient is fundamental also in the development of prosthetic devices, as it is not only expected to restore the physical appearance, but also most of the lost functions of the amputated body part. The final goal is to mimic the human motion pattern, power requirements and anatomical features, as for now the popularity of prosthetic devices, especially for the upper limbs, is not adequately high due to their inability to meet the expectations of the user in real world and daily life activities [3].

It will be fundamental to increase the integration between the various systems to provide an interaction link with the outside world and to improve the lives of physically disabled people. If the future goal is to offer solutions to these people and

to augment their capabilities of interaction in real life, then the new and improved technologies must be combined with existing assistive technologies (AT).
This includes the development of hybrid technologies that integrate BCI systems, the design of new optimized algorithms, the use of mental states to make the assistive devices react to the user, the improvement of usability of the new devices and of the devices themselves.
Especially for BCI, permanent FES and all related technologies, it is clear that the major challenges that will determine the success of future applications are closely linked to the long-term functionality of implantable devices and their wireless transmission to the actuators. Also the biocompatibility of the permanent implantable devices, as well as the efficiency of energy transfer from external batteries will have to be improved.
Some major problems will have to be overcome to achieve the required accuracy of these devices in real life, not only validating these technologies in experimental fixed situations.

The main concept is that any kind of technology should look to the long term as a final goal. It's not only about the transfer of the rehabilitation technology out of the clinical setting and into the user's home, but also to improve the patient's life condition on the long term, without compromising this duration with the subject's safety.

Many resources must be invested in research on rehabilitation in the pediatric field even though many difficulties may arise when treating children because of the rapid physiological changes, especially during growth spurts. This aspect is very critical because children are the ones who have the most life years to gain from the development and use of new technologies and treatments, and if needed they should have access to rehabilitation professionals especially during the periods of growth. This means that there is a need for effective and convenient treatments for children, in which the training is task-oriented and repetitive but at the same time motivating, for example through the use of compelling games.

In order to reach these goals a close collaboration together with a coordinated research between engineering and medical science are required [57], also to become able to provide safe, customized and motivating rehabilitation experiences to patients with all kinds of neurological impairment.

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Rehabilitation Technologies Application in Stroke and Traumatic Brain Injury Patients

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Abstract Neurorehabilitation plays a crucial role in the multidisciplinary management of brain injury patients. Emergent therapies based on rehabilitation technologies such as robots, bci, FES, and virtual reality could facilitate cognitive and sensorimotor recovery by supporting and motivating patients to practice-specific tasks on high repetitive levels during different stages of rehabilitation. Robots have become a promising task-oriented tool intended to restore upper limb function and a more normal gait pattern. Virtual reality environments by providing powerful sensorimotor feedback and increasing user interaction with a virtual scenario could improve gait, balance, and upper limb motor function. This chapter will provide an overview on

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the rationale of introducing rehabilitation technologies-based therapies into clinical settings and discuss their evidence for effectiveness, safety, and value for stroke and traumatic brain injury patients. In addition, recommendations for goal setting and practice of training based on disease-related symptoms and functional impairment are summarized together with reliable functional assessments.

1 Introduction

Stroke and traumatic brain injury (TBI) are major causes of long-term disability worldwide [32]. For each year, about 16 million people experience a first-ever stroke. This number is expected to rise to 23 million first-ever strokes in 2030 [135]. Globally, stroke is the second leading cause of death above the age of 60 years, and the fifth leading cause of death in people aged 15–59 years old [84]. An estimated 57 million people worldwide have been hospitalized with TBI [152], which is the leading cause of death and disability in children and adults from ages 1 to 44. At least 5.3 million Americans, 2 % of the U.S. population, currently live with disabilities resulting from TBI [76]. This means that there is an increasing need for rehabilitation strategies to enhance recovery, improve functional status, and promote quality of life, a current challenge for healthcare sectors, industries, financial systems, and aging societies as a whole.

There is strong evidence suggesting that the damaged motor system is able to reorganize in the presence of motor practice [6, 65, 74]. Further, recent research has shown that interventions that include high-intensity and repetitive task-specific practice are more effective than traditional approaches to enhance motor recovery after brain injury [75]. Relearning motor tasks requires an optimal set of practice conditions that promotes the maximum learning benefits [46].

Over the past decade, there has been an increasing interest in using technology for neurological rehabilitation [68]. The aim is to facilitate motor recovery by supporting and motivating individuals with impairments to practice-specific tasks on high repetitive levels. For example, robot assistance is able to support and alter ongoing movements by the application of forces through actuators. Robotic-assistive devices can also monitor performance and provide feedback to the user based on measurements made by the sensors within the system. Furthermore, in combination with virtual reality conveyed on a computer screen or head-mounted display, the technology can be used to convert repetitive movement practice into engaging functional tasks with game-like features. Overall, such developments have led to real-time multimedia exercise environments for clinical rehabilitation that are comparably or more effective than conventional therapy [74, 100]. Yet, in this still early stage of development, their full potential still remains to be determined.

1.1 Recovery After Stroke and Traumatic Brain Injury

The primary goals after stroke and TBI are to reduce brain tissue damage and promote maximal tissue preservation and recovery. Rapid detection and appropriate emergency medical care are essential in the acute phase [56]. Once a survivor is medically stable, the focus shifts to rehabilitation. The goals of the subacute phase include preventing secondary health complications, minimizing impairments, and achieving functional gains that promote independence in activities of daily living [35].

Early and spontaneous neurological recovery is often attributed to the resolution of edema or return of circulation within the ischemic area and may continue for up to 8 weeks [7, 55, 81]. Later recovery, based on neural plasticity and reorganization, plays an important role in the restoration of function and reduction of impairment. Neural plasticity and reorganization of the brain leads to functional changes in the surrounding brain tissue and in remote locations that have structural connections with the injured area [48, 101, 121].

It has been reported that most neurological recovery occurs within the first 3 months post injury, and recovery may continue at a slower pace for at least 6–12 months [58]. Progress toward recovery may plateau at any stage with only a very small percentage of individuals achieving full recovery [34, 39, 58]. Recent clinical practice guidelines recommend that rehabilitation therapy should start as early as possible, once medical stability is achieved [35].

2 Clinical Problems: Disability and Recovery After Stroke and Traumatic Brain Injury

The types and degree of disability depend upon which area of the brain and degree of tissue damage. It is difficult to compare one individual's disability to another, since every patient can sustain damage in slightly different sections of the brain and in different amounts. In general, five types of disabilities can be defined: paralysis or problems controlling movement; sensory disturbances including pain; problems using or understanding language; problems with thinking and memory; and emotional disturbances.

Paralysis and motor control problems are the most common disabilities. Patients have difficulty with everyday activities such as walking or grasping objects, and some have problems with swallowing (dysphagia). Damage to a lower part of the brain, the cerebellum, can affect the body's ability to coordinate movement (ataxia), leading to problems with walking, balance, and body posture. Patients may also lose the ability to feel touch, pain, temperature, or position. Sensory deficits also may hinder the ability to recognize objects held and can even be severe enough to cause loss of the ability to recognize one's own limb. Some patients experience pain, numbness, or odd sensations of tingling accompanying paralyzed or weakened limbs (paraesthesia). The loss of urinary continence is fairly common immediately after an event. Patients may lose the ability to sense the need to urinate or the ability to control bladder muscles. Patients frequently have a variety of pain syndromes resulting from damage to the nervous system (neuropathic or centrally mediated pain), e.g., shoulder pain. An injury to any of the brain's language-control centers can severely impair verbal communication (aphasia). The most severe form, global aphasia, is caused by extensive damage to several areas of the brain involved in language function, thereby patients lose nearly all their linguistic abilities; they cannot understand language or use it to convey thought. Stroke or TBI can cause damage to parts of the brain responsible for memory, learning, and awareness. Survivors may have dramatically shortened attention spans or may experience deficits in short-term memory. Individuals also may lose their ability to make plans, comprehend meaning, learn new tasks, or engage in other cognitive activities. For example, patients who develop apraxia (loss of ability to carry out a learned purposeful movement) cannot plan the steps involved in a multistep task and act on them in the proper sequence. Finally, many survivors feel fear, anxiety, frustration, anger, sadness, and a sense of grief sometimes related to their physical and mental losses. These feelings are a natural response to the psychological trauma or because of damage to mood control centers.

2.1 Upper Limb Impairment in Stroke and TBI

Severity of upper limb paresis in the first month after brain injury remains the best predictor of recovery of arm function and reflects the degree of damage in cortical motor areas and corticospinal tract. Depending on lesion location, there could be a different probability of recovery, for example, there is greater recovery from hemiparesis resulting from cortical lesions than subcortical or internal capsule located lesions, presumably due to convergence at this level of most axons coming from the primary motor cortex [130]. However, hemiparesis could be the result of a wide variety of lesion location and no correlation between specific kinematic and dynamic abnormalities with lesion location has been found [71].

Upper limb cortical mechanisms that control shoulder and elbow are integrated with those more distal-like wrist and hand, as part of a system subserving reaching, prehension, and manipulation. Early presence of proximal upper limb active motion could be determinant for functional recovery because upper limb proximal motor control is related to the sparing of crossed corticospinal tracts, which are considered crucial pathways for hand control [54]. This fact has important implications for clinicians in terms of pursuing upper limb proximal rehabilitation even in the absence of distal motor function that potentially could appear at a later time.

In stroke and TBI patients, the upper limb may be hypotonic or flaccid without any volitional movement initially, or rigidly spastic later on. Moreover, undesired motor synergies could appear limiting independent control of single joints. There is scarce evidence about spasticity significantly interfering with voluntary movement, and in

contrast no relationship has been found between spasticity, weakness, or loss of dexterity [132].
However, other abnormalities after stroke cannot be explained by spasticity, weakness, or sensory loss. Thus, apraxia a cognitive and execution impairment is characterized by a loss of ability to perform a prior-learned action. It occurs more frequently in right hemispheric lesions but could occur on both sides of the body. Abnormalities in interjoint coordination are observed in these patients and seem not to be related to motor synergies, spasticity, or weakness. They are characterized by an imbalance between shoulder, elbow, and hand motions with deficit in transforming the planned trajectory into an appropriate motion, resulting in disorders of the kinematic and dynamic multijoint movements [10].
Introducing a repetitive, intensive, and varied task-oriented therapy appears to be crucial to overcome these impairments and to increase generalization of new learned tasks. Impairment of upper limb sensory and proprioceptive function is a predictor of poor functional recovery even though motor function is intact or minimally impaired. This could be due to an interruption of projections from the cortical areas that represent upper limb dynamics [122].

2.2 Gait Disorders in Stroke and TBI

Gait dysfunction is a common clinical manifestation of neurologic disorders in stroke and TBI. Patients usually show a gait pattern with loss of symmetry, decreased stance time and increased swing time for the affected limb, increased stance time on the unaffected side, and decreased step length. Swing phase appears delayed and could be associated to compensatory hip elevation (hicking), lateral trunk displacement, ankle equinus, and cincumduction movements (Fig. 1). Speed of ambulation is decreased and influenced by weakness of hip flexors, knee extensors, and ankle plantar flexors [145].

Fig. 1 Hemiparetic gait

TBI patients usually walk slightly faster than patients who had a stroke, with an increased step length. Compared to stroke in patients with TBI, the stance time for the affected limb is diminished, even though it remains increased for the unaffected limb [103]. Lesions affecting the frontal lobes can result in apraxic gait with a rigid pattern and the feeling of being stuck to the ground. This kind of gait is characteristically hypokinetic with slow-speed gait and limitation in limb advancement.

In summary, both patients with stroke and TBI can show a spastic hemiparetic gait pattern. Abnormal muscle activation pattern could lead to problems in motor coordination. In many cases, the cause of the deficits maybe related to spasticity but frequently this is accompanied by muscle weakness with decreased ability to recruit motor units, muscle atrophy, loss of muscle contractile properties, and agonist–antagonist cocontraction. All these factors may adversely impact the generation of functional movements during gait [102].

3 Technology in Rehabilitation

3.1 Biofeedback in Neuroplasticity and Brain–Computer Interface (BCI)

After stroke, 80 % of patients experience acute paresis of the upper extremity and only approximately one-third achieve full functional recovery [9]. Passive phenomena like reperfusion of the penumbra and resolution of brain oedema do account for some of the motor recovery post stroke or in traumatic brain injury. Nevertheless, recent discoveries that neurogenesis and neural reorganization can in fact occur in the adult after CNS injury have been revolutionary for the field of neurorehabilitation and contradict the dogma expressed by Santiago Ramon y Cajal back in the late nineteenth century. Evidence of such neuroplastic changes have been reproduced in both animal [3] and human models [150]. Thence, research on how these neuroplastic phenomena can be exploited for motor recovery is currently a key focus, with neurochemical [11, 20, 134] and neurophysiological [86, 139] evidence of recovery-related neuroplasticity supporting the direction of this work.

A fundamental element in any process of learning is the presence of feedback. From a child who is learning to walk, to a gymnast who is training for a somersault, a real-time stream of multisensory data is continuously flowing to the brain during motor tasks. The integration of data from proprioceptive, visual, auditory, and sometimes even pain receptors helps the brain get a complete picture of the body's position, motion, and end result of any motor intention. Relaying of such data to the cerebellum, prefrontal, and motor cortices, over a repeated number of successful and failed attempts, forms the basis of motor skill learning [59, 123].

Following stroke or traumatic brain injuries, this motor execution → feedback loop is often disrupted. Damage to motor pathways, either at a cortical or subcortical level, leads to difficulty or complete inability to execute motor intention, which thus breaks the feedback loop very early on. The core of most neurorehabilitation strategies is the aim of reclosure of this loop, either by aiding movement completion or by giving some form of feedback to the central nervous system that is coupled with the initial motor intention.

If one looks at even the most basic of physiotherapy strategies like passive arm movement, the assisted physiotherapist-guided motion is allowing for proprioceptive sensation and visual feedback to reach the brain. A more affective approach—and currently a gold standard in the physiotherapy field—is the use of repetitive, task-specific training for relearning of motor skills needed for activities of daily living [118, 140]. This directly addresses one of the goals of neurorehabilitation as proposed in the latest clinical guidelines, which is to empower patients and families by helping motor function improvement and achievement of the highest level of independence in activities of daily living [99].

3.1.1 Electromyographic (EMG) Biofeedback

With this current knowledge on neuroplasticity in mind, one can start to appreciate the rationale behind the more recent technology-assisted strategies in the field of neurorehabilitation. One of the earliest technologies developed for biofeedback in the field of neurorehabilitation is EMG biofeedback. The mechanism behind this approach is the detection of attenuated electrical activity which occurs in paretic muscles upon motor intention and the conversion of this ineffective data to visual or auditory feedback to the patient—thus reclosing the loop. Research on such setups go as far back as the 1960s and within merely a decade it had become a standardized rehabilitation tool used commonly by physiotherapists [41, 155]. A recent Cochrane review exploring the efficacy and benefits of EMG biofeedback in motor recovery post stroke has identified a number of trials publishing evidence of benefit for motor power, function, and gait recovery when this technology was added on to the standard physiotherapy regime but this has yet to reach statistical significance in view of the limited size of trials and robustness of results [157].

3.1.2 Brain–Computer Interface

Recent advances in neurophysiological signal acquisition and processing techniques have opened the way to a higher form of neurorehabilitative feedback approach, which can completely bypass the peripheral physiological outputs of the body—*brain–computer interface (BCI)* [13]. Neurophysiological acquisition methods may range from noninvasive technologies like electroencephalography (EEG), magnetoencephalography (MEG), functional near-infrared spectroscopy (fNIR), and functional magnetic resonance imaging (fMRI) to invasive electrocorticography (ECoG). EEG technology still holds several limitations with respect to spatial resolution and quality of brain signal pick-up. Nevertheless, its safety, noninvasiveness, and excellent time resolution makes it one of the most popular signal acquisition media

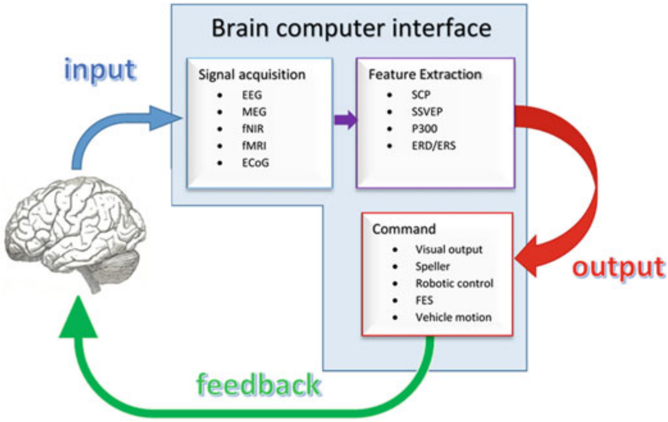

Fig. 2 Brain–computer interface system and the feedback loop

for BCI. Among the earliest accomplishments in the world of BCI was Birbaumer et al.'s success in enabling two 'locked-in patients' to communicate using a BCI speller [12]. One of these patients was reported to have eventually learnt to use the BCI on his own to write letters and communicate with his friend [98].

Brain–computer interface systems take advantage of a number of different neurophysiological changes and patterns that have been noted to be associated with particular mental states and tasks [156]. Some of these modalities are dependent on the subject's intention and can be modulated actively through training. These include the $P300$ response (a positive EEG deflection 300 ms after a target stimulus is presented to the subject) and the *slow cortical potential* (SCP) (changes in amplitude that correlate with level of cortical activation). Both of these paradigms have been employed most notably for BCI spellers. Other BCI paradigms are based on passive, natural responses to present stimulus and need no training, like the *steady-state visual evoked potentials* (SSVEP) (change in the frequency of occipital cortex oscillations that matches the frequency of flashing light presented). These three modalities of BCI are mostly used for ***assistive*** purposes, substituting a function that was lost due to motor or speech impairment following conditions like stroke, amyotrophic lateral sclerosis, or traumatic brain injury (Fig. 2).

The fourth major modality of BCI is based on motor imagery related changes in oscillatory activity like *event related (de)synchronization* (ERD/ERS). Desynchronization of EEG activity can be observed following both motor imagery and motor execution initiation, over the motor cortex, in the Mu and beta frequencies, followed by re-synchronization shortly after motor activity. This has become the modality of choice for BCI-based motor rehabilitation i.e., for ***restorative*** rather than assistive purposes [131]. Motor imagery (MI) itself has been shown to be associated with motor cortex activation [107, 128]. More importantly, repetitive MI tasks coupled with conventional (physiotherapy and occupational therapy) rehabilitation has been shown to have an added benefit in motor recovery [161]. This is of particular interest when dealing with patients with negligible residual muscle function, in whom standard task-specific or constraint-induced therapy would not be possible.

Initial BCI studies in stroke and traumatic brain injury patients focused on control of mu rhythm via either motor imagery or motor execution in order to either move cursors on screen or move hand orthoses [16]. These assistive approaches were subsequently followed by restorative BCI systems, with or without the use of haptic devices [4] or functional electrical stimulation [29] for proprioceptive feedback. Two examples of BCI-based therapeutic setup with purely visual feedback will be briefly introduced next, while further technological devices will be discussed in subsequent sections.

The first is a computer game-based neurofeedback system developed by Prasad et al. [115] for the rehabilitation of persons with chronic hemiplegic after stroke. The setup consisted of EEG signals acquired from C3 and C4 electrodes (overlying the motor cortex) which are processed online to translate into left and right movements of a ball on a computer screen. Subjects were required to maneuver the ball into a basket by imagining left- or right-hand movement according to the direction required (Fig. 3). Performance throughout the sessions was based both on accuracy classification during the MI task and periodic motor function recovery scores as measured by action research arm test and grip strength. After a 6-week period, improvement in at least one modality of function was noted in all patients and every patient managed to operate the BCI successful with an average accuracy of 60–75 %, suggesting feasibility of such a setup in the context of post-stroke rehabilitation. [115].

In a more recent publication by Cincotti et al. (2012), an elegantly designed BCI-based upper limb rehabilitation system for patients post-stroke is presented. The system is composed of a 32-channel EEG input, driving a BCI software that delivers two concurrent outputs when the patient's EEG signal is compatible with hand opening/closing motor imagery. The first output is intended for the assisting physician and is in the form of a moving cursor, representing the patient's mental activity. The second output is a visual feedback intended for the patient and is in the form of realistic images of moving hands, projected onto a white sheet that is placed over both of the patient's hands (Fig. 4). In this way, attempts at hand movement

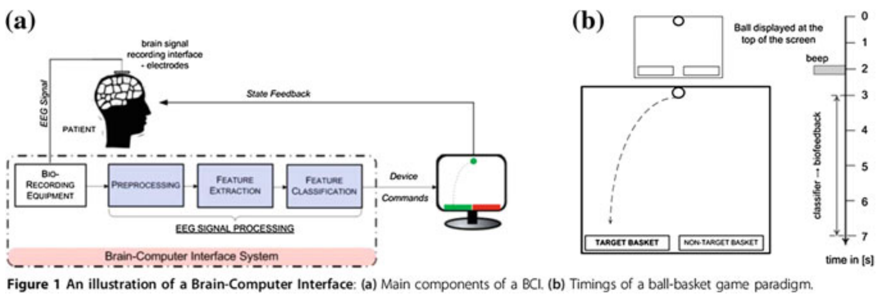

Fig. 3 A computer game-based neurofeedback system driven by EEG-based brain–computer interface—*Reproduced with permission from* Prasad et al. [115].

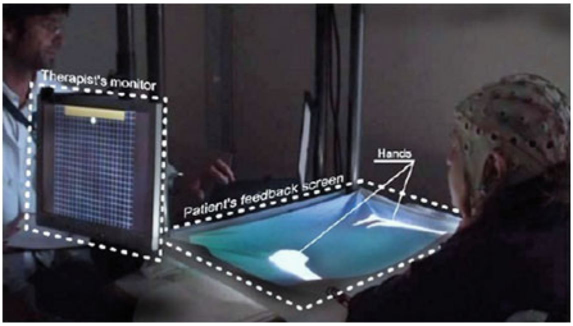

Fig. 4 EEG-based BCI upper limb rehabilitation system, giving both motor imagery information to the therapist and visual realistic hand motion feedback to the patient—*Reproduced with permission from* Morone et al. [94]

lead to the visual illusion of the paretic hand moving, as projected onto the screen superimposed on the paralyzed hand. This system was installed in a rehabilitation ward and tested on 29 stroke patients in whom increased alpha and beta reactivity was noted post training, along with moderate increases in functional outcome measures when compared to control subjects testing non-BCI MI practice.

3.1.3 Conclusion

As its name implies, brain–computer interface is merely a new interface that can translate a person's intentions into numerous outputs of various forms. Thus, the present challenge in neurorehabilitation research is the development of useful BCI applications and platforms that can offer more effective and efficient motor recovery to patients suffering from stroke and traumatic brain injury.

To date, most studies explore the benefits of MI-BCI rehabilitation in conjunction with standard physiotherapy, and so robust statistical evidence of superiority of MI-BCI-driven rehabilitation over standard active motor training is still difficult to prove and further randomized trials need to take place. Confounding factors to the observed beneficial effects of MI-BCI rehabilitation—albeit desirable themselves—include the increased willingness and time spent by patients doing active motor training within the BCI setup itself when compared to those in the standard, repetitive task-training groups.

The potentials for BCI in this context are various: visual, proprioceptive or, any other output that is coupled with motor imagery/intention can reinforce biofeedback to the patient and provide valuable information to the clinician regarding the patient's engagement and performance in these previously invisible MI tasks. Finally, innovative outputs and applications driven by MI-BCI can increase patient's motivation and engagement in his rehabilitation process, through the use of media like video games, engaging work-out sessions, or simply through the confidence-boosting sight of his arm actually moving on command, made possible only through BCI-driven robotics or functional electrical stimulation.

> "If I can't do it once, why do it a hundred times?"
> Quote from a severe hemiplegic patient on conventional table exercises
> - Reinkensmeyer and Housman, 2007

3.2 *Virtual Reality-Based Rehabilitation*

Rehabilitation technologies such as virtual reality are based on motor learning principles and could be implemented in order to compensate, restore, and recover cognitive impairment and loss of sensorimotor function caused by stroke and TBI.
Virtual reality can be defined as an approach to user–computer interface that involves real-time simulation of an environment, scenario, or activity that allows for user interaction via multiple sensory channels [17].

The rationale for using virtual reality training on brain injury rehabilitation is because during therapy a repetitive massed practice of relevant functional tasks based on imitation and movement observation could be useful to facilitate targeted brain networks and potential neuroplastic changes. Functional and motor recovery observed during virtual reality task-oriented therapy may be linked to induced neuroplasticity changes with a mirror-neuron system activation, reorganization of damaged motor cortex, decreased aberrant cortical hyperexcitability on unaffected hemisphere, and at synaptic level synthesis of neurotrophic factors (BDNF) that encourage axonal sprouting and dendritic spine formation [15, 109, 159].

Virtual environments are characterized as immersive, where a three-dimensional environment is displayed allowing to change visual perspective with head movements (head-mounted visual displays, virtual caves), semi-immersive with three-dimensional fixed visual perspective presentations, or nonimmersive in the case of two-dimensional presentations displayed on a screen with or without interface devices as keyboard, computer mouse, or a joystick. There are some commercially available devices such as the IREX system (from GestureTek, Canada), Nintendo Wii , Sony Playstation EyeToy, Microsoft Kinect (Fig. 5). Furthermore, there has been virtual reality systems designed to be coupled to haptic and robotic devices to provide interaction forces and sensorimotor feedback between the user and the virtual environment. Examples of combined robotic and haptic systems include the Rutgers Ankle Rehabilitation system, Cybergrasp, CyberGlove, Gentle-S, PneuWrex , Mit-Manus, and Armeo Power. They all have been used with the purpose of increasing the feeling of immersion and user interaction into the virtual scenario. Haptic devices add precision to tracking motion, providing a powerful multisensory feedback that contributes to improve real-world activity level motor outcomes [19].

Feedback is crucial for user's engagement, motivation, and concentration during virtual therapy and has been determined essential to increase effect . In addition to visual and auditory feedback, tactile and force feedback provided by haptic devices

Fig. 5 A kinect-based virtual reality system. With permission of Complejo hospitalario de Toledo-Spain

increases the user interaction with the virtual environment and objects. Augmented feedback also could be implemented during sessions using knowledge of results (KR) or knowledge of performance (KP- desirable/ undesirable movement patterns).
Usually, virtual reality therapies are applied to patients with low or moderate spasticity (Ashworth scale score equal or less than 2), and mild or moderate upper limb paresis. The presence of certain degree of active movements and manipulation ability (active wrist extension above 20^{o}, metacarpophalangeal finger extension above 10^{o}, and approximately between 30 and 42 points in upper extremity Fugl-Meyer assessment) seem to be necessary for participation in virtual therapy programs. Hand dexterity scores lower than 45 in Box and block test could be also considered a criterion for therapy admission.

Treatment sessions can vary widely in terms of number and duration between different studies. Duration of 40 min to 1 h, delivered 3–5 days a week along a three–four week period, is common [83].

Usually, patients with both types of stroke, ischaemic, or hemorrhagic are included in virtual reality therapy. A recent study has shown, in line with previous data with more classical interventions [104] a differential response depending on etiology of stroke. Although all participants achieved motor improvements, patients affected by hemorrhagic stroke improved significantly more on FIM scores and kinematic parameters compared to ischaemic stroke patients [64].
Majority of patients are treated predominantly during a subacute or chronic phase (greater than 3–6 months) after brain injury, because in many cases acute phase deliver of this therapy results in impractical due to an unstable medical condition or severe plegia.
Virtual reality therapy is typically applied to patients without cognitive impairments, but many times stroke and TBI patients show cognitive and perceptual disorders. The minimal cognitive and perceptual requirements to use virtual rehabilitation in an effective manner still remain unidentified.

3.2.1 Virtual Reality for Upper Limb Rehabilitation in Stroke and TBI

An increased number of studies have been proposed in the last decade to evaluate the scientific evidence for the effectiveness of virtual reality in upper limb rehabilitation after TBI or stroke.

Regarding virtual reality effectiveness for upper limb motor recovery in stroke patients, a moderate beneficial effect has been reported. In a systematic review by Henderson et al., the authors found that compared to conventional therapy, there is a moderate level of evidence (2b) on the effectiveness of using nonimmersive virtual reality training for upper limb rehabilitation [50].

In a meta analysis that reviewed five randomized controlled trials about virtual reality therapy for subacute and chronic stroke patients (daily sessions, 5 days a week, during 4–6 weeks), authors found improvements on upper limb motor function, with increasing Fugl-Meyer scale scores between 13.7–20 %, at the end of treatment when compared to controls (3.8–12.2 %) treated with conventional occupational therapy [124].

A recent Cochrane review [78] analyzed 19 studies with 565 participants. In three of them (101 participants), they achieved significant statistically differences regarding ADLs performance in patients with virtual reality therapy (standardized mean difference 0.81; IC 95 % [0.39–1.22]). However, authors concluded that there was insufficient evidence about the effectiveness of virtual reality therapies to significantly increase grip strength.

A recent review of current state of post-stroke virtual rehabilitation [42] analyzed eight studies of upper limb and concluded that virtual reality could induce a moderate improvement on upper limb motor function with a small additive effect in terms of real-world activity daily living motor outcomes in subjects performing intervention with haptic feedback.

Another recent study [79] reviewed ten studies examining effectiveness of virtual reality-based rehabilitation regarding upper limb and hand fine motor skills in chronic stroke patients. Significant improvements were found in finger fractionation, finger tracking, and time from peak hand velocity at the moment an object was lifted from a table. Moreover, in five of the ten studies of this review, significant improvements were reported regarding transfer of virtual reality gains to real-world tasks when assessed by the Jebsen Taylor hand function test.

In a recently published systematic review and metaanalysis, twenty six upper and lower limb controlled trials compared virtual reality to conventional therapy in stroke patients [82], demonstrating a moderate effect in favor of virtual reality therapy. Time post-stroke and type of virtual therapy intervention (commercial gaming, semi-immersive, immersive virtual environments) did not significantly affect the outcomes. In addition, virtual reality therapy induced significant improvements across domains of International Classification of Function, Disability, and Health. (ICF-World Health Organization. Geneva, 2001). For body function level, there was a significant benefit of virtual reality therapies compared to conventional therapy, with an overall effect size G= 0.48, 95 % CI [0.27,0.70]. For activity level outcomes, they found the same benefit with an overall effect size G=0.58, 95 % CI [0.32, 0.85], whereas for participation level outcomes, the overall effect size was $G = 0.56$, 95 % CI [0.02,1.10]. However, authors accept that results should be interpreted with caution due to considerable variability within interventions.

The evidence in favor of using virtual reality for upper limb rehabilitation in TBI patients to improve motor function still is very limited.

In a four-patient study, [52] used a virtual reality system consisting of a computer, software, and a motion-tracking device. Prerecorded arm movements of a virtual "teacher" and the patient arm movements using a motion-tracking capture system were displayed on a computer screen. The patient was asked to mimic the virtual teacher movements, and the difference between movement trajectories provided augmented feedback. In this study, three out of the four patients improved upper limb function, and movement trajectories were smoother, straighter, and more accurate after the therapy. Moreover, patients achieved higher Fugl-Meyer scale scores and were able to generalize learned skills to real-world performance.

Virtual reality systems for TBI patients seem to improve accuracy of movement for both hands (left $p = 0.01$; right $p = 0.02$), speed and efficiency for right hand ($p = 0.01$ and $p = 0.002$, respectively), and bilateral hand dexterity assessed by Box and Block Test [95].

Appropriate arm-postural coordination is crucial to perform reach and grasp activities without abnormal compensatory strategies (trunk displacement) and to carry out activities of daily living in standing position (bathing, dressing, cooking).

A study of a virtual reality system for arm-postural coordination using the World Viz Vizard software (Santa Barbara CA), integrated with a six-camera system for motion capture and a custom-made 3D- immersive videogame. Patients use large arm movements to control their avatar trying to reach the maximum number of targets. Participants with mild-to-moderate TBI using this virtual system improved arm movement time, arm postural coordination and movement trajectory, forward reach, and single-leg standing [143]. There was no follow-up to assess retention and duration of improvements.

3.2.2 Virtual Reality for Lower Limb Rehabilitation in Stroke and TBI

Efficacy of virtual reality technology to improve walking and balance for post-stroke and TBI patients has been studied for its clinical application during the last ten years. Hardware and software of virtual reality systems created for this purpose ranged from fully immersive systems combining motion platforms, instrumented treadmills, motion capture systems, and surround sound systems (i.e., Computer-Assisted Rehabilitation Environment-CAREN) to nonimmersive gaming-based commercially available systems (i.e., Nintendo Wii), and virtual reality systems coupled to haptic or robotic devices (i.e., Rutgers Ankle Rehabilitation System).

Improvements on balance and ambulation could be due to task-specific training and the virtual reality elements that simulate real-world environments and motivate patients to practice.

For stroke patients, most studies have been carried out during the chronic phase post stroke. In this population, combining virtual gait training with conventional therapies seems to be more effective than application of virtual training alone.

Some studies show that chronic stroke patients who received additional 30 min per session of virtual reality walking therapy added to conventional physical therapy achieved significant improvements on balance, gait velocity, cadence, and step length, compared to controls without virtual therapy [24, 63]. Therefore, even a short time of virtual training a day could yield significant gait improvements.

A differential effect in terms of biomechanics and functional outcomes has been found between nonimmersive and immersive haptic–robotic virtual systems.
A positive impact on gait biomechanics has been shown when patients are trained with a force-feedback robot interfaced virtual reality system. In a single-blind randomized control study, subjects in the robot interfaced virtual reality group demonstrated significantly larger increase in ankle power generation, ankle range of motion (ROM), and knee ROM during swing phase of gait, compared to controls [93].

In contrast, a randomized controlled trial [44] showed that chronic post-stroke patients that followed balance and gait training with a nonimmersive video-gaming system did not achieved significant improvements on Fugl-Meyer assessment, Berg balance test, time up and go, and 6-min walk test compared to controls that continued with normal activity without receiving any special intervention. However, additional studies are needed to establish real efficacy of nonimmersive commercially available devices for virtual gait training.

Evidence about virtual reality therapy for gait and balance recovery in acute stroke patients is still limited. In a recent randomized controlled trial [91] that studied 59 acute stroke patients, the treatment group (n = 30) received standard rehabilitation plus virtual reality therapy (10–12 sessions, 30 min per sessions, 3 weeks) that included some exercises that challenged balance while standing (soccer, snowboarding). The control group (n = 29) received the same conventional rehabilitation plus identical exposure to virtual therapy without balance challenging exercises (performed sitting). Patients in virtual training balance exercises achieved after therapy greater improvements on 2-min walk test and time up and go test, diminishing lower limb impairment assessed by Chedoke-McMaster Leg domain compared to controls.

Studies with acute TBI patients and virtual reality-based gait training are also scarce, but at least for chronic patients some studies had shown feasibility and efficacy of this therapy, with improvements on gait and balance confidence [138, 141].
For mild-to-moderate chronic TBI patients, arm–leg coordination movements and dynamic postural stability gains have been found using an Xbox Kinect sensor with an interactive customized virtual reality games and scenarios [144].
In addition to this evidence of efficacy, studies point to the feasibility of virtual therapy implementation. Thus, nonimmersive virtual training added to conventional therapy could lead to improvements on walking distance, gait speed, and balance compared to usual therapy, with high therapy compliance and patients attending the majority of sessions without any reports of adverse events [89].

3.2.3 Conclusions

At the present time, studies indicate moderate evidence about the effectiveness of virtual reality technology to improve gait, balance, and upper limb motor function in stroke and TBI patients. Combined interventions adding virtual training to conventional rehabilitation appear to yield better motor and functional outcomes than a single intervention.

There are still some challenges to attain effective translation of learned motor skills in virtual environments to real-world activities of daily living performance. Emerging evidences suggest some progress in this issue, as represented by the positive impact found with virtual therapies across ICF domains.

Nevertheless, outcomes obtained from different studies should be interpreted with caution due to considerable variability within interventions (dosage, intensity, duration), small sample sizes, variable design quality of studies, and lack of detail provided about "conventional therapy." Finally, reports of cybersickness or adverse side effects (dizziness, headache, pain) after using virtual reality are scarce or minimal. Future studies should be considered to determine whether virtual reality training could affect patients condition, facilitate recovery, or interfere directly or due to adverse effects with functional recovery.

3.3 Robotics and Haptic Devices

Robotics in the medical field requires the convergence of expertise in robotics, medicine, and computer science, and the identification of specific robotic system design demands is in various stages of development.

In recent years, there have been significant developments in the design of robotic system for applications in surgery, rehabilitation, prosthetics, and assistance directed at the elderly or the disabled.

In particular in the field of rehabilitation, robotic systems may have the potential to reduce the demands.

Human operators in order to cope with the increasing growth demand and potential for injury by reducing the staff effort introduce more effective rehabilitation protocols.

Robotic systems are also called upon to address the demands for home care for the elderly, especially in relation to the execution of repetitive tasks.

Robotic technology can provide support to rehabilitation therapy [146]. Early robotics, starting in the late 1950s, focused on large manipulators to replace workers in factories who were performing dirty, dangerous, and undesirable tasks. The rehabilitation robots were based on previous designs in the field of prosthetics, where devices have been developed for the substitution of function of upper and lower limbs, some of which are in widespread use in rehabilitation clinics. This chapter will focus on devices for the rehabilitation of the upper limb and review some of the most used.

3.3.1 Robotics Devices

Robots for upper limb rehabilitation generally consist of robotic arms with several degrees of freedom, the end of which is connected to the hand or arm of the patient. Many research groups have developed robotic devices for upper limb rehabilitation, for example, Massachusetts Institute of Technology (MIT) Manus [69], Assisted Rehabilitation and Measurement (ARM) Guide [116], Mirror Image Motion Enabler (MIME) [18], Bi-Manu-Track [51], GENTLE/S [26], Neurorehabilitation Robot (NeReBot) [120], REHAROB [142], Arm Coordination Training 3-D (ACT^{3D}) [136], and ARMin [97].

Generally, you can follow on the computer screen a representation of the movements of the robot. The interaction between patient motion and movement of the robot can be done in various ways. The robot can drive limb movements of the subject completely, without any subject active participation; or you may demand a greater participation by the user, who must strive to make the move. The user must prioritize positioning task performance, e.g., move the robotic arm so that its position in space, represented graphically on the computer screen, coincides with a desired position, also shown in the form of a 'target' on the screen. The task of the robot, in these scenario, is to encourage parallel movement of the patient, e.g., applying guiding resistance in the event of deviations from the desired trajectory, or to apply assistance if the patient has difficulty initiating or continuing the movement. The utility of these robot systems is shown by numerous clinical studies [114].

3.3.2 Haptics Devices

Haptics is a term that was derived from the Greek verb "haptesthai" meaning "of or relating to the sense of touch." It refers to manual sensing and manipulation of surrounding objects and environments through the sense of touch. The "touching" of objects and or environment can be made through these devices and the objects and environments can be real, virtual, or a combination of both. Also, the interaction may or may not be accompanied by other sensory modalities such as vision or audition [38].

The training with these devices is based on exercise therapy modalities that the literature and/or clinical practice indicate may help restore upper limb motor control and function [37].

There are two modalities to restore mobility, passive, and active mobilization. In the passive mode, the robotic device moves the patient's arm. In the active mode, the movement is either partially assisted by the robotic device, or resisted by the robotic device. An example of passive motion intervention is a system that provides bimanual mobilization, where the movement of the unaffected arm is mirrored by simultaneous passive movement of the affected arm provided by the robotic device.

For example, the device Phantom permits simulation of fingertip contact with virtual objects. A pen-like stylus tracks the pitch, roll, and yaw and x, y, and z Cartesian coordinates of the virtual point probe. Its actuators communicate forces back to the user's fingertips as it detects collisions with virtual 3-D objects, simulating the sense of touch [88]. Other haptics devices are Omega3 [45], Falcon [87], and haptic knob for rehabilitation of hand function [72].

For ambulation rehabilitation, the science behind exercise in persons with neurologic disease supports treadmill training over "conventional therapy [33]. What constitutes "conventional therapy" is highly variable and not well described in the literature. This area only recently has been given more study attention [30]. Traditionally, the conventional physiotherapy approach focuses on strengthening and practicing single selective movements or various neurofacilitation techniques. Conventional therapy methods, however, do not specifically emphasize the activity of ambulation. Limited evidence exists to support the effectiveness of these techniques in the restoration of walking ability [47, 67, 80, 148].

Many rehabilitation paradigms have been developed to promote recovery of lower extremity function and walking through task-specific training. Walking on the treadmill alone [77, 119] or in combination with body weight support (i.e., body weight supported treadmill training [BWSTT]) [27, 149] has become an increasingly popular option in the past several years. Although recent reviews of the literature have not demonstrated different outcomes of BWSTT for patients who have had a stroke [31, 36] based on task-specific approach, gait training is the best way to improve the walking pattern [28]. Such repetition is thought to facilitate the integration of remaining and altered sensorimotor systems in persons with either an acute or chronic brain injury [53, 137].

Positive changes in larger cortical representation have been demonstrated in patients with a TBI [60, 105]. Rehabilitation efforts that promote motor recovery of ambulation activity through task specificity and repetition for persons with a TBI can be complicated by a number of different factors: (1) the potential for multiple motor impairments, both of a pyramidal and extrapyramidal nature; (2) the presence of cognitive or communication impairment; (3) the need for a high number of repetitions as part of the training; and (4) the high level of manual assistance required to help the patient during gait training. These factors combine to make task-specific training for persons who have sustained a TBI very labor intensive, time consuming, and costly. To address some of these limitations, locomotor therapy with a robotic device has been introduced as a task-specific technique to apply precise movement training that may increase the efficiency and/or effectiveness of this type of intervention. Some of the benefits of robotic-assisted treadmill training include more intensive and prolonged training modes, consistent movements, and a reduction in manual labor required from the therapist. Although considerable literature exists on the effectiveness of locomotor training with robotic-driven therapy on spinal cord injury populations [25, 57, 153], surprisingly little published research is available regarding persons with a brain injury. In some studies of persons who had a stroke, investigators found better outcomes with robotic-assisted training compared with conventional training [127].

A Cochrane Review [92] on patients who had a stroke found that RATT in combination with physical therapy improves some gait parameters but not others. As for research on patients with a TBI who were treated with robot-assisted therapy, only a few studies are available using this training modality or comparing the effectiveness of the different interventions [40, 43]. In a randomized study with 16 subjects with TBI, there was evidence that BWSTT with manual and robotic assistance at participants' preferred walking speed and adjustments made on the basis of their velocity gains are an effective approach to increase self-selected and maximal walking velocity. RATT-trained participants had significant improvement in step length symmetry. Participants in both groups expressed significant improvement in their mobility. On the basis of between-group differences, no training technique appears to be superior to the other; however, the Lokomat required fewer staff and less manual effort from the staff was reported, with decreased staffing costs. Although the literature has demonstrated that gait training with either manual or robotic BWSTT is equivalent in persons who have had a stroke, this study provides the first reported evidence of this finding in the TBI population [40].

3.3.3 Guidelines

Robot therapists must present certain features that are crucial if they are to be really effective [21]. Some of these are summarized below. Robot interventions must

i. Have a high level of compliance; a highly compliant robot that is a system that can be easily moved even with a very small force is applied and, at the same time, that does not oppose the movement of the patient but facilitates it by means of gently modulated forces [21].
ii. Have a wide range of forces; in skilled therapeutic treatment, it is necessary to find the right combination of guiding and resisting forces, according to the individual's performance and the nature of the task.
iii. Adhere to a minimal force assistance-level criterion; This criterion is motivated by the requirement of compatibility with the schema theory of "assist as needed principle" of motor learning [21] or the "minimal assistance strategy" [154].
iv. Promote improvement of proprioceptive awareness; considering the fact that motor deficits are highly associated with proprioceptive deficits or deficits of spatial representations that affect the integration of the body schema. In many cases, such deficits are even more disabling than the purely motor deficits, but are not adequately considered [21].
v. Have a high degree of system intelligence; the figure below Fig. 6 illustrates the basic elements that characterize information flow: (1) a haptic robot; (2) a force field generator; (3) a performance evaluator; and (4) an adaptive controller. In other words, an efficient therapeutic robot must not be a purely executive electromechanical device but must provide the patient with a rich interactive environment.
vi. Be designed in a modular way; the complexity of the therapeutic robot, in particular the number of degrees of freedom employed, should be as small as possible and selected based on each patient need [21].

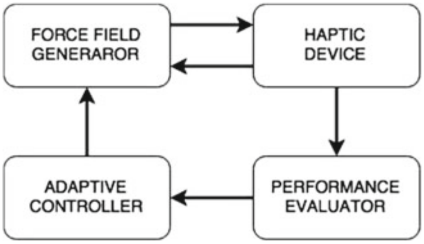

Fig. 6 Basic elements that characterize the flow of information

vii. Facilitate synergy between physiotherapy and therapeutic robot; the general principle is that robot therapy and physiotherapy should be synergistic and cooperative. The appropriate division between robot and human therapy can, in general terms, be formulated as follows: (i) the robot therapist trains the patient to improve basic motor coordination; and (ii) the human therapist exploits the improved coordination in a functional context by challenging the patient with tasks that require increasingly skilled actions [21].

3.4 Neuromuscular Electrical Stimulation in Rehabilitation of Upper Extremities

Electrical stimulation of the peripheral nervous system (PNS) can be used as a therapy and/or assistive devices for patients with TBI and stroke [8, 23, 113]. Neuromuscular electrical stimulation (NMES) refers to electrical stimulation of intact lower motor neurons hereby eliciting contractions of the otherwise paretic or paralyzed muscles [14]. Functional electrical stimulation (FES) is the use of NMES to activate muscles in a precise sequence and intensity, mimicking efferent signals from the central nervous system (CNS), in order to accomplish functional tasks [106].

NMES is applied as waveforms of electrical current which are characterized by stimulus frequency, pulse amplitude, and width. The quantity of recruited muscle fibers depends on the pulse amplitude and width of the stimulation, whereas temporal summation is reliant on the stimulation frequency. Thus, the strength of the elicited muscle contraction is tuned by adjustment of the stimulus parameters [106, 129]. Normally, stimulation frequencies in the range of 12–16 Hz is used in upper extremity applications in order to achieve muscle responses, without generating muscle fiber fatigue and rapid decline in contractile force [129]. It has been documented that NMES can improve neuromuscular function in stroke and TBI patients by strengthening of atrophied muscles, moderation of spasticity, decreasing pain, increasing motor control, and range of motion [111, 126]. Further, it has been suggested that NMES leads to relearning of motor function through the same mechanisms as conventional repetitive movement training [129] where afferent input is increased during the training [126]. In such case, NMES is denoted as therapeutic electrical stimulation (TES) [111–113, 126].

NMES devices are classified according to their mode of current application and the stimulation parameters utilized. Three modes of current application are described:

- Surface NMES systems where surface electrodes are placed over the motor point or the nerve innervating the target muscle and the entire system is external to the body.
- Implantable NMES systems where electrodes (e.g., cuff-, epimysial, or intramuscular electrodes) are placed around the nerves that innervate the targeted muscles, or at the motor point of the targeted muscles. An implantable stimulator is placed in the vicinity of the electrodes, and controlled via a control unit which is placed external to the body.
- Percutaneous NMES systems where needle- or wire- electrodes are inserted close to the motor point of the targeted muscles and the remaining part of the system is external to the body [106].

Similarly, three stimulation methods exist:

- Cyclic NMES where stimulation parameters are preprogrammed and triggered via the NMES system without any concurrent voluntary contraction of the target muscles by the subject.
- Electromyography (EMG)/biofeedback-mediated NMES where stimulation is triggered by EMG or positional feedback of the upper extremity obtained directly from the subject, which is actively participating in the rehabilitative exercise.
- Neuroprostheses where NMES in combination with the prostheses is used to facilitate functional and meaningful behavioral tasks [23, 70, 129].

Each of the NMES modalities has their own strengths and weaknesses which are going to be described in detail in the following sections.

3.4.1 Surface NMES

Surface NMES most often are voltage regulated in order to avoid tissue damage due to the changing resistance of the electrode–skin interface. Voltage regulation though might lead to variable motor responses due to decreased current induction as a function of increased impedance of the electrode–skin interface [129]. Surface systems are especially well suited for short-term rehabilitative use due to their low-cost, simplicity, and ease of use [106]. However, lack of deep muscle selectivity, potential skin irritation and pain, and unappealing esthetics are drawbacks of the surface systems. Choosing the optimal electrode dimensions and position in order to avoid pain and skin irritation while trying to recruit the appropriate muscles is a very complex task [110]. As a consequence, surface systems are most often utilized in the clinic, where skilled personnel secures repeated placement of the electrodes in the appropriate positions [106]. As a result of the aforementioned, surface NMES systems are considered to be temporal systems.

3.4.2 Implantable NMES

In implantable NMES systems, it is possible to use current-regulated stimulation due to elimination of skin resistance which results in a more homogeneous electrode–tissue interface [129]. By doing so, it is possible to achieve consistency and repeatability in the elicited motor responses with less pain [129]. Implantable NMES systems are intended for long-term use and since none of the leads of the system need to protrude the skin they can be made larger and more durable [106]. The implant is powered via batteries (rechargeable or disposable) or through radio frequency telemetry link from an external control unit (see Fig. 1) [106].

Cuff electrodes, used in implantable NMES systems, can either have a spiral or tube shape, and the geometric dimensions (e.g., internal diameter, longitudinal length) of the electrode are made to fit the targeted nerve [49, 110]. Cuff electrodes are made of polymer, and can be fabricated with various mono-, bi-, and tri-polar configurations [110].

Epimysial electrodes are disk-shaped electrodes which are surgically placed on the muscle near the motor point [110], and are well suited for activation of broad superficial muscles [129].

Intramuscular electrodes are wire or needle electrodes which are inserted into the target motor point using a hypodermic needle. They allow high degree of stimulation selectivity and can recruit deeper muscles [106].

3.4.3 Percutaneous NMES

Similar to implantable NMES systems, percutaneous systems most often are current regulated. The advantages of percutaneous NMES systems are that they can recruit deeper muscles, and have high muscle selectivity and repeatable responses over time. The intramuscular electrodes are inserted by a hypodermic needle through the skin [106, 110] and the leads of the electrodes exit the skin and are connected to an external stimulator unit. A large surface electrode is used as anode (see Fig. 1). Percutaneous stimulation is less likely to be painful since the stimulation pulses bypass the afferent receptors in the skin [106]. As with surface systems, percutaneous NMES systems are considered to be temporal systems, because there is a risk of breakage or displacement of the electrodes over time, and risk of infection at the point of electrode leads entry. As a consequence, use of percutaneous electrodes is limited to less than 3 months when it needs to be replaced [129].

3.4.4 Cyclic NMES

Cyclic NMES consists of electrical stimulation of the paretic or paralyzed muscles, whereby muscle contractions are elicited. Cyclic NMES is applied while the subject is passive, but it has been shown that the effect of this type of stimulation can be enhanced by instructing the subject to actively accompany the movement via thought and, if the subject has any voluntary control of the limb, by actively tensing of the muscles [126].

3.4.5 EMG/Biofeedback-Mediated NMES

EMG or biofeedback-mediated NMES requires larger degree of cognitive investment, since the subject is actively taking part in the rehabilitative exercises. In EMG-mediated NMES, stimulation is initiated when volitionally generated EMG activity exceeds a predefined threshold, whereas for biofeedback-mediated NMES, joint translation resulting from voluntary muscle contractions can be used as a threshold for initiation of NMES stimulation [70]. Specifically, NMES stimulation is triggered after the subject has performed the initial part of the predefined movement and NMES helps complete the remaining part of the movement [129]. Feedback-mediated NMES is believed to result in larger rehabilitative gains than cyclic NMES, due to the cognitive involvement in the exercises which can facilitate neural plasticity. Firm scientific evidence of greater rehabilitative gains through feedback-mediated NMES though still is lacking and has the additional prerequisite of some degree of voluntary control of the affected limb [23, 70, 129].

3.4.6 Neuroprostheses

Neuroprostheses are developed with focus on augmenting the independence of the user by safely and efficiently facilitating the completion of functional tasks [23, 110]. Neuroprostheses are mainly for patients with severe paralysis where motor relearning strategies are thought to have limited potential [23]. Neuroprostheses can have different sources of control signals to trigger or adjust the stimulation patterns. Some examples of sources of control are

- Contralateral hand joysticks.
- Wrist movement.
- EMG activity of agonistic muscles.
- Switches located on various places on the body [110].

Several neuroprostheses for grasping have been developed, and they are mostly designed as bracelets (e.g., the Handmaster [1, 2]) where NMES is applied through surface, percutaneous, or implantable electrodes [110].

3.4.7 Rehabilitative Effect of Neuromuscular Electrical Stimulation

In general, the literature supports that the most effective approach when aiming at restoring motor functions is to begin NMES as soon as possible [14, 113], since the rehabilitative effect of NMES appears to be more pronounced and enduring for acute stroke survivors. Furthermore, there are indications that patients with milder impairments have a greater benefit from NMES than those with severe involvement [23, 129]. This may be related to the patients with milder impairments being able to take active part in the rehabilitation [23]. Based on the current knowledge about motor relearning and post-stroke recovery, [70] stated that rehabilitative NMES training should include the following key elements: should be repetitive, intensive, attention demanding, task-oriented, and provide feedback. This implies that the NMES system should be highly flexible and adjustable in order to be adapted to the progress and actual needs of the patient. In this way, [113] suggests that the early use of NMES should be conducted with surface systems since these provide sufficient flexibility to change stimulation parameters and electrode position. In relations to surface electrodes, a novel electrode array with 64 channels has been developed and presented in [62]. The electrode array is embedded in a garment which can be applied to the arm. Real-time switching of the location and number of active electrodes is possible, hereby making the array very flexible and adjustable while avoiding the need to physically readjust electrode positions [61].

The appropriate stimulation paradigm would be based on the subject's clinical condition. If the subject is severely involved, cyclic NMES is preferred in order to facilitate muscle strengthening, range of motion, moderation of spasticity, decreasing pain, and increasing motor control [113]. Afterward, functional training is introduced preferably using EMG/biofeedback-mediated NMES [113], since there is indication that this type of stimulation might have a better effect than cyclic NMES [70]. In case voluntary movement of the upper extremity is present at initiation of rehabilitation, EMG/biofeedback-mediated NMES might be initiated at the beginning of rehabilitation.

Recently, [66] has suggested contralateral controlled NMES denoted as contralateral controlled functional electrical stimulation (CCFES) as a novel approach to improve recovery of volitional hand function in patients with stroke. The source of control signals and triggering is a glove which is worn on the unaffected hand and detects the degree of hand opening. The degree of hand opening then translates to a stimulation pattern which elicits finger and thumb extension of the paretic hand. In this way, movements mimicking the unaffected hand are elicited in the paretic hand. The preliminary findings from subacute post-stroke patients suggest that CCFES produces larger improvements than cyclic NMES [66], and in this way CCFES might be a future alternative to cyclic NMES as the initial intervention.

In the chronic phase after stroke or TBI when the initial rapid improvements caused by spontaneous recovery and rehabilitation have taken place, it might be beneficial to use percutaneous or implantable NMES systems in order to diminish the risk of pain and skin irritation caused by surface stimulation [113].

Rehabilitation in the chronic phase could be conducted with the use of EMG/biofeedback-mediated NMES and/or via use of a neuroprosthesis. A neuroprosthesis is potentially very useful for the patient once in the chronic phase since he/she might not benefit further from the NMES rehabilitation. In such case, the neuroprosthesis can function as assistive devices to assist in activities of daily living (ADL) [113].

3.4.8 Conclusion

NMES can be used to improve post-stroke and TBI rehabilitation, by initially strengthening muscles, augmenting range of motion, moderating spasticity, decreasing pain, and increasing motor control. Furthermore, it is suggested that NMES provides intensive traffic of neural information toward the brain promoting neural plasticity and motor relearning and resulting in enduring improvement of motor function.

The optimal NMES system for a given patient depends on the severity of the injury and how much time has elapsed since the injury. In general, rehabilitation should be initiated as quickly as possible in which case surface NMES is preferred due to a its flexibility with adjustable stimulation parameters and electrode positions. In less compromised patients who have voluntary movement of the affected upper extremity, EMG/biofeedback-mediated NMES is initiated in early phase, whereas severely affected patients should use cyclic NMES rehabilitation. The 64-channel electrode array developed by Keller and the contralateral controlled NMES system suggested by Knutson could be very beneficial additions to NMES systems for use during the acute phase after TBI and stroke rehabilitation.

Percutaneous and implantable NMES systems can be used to reduce pain and skin irritation commonly observed when using surface stimulation systems. Although percutaneous and implantable systems should first be used after the initial rapid recovery of function has declined, they are not as flexible as surface NMES system and thus not allow the same adjustability to respond to changes in the patient condition. Similarly, neuroprostheses can be used in the chronic phase as an assistive device to perform ADL.

4 The "Wish List"

4.1 Game on!—delivering technology to the golden years.

The last couple of decades have been revolutionized by the power of personal computers, smart phones, game consoles, and other technologies that are now used by people from all walks of life on everyday basis. This new phenomenon has important implications in shaping the needs and expectations of the patients of today and tomorrow. With every passing year, increasing proportions of older adults and elderly are becoming technology oriented, connected to the virtual world and dependent on gadgets for communication, information, and recreation. Today, more than 90 % of people over 65 years of age report the use of internet at least weekly [133]. This goes against the traditional image of elderly patients with nonexistent computer literacy and a tendency to drift into nostalgic trips to simpler lives.

A shift in perception toward the use of technology with the elderly has become crucial. The integration of technological applications into activities of daily lives of older patients is soon becoming a necessary step in order to engage patients, leading to a more driven and effective course of recovery. A promising niche in this context is the use of video games in stroke rehabilitation.

Today, between 40 and 50 % of the elderly population report weekly use of computer games [133]. This is only expected to rise with each passing year. Research on the use of computer games by the elderly has early roots [151] yet the rise—and availability—of more active gaming platforms like the Nintendo Wii® [125] and Microsoft Kinect® [73] has heightened the interest in their use for neurorehabilitation.

The vision is that in the near future, such technology-based rehabilitation tools and games become common house-hold gadgets. The aim is to have a rehabilitative platform that is engaging and enjoyable, instigating higher number of hours in rehabilitative training and making the process of motor recovery more efficient and less burdensome. With increased affordability, more versatile applications, and broadening of target population in the marketing phase, these "exergaming" devices [147] could ultimately find their way into the homes of the general elderly population, with more seamless transitioning between maintenance and rehabilitation of motor function and fitness.

4.2 Virtual Reality Technology

Application of virtual reality technology for motor and functional recovery in stroke and TBI patients seems promising. A more extended use of virtual reality systems coupled to haptic devices that increase user interaction with the virtual environment and objects could be important for functional recovery in terms of obtaining better real-world activity level outcomes. In the next future, patients with severe upper and lower limb paresis could also be treated using hybrid virtual reality systems coupled to brain computer interfaces (BCI), and exoskeleton or robotic devices, but at the present time, cost-effectiveness and a probably greater time of training remain as potential limitations to extent application of these systems in clinical settings. Finally, many virtual reality applications designed as rehabilitation tools are still expensive and compatibility between different hardware, software, drivers, and protocols is a problem that still remains unsolved. It would be desirable that gaming industry introduces changes in design of gaming consoles in terms to be more user-friendly for disability people, allowing them to play at different speeds or difficulty levels, developing as well on line available games for telerehabilitation and home use.

4.3 Technological Wishes from a Rehabilitation Clinician

Still at present, neurological rehabilitation is more an art than a science. Most of evaluation metrics are based on observational charts and therapies depend on the personal experience and education of the single physiotherapist. Technology today can provide sensors of many types capable of monitoring virtually all relevant characteristics of movement. Muscular activity, force, kinematics, balance, and activity of the cerebral cortex are all parameters that can be collected and processes while performing rehabilitation exercise. Through these sensors, patient participation, as well as brain and muscular changes associated with the exercise, can be monitored and used to measure the effects of the interventions and to guide the rehabilitation therapy. On the other hand, robotic device can provide support for any movement and function. Although already theoretically possible, a robotic rehabilitation based on multisensory human–machine interactions has been only seldom applied and only in laboratory conditions. On the other hand, also in this highly technical environment, results have been more of importance for the understanding of neurophysiological and recovery mechanisms than for clinical applications. The hope is that through simplification of the technical approaches and through development of technology-based evaluation and of treatment, protocols will became a part of the routine in neurological rehabilitation. Neuroengineering-based tools will then leave the research lab, becoming the everyday companion of neurological rehabilitation professionals.

5 Conclusions

Stroke and TBI are disabling diseases with high social costs and neurological rehabilitation is the best approach to reduce disabilities. Once considered only necessary in the early months after brain damage, evidences are summing up in indicating that neurological rehabilitation is a lifelong endeavor needed to reduce disability and to improve function even years after the lesion [5]. Within this framework, the need to provide cost-effective rehabilitation is becoming mandatory. Neuroengineering has the potential to provide effective intensive rehabilitation at a lower cost. In spite of these promises, more than a decade of research and clinical applications have provided limited impact on everyday treatments. Nevertheless, much work has been completed to demonstrate the value of robotic-mediated rehabilitation for upper and lower limb in patients after stroke and TBI. Advantages of using this technology include reduce staff utilization, and increase intensity of therapy and subject engagement with either equivalent or better results than traditional care in most cases. Other modalities such as electrical stimulation combined with robotic therapy appear to offer further advantages but only small trials are available to support these findings. Comparative trials of different robots are spars and additional studies should be considered.

Collaborative development by engineers and clinicians of robots that are simpler in design, more directly linked to functional use, and with less cost will allow further deployment of the technology to a larger section of patient population that may benefit and eventually allow development of wearable robots that can easily be used at home, altogether allowing increased time use with resulting benefits for this population.

Another aspect of high expectation relates to the understanding of the biological substrate of recovery and most importantly the capacity to directly link rehabilitation exercises with brain changes. This is already feasible in laboratory condition. By recording different biological signals from muscle or brain, it is possible to follow changes in activation and connectivity patterns linking them with treatment and recovery [90, 108]. These findings may serve to guide the correct timing for the exercise intervention by the physiotherapist as well as by a robot [158].
All these findings are promising and are helping to close the knowledge gap between rehabilitation interventions and induced brain changes. Controlling and quantifying the biological effects of a rehabilitation protocol will allow to base neurological rehabilitation on solid scientific ground.

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Rehabilitation Technologies for Spinal Injury

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Abstract Spinal cord injury (SCI) results in a temporary or permanent impairment in the spinal cord's normal motor, sensory, or autonomic function below the level of the lesion causing significant functional impairments in individuals. Restoration of gait is one of the major rehabilitation goals for SCI patients, along with recovery of upper limb control and other functions. When treating an individual with SCI, the ultimate objective is complete reparation of the functional damage, which is presently not yet possible. However, both human and animal studies in neuroplasticity have shown that the spinal cord has some potential to reorganize despite the loss of supraspinal input and utilize the remaining peripheral input to control stepping and standing. Therefore, optimally leveraging the interaction of neuroplasticity with technological devices to restore functionality in these individuals is the main focus of current research efforts in neurorehabilitation. In this chapter, we briefly review the clinical aspects of SCI and present a summary of the present and future approaches for rehabilitation of

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SCI patients and discuss how these techniques may restore function and potentially promote recovery in these patients.

Keywords Rehabilitation · Spinal cord injury · Neural circuitries · Neuroplasticity · Neurotechnology · Robotic therapeutics · Brain–machine interfaces · Brain–computer interfaces

1 Introduction to Spinal Cord Injury

Spinal cord injury (SCI) can be a devastating clinical condition due to resultant sensory-motor impairments and consequent loss of functional independence. The limited spontaneous recovery and lack of curative treatments [17], coupled with higher rates of incidence in younger adults (Spinal Cord Injury: WHO Fact Sheet, 2013), leads to considerable long-term disability and creates significant socioeconomic burden to affected individuals, caregivers, and society at large

SCI comprises any spinal cord lesion that can cause changes in movement, sensation, or function below the level of the injury [54]. The origin of the injury can be traumatic, non-traumatic, or congenital (infectious, neoplastic, vascular, autoimmune, inflammatory, demyelinating, idiopathic, and iatrogenic). The level of injury (see Fig. 1) is defined as the spinal cord segment located above the highest affected segment, and so a lesion may have different motor and sensory levels, and consequently affect function differently across both sides of the body [2]. In complete

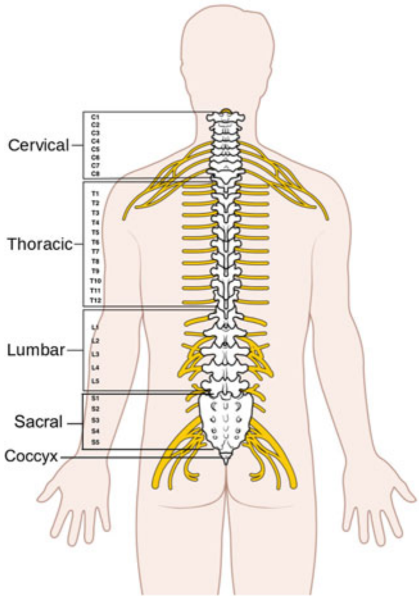

Fig. 1 Spinal cord segments (Modified with permission from Cancer Research UK/Wikimedia Commons)

SCI, there is no function, sensation, and movement below the level of injury; both sides of the body (ipsilateral and contralateral to the lesion) are equally affected. On the other hand, in incomplete SCI, some function is preserved below the level of the injury. A person with an incomplete injury may have asymmetries between both sides of the body in terms of mobility or sensation. Clinically, complete SCI occurs less frequently than incomplete SCI, and therefore, most patients experience some functional recovery after the initial stage of spinal shock and inflammation (acute phase of the injury).

2 Clinical Evaluation of SCI

Individuals with SCI typically present with a gamut of neurological and functional impairments, depending upon the spinal level of the lesion and the extent of the injury. Furthermore, the clinical signs and symptoms also change with time (starting from onset of the SCI) as the acute inflammatory processes subside, and intrinsic recovery starts to occur. Therefore, it becomes very important to document the clinical signs as well as the functional performance in order to monitor patient's progress and appropriately adjust therapeutic strategies and goals to maximize functional outcomes. Given the physical rehabilitation focus of this chapter, the scales pertinent to assessing sensory and motor function are primarily discussed below, while assessments of the autonomic nervous system function are excluded.

- American Spinal Cord Injury Association (ASIA) Scale:
  The neurological assessment in SCI is performed based on the guidelines of the ASIA scale [33, 38], which relies on a systematic exam of the motor and sensory functions. The motor evaluation component comprises the testing of 10 muscles: 5 in the upper limbs (UL) and 5 in the lower limbs (LL) wherein muscle strength/function is scored between 0 and 5 according to the guidelines presented in Table 1.
  Sensation is also assessed and scored on a scale of 0–2 in which 0 indicates anesthesia; 1, altered sensitivity (including hyperesthesia); and 2, normal sensory function. Table 2 presents the five levels of neurological impairment in SCI (ASIA).

- Penn Spasm Frequency Scale (PSFS):
  Penn et al. defined a 5-point scale (see Table 3) categorizing the frequency of occurrence of spasms, [27, 44]. Priebe et al. in [46] modified the Penn spasm frequency scale (PSFS), adding a second index to account for the individual's level of spasticity.

- Walking Index for Spinal Cord Injury (WISCI) Scale II:
  The WISCI II indicates the ability of the user to walk after a SCI [15]. This scale scores the individual between 0, indicating most severe level of disability, and 20, indicating minimal impairment.

Table 1 ASIA motor grading scale

Index	Description
0	Total paralysis
1	Palpable or visible contraction
2	Active movement, full range of motion (ROM) with gravity eliminated
3	Active movement, full ROM against gravity
4	Active movement, full ROM against gravity and moderate resistance in a muscle-specific position
5	(Normal) Active movement, full ROM against gravity and full resistance in a muscle-specific position expected from an otherwise unimpaired person
5*	(Normal) Active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e., pain, disuse) were not present
NT	Not testable (i.e., due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of >50 % of the range of motion)

Table 2 ASIA Impairment scale (AIS)

Index	Description
A	Complete sensorimotor injury
B	Incomplete sensory, complete motor injury
C	Nonfunctional incomplete sensorimotor injury
D	Functional incomplete sensorimotor injury
E	Normal sensorimotor function

- Ashworth and Modified Ashworth Scales of Spasticity:
  Spasticity, defined as a velocity-dependent response to passive stretch [30, 35], is one of the most important consequences of central nervous system lesions [7]. The Ashworth spasticity scale was developed as a simple clinical classification for assessing the effects of an antispasticity muscle relaxant drug (Carisoprodol) in multiple scleroses [4]. Ashworth scale (AS) is a 5-point scale based on subjective clinical assessment of patient's muscle tone [27]. Modified Ashworth scale (MAS) adds an extra value to the scale (1+) to include hemiplegic patients [27]. Due to its simplicity, therapists have adopted AS and MAS scales for quantification of spasticity in wide a variety of diseases and conditions, including SCI [23]. MAS scale is shown in detail in Table 4.

Table 3 Penn spasm frequency scale

Index	Description
0	No spasms
1	Stimulus induced spasms
2	Spasms occurring less than once per hour
3	Spasms occurring more than once per hour
4	Spasms occurring more than ten times per hour

Table 4 Modified Ashworth scale for spasticity

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

3 Rehabilitation Techniques for Spinal Cord Injury

Restoration of functional independence in activities of daily living (ADL) is a priority for individuals with SCI, along with bladder and sexual functions, and mitigation of circulatory and respiratory issues, pressure sores, and psychological problems. Therefore, physical rehabilitation continues to remain a mainstay in the treatment of SCI. Some decades ago, SCI meant confinement to a wheelchair and a lifetime of medical co-morbidity [50]. Advances in neuroscience have provided hope for stimulation of spinal cord regeneration and eventually complete functional restoration. Various solutions have been explored for SCI treatment and rehabilitation, each with its own advantages and limitations. Traditionally, rehabilitation has focused on functional restoration by maximizing residual motor skills through therapeutic exercise, or by overcoming losses with teaching of compensation techniques and use of assistive devices in patients.

While the complete repair of injury by regeneration techniques would be ideal, such techniques are still in early development (including stem cell therapies), and will need to be translated from preclinical to clinical therapies (for additional details refer to the section Rehabilitation Techniques for Complete SCI: Neural Regeneration). Nevertheless, for such neural repair to work, neurons within the spinal cord involved in generating rhythmic movements still need to be functioning. Therefore, the physical rehabilitation techniques currently used for functional restoration could be seen as a means of keeping neurons active until regeneration treatments become viable [21].

Clinical approaches for functional restoration are usually based on neuroplasticity to some extent, which consists of facilitating the adaptive reorganization of the sensory-motor systems within spared neuronal circuits to the loss of function due to injury/lesion [14]. There are several potential techniques for rehabilitation of SCI subjects. These approaches can typically be classified based on the severity and level of the injury, as treatment approaches will vary depending on the lesion. According to Table 5 [14], the goal of rehabilitation guides the selection of the most appropriate treatment approach based on the completeness of injury, such that it can maximize functional outcomes.

Table 5 Classification for SCI rehabilitative approaches (Based on [14])

Severity	Treatment	Goal	Current state
Complete SCI (AIS A)	Compensation by assistive devices (such as BCI)	ADL independence	Established
	Neural repair	Low level of motor function (hand or locomotor)	Still in translation to human
Incomplete SCI (AIS B/C)	Epidural electrical or pharmacological stimulation.	Low level of motor function (hand or locomotor)	Still in translation to human
	FES (Functional Electrical Stimulation) and orthosis	Tenodesis grasp	Established
		Assisted stepping	Established
	ISMS (Intraspinal Microstimulation)	Restore limb function	Still in research
	Intracortical Microstimulation	Restore sensation	Still in research
Incomplete SCI (AIS C/D)	Functional training	Active hand function	Established
		Restricted locomotor function	Established

3.1 Rehabilitation Techniques for Complete SCI

The treatment approach for complete injury usually is more focused on compensating the functional movements required for activities of daily life (ADL) with assistive devices such as powered wheelchairs, and more recently powered robotic lower limb exoskeletons ([42]. Another issue that is still in development is the neural regeneration aiming to achieve the recovery of the lower level motor functions to some extent so that the patient can self-initiate the movement of an assistive device.

- **Neural Regeneration**
  According to [21], while the peripheral nervous system (PNS) has the capacity to regenerate itself, the central nervous system (CNS) has limited capacity of regeneration after a damage occurs. In order to make the correct connections, i) cells have to be alive or be replaced (neural or tissue transplantation), ii) the environment has to be permissive for axonal growth, iii) correct signaling to select the desired target has to be provided, and iv) axonal remyelination has to be allowed. Some studies have demonstrated that application of electrical fields can directly affect the orientation and regeneration of axons [24]. Apart from this, spinal cord prosthetic devices to promote host tissue regeneration, rewiring, and plasticity are also being developed [22]. Passive SC prostheses are usually based on artificial scaffolds impregnated with cytokines to promote the surrounding tissue regeneration. On the other hand, the use of active SC prostheses is also aimed to the treatment of pain, bowel or bladder dysfunction, spasticity management, and motor control of limbs and trunks. Regeneration is considered as the solution for the complete repair and restoration; however, it is still under investigation and some promising results have been recently published [57]. In this Phase 1 clinical study, three human subjects with SCI were transplanted with autologous mucosal olfactory cells in the injured SC segments, and were provided with post-operative neurorehabilitation. Interestingly, neurophysiological examinations showed improvement in spinal cord transmission and activity of lower extremity muscles in surgically treated patients but not in patients receiving only neurorehabilitation. These initial results are encouraging and further investigations with a larger population will elucidate the mechanism of neural recovery after such transplantation, and will help develop more targeted and effective treatment approaches.
- **Neuroprostheses and Brain–Computer Interfaces**
  When there is a severe paralysis due to SCI, assistive devices normally help achieving independence in activities such as grasping, driving a wheelchair, or triggering an active orthosis. In this context, neuroprostheses have attracted considerable attention, as they can serve as a potential tool for intuitive user-driven control of an assistive device. This approach is typically useful for providing intuitive control in extreme disability to provide potential command signals to operate switches, joysticks, etc., via voice, eye movement and gaze tracking, electromyography, electroneurography, electrooculography, electroencephalography, etc. Neuroprostheses typically consist of electrodes that interface with the nervous

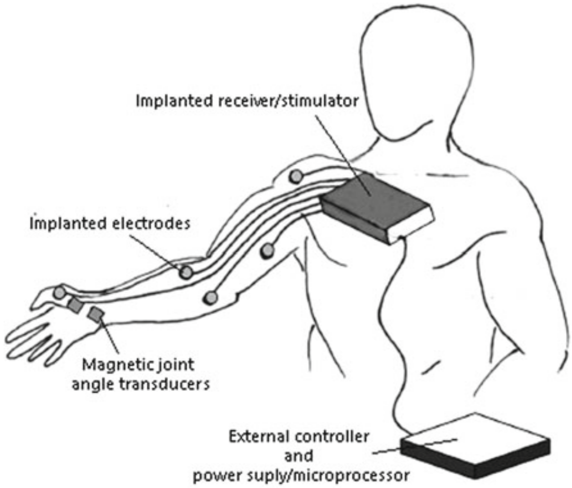

Fig. 2 The freehand grasp system (Edited from [22])

system and aim to restore lost motor, sensory, or autonomic function. To this end, neuroprostheses can stimulate specific muscles, nerves, or the spinal cord to produce function in end effectors below the level of spinal lesion. Alternatively, the intended movement-related neural activity that is recorded via one of the aforementioned approaches can serve as the control signal for an active orthosis that compensates for the loss of limb function [36]. In this context, neural prosthetic devices that decode intended motion trajectories from the motor cortex to control functional electrical stimulation (FES) devices have been developed [24]. For example, the Freehand System (NeuroControl, Cleveland, OH, USA), shown in Fig. 2, consists of an implantable neuroprosthesis intended to restore hand function in individuals with motor complete injury at the C5/C6 level [59]. It can stimulate specific muscles in the arm and hand in order to produce a useful grip and key pinch. The system consists of a surgically implanted receiver unit incorporating an eight-channel stimulator and electrode combination with an external controller and power supply/microprocessor [31]. Even though it has been shown to positively impact ADL in patients, the Freehand product has been discontinued, primarily due to issues with low market size and high production costs. Neuroprostheses can also stimulate intact peripheral nerves, providing functional restoration of various body organs [24], such as bladder function. In summary, neuroprostheses serve as compensatory functional tools in patients when voluntary movement is impossible due to paralysis. Therefore, this technology has the potential to significantly increase functional quality of life (QOL) in patients with complete SCI and paralysis, and even more so in chronic SCI.

Another recent approach that has contributed to improving SCI therapy is brain–computer interfacing (BCI). These BCIs can record movement-related neural command signals directly from the brain, via intracortically with microelectrode arrays implanted in the motor areas of the brain or extracortically with electrocorticogram or electroencephalogram electrodes. Most of the current BCI designs are based on the principle of recording neural signals and decoding the user's movement intention to operate an assistive device. BCI has been shown to not only be useful for assistive device control ([34, 49]), but also suitable for rehabilitation due to its therapeutic effects as an adjunct with physical therapy [48, 49]. Therefore, BCIs can be used for neural biofeedback-based training that can assist in rehabilitation as well as act as control mechanisms for neuroprostheses. This dual functionality provides the advantage of using this technology for rehabilitation in patients with acute complete and incomplete SCI to help engage intrinsic neuroplastic recovery mechanisms, and in patients with chronic complete SCI and paralysis. An important caveat to consider in the clinical translation of BCI technologies is that accuracy of decoding movement-related signals has been found to be lower in patients when compared to healthy subjects; further research in developing robust BCI decoding algorithms is necessary [19, 41]. Recently, promising results have been demonstrated in augmenting powered robotic gait assistive exoskeletons with noninvasive electroencephalography (EEG)-based BCIs for direct control by SCI patient user's movement intents [11, 32]. Such findings suggest that decoding algorithms for BCI-based therapies are improving, and future developments could significantly enhance the use of BCI technologies in rehabilitation of patients with complete SCI.

An alternative to EEG-based BCIs is the use of chronically implanted intracortical, microelectrode arrays to record motor cortical single-unit or multiunit ensemble spiking activity from a person with tetraplegia and use it to control an assistive device such as a robot arm or computer cursor. This approach generally uses the relationship between intended limb movement kinematics and neuronal spiking [39] to decode movement intention [37, 63] in contrast with EEG-based BCIs, which typically map the relationship between whole brain cortical dynamics and movement intention. The intended movement commands are then used to produce corresponding real-time movements in an external device. Ongoing clinical trials are exploring the feasibility of this approach for clinical rehabilitation of tetraplegia due to SCI and other severe movement disorders [10, 26]. Due to challenges posed by the lack of stability of single-neuronal ensemble recordings [45], other approaches have recently explored the use of larger-scale intracortical signals such as local field potentials [20, 28], multiunit activity [55], and electrocorticograms [53, 61]. We refer the reader to Chapter 7 of this book for further information on applications of BCI systems in neurorehabilitation, which further describes current approaches, issues, and applications of this technology.

3.2 Rehabilitation Techniques for Incomplete SCI

Rehabilitation approaches for individuals with incomplete SCI are focused on a combination of compensation, adaptation, and promoting extant neuroplasticity.

As a result of these techniques, more than 80 % of individuals with motor-incomplete SCI regain some locomotor function [18]. This can be achieved by activity-dependent plasticity, i.e., an appropriate sensory input can be used to normalize the reflex output of the spinal cord that is disrupted, such as the rhythmic input from a treadmill. Neuroplasticity can also be harnessed by simultaneously training upper and lower limb movements trying to optimize the functional outcome. In the last decade, robotic devices and technology have been integrated into these training programs with promising results [36]. However, depending on the level of the injury, treatments usually apply varied approaches due to differences in rehabilitation goals based on each individual's need. In the subsequent sections, several rehabilitation approaches based on the severity of injury on ASIA impairment scale (AIS) classification are discussed.

3.2.1 Rehabilitation Approaches for AIS B/C

Patients with a level of lesion ASIA B or C are less likely to achieve neural adaptation or plasticity, due to the severity of the injury. The most commonly applied techniques are epidural stimulation of the spinal cord and functional electrical stimulation (FES) of muscles.

- **Epidural Stimulation**
  This technique consists of pharmacologically or electrically stimulating the spinal cord, which remains functional after complete or incomplete SCI. This enables more natural, coordinated recruitment of synergistic muscle groups and consequently causes less muscle fatigue in comparison to functional electrical stimulation (FES) [14]. This approach may also be suitable for treatment of intractable pain and spasticity, but those applications are still under investigation. Epidural stimulation involves activating central pattern generators (CPGs) for locomotion [9]. These CPGs are autonomous networks of neurons capable of generating locomotor patterns irrespective of the state of supraspinal input [21]. However, the main limitations of the approach include the invasiveness of surgically implanted electrodes and the fact that therapeutic benefit is primarily restricted to lower limb function compensation.

- **Functional Electrical Stimulation (FES)**
  This approach uses electrodes to electrically stimulate denervated muscles or intact peripheral nerves to produce functionally relevant movements via contraction of key muscles/muscle groups [21], restoring or improving their function [14, 36]. Although it has been researched for decades, there are still some major challenges and limitations [9]. The muscle tissue below the level of the lesion usually changes due to disuse or denervation, and the prolonged lack of supra spinal influence leads to progressive disuse atrophy. Besides, muscle atrophy produces pressure sores and cardiovascular diseases, complicating the application of FES. Importantly, muscle fibers also tend to fatigue and this limits stimulation duration. There is therefore

a trade-off between maintaining optimal levels of muscle endurance (i.e., by preventing muscle fatigue) and muscle strength. In the case of upper extremity, surface FES system for grasping such as the NESS H200 (Bioness Inc.) has already been commercialized. However, denervation and lack of voluntary control of the stabilizing musculature normally require surgical interventions before the devices can be useful to the patient. Commercial FES walking systems based on surface electrodes are also available, such as the Parastep (Sigmedics Inc.). However, loss of sensation in SCI further compromises balance and natural gait, which necessitates combination of FES systems with an orthosis in order to improve balance and reduce energy requirements. Research combining EMG-based forward dynamics with biomechanical modeling of the musculoskeletal system is being performed in order to quantify residual capabilities [22, 52]. This could lead to the development of a hybrid system [12, 29] based on individually tailored predictive algorithms to optimize neuromuscular control achieved by the FES based on each patient's residual capability.

- **Intraspinal Microstimulation (ISMS)**
  Locomotion consists of interactions of the nervous system and skeletal muscles in a rhythmic sequence, which is governed by CPGs. Therefore, in this technique, spinal cord locomotor circuits (or CPGs) are directly stimulated by intraspinal electrodes with the aim to restore limb movement [3, 24, 43, 51]. ISMS can be also useful for bladder function restoration. It is achieved by means of an implanted multichannel stimulator connected to an electrode array to selectively activate spinal nerve fibers, and therefore corresponding peripheral nerves and muscles, depending on which electrodes are activated [9]. Although powerful due to its ability to achieve precise stimulation, this technique still requires significant technical advances before it can be clinically deployed as a therapeutic device [22].

- **Intracortical Microstimulation (ICMS)**
  This approach consists of microelectrodes implanted in the cerebral cortex in order to restore a variety of sensorimotor functions, activating neurons that would normally be responsive to a now-disconnected sensory input or motor output. As proprioception is involved in the learning and control of motor action, its loss can have significant effects on a person's ability to move with or without a visual input. Therefore, ICMS devices can help simulate proprioceptive feedback loops within the CNS to help these individuals relearn optimal sensory-motor control in the context of novel robotic assistive orthotic and prosthetic devices. More importantly, this approach can help create a more complete cognitive percept of functional actions in these individuals, which can significantly improve their overall quality of life (QoL).

3.2.2 Rehabilitation Approaches for AIS C/D

Functional training, i.e., direct or task-specific training of a motor function, is the most effective and least invasive approach to enhance plasticity for the recovery of motor functions [14]. Focusing on locomotion, step training can help to reorganize the intrinsic spinal cord connections and harnesses its plasticity to relearn aspects of locomotion. Over the past few decades, the most common intervention in rehabilitation programs has been manual assistance by clinical staff, to perform lower limb stretching and cyclical movements. Thus, support systems such as crutches, walkers, or parallel bars are commonly used as stabilizing and unloading systems during these processes. In recent years, therapists have incorporated the use of body weight support (BWS)-based systems, since they are supposed to help reactivate gait patterns as well as provide other important benefits, such as physiological and psychological benefits associated with standing [25]. These primarily include improvements in cardiopulmonary, bowel, and bladder functions, and further also help alleviate pressure points on the skin and integumentary systems.

The body weight support treadmill (BWST) system is one of the most well-established techniques at many rehabilitation centers [29]. It consists of task-specific training that can promote supraspinal plasticity in locomotion motor centers. Studies measuring fMRI before and after rehabilitation with BWST have revealed greater activation in sensorimotor cortical regions and cerebellar regions due to BWST [36]. Progression can be achieved by decreasing BWS and increasing speed across the rehabilitation sessions [5]. However, these systems require at least two therapists in charge of moving the patient's legs. Therefore, manual assistance with BWST has several limitations due to the intensive physical effort needed from the therapists. As a result, sessions are limited by the lack of staff. In this regard, BWST systems can be automated with the incorporation of a robotic orthosis, such as the Lokomat (Hocoma) [13], releasing the therapists from continuous manual assistance. These devices, therefore, provide the therapists with greater opportunities to focus on changing/altering task demands depending upon the individual's progress and needs. These adaptive variations in the task demands help continually engage the user in his/her own rehabilitation and consequently recruit neuroplastic mechanisms more efficiently.

The technological support afforded by these robotic rehabilitation tools has significantly enhanced the ability to provide functional training, since it permits a higher number of movement repetitions, and can also monitor changes and adaptations in movement along the rehabilitation program. Therefore, these devices serve both therapeutic and diagnostic functions, which allows to more effectively documenting the functional outcomes within and across rehabilitation sessions. This in turn helps the therapist adaptively modify the rehabilitation paradigm in a personalized manner to elicit the best possible therapeutic benefits.

Moreover, there are other devices such as HapticWalker, more focused on performing ADL tasks such as climbing stairs or ramps. In general, these systems have in common the use of a treadmill. However, new systems have appeared in recent years such as the WalkTrainer [56], HYBRID [60], the Vanderbilt exoskeleton [47], NeuroREX system [11] as well as the Hybrid Assistive Limb (HAL) system [1], which combine a robotic gait orthosis with an unloading system, to respond to the needs for a more natural gait on level surfaces, allowing the user to stand and move around in normal walking environments. In this context, a robotic exoskeleton developed by REX Bionics, namely the RehabREX, is the only self-balancing exoskeleton that can completely support the body weight of an individual in the absence of assistive devices such as canes and crutches. This helps free the upper limbs of the user for performing other functional tasks, and can also be used in individuals with high cervical spinal injury (quadriplegic patients) who have limited upper extremity function. This automated, gait orthoses-driven, ambulation training significantly reduces the workload on therapists. Orthotic devices can also be beneficial as a means to improve the performance and accuracy of the functional movement. Further, robotic rehabilitation technologies for upper limbs have also shown some benefit in promoting functional recovery in incomplete SCI. [64] demonstrated in a case report that training with a novel upper limb robotic elbow–forearm–wrist exoskeleton helped improve upper limb function in an individual with incomplete SCI. These results are promising and provide evidence to support upper extremity functional training as well using these novel robotic technologies.

Automated BWST and active orthoses can be combined with the closed-loop control of FES [29], aiming to detect the user's intention, and actuate the appropriate joints as necessary. For example, feedback controllers that induce the FES to move the leg according to measurements of specific gait descriptors can be included [12], wherein a combination of a robotic orthosis with a closed-loop controlled FES system has been successfully demonstrated to induce user's leg movement, while simultaneously assessing associated muscle fatigue. Also, biologically based neural network controllers that model the spinal locomotor circuitry are used to trigger FES systems. This approach provides an excellent framework for developing rehabilitation technologies that combine several novel approaches that not only deliver therapy, but also perform diagnostic functions to continuously monitor the user's state, which helps drive a more optimally functioning closed-loop therapeutic system in SCI patients.

An important issue to consider is that the robotic device should not overtake functions, since active involvement/engagement of the patient is required to maximize functional recovery by recruiting neuroplastic mechanisms. If the training process is based on a fixed gait pattern, the patient will remain passive because variability, which is an intrinsic property of neuromuscular control (to prevent habituation to sensory input), will be lost [8]. Neural and muscular elements must be involved in the generation of movement, where the sensory system can serve as a control system for the spinal circuitry. Robotic devices can be useful in manipulating this sensory input. As a consequence, control schemes that take into account the patient–orthosis interaction [29], i.e., the assist-as-needed (AAN) paradigm, provides a high probability of successful rehabilitation in gait rehabilitation [6]. Robots working in an AAN mode can quantify the amount of work and power generated by the device in relation to that generated by the patient. Its effectiveness is based on the hypothesis that the spinal cord can relearn to walk more effectively if it is constantly challenged during locomotor training via adaptive training patterns. In this way, training algorithms that allow this intrinsic variability in the activation of motor pools may permit the spinal circuits to explore multiple patterns of activation, optimizing training effectiveness [8].

Therefore, more efficient robotic rehabilitation devices can provide a multitude of benefits such as enhance recovery of the neuromotor function; motivate the patient (by providing feedback about the rate of progress); and finally, reduce the cost of the therapy by minimizing therapist work time, allowing longer training times, and can be used more effectively at home as well [16]. These robotic rehabilitation technologies, however, have a limited memory, i.e., their effects last for a limited period of time if training is suspended. So treadmill or active orthoses gait training is relatively a more temporary solution than a long-term treatment [21]. Therefore, the best solution is the combination with alternative therapies. Combining FES with treadmill or walking aids can improve locomotion in incomplete SCI, and it can also help strengthen muscles in complete SCI, while standing or walking training. Other alternatives are based on the combination of functional training with pharmaceutical approaches, SC stimulation, or tissue regeneration, which would be the key to more permanently aid the restoration of function.

4 Future Directions

In summary, recent technological advances have significantly helped advance the state-of-the-art in neurorehabilitation after SCI. These approaches vary along the gamut of promoting functional recovery to substituting for lost function, and thereby help patients with varying levels of function based on their injury type and level. While many of these approaches are still under investigation to document definitive clinical efficacy, initial studies have shown promising results, which encourages further larger-scale clinical investigations. Another theme that becomes apparent in the literature is that the treatment of SCI should not be limited to only one method, but rather be based on a combination of therapies in order to be more effective by achieving a synergistic interaction between biological, pharmacological, and electrical stimulation [24]. For example, in complete SCI, the optimal therapy will lead to complete repair using regeneration techniques, which are still currently under investigation. However, while these therapies are being developed, it is critical to maintain functionality of the neurons within the CPG circuits. For this purpose, functional training in the treadmill or with active orthoses can serve to keep these neurons active until regeneration therapies are perfected to be applied in human subjects. This represents a best practice case for therapeutic practice wherein the most effective treatment is based on a combination of neural regeneration (cellular transplant or artificial scaffolds) and plasticity facilitated with technology or robotic devices.

Several important factors warrant further consideration in subsequent research during the course of translation of rehabilitation technologies to develop therapies for SCI. These include a) sharing control between the rehabilitation technology and user; b) permitting adaptive modifications in the control algorithms for the rehabilitation technology; and finally c) development of sensitive clinical metrics to measure functional progress and recovery. It is important to note that the design of these rehabilitation technologies should be centered around the needs of the user, i.e., individual with SCI in this case. For instance, wearable exoskeletons need to be form-fitting and comfortable, and should permit easy donning and doffing for users. Importantly, esthetic aspects of the device are important to motivate consistent use by the user to reap longitudinal benefits.

In this context, shared control becomes an important factor when considering BCI augmentation of robotic rehabilitation devices, wherein higher order cognitive features are extracted and play a big role in the implementation of the control algorithm. These higher order features can sense user motivation, emotion, etc., which play an important role in determining the outcome of each rehabilitation session and permitting the user's mental state to drive the use of device can help significantly improve user's experience and reduce frustration. This will ensure longitudinal compliance with use of the therapeutic device. Similarly, these technologies should be adaptive to the continuously changing user demands and needs. For example, as a patient with paraplegia following an incomplete SCI starts to recover function, designing modular devices can help adapt to the user's needs and use appropriate lower limb joint actuators in order to optimize the therapeutic intervention. In this regard, robotic assistance mode can be switched to resistance mode to maintain a certain level of challenge within the treatment session, and therefore keep the user engaged and motivated during therapy. Similarly, if a combined FES approach is used, then an appropriately designed control algorithm will adaptively modify the amount/duration of stimulation in order to maintain a certain level of task difficulty for the user. Overall, an adaptive system will constantly challenge the user and help maximize therapeutic benefit by recruiting intrinsic CNS neuroplasticity—both spinal and supraspinal. An important collateral benefit in this case is that adaptive algorithms can help systematically document task variations across therapy sessions, which can help inform development of targeted rehabilitation protocols in the future.

An important point to note in this discussion is that current clinical evaluation scales are very coarse, and measure function at a much higher level of granularity. With the advent of these novel rehabilitation technologies, it is expected that patients will progress along the spectrum of functional recovery at a much faster rate than earlier. Therefore, it becomes critical to measure the user's functional state more accurately at a much finer level of granularity. Thus, novel clinical metrics that are sensitive to subtle changes in function need to be developed and validated in order to track the individual's progress as he/she is treated with these novel therapies. This should be an important focus in subsequent research efforts. Input signals for BCIs and neuroprostheses, and parameters for neural and muscular stimulation can also serve as important markers of nervous system function as they depend on threshold activity of the CNS at any given point in time. Given the collection of these rich datasets, analytics and algorithm development can help mine these data to create novel markers/metrics to document the functional state of the individual at a much finer time scale. With careful research and validation, these metrics could serve as important clinical markers of plasticity and help inform the rehabilitation clinicians to appropriately review and adjust treatment parameters to suit the user's clinical needs at all times. This will permit development of a rehabilitation technology ecosystem, which will be centered around the user/patient and consequently optimize resources to maximize functional outcomes in the patient at all times.

Finally, it is important to also briefly discuss other physiological factors that can directly impact the outcome of rehabilitation in SCI, precluding application of these novel technologies. Chronic pain is a significant issue in SCI, which can alter functional QOL and also user's ability and motivation to actively participate in rehabilitation. Various pharmacological therapies as well as electrical stimulation, i.e., epidural stimulation, are actively used in controlling chronic pain in SCI survivors. More recently, noninvasive cortical stimulation approaches have also been used in SCI patients and show some promising results in helping mitigating chronic pain (for a more detailed review, please see [40]), which can subsequently help maximize rehabilitation outcomes. Similarly, skin and integumentary function need to be duly taken care of in order maximize use and benefits of these rehabilitation technologies. In this regard, it would be worthwhile to consider integrating pressure sensing mechanisms built into these rehabilitation technologies, most of which need to be strapped on to the user in one form or another. That way, the individual can be alerted about increasing pressure points that need attention in an audio/visual method given the absence of normal sensations due to injury [58]. Such systems can also serve to engage the user more directly in the treatment, increase confidence in the technology, and motivate him/her to use it to its maximal potential.

5 Summary

In conclusion, Fig. 3 shows the current and future possible routes for SCI rehabilitation devices, based on the study by [22]. Peripheral neural stimulation technologies are well established, and thus control signals drawn from intact CNS, PNS, or user motions can be used to control peripheral orthoses/exoskeletons, spinal (epidural or ISMS), or peripheral stimulation (FES), making it possible to enhance any residual function. Advances in invasive and noninvasive BCI control algorithm development have also greatly helped this process. Future work in these research areas will also benefit from improved neurotechnology for reliable long-term acquisition of BCI signals. ISMS can be a potentially powerful technique, but requires further research and testing. One of the main rate limiters in development of more effective ISMS protocols is the fact that our knowledge of the functional mechanisms of spinal circuitry is still largely incomplete. Therefore, subsequent basic research efforts should also be aimed at understanding the intrinsic functional mechanisms of spinal circuits as well as characterizing the role of supraspinal influence on these mechanisms. Together, these combined basic and clinical research efforts can help develop the most efficient rehabilitation technology systems that can significantly alter the trajectory of functional recovery after SCI. This will help reduce the overall healthcare burden associated with lifetime clinical management of SCI survivors. More importantly,

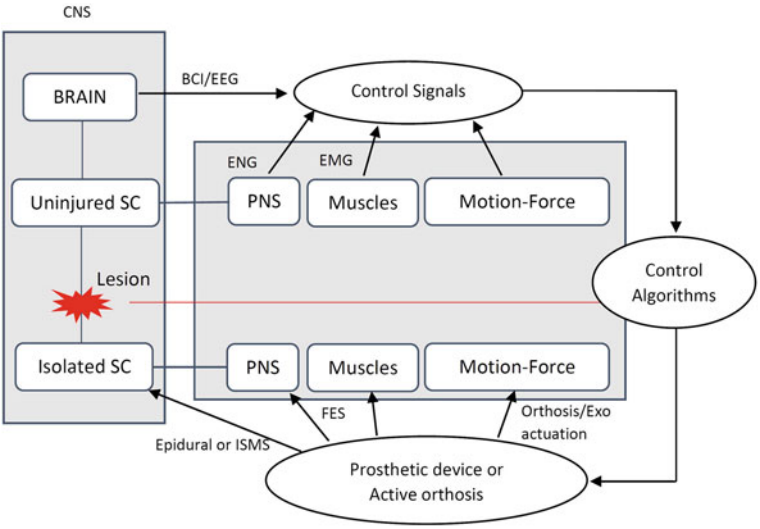

Fig. 3 Possible routes to restore and provide function in SC subjects (Edited from [22])

advances in these therapeutic technologies can greatly improve treatment for other forms of neuromotor injuries and disorders.

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Rehabilitation Technologies for Cerebral Palsy

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Abstract Cerebral palsy (CP) is the most common motor disorder of childhood. It is characterized by abnormal muscle tone and is caused by a nonprogressive injury to the developing brain. The hallmark of abnormal posture and movement occurs as the child develops fundamental motor skills. Thus, it is critical to make opportunities for infants and young children to interact with the environment. It is recognized that assistive technology can improve the functional capabilities limited by CP. In this chapter we will explore four distinct current innovative strategies that promote rehabilitation functional outcomes. The first two will focus on the output side of treatment that of robotic control systems with virtual reality to increased practice performance in locomotion and activity of daily living. The second contribution describes the state of the art of wearable sensors providing feedback for improving motor performance including communication. The third will focus on noninvasive

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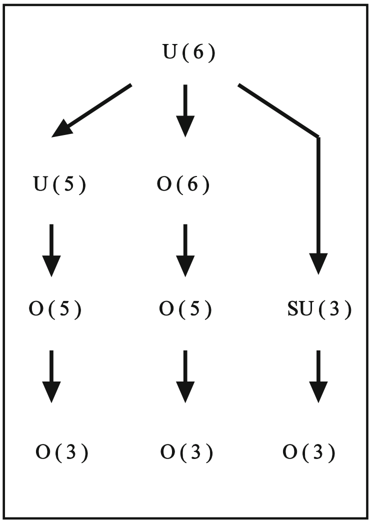
brain stimulation for CP rehabilitation. The next contribution provides analogues strategies used with stroke research that may be translated to children. Finally, we summarize the assistive devices for rehabilitation of people with CP from a parents perspective describing the challenges achieved and the future work required.

1 Introduction

The challenges of applying robotics and studying rehabilitation in childhood are complex but not insurmountable. The hallmarks that distinguish children are development, an acquisition of skills and growth a change in size. These two processes create a moving target when utilizing adult robotics and in turn analyzing movement, motor control, and functional outcome. The maturing brain and musculoskeletal system are in flux during childhood with critical periods and growth spurts. Critical periods of brain formation affects presentation of impairments and function. Advances and applications in bioengineering provide robotic tools for quantification that discriminate the patterns and shed light on mechanisms of injury and recovery, [1–3]. Although developmental sequences are orderly with known age ranges in typical children, those with developmental disabilities have considerable variability. Sequencing of developmental postures, for example a priority for children, does not naturally apply to the adult. Cerebral palsy is the most common motor disability of childhood, [4]. Abnormal muscle tone is one of the important features that influence movement and function in the child with CP. Objective measurement of tone, strength, and limitations of movement are body structure and function parameters or domains that are enhanced with robotics, [5]. Known variability among children with cerebral palsy make cohort comparison and control groups difficult for research. However, the GMFCS, which is now in standard use makes it possible to create more homogeneity, [6]. Another example of the moving target conundrum of childhood, or in particular cerebral palsy, is that the motor type and clinical presentation has changed and will continue to change as successful neonatal treatment occurs. Kernicterus is now rare but was once a common cause for cerebral palsy. As the field of neonatology advances the care of the neonate is modified, which creates different patterns of recovery from injury with the goal of reducing perinatal morbidity. Currently, babies born as young as 22-weeks gestation survive with new clinical presentations, [7]. In all countries there are important ethical issues surrounding the study of children. Typically, ethical review boards have additional protections for minors and scrutiny of research with vulnerable populations. Working with children though is made simpler now with IRB or ethical review board templates for assents, verbal and written and parent consents written at different age levels.

2 Robotics for Lower Limb Rehabilitation: Effects Beyond the Intervention

One of the main goals of neuromotor rehabilitation is recovery of the locomotion ability as it allows the patients to improve their independence and quality of life. Traditionally, physical therapy has played a critical role in lower limb rehabilitation. Treadmill training, usually with a partial support of body weight (Body Weight Support Treadmill Training or BWSTT), is also gaining importance as the therapy is provided in a controlled and safe way, [8]. Generally, training protocols include a gradual increase of difficulty level by decreasing the amount of body weight support provided, or by increasing the treadmill speed or the time spent walking.



A review of the effect of treadmill training on CP population by Willoughby et al. (2009) showed augmented speed of over-ground walking measured during a 10 m walking test (10 mWT) and improvements in gross motor skills (evaluated by means of Gross Motor Function Measure—GMFM). Moreover, walking endurance (measured with the 6 min walking test—6MWT) obtained some mild increase only in the more impaired group of subjects (with Gross Motor Function Classification System—GMFCS III or VI) [9]. The review by Damiano et al. (2009) confirmed the results highlighting that many studies noted positive, yet small, effects with a significant increase in self-selected gait speed after BWSTT.

Nevertheless, insufficient evidence is found for CP patients exercised with treadmill training, [10], and some drawbacks that can be highlighted include that the trunk and the lower limbs are difficult to control during exercise; thus BWSTT demands high physical effort especially for severely impaired subjects, [11]. In addition, treadmill training is conducted on artificial walking surface and neuromuscular feedback and sensation are different compared with over-ground walking, [8].

In this framework robotics is emerging as a leading technology for motor rehabilitation of subjects with neurological impairments and, in particular, for recovery of walking. In fact, Robot-Assisted Gait Training (RAGT) has some possible promising advantages with respect to traditional training or BWSTT including the fact that it is intensive, controlled, repetitive, and provided with goal-oriented tasks that are known to be related to the cortical organization and motor learning process, [12]. These are particularly important for the pediatric population that could obtain better results thanks to their greater neuroplasticity. Moreover, it can be performed in a safe manner and allows hand-free operation by therapists, which in traditional therapy has a high physical burden. Finally, robotic rehabilitation is often delivered in conjunction with virtual reality (VR) resulting in cognitive engaging tasks that stimulate the subject's active participation, [13].

2.1 Clinical Results

Interesting results were obtained with RAGT on 999 stroke adult subjects, [14] and on SCI, [15], assessing significant improvement after RAGT, and also with respect to traditional treatment and BWSTT. Only a few studies assessed the positive effect of robot-assisted lower limb training on the pediatric population, [16].

Till date, few robotic devices are available for the pediatric population and, among them, two are primarily used: Lokomat (Hocoma AG, Switzerland) and Gait trainer GT I (RehaStim, Germany), [16]. These robots follow two different training principles: the first principle provides training with a driven orthosis that guides the lower limb in a sequence of gait cycles on a treadmill. The second uses the end-effector paradigm: the lower extremities are fixed on two moving plates that are moved in a sequence similar to the gait cycle. During the training, both provide the body weight support allowing the fruition of training for subjects with different levels of impairment.

Some positive results on the CP population are reported in the literature. Borggraefe et al. (2010) showed positive effects with 12 sessions of training with Lokomat and described improvements in standing and walking ability (dimensions D and E of the GMFM, respectively) in 20 children with bilateral CP, which were maintained after a period of 6 months, [17, 18]. The authors also reported a dose-dependence efficacy of the intervention as the improvements of the task specifically trained (walking) measured in dimension E of GMFM are positively correlated with higher distance and time walked. Lokomat has also been used by Meyer-Heim et al. (2009), who obtained some significant improvements in terms of 10 m walking test (10 mWT) and dimension D of GMFM-66 after 12–20 sessions of training 22 CP children, [12].

Two randomized controlled trials studied the difference between robot-based therapy and conventional therapy with Lokomat (20 sessions), [19] and Gait Trainer (10 sessions over 2 weeks), [11]. Druzbiki et al. (2013), [19] recruited 52 CP subjects that underwent 20 sessions of 45 min each with either Lokomat or traditional physiotherapy (N = 26 each). They observed only few improvements (not statistically significant) in spatiotemporal parameters and kinematics of gait analysis both in the study group and in the control group. Differently, Smania et al. (2011), [11] analyzed the results of 18 diplegic and tetraplegic CP trained with 10 sessions of 40 min each. Nine children of the study group underwent 30 min of RAGT with Gait Trainer + 10 min of traditional training while nine of the control group had 40 min of traditional training. Results assessed significant improvements in terms of 10 mWT and 6 min walking test (6 MWT) only in the study group, while no groups gained significant improvement in an index of activities of daily living (Functional Independence Measure for Children—WeeFIM). The controversial results of these studies suggest that the RAGT therapy seems to be ineffective in modifying motor strategy consolidated in chronic disorders like cerebral palsy, thus the gait analysis cannot highlight modification in the kinematics pattern. However, improving muscular strength or reduction of energy expenditure could intervene in obtaining the overall effect of augment speed or endurance during walking observed in other studies, [11, 18] sustainably. The results remain uncertain, thus they should be regarded as preliminary with further studies necessary in RAGT in the CP population.

2.2 Rehabilitative Factors

2.2.1 Subject-Specific Responsiveness to RAGT

Recently, some evidence on pediatric treadmill training suggests a possible heterogeneity in the response to task-specific therapies in children, [20]. In particular, some studies assessed possible different outcomes following training for subjects with different impairment levels at baseline [9, 18, 20].

Borggraefe et al. (2010) observed that patients with moderate to severe cerebral palsy achieved less improvements after the robotic training compared to mildly affected patients. Schroeder et al. (2014) suggest that gross motor function at baseline can be considered as an independent determinant of improvement in GMFM-66 total score and GMFM-E score, meaning that patients with higher motor abilities at baseline improved more during RAGT than patients with lower gross motor abilities at baseline, [20]. These results are in line with findings by Hanna et al. (2008), who observed that CP patients with GMFCS levels of I and II exhibit a higher potential to gain motor function over time compared to severely affected patients using developmental curves of GMFM-66, [21].

However, a different trend was highlighted in a review for BWSTT: greater benefits were gained by children with more severe functional involvement (GMFCS III and IV), [9].

This inconsistency might be related to the heterogeneity of the studies analyzed (the first two related to the use of RAGT and the third one to BWSTT) and the use of different outcome measures to analyze data. It should be noticed that even if children with severe walking impairment (GMFCS IV) may be expected to obtain only reduced changes in functional abilities after training, they may obtain other potential benefits that can have an enormous impact on the children's health and well-being, [9].

Schroeder et al. (2014) provided a wider evaluation of the patient-specific responsiveness to RAGT, [20], considering also other factors that could influence the recovery (age, gender, etiology, and add-on botulinum toxin therapy). In their study they recruited 83 children (aged between 4 and 18 years) with various developmental disorders (bilateral spastic CP, unilateral CP, ataxic CP, hereditary spastic paraparesis, and genetic syndrome). The patients underwent 12 sessions of training within 3 weeks with Lokomat and were evaluated before and after the training by means of GMFM, obtaining some improvements in GMFM-66 and GMFM-E. The correlation between the results obtained and the other factors considered revealed that age seems to have an inverse effect on the improvement of standing abilities (GMFM-D), while no correlation was found between GMFM, gender, etiology, or previous intervention with botulinum toxin treatment.

2.2.2 Effects of Enhanced Active Contribution on Clinical Outcomes

Active participation of the subjects involved in training is recognized as one of the more important determinants of positive outcome, [22].

Some research groups investigate it analyzing the muscular activity during robot-assisted locomotion. Two studies assessed that the EMG activity of quadriceps and hamstrings is reduced with robot-assisted training with respect to therapist-assisted treadmill training [23, 24], but this difference is reduced if during RAGT subjects were vocally encouraged to maximize their effort, [24]. Schuler et al. (2013) observed that muscular activity follows a more physiological activation timing with respect to training on treadmill without orthosis, [25]. The reduced active contribution during robot-assisted training could be one of the responsible facts for the controversial results described in the literature, as it is recognized as a principle factor in eliciting performance improvements, [22].

Virtual reality has been suggested as an effective means to encourage subjects' motivation and active participation during training, especially in the pediatric population. Evaluation of EMG patterns on nine children with motor impairment and eight healthy subjects showed that there is an increased EMG activity during tasks with virtual realities than during normal walking conditions for both groups, [26]. These results are confirmed by two other studies, [25, 27] that, robot assisted treadmill training showed that the EMG activity of the hip muscles in the swing phase is significantly correlated with the presence of virtual reality, together with the encouragement provided by physiotherapists.

To conclude, RAGT seems to be a promising strategy to provide rehabilitation treatment in children affected by cerebral palsy and its effectiveness may be enhanced in the presence of active participation, promoted by therapists and/or virtual reality.

Definitive conclusions about RAGT cost-effectiveness cannot be drawn. Crucial elements to be considered for future studies include the small sample size, especially on the pediatric population, the absence of a randomized control trial design, and the lack of instrumental evaluations. There is no clear evidence of benefits of the robot-assisted training in cerebral palsy, also with respect to traditional training. Explanation for this might be due to different methods and protocols during intervention/group of patients studied as there are no well-established protocols shared by clinics to provide training. Moreover, it should be considered that there are only few effective assessment methods able to identify possible variation after training in a quantitative and not operator-dependent fashion. Changes to body structure and function (e.g., muscle tone, energy expenditure, muscle strength, bone density) are not often considered although they could be critical to provide a comprehensive evaluation of the training. Finally, some studies suggest that the effects of training are patient-dependent and a lot should still be done to identify specific factors that allow for prediction of the training efficacy and that could provide important indications to clinicians to customize the rehabilitation treatment.

3 Biofeedback as Rehabilitation Tool Using Physiological Sensors

Biofeedback, for use in treatment of children with cerebral palsy, can be defined as the use of sensory feedback through which objective performance observation related to a specific motor task is presented to provide the child with immediate, consistent feedback of performance, [28]. The aim of providing patients with biofeedback during exercise is twofold. First of all, to improve the effectiveness of the rehabilitation treatment, both by allowing patients to adjust their movements according to the feedback of performance and by providing an incentive to exercise. In the second instance, recording the physiological parameters to be fed back to the patient provides quantitative monitoring and documentation of patient progress during treatment. The latter feature is particularly important when the rehabilitation treatment is extensive and prolonged, which is typically the case with patients with CP.

3.1 Underlying Mechanisms

The neurological mechanisms underlying biofeedback training are still not completely clear. One of the primary problems for children with abnormal movement may be inefficient sensory information. Harris postulated that biofeedback devices that provide augmented or exteroceptive sensory information can be used by children with cerebral palsy to better calibrate the proprioceptive information they receive and, therefore, help them to achieve improved motor control, [29]. Biofeedback may enhance neuralplasticity by involving auxiliary sensory inputs, thus making it an appropriate tool for neurorehabilitation.

3.2 Biofeedback Modalities

Modalities of biofeedback are diverse and the appropriate sensors to use in a biofeedback system depend on the motor control mechanism, the training task, and the therapeutic goal. Clinicians may use sensors that detect such parameters as brain waves, muscle activity, reaction forces, joint angles, or positions. In neurofeedback training, surface sensors are placed on selected areas of the scalp to record EEG activity, thus teaching participants to control the frequency content of the EEG signal and gaining self-regulation of brain functions, [30]. For EMG training, surface EMG electrodes are attached to the skin over the muscle(s) being targeted. The goal of the EMG-based biofeedback is generally to provide subjects with enhanced information about their muscle activity to improve basic motor control skills, coordinated recruitment of synergistic muscles, or functional use of an impaired muscle during daily activities, [31]. Force platform biofeedback systems are used to measure the ground reaction forces generated by a body standing or moving on them. These systems are usually employed in protocols aimed at enhancing stance symmetry, steadiness, and dynamic stability, [32]. Inertial measurement units (IMUs) are systems typically based on accelerometers and gyroscopes that have been used to examine and quantify human movement, [33]. Because of their small and unobtrusive dimension, they have been used in several biofeedback protocols during static and dynamic balance training, [34, 35].

Since biofeedback therapy always involves a monitoring instrument capable of providing accurate physiological information, new and innovative sensor technology is particularly important in order to provide participants with a significant, accurate, and low-latency clue, thus improving the training outcome.

3.3 Early Studies

Starting from the 1970s, scientific studies investigated the effects of biofeedback therapy on the treatment of motor deficits in cerebral palsy. In an early work, Wooldridge and Russell, [36] tested a mercury-switch device to provide 12 cerebral palsied children with auditory and visual information regarding the spatial position of the head. It was concluded that the head position trainer was effective in the development of head control and position awareness in children with cerebral palsy. Postural control was also investigated in another early study, [37], where a pressure switch that activated a videocassette recorder was placed in the seat insert of five children with spastic diplegia or quadriplegia with inadequate trunk control. Based on the amount of time they exerted pressure against the switch, the study showed that children improved their sitting posture by voluntarily extending their trunk. In one pioneer study, Nash et al. [38] used the gain of the tonic stretch reflex of the gastrocnemius muscle derived from the level of EMG activity while the child's joint was rotated by the operator, to control video games. The protocol was tested on three spastic diplegic children with normal intelligence and aimed at facilitating the control of the reflex sensitivity, thus reducing spasticity. They reported that the range of voluntary joint rotation increased significantly, but that only one subject had a significant reduction in spasticity. They also highlighted that the protocol made the training interesting and enjoyable for all the children.

3.4 State of the Art

Early approaches have several limitations that prevent long-term use in children. In the first place, the types of cues used to convey the information to the subject were relatively simple, usually employing analog, digital, or binary values. A common form of performance information employed response-contingency systems, in which a desirable event such as the operation of a television set occurs as long as the required activity occurs, [28, 36]. Such feedback requires attention and can be distracting to the child and to other children nearby, preventing its use, for instance, during school. To have a significant effect on brain plasticity, it seems desirable to have the child training for several hours a day during daily activities. To address this limitation, Bloom and colleagues, [39] developed a wearable device that provided the subject with a mechanical tactile stimulation. The device was based on a mechanical vibrating stimulator attached to the skin, which provided the patient with a vibration proportional to the activity of the most impaired muscle and it was tested on 11 cerebral palsy children during daily activity. Results, based on parental questionnaires and Goal Attainment Scale assessments, showed significant clinical improvements in all the children who completed the study.

Another limitation of early studies is the reduced information available to the patient, typically limited to one or two channels so as not to overwhelm him during movement execution. Therefore, an effective task-oriented biofeedback system requires synergistic feedback of multiple channels that characterize the task performance without overwhelming a patient's perception and cognitive ability. Bolek et al. [40] developed multiple-site performance-contingent feedback to treat motor dysfunction in two patients with cerebral palsy. Specifically, they conveyed information from four muscles of the lower limb to train postural stability while sitting. Right and left gluteusmedius were targeted to remain above threshold, while the right and left gluteus maximus were required to be below threshold. When this constellation of muscle groups was on target, a reward was activated. Failure to maintain any muscle at the therapeutic threshold terminated the reward. The aim of this approach was to internalize the correct muscle pattern recruitment rather than individual muscle activity. Improvement, expressed in percent of time the threshold was met, was reported for both the participants.

One more shortcoming of earlier biofeedback approaches was that the information presented often took the form of lines or bars on a computer screen or simple beeps. These were neither intuitive nor attention grabbing. Motivation and attention are two key factors for biofeedback training. The success of therapies aimed at inducing neuroplasticity is strictly related to the amount of time spent on active training. As a result, the training task should be attractive and motivating to keep the subject attentive for several repetitions of the task. This feature is particularly important when working with children who get tired and distracted easily, [38]. Multimedia-based technology uses computerized graphics and animation, together with sound and haptic stimulation, to immerse the subject in a constructed virtual reality (VR), [41]; thus it can be exploited to design biofeedback cues with the required features. Novel VR-based biofeedback systems have the potential to promote sustained attention, self-confidence, and motivation of participants during the repetitive task therapy. Therefore, there is widespread interest in using VR in rehabilitation of children with cerebral palsy, to address upper extremity, [42, 43] and lower extremity motor functions, [44]. Yoo and colleagues, [43] investigated the effectiveness of a combined EMG biofeedback and VR intervention system to improve muscle imbalance between triceps and biceps during reaching movements in three children with spastic cerebral palsy. Results reported an improvement in the muscle imbalance ratio between triceps and biceps compared to a traditional EMG-based biofeedback training. Another case report, [45] investigated the effects of VR therapy on cortical reorganization and associated motor function in an 8-year-old children with hemiparetic cerebral palsy. After VR therapy, the altered activations disappeared and the contralateral primary sensorimotor cortex was activated. This neuroplastic change was associated with enhanced functional motor skills, which were not possible before the intervention.

An important feature of these novel systems is that virtual applications that are Internet-deliverable pave the way for possible home-based rehabilitation, which has the potential to reduce the costs associated with long periods of hospitalization or traveling long distances, [46]. Interactive technologies also provide children with movement disorders with the chance to be involved without being judged because of their disability [47]. In this framework, Golomb and colleagues, [48] carried out a 3-month proof-of-concept pilot study on three adolescents with severe hemiplegic cerebral palsy, where they tested a VR video-game telerehabilitation system using a sensing glove fitted to the plegic hand, [49]. Based on several outcome measures, such as occupational therapy assessments, fingers' range of motion (ROM), dual-energy x-ray absorptiometry (DXA), and peripheral quantitative computed tomography (pQCT) of the plegic forearm bone health, functional magnetic resonance imaging (fMRI) of hand grip task, the study reported improved hand function and forearm bone health for patients who practiced regularly. To address the need for technologies that facilitate children's acquisition of play experiences, another group tested the effectiveness of an affordable home-based musical play system (the movement-to-music system (MTM)) on children with severe physical disabilities, who are typically limited to play and create music, [50]. The results, based on parental interviews, showed that the MTM technology had the potential to improve children's body functions and enhance their participation in family activities. Another study developed a low-cost VR therapy system based on commercially-available game consoles (Sony PlayStation 2 equipped with an EyeToy video camera) to elicit practice of targeted neuromotor movements in five children with hemiplegia. The evaluation, based on the Quality of Upper Extremity Skills Test and on caregivers and parents questionnaires, showed that the system successfully elicited targeted neuromotor movements of the hemiplegic limb, [51].

The use of biofeedback techniques looks well suited for rehabilitation of children with cerebral palsy as a natural part of their daily activities. Findings indeed report a positive effect in motor rehabilitation, with improvements in motor control, spatial orientation skills, mobility, and an increase in motivation to practice even for children with severe grades of disabilities. However, even if at present studies report a general positive effect, there is scarcity of evidence of a strong beneficial effect, especially when it comes to VR studies. Indeed, studies that address the use of VR for rehabilitation of children with cerebral palsy are few, and the level of evidence is primarily limited to experimental and pilot studies with small samples. The large variation in outcome measures makes it hard to compare and integrate the results. In some studies, the assessment is based on qualitative interview, while there may be the need for more sensitive outcome measures that have the capacity to capture small motor changes. To conclude, the results show that the use of biofeedback and VR-based biofeedback in rehabilitation of children with cerebral palsy is a highly promising area in which further research is encouraged. In particular, further efforts to develop sensitive outcome measures and a common vocabulary within this research field is needed.

4 Noninvasive Brain Stimulation for Cerebral Palsy Rehabilitation

Noninvasive brain stimulation is growing as a very active research line because of its possibilities to enhance cognition, motor performance, rehabilitation after brain damage, and treatment of different psychopathologies. Basically, brain activity can be modulated by manipulation of neuron resting potential, rendering cells more prone to be activated if depolarized or reducing the probability of firing if hyperpolarized. Both effects, activation and inhibition, are reached by passing through the scalp a magnetic pulse or a weak electrical current, [52]. Transcranial Magnetic Stimulation (TMS) is based in a stimulator device that generates high intensity electrical pulses into a coil, superimposed above the scalp, to induce magnetic fields that easily pass the skull and modify actual electrical currents inducing activation or inhibition of cells. If the magnetic pulse is strong enough firing of neurons can also be induced. There are two main types of magnetic stimulation: single pulse (TMS) and repetitive transcranial magnetic stimulation (rTMS), [53]. Transcranial Direct Current Stimulation (tDCS) is based in an electrical device, battery powered, that delivers continuous current to a pair of electrodes situated above the scalp. The device contains specific software for programming the experimental setup and for maintaining a constant current intensity in function of variation on skull impedance. Electrodes are positioned to direct current flow between them, in such a way that tissue under anode is expected to become depolarized while brain tissue under cathode is said to be hyperpolarized. Electrical intensity is weak enough, between 0 and 2 mA, to ensure that no neuronal firing is triggered, [53].

Both techniques are being actively investigated for, directly or indirectly, enhancing neurorehabilitation. Thus, different reports show better performance on learning tasks (motor, sensory, or cognitive) of healthy participants as well of patients with brain damage (stroke, TBI, Alzheimer, Parkinson, epilepsy, amyotrophic lateral sclerosis, cerebral palsy, etc.), [52, 54]. Specifically the problem of spasticity has been targeted in various reports, mainly focused on stroke patients but also in cerebral palsy children. Two approaches can be indentified in the literature: direct modulation of spasticity by direct modulation of brain activity or modulation of typical motor training programs. Primary motor cortex, M1, sends out projections directly to the spinal cord, where it modulates spinal interneurons and reflex. Damage to M1 can result in spasticity because the absence, or reduction, of high-order motor commands imply the reduction of spinal inhibitory processes and a consequent overactivation of muscles. Thus, noninvasive M1 stimulation should increase spinal inhibition and spasticity. Working with this hypothesis has shown temporal reductions in upper or lower limb spasticity in stroke patients by stimulation itself but also by combination with physiotherapy or other functional motor tasks [55–57]. In 2007 Valle et al. [58], stimulated for 5 days the primary motor cortex of 17 CP children from 5 to 18 years old. 5 Hz stimulation, but not sham or 1 Hz, produced modest benefit in some, but not all, measures taken, namely upper limb joints range of motion. The more important information about these reports rely in safety data as no side effects were noted and no convulsions were generated in well-medicated patients diagnosed of epilepsy.

tDCS has been tested in the context of rehabilitation of CP children with the objective of improving functional training. Thus, Grecco et al. [59] compared 12 ambulant children with CP (GMFCSI-III) with 12 control children with the same characteristics. All of them were subjected to treadmill training; the experimental group was stimulated 5 days/week for 2 weeks with 20 daily minutes of 1 mA of anodal tDCS over the primary motor cortex, while control group was sham stimulated. Gait performance improvements were recorded for the experimental group both at the end of treatment and 1 month later. Cortical excitability, measured by TMS stimulation of motor cortex and motor evoked potentials, was also modulated by tDCS treatment, [60]. In a following paper the same group has shown that simultaneous tDCS M1 stimulation (1 mA) during 20 min of treadmill training resulted also in improvements of static balance and functional balance that lasted for 1 month, [60, 61]. Thus, tDCS also seems a promising technique for CP neurorehabilitation. In fact, just a single session of stimulation with the same parameters has shown improvements in oscillations during standing as well as gait velocity, [60]. In these experiments it is supposed that anodal stimulation, by depolarizing underlying tissue, will help in motor activation and plasticity, and as a consequence improve treadmill motor training. But anodal M1 1 mA stimulation has also been shown to reduce spasticity in children with CP; a reduction of spasticity would, for sure, improve motor learning. Thus it is important to discern the exact mechanism for this beneficial effect over treadmill motor learning.

Nevertheless, safety issues about both techniques are not convened for the pediatric population. Thus a plus of prudence is claimed by some authors: brain surface and physiology varied between children and adults together with skull and meningeal volume. It is important, then, to perform safety studies and, probably, basic research using animal models to ensure that actual stimulation parameters and, perhaps more important, a chronic stimulation schedule is safe for a developing brain, [62, 63].

5 Potential Effectiveness of Devices Designed for Stroke in Cerebral Palsy

5.1 Introduction

Stroke is the leading cause for adult disability in the US, [64], and accordingly, much of the novel technology-based rehabilitation research has been focused on treating adults with stroke. However, approximately 500,000 children and adults are also living with motor impairments caused by cerebral palsy, yet relatively little research has been done on how to best address current impairments and prevent further deterioration of movement abilities. Even with all the dedicated therapy research, there are no current widely accepted comprehensive clinical therapies that completely address impairments of the arm and hand for any condition. Inability to fully use either or both hands can have a major effect on performing both basic daily tasks and meaningful vocational activities. Providing therapy for the upper-extremity after stroke is especially challenging because of highly varied combinations of impairments such as spasticity, [65], weakness, movement inefficiency [66, 67], joint discoordination, [68], limited ranges of motion, increased trunk compensation, [69], and reduced movement speed, [70]. Because each stroke survivor has a unique array and severity of impairments, as well as potentially confounding neurological and mobility conditions caused by the stroke or other pre-morbid conditions, prescribing one therapy to adequately address movement behaviors throughout the recovery period is difficult. Many of the motor impairments and confounding factors are similarly seen in people with cerebral palsy, and this section will explore different types of upper-extremity therapies from theoretical, clinical, and technological angles and discuss how each therapy might translate to the treatment of children and adults with cerebral palsy. Therapies discussed include assistive robotics, virtual reality and feedback-based rehabilitation, constraint-induced movement therapy, vibration therapy, and functional electrical stimulation.

5.2 Assistive Robotic Therapy

One of the most popular ways to use robotic therapy is as a physically assistive device. This involves a robotic device that interfaces directly with the affected limb(s) and either assists the movement or moves the passive limb without any action from the user. Robotic devices such as these can be used as a stationary device that the person interacts with or as an ambulatory, wearable exoskeleton, or a combination of both types [71–74]. Assistive wearable robotic devices have been created to address issues of the hand, arm, and gait. Many of these robots also use a computer screen to provide some feedback to the user and create incentive for use. The Hand Mentor (KMI) is a commercially available repetitive task robot that passively moves or actively assists the hand in a way to practice wrist flexion/extension movements, [75–77]. This product has a small computer screen associated with the exercise so the user can play a game with the movements of the hand. The same company has also created the Foot Mentor, which uses similar principles to train ankle range of motion. The MIT Manus is another hand and arm robot where the user grasps a cylinder and the user's forearm is strapped onto the robot. The user can perform active anti-gravity movements, or if needed, be assisted by the robot, while they are playing a rehabilitation game, [78]. While assistive robotics can be extremely useful in augmenting a therapist's ability to help patients produce repetitive movements with a high frequency, they have also tended to focus on the technology, rather than on the specific clinical benefit. Many robots are designed to move the limb completely independently, which greatly limits the patient's opportunity to engage in active motor learning. The robots may also fail to adapt to the patient's specific movement impairments or to change the assistance based on improvements in movement or function. Because repetitive movements can become tedious even with assistive robots, robotic protocols often include visual feedback or games to incentivize the user to practice more often and for longer time periods. The feedback can also help the patient improve the movement in conjunction with the intervention of the robot.

The field of rehabilitation robotics has grown substantially during the past 15 years. Studies of upper limb robot-assisted therapy for adults with moderate to severe hemiparesis after stroke have shown significant gains compared with usual care in isolated control, coordination, and strength in the paretic arm. Researchers have recently extended their focus to children with neurologically based movement disorders arising from cerebral palsy and acquired brain injury or stroke. Section 2 has described the state of the art of robotic devices for gait pediatric rehabilitation. Some devices as InnoSmart (from Made for Movement) and Lokomat are examples of robotic systems that offer a specific version for children.

There are currently a limited number of robotic systems targeting the upper extremity that have been applied to children with CP, [79]. These devices propose goal-directed tasks and reaching movement to rehabilitate the hand and arm function. The InMotion2, also called shoulder-elbow robot, is an end-effector robot, a commercial version of MIT-MANUS (Interactive Motion Technologies), [80], which is capable of continuously adapting to and challenging each patient's ability. This device aims to improve the range of motion, coordination, strength, movement speed, and smoothness. 117 subjects with stroke were trained with InMotion2, and during the training patients were able to execute shoulder and elbow joint movements with significantly greater independence. At the end of the experiment, subjects were better able to draw circles, [81]. In most cases, studies conducted with patients with stroke have encouraged new experiments with people with CP. This is the case of an experiment where 12 children aged 5–12 with cerebral palsy and upper-limb hemiplegia received robotic therapy twice a week for 8 weeks. The children showed significant improvement in the total Quality of Upper Extremity Skills Test (QUEST) and Fugl-Meyer Assessment Scores, [80]. Following the distal approach, Interactive Motion Technologies has developed the MIT-Manus InMotion3. This robotic handle works with flexion and extension, as well as pronation and supination of the affected wrist. The results are similar to with InMotion2, but in this case, InMotion3 can operate both as a standalone device and as an InMotion2 module. There are no studies using InMotion3 by children with CP.

5.3 Constraint-Induced Movement Therapy

Constraint-induced movement therapy (CIMT), [82] was a method pioneered to encourage use of the affected arm. The patient puts a restrictive glove or mitt on their less affected hand and therefore is forced to use the more affected hand for activities of daily living (ADLs). As the person is restrained from using the less affected hand and arm, they must adapt to using the more affected arm in everyday real-world scenarios, which creates more natural practice than controlled therapy tasks. Constraint-induced movement therapy has been shown to increase movement and function of the affected arm, but studies have linked the higher amount of use to increased compensatory strategies and not to the recovery of pre-morbid movement patterns, [83]. Other studies have also shown that practice without a focus on improving movement quality may increase function, but will have an adverse effect of increasing compensation or inefficient movements, [84]. Another disadvantage of CIMT is that rendering one hand unusable severely restricts the performance of bimanual tasks that are crucial to many ADLs. The therapy may also not be ideal for people suffering from bilateral impairments, as they do not have a good arm to be constrained and may need to practice using both hands.

5.4 Feedback Systems

Feedback-based rehabilitation systems collect bio-data from sensors placed on the body and transform the data into usable feedback to allow the patient to alter their performance in some way. Sensors can collect muscle signals (EMG), kinematic data (motion capture or joint angle sensors), force, galvanic skin response, or brain signals (EEG) among others. The purpose of such systems is to encourage or correct certain patterns detected through the sensors. An EMG biofeedback system, [85] uses electrodes placed on the upper arm, whose signal control is a computer cursor. The cursor is used to play a game and can only be controlled correctly through the reduced use of abnormal muscle synergies. This can help retrain correct muscle activation patterns, although transference to significant increase in daily use or function. Another group, [86] has used combined EMG and kinematic signals to provide visual feedback on elbow extension, however, this system has not yet been used in active retraining movement patterns. Kinematic-based feedback can also be used to provide people with stroke useful information on their speed, trajectory efficiency, targeting accuracy, joint angles, and compensation, [87], but it is currently very difficult to provide high-level feedback on hand function as the movements are complex and difficult to measure. Feedback systems are also generally associated with complex and long setups to apply the sensors correctly and reducing the sensor set for an easier setup may result in lost important data. These systems are also not yet at the point of training functional, complex tasks. More research needs to be done on the best ways to provide multisensory integrated information about key movement features in a way that is intuitive and useful to the patient. Section of this chapter describes different studies using biofeedback for cerebral palsy.

5.5 Functional Electrical Stimulation and Vibration Therapy

Functional electrical stimulation (FES) uses electrodes to electrically stimulate weak or paralyzed muscles after stroke. FES has been used to reduce shoulder subluxation and reduce pain in the shoulder, which may potentially increase the use of that joint, [88]. However, repetitive task training has been shown to significantly increase active use of the hand when compared to FES therapy, [89]. However, the FES intervention may have been involved reducing spasticity in the hand flexors. This indicates that FES may be most beneficial in combination with other types of therapy as a way to reduce unwanted EMG signals or to enhance voluntary EMG signals during other types of occupational or physical therapy. The complexity of the FES setup as well as the inability to selectively activate smaller or more internal muscles could limit its overall usefulness in the clinic. Muscle vibration therapy is another way to reduce muscle tone and spasticity in the upper limb after stroke, [90]. Vibrations of the muscles are thought to increase corticospinal excitability as well as inhibitory neuronal activity in the antagonist muscle, [91], which could explain the reduction in spasticity. However, reduction in unwanted muscle activity may not lead directly to increases in voluntary functional usage of the affected limb, but instead may be another way to augment more traditional therapies. Coupling tendon vibration with assistive movement may also augment sensory information related to movement, but the outcomes may be most significant in people with severe impairments, [92]. Additional work is still needed to determine if vibration therapy can be beneficially coupled with active relearning of complex movements. There are very limited numbers of studies of children with cerebral palsy. Ruck et al. [93] showed that 20 subjects receiving 9 min of side-alternating whole-body vibration in addition to physiotherapy increased the average walking speed in the 10 m test. Katusic et al. [94] evaluate the effect of sound wave vibration therapy on spasticity and motor function of children with CP. Eighty-nine children with CP participated in the study. The Asworth Scale and GMFM-88 were used as outcome measures, describing significant differences after 3 months' intervention.

6 Rehabilitation from a Parent's Perspective

Children with cerebral palsy and their parents are very eager to seek and improve physical function through the therapeutic use of robotics. To include the perspective of parents, the president and co-founder of the International Alliance for Pediatric Stroke was asked to contribute and conclude the chapter.

Rehabilitative therapy has been proven to improve the quality of life for children, but it only works if the child participates. It is difficult to keep a child engaged and motivated in an ongoing, consistent rehab program as the child gets older. School work, activities, family life, and playtime start becoming more and more important. Therapy becomes boring and a nuisance for the child. In addition, older children become accustomed to instant gratification through their use of social media, video games, and technology. Typical therapy does not provide this. Similarly, in school, children are rewarded for their hard work with good grades. However, telling a child that therapy will reward them in the future does not seem attainable in the present.

In order to keep children interested and get them to actively participate in rehab, we need to find a similar instant feedback or measurable goals scenario for children and teens. This is where innovative rehabilitation technology becomes a valuable resource. Technologies such as Biofeedback, Robotics, VR Therapy, and Transcranial Stimulation are excellent methods to provide the goal and instant feedback that would increase the child's participation. Additionally, it provides the use of technology which children thrive on. Typical therapies are not able to provide this type of feedback and stimulation that children are familiar with.

Accessing these types of technology and making them affordable to families will be the challenges however. We live in North Carolina, but a few years ago my daughter was able to try out the Intellistretch at Rehabilitation Institute of Chicago. She came home very excited about the prospect of using this on a regular basis because this was something that would keep her motivated. Unfortunately, the device was not available in our area.

Speaking from experience, I see these technologies not only as innovative and promising for children, but necessary to improve their quality of life. These types of rehabilitation therapies will be the key to keeping children motivated, enthused, and eager to stick with the programs because they will see the improvement. Therapy will be something they "want" to do, instead of something they "have" to do. Moving forward, we will need to find a way to make these technologies affordable and readily available for these children.

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Neural and Musculoskeletal Modeling: Its Role in Neurorehabilitation

M. Ali Akhras, Roberto Bortoletto, Forough Madehkhaksar and Luca Tagliapietra

Abstract Human NeuroMusculoSkeletal systems (NMS SYs) are very complex and have redundant anatomical degrees of freedom (DOFs) at muscles and joints. These features enable them to easily perform dexterous tasks since the childhood. NMS SYs have attracted many researchers from different scientific domains such as neurophysiology, robotics, biomechanics, and neuro-rehabilitation engineering because of its multi-task functionalities. Humans can perform hundreds of tasks and dynamically interact with external environments in a very efficient way without thinking about the complexity of the motor task. Thinking about twirling a coin or writing tasks, the many complex operations needed to perform such actions rise important questions like "do we really perform very complex computations to control our musculoskeletal system?" or "how do we control our musculoskeletal system to perform such actions?" and "what is the main contribution of our biomechanical structure in the motor control task?". Recently, scientists have paid more attention not only to the neural commands but also to the biomechanical properties of NMS Sys and their role in simplifying the motor control tasks. Muscles are the main building blocks in our biomechanical systems. They can be continuously co-activated to produce and to coordinate movements maintaining the stability. Muscle-tendon actuators have been physically modeled, based on Hill-Type model, to study their non-linear behaviors

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and characteristics. Those models were then integrated with neuron models to provide a better understanding of the local control mechanism of a motor unit (e.g. spinal cord motor neuron and muscle-tendon actuator). Motor unit behaviors are observed through the muscle activity: the physiological process of converting an electrical stimulus to a mechanical response. This process is fundamental to muscle physiology, whereby the electrical stimulus is usually an action potential and the mechanical response is contraction. The transformation from Electromyographic (EMG) signal to muscle activation is not trivial and can occur through several steps. Muscle activation dynamics is the physiological process described by those steps. In general, the control of NMS models can be achieved also by combining together the EMG signals to retrieve muscle synergies. Apparently, humans use different motor control strategies to command their actions, some already exist in the Central Nervous System (CNS) with their birth and many others are developed and/or adapted during their life and gained experiences. However, both views of control strategies suggest a task dependency of the neural control. More details on description of muscle co-activation patterns based on the two views of the task dependent motor control strategies are provided in this chapter which will give an insight not only on a higher level of neural control but also at a lower level control of muscles in the CNS. Computational musculoskeletal models can provide an accurate knowledge of the physiological loading conditions on the skeletal system during human movements and allow quantifying factors that affect musculoskeletal functions, thus it can significantly improve clinical treatments in several orthopedics and neurological contexts. Every patient is different and possesses unique anatomical, neurological, and functional characteristics that may significantly affect optimal treatment of the patient. Therefore, personalized computational models of NMS systems can facilitate prediction of patient-specific functional outcome for different treatment designs and provide useful information for clinicians. Personalize computational models can be derived by generic models or subject-specific models with different levels of subject-specific details. In this chapter, we describe NMS systems in a bottom-up fashion. First we provide a deep insight on muscle contraction dynamics and musculoskeletal system properties. Then we discuss how a musculoskeletal system is locally driven by neuromuscular controls. Afterwards, we define how central motor commands are mapped through muscle synergies into low level controls. We discuss the two visions on the motor control strategies that CNS might use to perform motor control tasks and some related aspects inspired from neurorehabilitation studies and motor control experiments. Finally, we describe the importance and application of personalized subject-specific musculoskeletal modeling in neurorehabilitation.

Keywords Neuromusculoskeletal modeling · Muscle-driven simulations · Muscle-tendon activation · Model calibration and validation · Motor control · Muscle synergies · Muscle co-contraction

1 Musculo-Tendon Models and Parameters

The CNS generates neural commands to activate the muscles in order to control the human body movements. Subsequent forces produced by muscles are transmitted through tendons to the skeleton to perform a motor task. Thus, muscles and tendons are the interface between the CNS and the articulated body segments. A firm understanding of the properties of this framework is important to scientists in order interpret kinesiological events in the context of coordination of the body, and to engineers in order to design prosthetic, orthotic, and functional neuromuscular stimulation systems that helps to restore lost or impaired motor function. Biomechanical models have been used in several studies to predict muscle forces and joint torques along with human body motion. One of the first muscle's mathematical models was proposed by Hill [74]. Gordon et al. [66] refined such model by incorporating the dependence between changes in muscle force as function of muscle lengths and contraction speeds. Zajac extended the Hill's model introducing a muscle-tendon model [136], which is known as Hill-type muscle force model.

Hill-type muscle model is an important component of most of the adopted musculoskeletal models, yet it requires specific knowledge of several muscle and tendon properties. These include the Optimal Muscle Fibre Length (OMFL), the length at which the muscle can generate maximum force, and the Tendon Slack Length (TSL), the length at which the tendon starts to generate a resistive force to stretch. Both of these parameters extremely influence the force-generating behaviour of a musculotendon unit and vary with the size of the person. However, these properties are difficult to be directly measured in vivo and are often estimated using the results of cadaver studies, which do not account for differences in subject size [129]. The difficulty associated to the direct measurement of important variables, including the forces generated by muscles, is one of the main limitations related to the use of experiments only. As argued by Delp et al. [41], a theoretical framework is needed, in combination with experiments, to investigate the principles that govern the coordination of muscles during normal movement, to determine how neuromuscular impairments contribute to abnormal movement, and to predict the functional consequences of treatments. A dynamic simulation of movement that integrates models describing the anatomy and physiology of the elements of Neuromusculoskeletal (NMS) system and the mechanics of multijoint movement provides such a framework [41]. Muscle-driven simulations rely on computational models of musculotendon dynamics. These models are commonly subdivided into two classes: cross-bridge models [49, 72, 135] and Hill-type models [50, 131]. Although cross-bridge models have the advantage of being derived from the fundamental structure of muscle, they include many parameters that are difficult to measure and rarely used in muscle-driven simulations involving many muscles. For this reason and due to the fact that they are widely used in muscle-driven simulations thanks to their computational efficiency [2, 8, 13, 71, 78, 86, 118, 121, 137, 138], we focus here on Hill-type models.

1.1 Architecture of Muscle Tissue

Musculotendon actuators are assumed to be massless, frictionless, extensible strings that attach and wrap around bones and other structures [97]. Muscle are considered to be a collection of equally long coplanar fibers arranged in parallel, where all fibers are oriented either in the direction of the tendon or at an acute angle, also known as Pennation Angle (PA), $\alpha > 0$, to the tendon [136]. A common assumption is that muscle maintains a constant volume and the distance between the aponeurosis of origin and insertion is constant. The major effect on musculotendon function is that α increases as fibers shorten. Thus, muscle fibers shorten in a direction that is not colinear with the direction in which tendon stretches.

The length at which active muscle force peaks, L_0^M, is called OMFL. Notice that the shortest length at which passive muscle tissue develops force is L_0^M. Given the OMFL and the corresponding PA, α_0, at which the muscle develops the Maximum Isometric Force (MIF); the relationship between PA and Muscle Fiber Length (MFL), L^M, can be expressed as the following [62]:

$$\sin(\alpha) = \frac{L_0^M \sin(\alpha_0)}{L^M} \tag{1}$$

$$\cos(\alpha) = \sqrt{1 - \sin^2(\alpha)} = \sqrt{1 - \left(\frac{L_0^M \sin(\alpha_0)}{L^M}\right)^2} \tag{2}$$

For muscles with a small PA, the PA will have little effect on the force in the musculotendon unit. However, a large PA (i.e. greater than 20°) can have a significant effect on muscle force. PA can be directly derived from Eq. 1, at time t:

$$\alpha(t) = \sin^{-1}\left(\frac{L_0^M \sin(\alpha_0)}{L^M(t)}\right) \tag{3}$$

A muscle can be represented by n motor units being controlled by n nerve axons originating from the CNS, each with its own control $u_i(t)$. The muscle fibers of each motor unit i collectively develop a motor unit force F_i^M, which is most likely assumed to sum with the other motor unit forces to produce the net muscle force F^M. This assumption allows us to represent musculotendon actuators with a wide range of architectures with a single dimensionless model [14].

1.2 Hill-Type Muscle-Tendon Model

The general arrangement for a muscle-tendon model has a muscle fiber in series with an elastic or viscoelastic tendon (Fig. 1). The muscle fiber has a contractile component in parallel with an elastic component [25]. The Hill-type muscle model

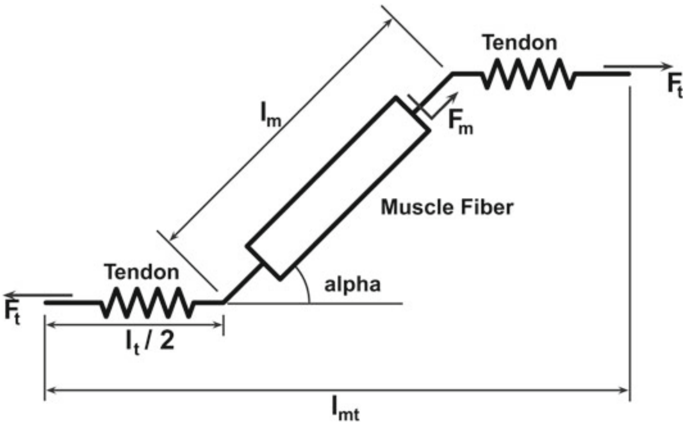

Fig. 1 Schematic of muscle-tendon unit showing muscle fibre in series with the tendon

is used to estimate the force that can be generated by the contractile element of the muscle fiber, using a Force-Length-Velocity (FLV) relation controlled by muscle activation. The general form of the function is given by:

$$F^M(t) = f(l)f(v)a(t)F_0^M \tag{4}$$

where $F^M(t)$ is the time varying muscle fiber force; $f(l)$ is the normalized length dependent fiber force; $f(v)$ is the normalized velocity dependent fiber force; $a(t)$ is the time varying muscle activation; and F_0^M is the MIF. Commonly, Hill's equation [74] is modified and used as an expression [16, 131], although nothing precludes the use of other expressions [73].

Muscles could be imagined having an active part which generates force when activated, like a motor, and an in-parallel passive part that applies a resistive force when stretched beyond a resting length, like a rubber band [25]. Sometimes a muscle elastic element, distinguishable from tendon elasticity is included in series with the active part, which is due to the contractile elements [136]. These yield a MIF when the sarcomeres are at an OMFL (i.e. when there is optimal overlap of the actin and myosin myofilaments). When the muscle length is above that optimal length, it cannot generate as much force because there is less actin-myosin overlap which reduces the force-generating potential of the muscle.

1.2.1 Force-Length Relation

The static property of muscle tissue is defined by its isometric Force-Length curve (FLc). This property can be studied when activation $a(t)$ and fiber length L^M are constant. Full activation ($a(t) = 1$) occurs when muscle tissue has been maximally excited ($u(t) = 1$). Conversely, muscle tissue that has been neither neurally nor electrically excited for a long time is said to be passive ($u(t) = a(t) = 0$) [136]. MIF, F_0^M, is assumed to be proportional to Physiological Cross-Sectional Area (PCSA), where PCSA is defined as the ratio between muscle volume and OMFL:

$$PCSA = \frac{Volume}{L_0^M} \tag{5}$$

Typically, the volume of a muscle is calculated from its weight multiplied by the density of muscle tissue: 1.06 g/cm^3 [100]. The proportionality constant relating F_0^M to $PCSA$ represents the Maximum Muscle Stress (MMS) [62].

The difference in force developed when muscle is activated and when muscle is passive is called Active Muscle Force (AMF), F_A^M.

$$F_A^M = f_A(l) F_0^m a(t) \tag{6}$$

where $a(t)$ is accounted for since the level of muscle activation determines the MIF produced by the muscle.

The muscle force-length is also coupled to the level of activation [70]. Lloyd and Besier [88] incorporated this coupling between activation and OMFL into the muscle-tendon model using the following relationship:

$$L_0^M(t) = L_0^M\,(\lambda\,(1 - a(t)) + 1) \tag{7}$$

The percentage change in OMFL defines how much the OMFL shifts to longer lengths, at time t and activation $a(t)$.

Mathematically, it is often more helpful to consider the force-length relationship in dimensionless units. Zajac [136] represented this property in terms of Normalized Muscle Force (NMF), $\tilde{F}^M$, and Normalized Muscle Fiber Length (NMFL), $\tilde{L}^M$.

$$\tilde{F}^M = F^M / F_0^M \tag{8}$$
$$\tilde{L}^M = L^M / L_0^M \tag{9}$$

As depicted in Fig. 2, the effective operating range of muscle begins at roughly $0.5L_0^M$ and ends at $1.5L_0^M$; muscle cannot generate active force beyond these lengths. Furthermore, when muscle is stretched to lengths greater than $1.2L_0^M$, it generates a significant amount of Passive Muscle Force (PMF), F_P^M. It is due to the elasticity of the tissue that is in parallel with the contractile element. Passive forces are very small when the muscle fibers are shorter than their OMFL, and rise greatly thereafter [117].

$$F_P^M = f_P(l) F_0^M \tag{10}$$

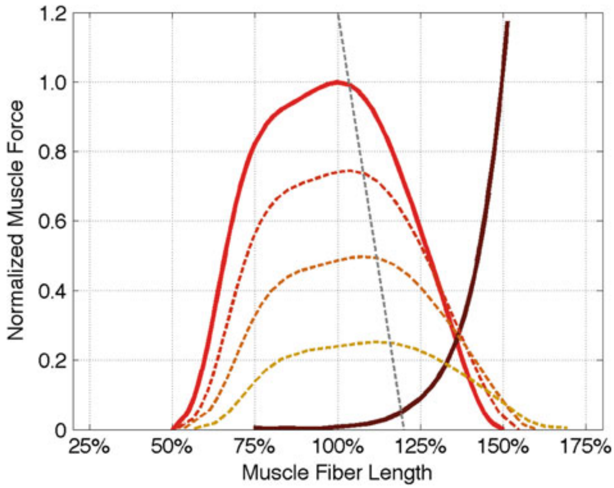

Fig. 2 Normalized forcelength relationship for muscle. Thick dark lines indicate maximum activation, whereas the light thin lines are lower levels of activation

The total normalized muscle force is the sum of the active and passive components, which can be scaled to different muscles to provide total isometric muscle force, F^M, by:

$$\begin{aligned} F^M &= \left[F_A^M + F_P^M\right]\cos(\alpha) \\ &= \left[f_A(l)a(t) + f_P(l)\right] F_0^M \cos(\alpha) \end{aligned} \quad (11)$$

It is also worth noting the importance of the fiber lengths operating range with respect to the required excursion of a muscle. Brand et al. [22] defined muscle excursion as the difference between the maximum physiological length, L_{max}^{MT}, and the minimum physiological length, L_{min}^{MT}, of the muscle: the extreme lengths of a musculotendon actuator when a joint is moved through its full range of motion. For muscles with a large excursion, one can expect the value of L_0^M to be relatively large; conversely, for muscles with a small excursion, the value of L_0^M should be relatively small. Unfortunately, the relationship between OMFL and musculotendon excursion has been shown to vary widely among muscles, and it cannot be used to define the value of L_0^M precisely. As discussed in [62], also the value of TSL, L_s^T, affects the relation between OMFL and musculotendon excursion. If we assume that the total length, L^{MT}, of a musculotendon actuator is given by the sum of muscle length, L^M, and tendon length, L^T, then the tendon length will affect the length of the muscle when the actuator is at L_{min}^{MT} and L_{max}^{MT}. If tendon is assumed to be sufficiently stiff so that a change in its length is negligible compared to a change in muscle length, then all variation in musculotendon length, L^{MT}, can be attributed to a change in muscle length. On the other hand, if an actuator has minimum and maximum physiological lengths which are both relatively large, then one can expect the value of TSL, L_s^T, to be large and the value of OMFL, L_0^M, to be small. Conversely, if L_{min}^{MT} is relatively small, then L_s^T should be small and L_0^M should be large. It is clear that L_0^M, L_s^T, L_{min}^{MT}, and L_{max}^{MT} are all related.

1.2.2 Force-Velocity Relation

Muscle tissue is subject to a constant tension when it's fully activated. It first shortens then stops (i.e. isometric contraction). The length at which shortening terminates corresponds to the length at which such a force can be sustained in steady-state [136]. From a set of length trajectories, obtained by subjecting muscle to different tensions, a Force-Velocity relation can be constructed for any length L^M, where $0.5L_0^M < L^M < 1.5L_0^M$. Finally, at OMFL, L_0^M, a Maximum Shortening Velocity (MSV), v_0^M, can be defined from the Force-Velocity curve (FVc). At this velocity, muscle cannot sustain any tension, even when fully activated.

The shape of the FVc determines the mechanical power output that active muscle delivers. During shortening, muscle delivers power (power output is positive), with peak power output occuring when muscle shortens at about $0.3v_0^M$ [136]. The shape of FVc during lengthening is very important during computer simulation of movement. Common assumption are that (Fig. 3):

1. The FV relation scales with length and activation in one of two ways: either the velocity-axis intercept remains constant under all conditions or decreases with $a(t)$ and L^M);
2. No discontinuity in slope at F_0^M exists, even though experiments and cross-bridge theory suggest one;
3. The FVc at any instant is unaffected by preceding events, even though it is known that prestretched muscle tissue subsequently shortens faster.

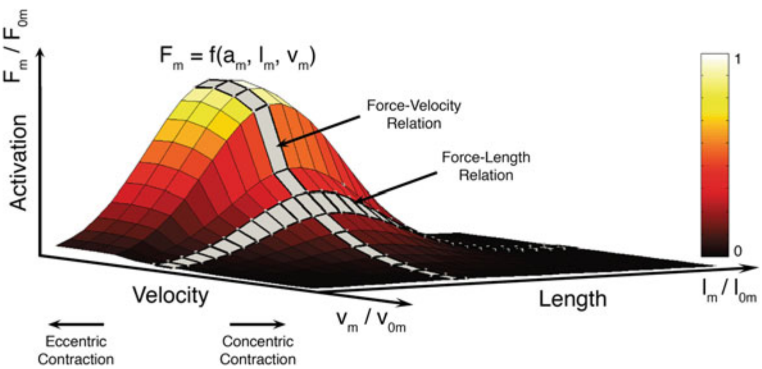

Fig. 3 The Active Force-Length-Velocity (FLV) surface of muscle is defined by the muscle's Optimal Fiber Length (OFL), Maximum Shortening Velocity (MSV), and Maximum Isometric Force (MIF). Active muscle force generation can be constrained to this surface and scaled by the level of muscle activation. Force-Length and Force-Velocity curves are highlighted in gray

MSV, v_0^M, is commonly defined as the number of OMFL per second, and it is treated as a constant. However, it could be varied depending on the relative fiber mixes in muscles. Yamaguchi et al. [134] listed the fiber mixture percentages to be considered as common starting point, but it is well known that people do have different fast-twitch to slow-twitch fiber ratios. A detailed discussion about the ways in which the force-length and force-velocity relationships could be most readily combined for shortening muscle can be found at [25].

Given a value of L^M, PA is calculated using Eq. 3. Subsequently, since the muscle-tendon length, L^{MT}, is a known input of the model (it is directly related to the musculotendon kinematics), the tendon lenght is computed as follows:

$$L^T = L^{MT} - L^M \cos(\alpha) \tag{12}$$

Once tendon length is established, also tendon force, F^T, can be determined (see Sect. 1.3). Given the total muscle force (Eq. 11), the corresponding normalized velocity dependent fiber force, $f(v)$, can be computed as follows:

$$f(v) = \frac{F^T - f_P(l) F_0^M \cos(\alpha)}{f_A(l) a(t) F_0^M \cos(\alpha)} \tag{13}$$

Once $f(v)$ is calculated, we can solve for fiber velocity, v^M.

1.3 Tendon Model

Tendons are commonly defined as a external portion to muscle passive elements that act like rubber bands. Tendons do not carry any load their length is below the TSL and generates a force proportional to the stretch distance if their length is above TSL. Given the tendon length, L^T, tendon strain (i.e. tendon stretch relative to its resting) can be defined as follows:

$$\varepsilon^T = \frac{L^T - L_s^T}{L_s^T} \tag{14}$$

Data suggest that the same strain is experienced throughout internal and external tendon. It is also convenient to assume that the Stress-Strain properties of external and internal tendon are the same, where the Tendon Stress, σ^T, is defined by the ratio of tendon force, F^T, to Tendon Cross-Sectional Area (TCSA), as follows:

$$\sigma^T = \frac{F^T}{TCSA} \tag{15}$$

Notice that the tendon force varies with the strain only when the tendon length is greater than the TSL, otherwise the tendon force is zero. Hence, tendon behavior can be modeled through a generic Force-Strain curve (FSc). As depicted in Fig. 4,

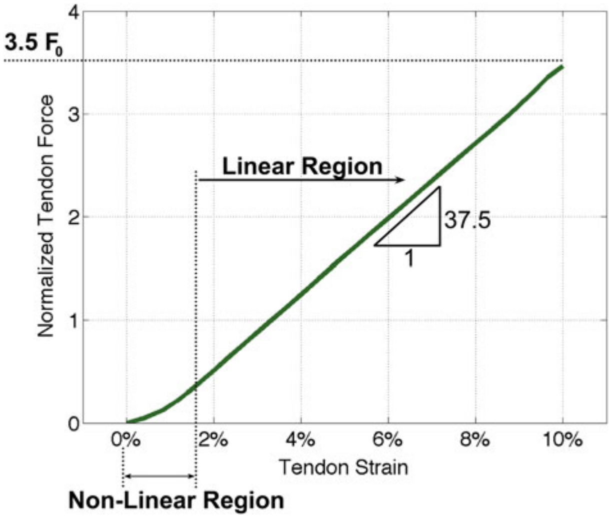

Fig. 4 Mechanical properties of tendon

the tendon tangent modulus of elasticity (i.e., the slope of the tendon stress-strain curve) increases with strain at low strains, and then is constant at higher strains until failure. Zajac [136] observed from the literature that the strain in tendon is 3.3 % when the muscle generates MIF, corresponding to a nominal value for σ_0^T of 32 MPa.

1.4 Musculo-Skeletal Kinematics

Once the muscle-tendon force is computed, it is important to compute the corresponding contribution to joint moment. This requires knowledge of the muscle's moment arm, r, which can be shown to be a function of the muscle's length [95]. To compute both the length and the moment arm for a musculotendon unit, a musculoskeletal model is required. Musculotendon kinematics estimations can be produced by a software that model the geometry of the bones, the complex relationships associated with joint kinematics, and the musculotendon paths wrapping around points and surfaces [41]. This is based on obstacle detection and may cause discontinuities in the predicted musculotendon kinematics [61]. On the other hand, it is desirable that musculotendon kinematics equations are continuously differentiable to enable the computation of analytical Jacobians for the forward simulation of the musculoskeletal system [2, 113].

Sets of differentiable polynomial regression equations have been proposed to estimate L^{MT} and r from nominal values of both parameters corresponding to combinations of discrete joint angles or Generalized Coordinates (GCs) [95]. This required gathering data sets on both L^{MT} and r and manually identifying the best-performing equations that depended on the muscle, number of GCs, and the fitted musculotendon parameter. This necessitated computing and storing coefficients for all equations for L^{MT} and r for each muscle before use. Alternatively, continuously differentiable multidimensional cubic splines can be used, but are yet to be examined as a means to estimate musculotendon kinematics. In [113] a single spline function per muscle was used to estimate L^{MT} and r.

2 From EMG Signals to Muscle Activation

This section covers some issues related to the neural controls for a NMS systems and models. In NMS simulation environments, the neural control signal or muscle activation level defines the input of the forward dynamics used to study the human motion. This physiological command indeed specifies the amplitude and the timing of the subject's muscle activation. It can be obtained directly from experimentally measured electromiographic (EMG) signals (EMGs control strategy) or from a synergy analysis (synergies control strategy). Both the control strategies require recording EMG signals from a set of subject's muscles, then a pre-processing of data to obtain a neural control signals utilized in the subsequent steps. EMG pre-processing aims to cut off different non-physiologic signal components due to the acquisition process, such as motion artifacts and 50 Hz noise. It also includes the low pass filtering, to match muscle characteristics, and the optional EMG normalization procedure.

In synergies control strategies, the muscle synergies are first calculated. The main idea behind this method is to express the experimental EMG signals as a weighted sum of a limited number of muscle synergies. This analysis aims to reduce the dimensionality and the redundancy of the human motor system.

Finally, the muscle activation dynamics represent the contribution of the neural control on the activation of each muscle. Once again this processing step is common to both the strategies.

2.1 EMG Pre-Processing

Electromyography is the study of muscle function through the analysis of the electrical signals from the muscles [136]. EMG signals are emitted before muscle contraction and can be detected through superficial non-invasive electrodes. Furthermore, the EMG signal is the result of all the motor unit action potentials occurring during the contraction. This activity, measured at a given electrode location, is expressed by an electric signal (in the order of millivolts) either positive and negative.

EMG signals recording could be affected by unpredictable variables such as: the placement of the electrodes on the subject muscle, the skin characteristics, the amount of tissue between the electrodes and the muscles, the cross talk from nearby muscles, muscle fatigue, the electrodes and amplifier quality and durability through the acquisition process, the electrical and magnetic noise, etc. The influence of these external factors must be removed, or at least smoothed, before computing the muscle activation [25]. This pre-processing phase can be addressed in different ways.

The first operation is to remove any DC offset and low frequency noise that can be due to the use of low quality amplifiers or electrodes, or due to the movement of the electrodes themselves. This can be done through a high-pass filter with a cutoff frequency in the range of 5–30 Hz, depending on the type of filter and electrodes used. A good strategy is to implement a digital zero-phase delay filter (e.g., forward and backward pass 4th order Butterworth filter). This way filtering does not shift EMG signals in time. The next step is to visually inspect each obtained signal to check the presence of 50 Hz electromagnetic interference. For the affected trials a 50 Hz notch filter (usually of order 10) should be used. Then the signal must be rectified based on its the absolute value for each sample to obtain a *rectified* EMG signal.

2.1.1 EMG Normalization

EMG signals are extremely sensitive to a large number of external factors that can not often be controlled in clinical settings. A very comprehensive review of this problem is available in [38]. EMGs normalization aims to reduce this variability facilitating the comparison of EMG signals across muscles, subjects, or acquisition session from same subject [38, 83]. A concise and precise analysis of the importance of EMG normalization can be found in [83] with a discussion of the dangers of misinterpreting the signals when this step is not preformed correctly.

The general procedure for the EMGs normalization requires to divide the EMG from a specific task by the EMG from a reference contraction or event of the same muscle. Recent papers [28, 32, 33, 38, 77] partially discussed the benefits and limitations of different normalization methods within a more general analysis while a more complete review and critical comparison of normalization strategies can be found in [29]. According to the available results, a standard normalization procedure is still far from being defined.

One of the most used strategies, suggested also by the Journal of Electromyography and Kinesiology (JEK), is the Maximum Voluntary Contraction (MVC) normalization. This strategy divide each EMG signal by the reference one recorded during an MVC task. Similarly, the SENIAM project [96] suggests to use as denominator in the normalization process the EMG from a reference contraction, and uses MVC as an example. Both strategies refer to static MVC although it could also be dynamic. However, non of them provides a guideline to define the best strategy depending on a specific objective. Either JEK and SENIAM advised electromyographers to report information about the joint angles of the subject during the MVC acquisition. The main benefit of using MVC as normalization method is the possibility to understand the level of activation of the muscle during the task in terms of percentage of the MVC. However, electromyographers should pay high attention that subjects are reaching their true maximum contraction during the MVC acquisition, otherwise the results could be uninterpretable.

Another widely used strategy concerns a division by the peak of the EMG recorded during the task or the acquisition. This approach does not need to perform ad-hoc trials. However, most of researches indicate that this method reduces inter–subject variability and has poor intra-subject reliability. Therefore it is better to avoid the use of this strategy to compare EMGs among different trials, muscles or individuals.

2.1.2 Muscle Filtering Effect

The normalized and rectified EMG signals should be low pass filtered to match the muscle filtering effect. Indeed, although the electrical signals that pass through the muscle have components over 100 Hz, the forces that the muscle generates is at much lower frequency. There are many mechanisms in muscle that require this filtering: calcium dynamics, finite amount of time for signals propagation along the muscle, and muscle and tendon viscoelasticity. The cutoff frequency typically used is in the range of 3–10 Hz.

This step is the last one in the pre-processing of the raw EMG signals. The output of this process can be used to directly evaluate muscle activation or elaborated to extrapolate muscle synergies.

2.2 Muscle Synergies

The concept of muscle synergy was proposed for the first time by Bernstein in 1967 [17]. The idea is that the CNS uses this strategy to reduce the redundancy in the motor control task of musculoskeletal system with multiple degrees of freedom. Recent interpretations suggest that afferent signals and supra spinal descending motor control commands interact, select, and correctly activate a low-dimension set of muscle synergies through time modulated activation coefficients. Synergies can be thought as neural networks produced at corticospinal levels, specifying an invariant profile of activation for the motoneurons innervating a set of muscles [31]. The result is a weighted distribution of the neural drives to different muscles. Experimental results, obtained both in humans and animals, support the hypothesis that biomechanical tasks reflect a synergistic muscle control. Moreover, there is evidence that different biomechanical conditions, such as speed and load, share the same synergies [30, 76].

Different studies have used low-dimensional sets of multi-impulse curves within musculoskeletal models of the human lower extremity assessing the mechanical role of muscles during human locomotion [4, 93, 102] and the conceptual idea of muscle synergies in relation to the biomechanics of human and animal movement [58, 79, 94, 123, 137]. Since the multi-muscular EMG patterns observed during motor behaviors have a lower dimensionality with respect to the number of muscles and associated motor units (MTUs) [19, 37], the same excitation patterns can be expressed using a low-dimensional set of muscle synergies. Hence, a low-dimensional controller of single-impulse synergies could be designed to be generic to subjects and motor tasks, but sufficiently selective to drive a subject-specific musculoskeletal model of the human lower extremity [112]. In this same work, the static behavior and simplified structure of the generic synergies have been compensated using the experimental joint kinematics as an error correction factor. This approach provides a musculoskeletal model of human locomotion which can be operated in an open-loop forward dynamics way without using numerical optimization to match the experimental joint moments, reducing the computational cost. Moreover, since the musculoskeletal is calibrated on a specific subject, it can estimate movement-specific joint moment even if driven by subject-generic and task-generic synergies. In this scenario no EMG recordings are needed for the model operation, allowing its use in the development of neurorehabilitation technologies simplifying the human-robot interface.

A common approach to muscle synergies identification is based on a Non-negative Matrix Factorization (NMF) technique [82]. A good practice when using this technique is pre-process the data with the peak normalization strategy for EMG amplitude (Sec. *EMG Normalization*) where the peak is evaluated across all the available tasks. Then, a normalization in time follows [65, 76]. Finally, a $m \times n$ matrix is created, where m is the number of recorded muscles and n is the number of trial frames per the number of trials per the number of subjects.

The NMF is applied to the matrix with a number of non-negative factors identified together with their associated weightings. The extracted, experimental non-negative factors are linearly combined with their associated weightings to produce an $m \times n$ matrix of reconstructed EMGs and then compared to the original EMG matrix. The NMF is iterated within an optimization procedure adjusting the non-negative factors until they minimize the least squared error between experimental and reconstructed EMG data. In this procedure the dimensionality of the non-negative factor set is increased until the accuracy of the reconstructed EMG data reach a pre-defined threshold. This is assessed by means of the Variation Accounted For (VAF) index, which is defined as:

$$VAF = 1 - SSE/TSS \tag{16}$$

where SSE (sum of squared errors) represents the unexplained variation and TSS (total sum of squares) is the total variation of the EMG data. A minimal VAF value of 80 % is a good choice for the threshold to consider the reconstruction quality as satisfactory [65].

Several other algorithms can be used to identify muscle synergies combination. In [126] these algorithms have been compared on both simulated and experimental data sets with the main goal of investigating their ability to identify the set of synergies from a common data set. The obtained results are quite similar for all the algorithms with no significant differences in performances or accuracy.

2.3 From EMG to Neural Activation

In order to account for the time varying features of the EMG signals, a detailed model of muscle activation dynamics should be considered. In this paragraph, we will refer with the term EMGs (e(t)) both to the pre-processed EMGs and to the synthetic EMG retrieved from the weighting of the muscle synergies.

The next processing steps are indeed common to both the control strategies. The first proposal for modeling the neural activation dynamics was the following first-order linear differential equation [25, 136]:

$$\frac{d\,u(t)}{d(t)} + \left[\frac{1}{\tau_{act}} \cdot (\beta + (1-\beta)e(t))\right] \cdot u(t)\frac{1}{\tau_{act}}e(t) \tag{17}$$

where τ_{act} is the time delay associated to the activation dynamics and β is a constant that can vary in the range (0, 1). This modeling approach captures very well the activation dynamics but requires to be solved numerically for a discrete signal, using a numerical integration approach, such as Runge-Kutta algorithm. Therefore, a more efficient model is required.

A critically damped linear second order differential equation has been used with quite good results [98]. An approximated version of this differential equation have been proposed [25, 110]:

$$u(t) = \alpha e(t-d) - \beta_1 u(t-1) - \beta_2 u(t-2) \tag{18}$$

where d is the electromechanical delay and the coefficients α, β_1 and β_2 define the second order dynamics. The electromechanical delay have been shown to be in a range from 10 to 100 ms [25, 36]. The selection of these four parameter is critical for the stability of the equation. Therefore the following relationships must be verified:

$$\beta_1 = \gamma_1 + \gamma_2 \tag{19}$$

$$\beta_2 = \gamma_1 \times \gamma_2 \tag{20}$$

$$|\gamma_1| < 1 \tag{21}$$

$$|\gamma_2| < 1 \tag{22}$$

Another condition that must be verified ensure the unitary gain of the equation:

$$\alpha - \beta_1 - \beta_2 = 1 \tag{23}$$

Through the combination of previous constrains only the three parameters d, γ_1, and γ_2 are required to fully describe the transformation.

2.4 From Neural Excitation to Muscle Activation

This paragraph illustrates how the nonlinear relation between the neural excitation $u(t)$ and the muscle activation $a(t)$ can be modeled. A possible explanation for this non-linearity can be found in the size principle, i.e. the size of the recruited motor units is related to the force that has to be expressed.

Several studies have shown that the effect of this nonlinearity is significant only at lower excitation (up to 30–40 % of the maximum). For this reason, a first attempt to model this relation, presented in [133], uses a power function in the first 30–40% and a linear function for the remainder. The power function is expressed as:

$$EMG = a \cdot FORCE^b \tag{24}$$

where the authors referred with EMG to the neural excitation $u(t)$ and as FORCE to the muscle force (linearly related to the muscle activation $a(t)$).

Both of them indicated in capital letters to underline that are normalized to their maximum value. The coefficients a and b were computed basing on experimental measurements. However, this approach has two main disadvantages: the need to evaluate two parameters and the not-smoothed connection between the two expression.

Another approach correct these disadvantages is proposed in [25, 91]. This solution uses a logarithmic function for the first 30 % and a linear expression for the reminder:

$$\begin{aligned} a(t) &= d\,ln(c\,u(t) + 1) && 0 \leq u(t) \sim 0.3 \\ a(t) &= m\,u(t) + b && \sim 0.3\ \leq u(t)\ <\ 1 \end{aligned} \tag{25}$$

where the coefficients d, c, m, and b can be simultaneously solved and therefore reduced to a single parameter A, which characterizes the amount of nonlinearity,

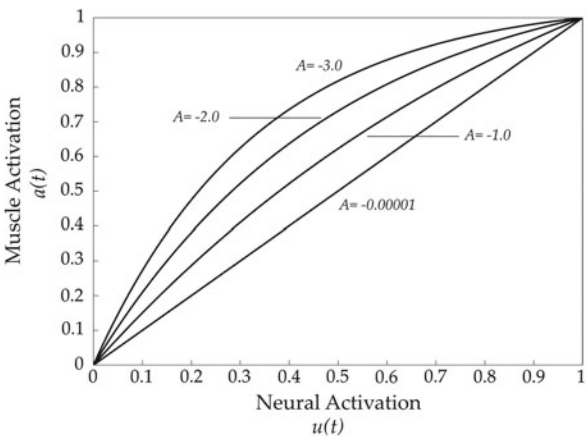

Fig. 5 Changes in the neural excitation u(t) to muscle activation a(t) curve depending on the nonlinear shape factor A

varying from 0 to approximately 0.12. A simpler formulation, [25, 88, 90, 92] is the following:

$$a(t) = \frac{e^{A\,u(t)} - 1}{e^{A} - 1} \tag{26}$$

The coefficient A in Eq. 26 is named nonlinear shape factor and it is allowed to vary from 0 to −3 where A = −3 indicates a linear relationship as shown in Fig. 5. The value of A is determined through the usage of the calibration procedure.

3 Differences in Task-Dependent Central Control Strategies for Same or Similar Joint Biomechanics

Neuromuscular control in humans is still unknown due to the high complexity of our neuro-musculoskeletal systems and its high motor redundancy [23, 81, 111]. Humans learn and adapt different dexterous tasks in an interactive manner with external environments taking advantage of their past knowledge of motor actions and their biomechanical structure. [18, 116, 130]. Many elements in the human body dynamically cooperate to perform tasks planned in the brain. Task parameters are planned in different areas in the brain, known as central control unit, to create a motor program that contain the necessary central motor command to perform the task. The central motor commands are then transmitted through the brain stem and spinal cord to alpha-motor neurons which are known are local controllers of the muscular system Fig. 6. Motor neurons in spinal cord drive the muscle contraction to actuate skeletal segments that in turn generate the desire motion and dynamic properties (i.e. forces and torque). Sensory signals are sent to local and central control units during the action execution to modulate the dynamic properties in the biomechanical system.

Scientists suggest that humans centrally control their movements in feed forward system and locally in feedback system [34, 75, 108], also known as open-loop

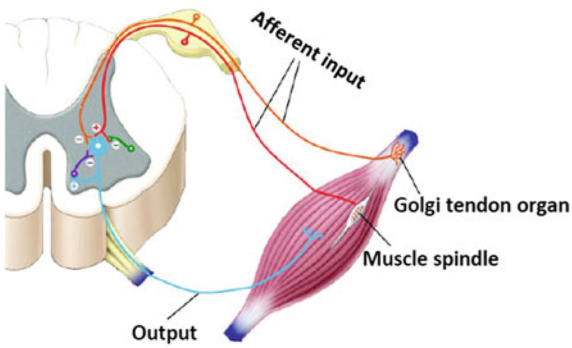

Fig. 6 Basic neural circuit describing the closed-loop control structure of a single muscle

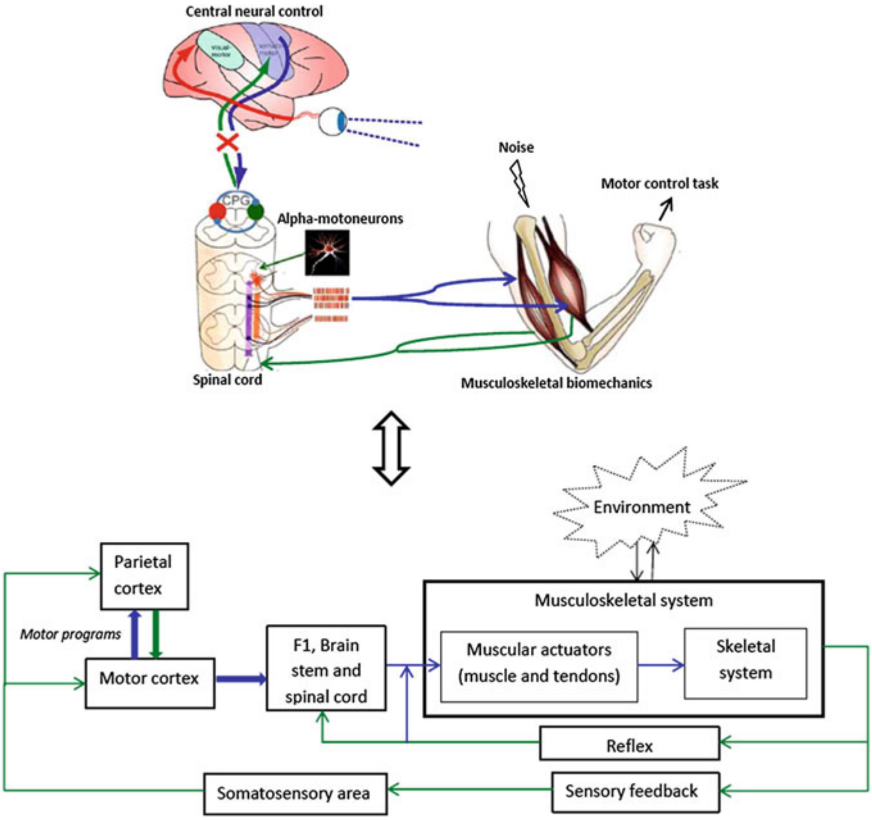

Fig. 7 Basic scheme of neuro-musculoskeletal systems. Blue arrows represent the motor information while green arrows stand for the sensory and feedback information

and closed-loop systems respectively as illustrated in Fig. 7. This basic motor control scheme describes different control levels and sensory information modalities integration in the CNS taking into account the delays caused by the sensory-motor loops that are crucial for some motor actions.

Muscles are the main components in any biomechanical system to generate forces. They are unidirectional force generators and can only contract, therefore they can only pull. Based on that fact, our joints are always actuated by at least two muscles known as agonist and antagonist muscles to bi-directionally control the joint movement like flexion and extension or abduction and adduction in digits. Muscles are activated when a neural signal arrives from an alpha motor neuron through its axons to a target muscle fiber. A large number of muscles can be activated simultaneously to produce a movement and consequently perform a task. Pointing toward an object with the index finger or reaching tasks are typical examples to describe the problem [120]. In robotics, three coordinates of the fingertip in the operational space need to be planned corresponding to three equations, but the number of joints and muscles participating in such a task is much higher which means that the number of unknown variables (Degrees of freedom) is higher than the number of equations [35]. In consequence, the motor control task can have an infinite number of neural solutions of joint angles and muscle forces. The motor control task could have different neural solutions among different people or even for the same person when solving it several times [69, 81, 109].

Some motor control researchers believe that this motor control redundancy problem is solved at the neural level by our CNS by optimizing (typically minimizing) a cost function (i.e. muscle energy, total muscle force) to select a neural solution [21, 25, 27, 109, 124, 125]. Static and dynamic optimization methods are usually used to describe this hypothesis and estimate the neural solutions. Other researchers, [52, 56, 80, 103, 105], believe that there are no computations of mechanical variables done at the neural level and the CNS cares only about the overall task performance and matching the task requirements beside of the detailed muscle activation characteristics (i.e. recruitment frequency of motor units). An example of this view is the Equilibrium Point hypothesis (EP), originally developed by Feldman in 1960, will be described in more details in this chapter. EP hypothesis is based on the idea of control with thresholds for activation of neuronal pools, it assume that all the mechanical variables (i.e. joint stiffness, muscle and join forces, muscle activity "EMG", etc.) are not directly planned in the CNS, but they emerge when reducing the difference between a referent configuration pre-programmed by the CNS and the actual one.

Muscle redundancy at a joint allows humans to perform isometric or isotonic tasks. A person can produce a constant net joint moment but different muscle activation patterns in static and dynamic tasks [122]. This leads to a variation in co-contraction levels of agonist-antagonist muscles with the net muscle activity with no change on the net joint moment. However, the main contribution of muscle co-contractions in the motor control task is still under-investigation. In this chapter, we presented two neural control frameworks, muscle activation control and equilibrium point control, that account for the muscle co-contraction control and its dependency on the control task.

3.1 Muscle Activation Control

Almost all the motor control hypotheses agree that the CNS controls the muscle contraction locally by alpha motor neurons located in the spinal cord [53, 84, 104] or the brain stem (for facial and neck muscles). Those neurons receive projections of central commands that describe the task parameters (desired spatial pose "position and orientation", velocity, total force... etc.) pre-programmed in the cortical areas of brain and reflex signal for fast movement. Muscle activation control models assume that the CNS pre-compute some unknown variables (i.e. mechanical parameters, muscle activation patterns, ... etc.) based on the task and biomechanical properties and actual state of the neuro-musculoskeletal system [88, 132].

3.1.1 Task-Dependent Muscle Activation Patterns for Static and Dynamic Tasks

Several studies have shown high evidence that the muscle activity patterns are task-dependent [24, 63, 67, 122]. Tax and his colleagues hypothesis suggested that central activation of motor units is different in the control of movement and isometric contractions. They compared the activation behavior of motor units in force task with two conditions of movement task, imposed movements and intended movements. They found that the CNS recruits the motor units during isometric contractions similarly during imposed movement contractions and differently during slow isotonic voluntary movements.

Ghez and his colleagues developed another hypothesis, called pulse-step control, suggesting that the CNS controls movements and isometric contractions by scaling muscle activation patterns. This assumption hypothesize that the projection of task parameters received by alpha-motor neurons is a sequence of a short-lasting pulse and long-lasting step. The hypothesis was then updated by the authors considering the pulse and step commands are separated in the CNS. During isotonic movements (movement task), the pulse amplitude would control the acceleration rate and its duration would define the movement amplitude (e.g. the trajectory of an effector). The step component of the sequence would control the co-contraction level of agonist-antagonist muscle to stop the movement at the final position. During isometric contractions (force task), the pulse amplitude would control the production rate of force and its duration would indirectly define the peak force (e.g. time profile of force). The step part of the command would stop the force production and therefore define the final steady-state force.

Buchanan and his colleagues tested muscle activation patterns in humans when performing two different static tasks, isometric (force control; when joint angles are fixed and joint torque is allowed to vary) and isoinertial (position control; when joint torque is fixed and joint angles are allowed to vary) tasks. In their study, they aimed to see if there is a difference in muscle activation patterns (e.g. muscle synergies) even though the joint angles and torques are identical. Their hypothesis suggests that the difference in synergic activations occur not only between static isometric and dynamic isotonic tasks but also between static isometric and isoinertial tasks. This switch in the central control strategy depends on the control task (i.e. force control for isometric tasks or position control for isoinertial tasks).

3.1.2 Muscle Co-Activation Patterns

As we showed in the previous paragraph, muscle co-contraction patterns vary not only with the length and force but also with the load characteristics (e.g. isometric, isotonic or elastic load) on the joint or its stability condition [39, 68].

De Serres and his colleagues have found a little effect of a stable load (constant or elastic) and a big effect of unstable load on the co-contraction of wrist flexor and extensor muscles. The muscle co-contraction was dramatically greater for the unstable load than the stable load. They also tested the effect of muscle co-contraction on the stretch reflex response and found a major effect for a stable load than for an unstable load. In consequence, the joint stiffness was more dramatically affected for a stable load than an unstable load. They concluded that the muscle co-activation patterns (e.g. muscle synergies) of the central control, and therefore the muscle co-contraction, are different depending on the load stability condition. They found no evidence of a significant contribution of phasic stretch reflexes in the joint stiffness although their results showed that magnitude of reflex response increases with the co-contraction level. Hence, they concluded that the stretch reflex modulation is independent from the tonic muscle activation control and dependent on the load stability.

Heiden and her colleagues explored the co-contraction patterns in Knee Osteoarthritis (OA) patients. They have shown that the level of muscle activation varies with the loading and the reduction of pain and adduction moments. Their study stated that the levels of net muscle activation increased during loading and early stance to possibly alter the stabilization and articular loading of knee joint. They found a significant difference in muscle activation strategies between OA patients and healthy subjects. OA patients utilize a directed co-contraction strategy to exhibit greater lateral muscle activation during loading, early stance and mid-stance while heathy subjects utilize it to predominantly exhibit medial muscle activation during the same tasks. Some studies showed that the increment of the co-contraction level does not increase the net moment (net moment = constant) but the net muscle activity [89]. They also observed that OA patients increase the level of net muscle activity and laterally directed co-contraction even as the same joint moment and posture while heathy subjects utilizes lower co-contraction levels. This result suggest that OA patients use this mechanism to reduce the pain resulted from external knee adduction moments. It is also worth noting that no difference in co-contraction level or net muscle activity was observed between control and stroke groups in late stance.

3.2 Threshold Position Control

As we mentioned above, a second view on neural control of muscles, called threshold (referent) position control or equilibrium point control, contrasts the muscle activation control hypotheses. It does not consider any particular computation of the unknown system variables at the neural level, but an emergence of those variables when the neuro-musculoskeletal system attempts to attain a referent configuration of an effector [53–55]. In other words, neither trajectories (i.e. trajectory of an effector, force/torque profiles, joint stiffness, etc.) nor motor commands (muscle activity “EMG patterns”) are directly specified by neural control levels but only a referent configuration and those mechanical variables emerge when reducing the difference between a referent configuration pre-programmed by the CNS with the actual one. This automatic mechanism occurs in alpha-motoneurons which reduces the error between a central input (referent control signal) and afferent input (feedback signals,

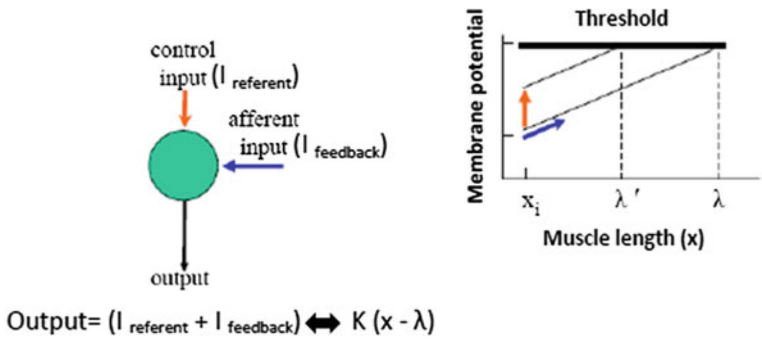

Fig. 8 Alpha-motoneuron is represented as a servo controller in the left-hand image. Regulation of threshold muscle length in neurons is shown in the right hand image. The neuron works as a servo controller to reduce the error between the actual muscle length and the control variable (lambda) to obtain a referent configuration of the body segment pre-programmed in the brain. parameter is projected from task parameters though muscle synergy mapping. It can be shifted by the CNS to define a new referent configuration

i.e. muscle spindle feedback), as illustrated in Fig. 8 (motoneurons). The central input is a projection of high level commands that describe a referent configuration. The afferent feedback provides the CNS information about deviation of the actual (emergent) position of an effector from their referent position specified by the brain. The neuron can generate action potentials when the neural membrane potential due to the input excitatory sources reaches a threshold according to all-or-non law. The neuron output changes the state of an effector. The frequency of action potentials generated by the neuron depends on all afferent excitatory signals.

Equilibrium Point hypothesis assumes that the CNS controls the muscle activation with thresholds for activation of neuronal pools, this neural control strategy is called threshold position control.

Threshold position is a parameter that pre-determines where, in spatial coordinates, muscles can work without pre-determining how they should work in terms of EMG patterns, forces and kinematics. The referent signal is normally lower the membrane threshold in healthy subjects otherwise the neuron will be always active generating action potentials at the highest possible frequency independently of the afferent feedback input. This is because the neuronal membrane potential is over the threshold. Hence, the membrane potential should depend on both referent control and feedback inputs. Based on threshold control hypothesis, the CNS regulates the membrane potential through the referent position control level as illustrated in Fig. 8. It is clear from the figure that a low level and a high level of referent control signal will lead to two different referent configurations (e.g. two different muscle lengths and forces). If the referent control level is constant, the neural membrane potential to reach the threshold will depend on the feedback source. If the referent control level is shifted to a higher level, the membrane potential will be closer to reach the threshold, and therefore the neuron will need less feedback excitation to fire action potentials. This mechanism will produce two different muscle lengths leading to two different configurations of the body segments or/and force production.

EP hypothesis suggests that the central control defines the set of R and C commands at the joint level which delivers information about the referent configuration intentionally planned (e.g.Θ). R command and C command are addressed as reciprocal and co-activation [52, 85]. These commands are then projected at the corticospinal level to provide control variable (λ) at the muscle level addressed as the threshold of tonic stretch reflex. This means that each muscle can have its own λ according to its fiber length and biomechanical properties and connections, but the same R and C command set corresponding to a referent configuration (e.g. joint angles Θ).

The transition previously described corresponds to a shift in the characteristic of muscle force-length. For agonist-antagonist muscle actuation, R-command leads to a unidirectional shift of the two muscle characteristics (R = sum (λ_1, λ_2)) while C-command leads to an opposite directional shift of the two muscle characteristics (C = diff (λ_1, λ_2)). Changes in R and C commands reflect a change joint movement and joint stiffness respectively. Based on EP hypothesis, it may happen voluntarily following a change in the central commands (R and/or C commands) which lead to a change in the threshold level of the tonic stretch reflex (λ) or involuntarily (R and C commands are constant, λ is constant) following a change in the external load as illustrated in Fig. 9.

EP hypothesis suggests that co-contractions of agonist-antagonist muscles are modulated through C-commands. Changes in this command reflect a variation in the joint stiffness and damping when the musculoskeletal system is deviated from its equilibrium states [52]. C-command can be modulated independently of R-command during static or dynamics task [85]. This result would suggest a multi-contribution of C-command in joint stability and movement speed.

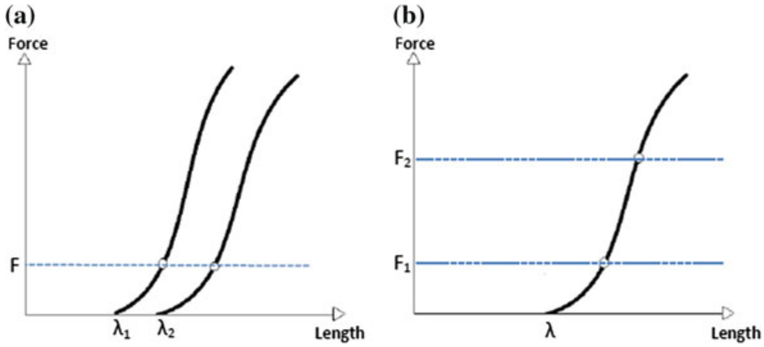

Fig. 9 **a** voluntarily movement produced by a shift in the threshold level of the tonic stretch reflex (λ) through a change in the central commands (R and/or C commands) **b** involuntarily movement produced by a change in the external load at constant intentional neural control (R and C commands are constant, λ is constant)

4 Personalized Musculoskeletal Modeling

Computational musculoskeletal models can provide an accurate knowledge of the physiological loading conditions on the skeletal system during human movements and allow quantifying factors (e.g. muscle moment arms, joint motions) that affect musculoskeletal function, Thus, it may significantly improve clinical treatments in several orthopedics and neurological contexts [10, 11, 15, 44]. Musculoskeletal models have been used to study stroke [5], spinal cord injury [9], bone fractures, joint osteoarthritis [64], orthopedic surgical procedures such as Arthroplasty and neurological disease such as cerebral palsy [42].

Muscle and joint contact forces during motion are currently not measurable in vivo with non-invasive devices. Computational modeling of the musculoskeletal system is the only practicable method that can provide an approach to analyze loading of muscle and joint. Computer and information technologies have recentrly advanced computational modeling to deal with important challenges in clinical biomechanics. The development of new modeling methods and numerical simulation algorithms, which are computationally efficient, are increasingly raising the interest in musculoskeletal modeling and simulation among the biomechanical and medical communities.

Every patient is different and possesses unique anatomical, neurological, and functional characteristics that may significantly affect optimal treatment of the patient. Personalized computational models of the NMS system can facilitate prediction of patient-specific functional outcome for different treatment designs and provide useful information for clinicians. Personalized models may reduce the likelihood that different clinicians will plan different treatments given the same patient data [58]. Depending on the intended clinical application, a personalized NMS model might account for patient specific anatomical (e.g., skeletal structure and muscle lines of action), physiological (e.g., muscle force-generating properties), and/or neurological (e.g., constraints on achievable muscle excitation patterns) characteristics, all within the context of a multibody dynamic model [58].

Personalized computational models can be derived by generic models or subject-specific models with different levels of subject-specific details.

4.1 Generic Models

The existing musculoskeletal models in use have some limitations. Several studies have used generic musculoskeletal models derived from average adult anatomy [51, 106]. In addition, many software packages for biomechanical analysis of muscle function are based on biomechanical studies of cadaveric specimens, and use the musculoskeletal geometry of a healthy, average-sized adult male with normal musculoskeletal geometry [9, 43, 44]. These generic models apply variations in subject size by scaling [46, 57, 87], based on three-dimensional positions of markers placed on selected anatomical landmarks and measured during a static, standing trial.

The lower-limb Delp model [44, 45] has been widely adopted for a variety of biomechanical investigations. This generic model is based on several experimental studies, and has been altered and refined to different purposes [6, 101]. But dataset inconsistency and limitation of in vivo measurements make some difficulties in the identification of model parameters. And the use of generic models in representation of a wide population may not be robust.

Two critical tasks in process of using personalized models are Calibration and Validation [58]. Since generic models are constructed from detailed anatomic measurements performed on cadaver specimens, a model personalization/calibration process is needed. Four proposed model calibration steps that should be performed in whole or in part to transform a generic model into a personalized model include geometric calibration, kinematic calibration, kinetic calibration and neurologic calibration. Validation of clinical predictions is the other major challenge faced by personalized models will ultimately require randomized controlled trials, where outcomes are compared between patients whose treatments were planned with a personalized model and those whose treatments were not [58].

In fact personalized models have the greatest potential to impact clinic practice, but generic models can still provide significant clinical benefits. Generic models were used to simulate bone deformities [10], risk of bone fracture [128], and tendon transfer surgeries [46]. However, a recent study has proved that such models provide inaccurate analysis of muscle function even for a healthy adult male [115].

A growing concern is being raised about the accuracy of scaled-generic models, since the musculoskeletal system is very intricate and large anatomical variations exist among individuals, scaled-generic models may not be able to fit to all variability of musculoskeletal geometry and tissue properties among individuals. This is particularly when the case of study is a pathological musculoskeletal condition. A recent study has proved that such models provide inaccurate analysis of muscle function even for a healthy adult male, this studies showed significant differences in muscle moment arm lengths, musculotendon lengths and gait kinematics calculated with subject-specific models created from MRI and scaled-generic models [114]. The musculoskeletal geometry determines moment arm and thereby the moment about a joint produced by a given musculotendon force. A study showed how variability of muscle attachments affects muscle moment arms (MALs) [48]. Also the effects of bone geometry on the moment-generating capacity of the muscles has been shown [45]. Thus, the different musculoskeletal geometry due to size or pathology can also affect the accuracy of results derived from generic models.

Since the results of simulations are often sensitive to the accuracy of the functional musculoskeletal model, individualized musculoskeletal models may be a better alternative.

4.2 Subject-Specific Models

Despite the growing concern on the use of scaled-generic model to investigate skeletal load, A few studies performed using different levels of subject-specific details [58, 127]. Few attempts have been made to create subject-specific models for skeletal load predictions, and it not clarified to which extent it is important to obtain different subject-specific parameters. Personalization process involve tissue geometries reconstructions, calculation of tissue inertial properties, definition of location and orientation of joint axes from anatomical landmarks, definition of musculotendon architecture. In addition to importance of validation problem of model predictions, it is difficult to collect all necessary data in the research and clinical practice. Another problem is the lack of valuable methods and frameworks to create subject-specific models and simulations. Developing these kind of methods requiring extensive effort with skilled expertise and time. The musculoskeletal geometry for a specific subject can be extracted from MRI or CT-scan images with a good accuracy and low level of invasiveness and it can be used to study in vivo the complex geometric relationships among the muscles, bones, and other structures. The level of subject-specific detail also involves additional measurements, e.g., body motion, ground reaction forces, muscle activity, which can be obtained through technologies for human movement analysis such as stereophotogrammetry, 3D fluoroscopy, EMG, force platforms.

As it is mentioned, one problem is about lack of valuable methods and frameworks available. The other problem is about availability of required data, collecting these data are dependent on mentioned technologies and cannot be always collected in the research and clinical practice and this arises time- and cost-related problems.

Important research has been performed to incorporate more accurate MR-based models of musculotendon geometry into multibody musculoskeletal models [12, 15, 20], however it is time-consuming and requires extensive imaging protocols to capture the muscle and joint geometry at different limb positions. Subject-specific musculoskeletal modelling also addresses the problem of image segmentation, which consists of extracting anatomical structures from medical image data such as MRI. Semiautomatic or fully automatic segmentation methods are fast but inaccurate since muscle distinction is often difficult or impossible to assess with currently used methods. Thus, muscles volumetric representations are most often and most accurately acquired by defining muscle contours manually.

4.3 Software for Personalized Musculoskeletal Modeling

Personalized musculoskeletal modeling and biomechanical load analyzing are increasingly performed by using commercial, freeware and in-house custom-built software. And also several generic models are available for the biomechanical community. As an example, OpenSim is a freely available musculoskeletal modeling and simulation application and libraries specialized for modeling, simulating, and analyzing the neuromusculoskeletal system [41]. OpenSim provides musculoskeletal modeling elements such as biomechanical joints, muscle actuators, ligament forces, compliant contact, and controllers; and tools for fitting generic models to subject-specific data, performing inverse kinematics and forward dynamic simulations. It performs an array of physics-based analyses to delve into the behavior of musculoskeletal models by employing multibody system dynamics codes. Models are publicly available and are often reused for multiple investigations because they provide a rich set of behaviors that enables different lines of inquiry (Fig. 10) [41, 119].

It is also possible to add subject-specific information to biomechanical models using these modeling and simulation environments. However the software users and developers have to necessarily set up specific modeling frameworks that involve an important pre-processing phase to create the models. Depending on the level of subject specific details, this process needs a skilled expertise to process imaging data, define the features of the multibody systems, create models and simulation setups in the appropriate file formats, and particularly develop codes to create efficient modeling frameworks.

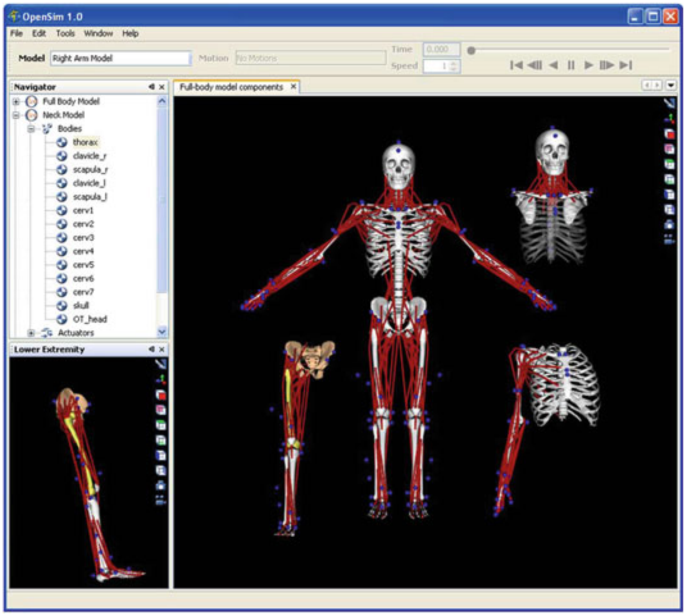

Fig. 10 Screenshot from OpenSim. Models of different musculoskeletal structures, including the lower extremity, upper extremity, and neck, can be loaded, viewed and analyzed [41]

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Spinal Cord Plasticity and Neuromodulation After SCI

Stefano Piazza and Jaime Ibáñez

Abstract Over the past several decades, it has been shown that the spinal cord exhibits significant adaptive plasticity during development and throughout life. This is normally a positive phenomenon, allowing the spinal cord to develop fundamental functions and learn novel behaviours. However, after a spinal cord injury, the pathways controlling the behaviours mediated by the spinal cord are interrupted and maladaptive plasticity can take place. The traditional approach to rehabilitation after spinal cord injury is to apply physical training exercises improving the overall condition and functioning of the patient, and thus to indirectly promote neural recovery. Emerging neuromodulation therapies that complement physical therapy have been proposed to directly stimulate and modify specific impaired neural pathways and thereby produce a more satisfactory functional state. This chapter presents an overview of these new treatment approaches.

1 Introduction

The term neuroplasticity refers to the changes or adaptations of the nervous system in response to endogenous or exogenous stimuli. Historically, the nervous system's neuroplastic properties were attributed solely to supraspinal structures and the spinal cord (SC) was seen as a hardwired neural structure with the capability only of reacting quickly and in a predictable manner to external and descending stimuli. According to this view, complex motor skills acquired through intensive practice (such as walking, dancing, or playing a musical instrument) are achieved by modulating only the supraspinal control of the unchanging SC.

This view that nervous system plasticity was limited exclusively to supraspinal structures endured despite the publication of studies showing long-term SC changes resulting from pathological situations or conditioning paradigms [29, 105, 115].

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During recent decades, numerous studies have revealed a better understanding and characterization of the modification of the SC as it learns new behaviours, as well as an understanding of how this process contributes to the adaptation of the SC after a neurological lesion.

At present, novel targeted neuromodulation techniques are being explored and developed to take advantage of the SC's plasticity to support and enhance motor recovery after a lesion. These rehabilitation approaches are especially relevant for people with spinal cord injury (SCI). In such cases, regaining basic functions (such as locomotion) may be empowered by modifying specific neural circuits and behaviours located in the SC that in turn may generalize to more complex and coordinated motor capabilities.

This chapter presents a general overview of new neurorehabilitation techniques that are targeted to improve lower limb function (mainly gait function) in people with SCI. The overall goal of these neurorehabilitation strategies is to induce focalized changes in the SC that result in better function after treatment. Experiments that generate modulation from descending supraspinal and peripheral pathways are considered. The first section of the chapter summarizes the main functional and neurophysiological impacts of a lesion in the SC, and describes the approaches that are currently being integrated in the rehabilitation interventions for people with SCI to improve locomotion. The next section describes the current understanding of the plastic properties of the SC that result from learning or injury or in experimental settings. Finally, the last section covers some of the most important approaches published during recent years describing rehabilitation using targeted neuromodulation strategies to improve gait function in individuals with SCI.

2 SCI: Impact, Neurophysiological Consequences and Current Therapies for Functional Recovery

SCI leads to a partial or complete interruption of the neural pathways between the brain and parts of the SC and the peripheral nervous system. Such disruption causes alterations in the sensori-motor and autonomic systems controlled by pathways at the lesion level or below. It causes an array of functional, structural, and neurochemical/molecular changes at multiple levels of the somatosensory core [36]. SCI-related dysfunctions affect cardiovascular, gastrointestinal, genitourinary, musculoskeletal, respiratory, skin, endocrinologic, and hematologic systems, as well as mobility and other voluntary functions. These dysfunctions can contribute to diminished autonomy and functional abilities which often cannot be completely restored with rehabilitation [110].

Many SCI-related dysfunctions, such as spasms, spasticity or neurologic pain, are caused by processes of maladaptive spinal plasticity [46]. After injury, the influence of the brain on SC functions is at least partially reduced leading to an altered supraspinal-spinal interaction [36]. The associated symptoms and signs of SCI are collectively called the 'upper motor neuron syndrome' and are classified as positive or negative. Positive symptoms and signs include muscular hyperactivity causing spasticity, hypertonia, hyperreflexia, clonus, spasms, and muscles coactivation. Negative symptoms include muscle weakness, loss of dexterity and fatigue [34].

In addition to traditional physical and occupational therapy, the most accepted approaches over the past few decades for the rehabilitation of SC function have been mainly based on functional training of the patient to recover function-specific spinal cord activation patterns. Current gait-rehabilitation strategies are based on a large body of evidence demonstrating that the adult mammalian spinal cord has a remarkable capacity for activity-dependent plasticity when trained to walk on a treadmill [9]. Over the past 30 years, the impact of treadmill walking on locomotion has been widely studied in animal models of SCI [65, 81, 107] and in people with SCI [1, 33, 68, 75, 83]. Locomotion in spinalized cats following treadmill training has been shown to be comparable to that in healthy cats and superior to that in spinalized cats without training [10, 30]. Comparable treadmill training in humans with complete or incomplete SCI has also been evaluated [31, 47, 48, 61, 134, 135]. Both in animal models and in humans with SCI, treadmill training-dependent improvement after the lesion persists over subsequent months and appears to mainly be due to activity-dependent plasticity in the SC [38, 54, 136, 143]. This conclusion is based on the induced synchronized patterns of afferent, efferent, and interneuronal activity produced during locomotor training [38, 72, 106].

These traditional approaches to rehabilitation from SCI might be improved upon with the use of other complementary technologies such as advanced neurorobotic or neuroprosthetic systems. Current therapies may have the potential to include complementary methods that target changes to specific neural pathways. Such targeted neuromodulation requires determining the properties of the impaired state and the desired neural changes that will produce improvement in the functional outcome of the person with spinal cord damage. To achieve this requires an understanding of the plastic behaviour of the SC.

3 Plasticity in the Spinal Cord

During the past several decades, an increasing number of studies have demonstrated unequivocally that changes in the SC and the corticospinal tract (CST) can occur throughout life as a result of normal development of the individual, in the process of learning new behaviors or following an injury [84, 100, 136].

Several studies have described significant differences in the the pattern and strengths of corticospinal and spinal connections during post-natal development and in maturity [78, 85]. Development encompasses important changes in spinal connections including elimination of transient terminations and growth to new targets. This refinement in the spinal neural connections is driven by supraspinal descending activity and by afferent feedback arising from sensory receptors located in the limbs [85, 136]. The motor control functions of the corticospinal system are not expressed until development of connectional specificity with spinal cord neurons and the formation of the cortical motor map is complete. This is especially significant in humans, where only reduced motor capacities in the SC are present immediately after birth in order to carry out the most basic survival behaviours (e.g., flexion withdrawal and feeding-related behaviours) [97].

In the adult, SC plasticity has also been demonstrated during learning and acquisition of new motor skills [10, 122, 138]. For example, professional ballet dancers have smaller soleus H-reflexes (muscles' reaction to stimulation of the sensory fibres) than those in non-dancers or even other elite athletes, suggesting an increased cortical control of lower-limb muscles in the former group [101]. Adult SC plasticity is also seen in the progressive adaptation of the soleus H-reflex in healthy subjects as a result of daily training of a non-automated motor task such as backward walking [111], or in the decrease of soleus H-reflex amplitude associated with skill acquisition in a cycling task with sudden impedance perturbations [89]. Since H-reflexes are largely monosynaptic and are spinally mediated, the changes observed in these studies appear to represent plasticity within the SC.

Finally, long-term plastic changes in the SC also occur as a result of injury or disease. It is well established that the damage or alteration of supraspinal descending modulatory activity due to a SC injury or disease in the mature individual often causes maladaptive changes leading to increased reflexes, appearance of mass reflexes, and spasticity [42, 64, 108, 138].

All this evidence of a spatially and temporally distributed plasticity in the CNS including the SC leads to an understanding of the SC as playing a more complex role than traditionally thought. Rather than operating as a hard-wired executor of descending influence from the brain, the SC is capable of task-induced plasticity, Wolpaw [137] describes a state of *negotiated equilibrium* in which the SC and supraspinal descending activity maintain spinal neurons and synapses in a state that successfully serves all the incorporated behaviours. Learning new skills (i.e., new SC behaviours) implies incorporation of finely tuned muscle contractions in response to concurrent sensory inputs. As described by Wolpaw and colleagues [123, 137], this process involves modulation of supraspinal signals descending from the brain, to adjust spinal pathways to a constantly and reiteratively revised state of *negotiated equilibrium* that accommodates newly acquired skills and those learned previously. For this to happen, ubiquitous activity-dependent plasticity in the CNS is essential [144].

The study of the mechanisms of SC plasticity offers unique opportunities to answer basic neurological questions regarding behaviour, learning, and the consequences of injury, and at the same time offers new opportunities for rehabilitation after injury in humans. The principal advantage of focusing on the SC to study plasticity in the CNS is the relative simplicity of its structure and behaviours (especially in the case of spinal reflexes) and the methods available to access and condition them either through multisensory afferents or through descending pathways. Plasticity produced by sensory inputs in the isolated spinal cord has been shown to produce short- and long-term effects (for a review see [143]). Thus both changes in simple reflex arcs (*e.g.* the flexion withdrawal reflexes and the proprioceptive reflexes) [80] as well as in functional tasks such as by training spinalized animals on a treadmill [10, 116] have been revealed.

Since the SC connects directly to motor behaviour, it is easier to link learning processes with visible behavioural changes. The study of SC plasticity is also of significant clinical relevance. The impact of lesions at different levels of the neuromotor system may severely impair functionally relevant capacities such as locomotion. The appropriate engagement and guidance of spinal cord plasticity could play a major role in restoring useful function after spinal cord injuries, stroke or other trauma or disease.

The SC integrates nondeclarative memory [10] (i.e., memory that does not require conscious thought). In particular, four principal learning mechanisms can be identified, which are at the basis of the currently available spinal neuromodulation protocols: habituation, sensitization, classical conditioning and operant/instrumental conditioning. Since these capacities are intrinsic to the SC, we will present examples studied in the isolated SC, where supraspinal input is absent. When the SC is not in complete isolation, the conditioning input may originate from the brain, and additionally the brain will be influenced by afferents from the lower structures.

3.1 Habituation

Habituation is one of the simplest form of learning, and is considered a prerequisite for more complex behaviours. Habituation is defined as a behavioural response decrement that results from repeated stimulation and does not involve sensory adaptation/sensory fatigue or motor fatigue [104]. Due to this mechanism, non-relevant stimuli are filtered out, allowing the CNS to focus on the important ones [104]. The first observations of the phenomenon of habituation in the SC of spinally transected dogs [113], cats [39, 125], and rats [103] indicated that the SC could learn from repeated activity, and demonstrated a form of spinal memory that manifested itself behaviourally. The absence of observable sensory receptor adaptation in the periphery, or changes in the neuromuscular junction, suggested that the memory for stimulus training history resided in spinal interneuronal synapses [46].

Habituation effects are stronger if the conditioning stimulation is delivered with constant and moderate intensity [35], and at fixed frequencies [58]. Despite extensive study of the effects of habituation on the SC, the neural mechanisms driving this phenomenon are still not completely understood [104].

3.2 Sensitization

In contrast to habituation, exposure to a single intense or noxious stimulus has the capacity to increase subsequent responsiveness to a variety of inputs. This is known as sensitization [6]. Sensitization is an essential warning mechanism that helps protect an organism from environmental dangers. It manifests itself both in the peripheral and central nervous systems. Sensitization is the reduction in threshold and increase in responsiveness of the peripheral ends of nociceptor neurons that occurs when these are exposed to inflammatory mediators or damaged tissues [77]. Central sensitization is an enhancement in the functional status of neurons and circuits caused by increases in membrane excitability, synaptic efficacy, or a reduced inhibition. The net effect is a state of facilitation, potentiation or amplification in which previously subthreshold inputs generate exaggerated neural output [77]. Sensitization may produce increased spontaneous activity, a reduction in the threshold for activation by peripheral stimuli, and increased responses to suprathreshold stimulation. Moreover, sensitized cells may also increase sensitivity to neural inputs which normally are not considered part of the neuron's receptive field. For example, when central sensitization is observed in nociceptive pathways, spinal neurons can become sensitive to input such as large low-threshold mechanoreceptor myelinated fibers to produce Aβ fiber-mediated pain [145].

In the presence of prolonged nociceptive stimulation, for example after an injury, peripheral and central sensitization produce pain hypersensitivity, a defense mechanism to protect the damaged tissue. This effect may last even when the tissue is healed, in the form of neuropathic pain. This type of pain represents an obstacle to rehabilitation and a form of maladaptive plasticity that reduces spinal learning [46]. Descending brain pathways can exert a protective effect limiting central sensitization [57]. However, the alteration or interruption of supraspinal input following SCI leaves SC plasticity uncontrolled and often leads to the manifestation of neuropathic pain [77].

3.3 Classical Conditioning

Spinal neurons are responsive to classical (Pavlovian) conditioning protocols. In classical conditioning, after the repeated paired delivery of a conditioned (CS) and an unconditioned stimulus (US), the relationship between the two stimuli is encoded and learned by the spinal interneurons. For example in an isolated spinal cord, when weak thigh stimulation (CS) and strong plantar foot stimulation (US) are presented in paired succession, the thigh stimulation ends by modulating the flexion withdrawal reflex [49].

Simple hind-limb motor responses to cutaneous or electrical stimulation are enhanced in animals with completely transected spinal cords, for example in spinalized cats with the modulation of flexion reflex by pairing saphenous nerve stimulation (CS) with superficial peroneal nerve stimulation (US) [40, 67], by stimulating superficial peroneal sensory nerve (CS) with a stronger electrical stimulus to the ankle skin (US) of the same leg [8], or in spinal dogs when mechanical or electric stimulation of the tail is combined with shock to the left hind paw [115].

3.4 Operant Conditioning

Instrumental conditioning, also known as operant conditioning, is a more sophisticated form of learning than those discussed thus far. It requires the acquisition of a behaviour in response to a conditioning stimulus. Evidence that the isolated SC is sensitive to operant conditioning was provided by [28] and [69] by training spinally transected rats with a paradigm that consists in the delivery of a nociceptive stimulation on the hind paw, when the leg was fully extended. After the training, the rats learned to maintain their leg in a flexed position, displaying an increase in the duration of a flexion reflex response that minimizes net shock exposure [28]. The same effect was not present if the SC was anesthetized with lidocaine, or if a lesion in the sciatic nerve prevented the afferent information from reaching the SC, indicating that the process of acquisition of an operant response depends on spinal cord neurons [28].

The characteristics of the conditioning stimulus are critical for learning to occur, in particular the intensity of the stimulation and the accuracy in the instant of delivery. [55] showed that if stimulus intensity is too weak, habituation takes place and the stimulus is ignored, but if the stimulus is intense, a strong impulsive reaction takes place, which manifests mechanically without showing evidence of an underlying learning process. With regard to the stimulation accuracy, [45] found that their learning protocol was not effective if the stimulation was not delivered immediately after the leg reached the target position (controllable stimulation). It was also shown that the ability of the SC to learn the new behaviour can be temporarily disabled for 24–48 hours, and impaired for 6 weeks, after 6 min of stimulation to the leg, when the stimuli were provided regardless of limb position (uncontrollable stimulation) [46]. It has been proposed that the uncontrollable stimulation may have promoted central sensitization, which was responsible for the spinal learning deficit, inhibiting the adaptive spinal plasticity promoted during the delivery of timely accurate (controllable) stimulations [46].

It has been suggested that adaptive plasticity mechanisms similar to the ones generated by operant learning may explain the improvements in functional walking, muscle strength and the coordination observed in commercially available foot drop devices [66]. These devices usually rely on external sensors (heel switch or built-in sensors) to trigger the onset of electrical stimulation to the ankle's flexors to elicit flexion during the swing phase of the gait cycle. In this paradigm, the stimulation is controllable and predictable for the SC, and it may promote the adaptive flexion behaviour in order to avoid the electrical stimulus [57, 66]. As for foot drop devices, the learning clues on adaptive and maladaptive plasticity provided by operant conditioning paradigms may be applied to a broader set of available rehabilitation therapies, to improve adaptive plasticity and reduce the chances of impaired learning from central sensitization [46, 56, 57].

4 Targeted Modulation

The accessibility and relative simplicity of the SC make it a suitable locus for targeting and precisely changing specific neural pathways that improve motor function in people with SC injury. Targeted modulation of SC networks can shift SC structure and function from a malfunctioning established equilibrium to a new more functional one, for example limiting maladaptive plasticity effects.

Since these neural rehabilitation strategies can target particular spinal pathways and can either weaken or strengthen the activity of these pathways, these modulation protocols can be designed to focus on each patients specific deficits and needs [124]. This flexibility and specificity are distinctive and desirable features of this new therapeutic approach, and they distinguish it from less focused interventions such as treatment with botulinum toxin or baclofen, drugs which simply weaken muscles or reflexes and may have undesirable side effects [121, 132].

The following sections of this chapter will present two different approaches to facilitate spinal cord rehabilitation based on targeted modulation of specific and functionally relevant spinal behaviours. First, we will review the main alternatives proposed for the modulation of spinal structures based on the induction of peripheral stimuli. Finally, we will describe a set of studies demonstrating functionally relevant, activity-dependent spinal cord changes that are modulated by descending activity from the brain.

4.1 Peripheral Modulation

The finding that animals with complete SCI can relearn to walk after intense treadmill training demonstrates the intrinsic capacity of the SC to integrate incoming proprioceptive and/or cutaneous information, interpret it, and respond with a functional motor output [9]. Successful afferent inputs can be proprioception, lengthening of muscle, cutaneous feedback, or load. Peripheral modulation protocols are designed to modulate SC neural circuits without directly stimulating the brain cortex. In this section, we present examples of the most promising approaches.

4.1.1 Stimulation of Cutaneous Afferent Pathways

Afferent input plays an important role in rehabilitation after SCI. For people with SCI, locomotor training is based on providing sensory cues consistent with normal walking, especially from lower limb stretch- and load-sensitive mechanoreceptors [62], although a plethora of other inputs are also activated during the exercise [107]. In this context, of particular interest are cutaneous mechanoreceptors from plantar foot afferents because of their accessibility and simple integration with the functional task.

Plantar cutaneous feedback contributes to maintaining balance and ensuring a stable walking pattern throughout the step cycle [90, 102]. This has been shown in animal models, of cats [26] and rats [118]. In cats, the loss of cutaneous input does not produce a strong effect on stable walking. [114] observed that, after complete cutaneous denervation of the hindlimbs, cats were still able to walk in a pattern similar to that in intact cats. Using gait analyses instrumentation, subsequent studies detected small changes in limb kinematics and muscle activity [41]. However, in challenging walking conditions, such as ladder or incline walking, or when lateral stability was compromised by unexpected perturbations, the kinematics and locomotor muscle activity were significantly modified, with compromised stability [11, 14]. Walking disruption was even more evident in spinalized cats, suggesting that the remaining intact input of muscles, joints and other receptors was not sufficient in these animals to compensate for the loss of cutaneous information [13]. In rats, which are plantigrade animals as are humans, the elimination of cutaneous input by hypothermic anaesthesia modified hindlimb kinematics to produce less efficient locomotion, with a larger ankle and hip excursion and decreased distance between the hip and the ground, leading to a significant functional deficit [130].

As in the animal models, in humans information from plantar cutaneous afferents plays an important role in postural and walking stabilization. These have been shown to determine postural responses in ankle muscles, to stabilize stance and gait [4, 102, 127, 147]. For example, after a temporary plantar desensitization, motor activity and ground reaction forces during a balance recovery task were reduced [120, 126] and postural adjustments prior to step initiation were compromised in a way that could not be compensated by other inputs [79].

Furthermore, [146] found that in humans, electrical stimulation of plantar cutaneous afferents during walking generates withdrawal responses during swing and stabilizing responses during stance; this phase-dependent behaviour indicates an integration of cutaneous afferent feedback into spinal locomotor networks. In fact, the contribution of plantar afferent feedback to locomotion is not limited to reactive responses: it extends from the modulation of spinal reflex excitability [52] to the selection of motor patterns and the alterations of central pattern generator (CPG) frequency [107].

After SCI, the loss of descending input from supraspinal structures increases the importance of sensory feedback from the periphery [88]. The processing of sensory input within the SC is altered [51] and considerable changes in reflex pathways develop over time as a consequence of the injury [25, 26]. Locomotor training after SCI is based on the fact that appropriate peripheral sensory input can reactivate and reorganize the spinal locomotor circuitry [109].

Critical input comes from proprioceptive signals from the muscles. For example, in incomplete SCI rats, locomotion rehabilitation based on swimming training improves locomotion [118]. However, the therapy is more effective when swimming is potentiated by cutaneous feedback provided by a matrix of buoyant tubes suspended from the bottom of the pool [118]. A similar result was previously observed by [98], using the same protocol to rehabilitate locomotion of hemisected chicks.

In this case, the phasic feedback from cutaneous plantar receptors was sufficient to permanently increase limb extension during swimming.

Cutaneous input is also critical for the recovery of stepping during walking training on a treadmill. For example, in cats, the chemical deactivation of the nerves from the low-threshold mechanoreceptors of the hind paws consistently decreased coordination between forelimbs and hind limbs, and between left and right legs, reducing walking stability and efficiency [117].

In humans, some neuromodulation protocols already take advantage of the strong interaction between feedback from plantar cutaneous afferents and spinal locomotor circuits, to restore a pathological or absent phase-dependent H-reflex modulation pattern or stimulate plastic changes to CNS microcircuits following injury [102]. For example, [52] applied electrical impulses to the sole of the foot to decrease the soleus H-reflex, showing that it is possible to modulate this reflex in both neurologically intact subjects and in subjects with SCI during walking and standing. These results were extended by [71], who used electrical stimuli to enhance sensory feedback during walking in subjects with SCI, producing phase-dependent normalization of H-reflex and tibialis anterior flexion reflexes.

4.1.2 Electrical Spinal Cord Stimulation

Electrical Spinal Cord Stimulation (SCS) is an invasive neuromodulation technique that entails the application of minute electrical impulses to the spinal cord to modulate segmental spinal and/or brain stem/spinal pathways. These techniques have been used to treat motor dysfunction associated with several degenerative diseases of the CNS and has been shown to improve a wide range of functions including motor function, posture, walking, and bladder control [24, 131]. SCS may be applied by epidural electrical stimulation (EES) or intraspinal microstimulation (ISMS).

EES is applied to the dorsal surface of the spinal cord by surgically implanted electrodes, to activate the dorsal root entry zones or dorsal columns. Its principal use has been for the treatment of neurologic pain [2, 23, 73, 74, 128]. However, when applied in association with partial body-weight support training, it has the potential to initiate and sustain locomotion in people with chronic incomplete SCI, even in cases where partial body weight support alone was not able to achieve functional over-ground ambulation [16, 63].

EES, in combination with physical therapy, has also been used in individuals with chronic complete SCI. For example, [3] showed that four subjects with complete SCI (AIS A or B) were able to recover voluntary movement soon after the implantation of the stimulation device, and their condition improved progressively in the following months with the combination of EES and body weight supported standing exercises or manual therapist-assisted locomotor training on a treadmill [3, 60]. The same therapies performed before the implantation of the EES device were not able to produce functional recovery in these patients.

Together, these results suggest that EESs effect on the spinal pathways may enhance the central excitatory drive to the motor neurons; at the same time, task-specific training may promote force generation and accuracy [3]. In addition, the fact that stimulating specific SC regions (L2 in humans, L5 in cats and between L2 and S1 in rats [53]) can induce or facilitate stepping, has been attributed to the activation of central pattern generators circuits (CPG) in the SC, i.e., neural circuits that generate coordinated alternating flexor-extensor neuromotor patterns in the absence of supraspinal or sensory modulation [50]. Nevertheless, it has not yet been shown whether muscle activity generated with EES will be sufficient in individuals with SCI to support the body during stepping, and what the long-term effects of such a treatment will be [32].

A similar and more invasive technique is ISMS [94]. In this method, arrays of microwire electrodes are implanted in the spinal cord to target the intermediate and ventral gray matter for activation of local circuits. ISMS potential for rehabilitation comes from its capacity to evoke, in the isolated SC, specific functional movements in the hindlimbs and forelimbs. This effect depends on the level and characteristics of the stimulation. For example, standing and stepping movements can be evoked by the application of ISMS to the lumbar SC in spinal cats [7, 59, 99], while forelimb movements can be evoked when ISMS is delivered to the cervical spinal cord in non-human primates [95, 148].

Since these SCS techniques require the use of implanted electrodes near to (EES) or within (ISMS) the CNS, complications may arise during and after the surgical implantation [24]. Principal intra-operatory complications include direct damage to the neuraxial structures and risks associated with the anaesthesia and surgery; in the post-operatory interval, principal risks include pain, seroma, lead migration and hardware failure, and infections [24, 70, 128].

A recent review of documented cases of EES stimulation provided an estimation of the risk of complication associated with EES [91]. Of the 787 patients considered in the review, those who were initially submitted to the EES initial trial lead placement, 11 % reported emergence of pain at the stimulation site and 4.5 % developed documented infections. After the test phase, 200 patients were excluded from the pulse generator implant, with an average implant-to-trial ratio of 75 %. For 38.1 % of the remaining 512 patients who were implanted with the stimulator, hardware related complications (lead migration, lead connection failure and lead breakage) occurred.

ISMS has not yet been tested in humans. The principal challenges of ISMS relate to the safety and durability of the implanted electrodes, since adverse tissue responses are still common following implantation of currently available electrodes within the CNS [92].

4.1.3 Electrochemical Spinal Cord Stimulation

Pharmacological treatments have also shown potential for activating locomotor circuits in rats and mice [5, 76]. [27] proposed an alternative approach to neuromodulation by combining specific pharmacological and electrical stimulation interventions, together with locomotor training [27, 129]. Combining injection of serotonin antagonists ($5HT_{1A/2/7}$), stimulation with EES and locomotor gait training induced full weight bearing bipedal treadmill locomotion in complete SC-transected rats. In other studies, [12, 133], it was shown that by automatically modulating electrochemical stimulation parameters, it is possible with a closed-loop controller to precisely control leg kinematics in rats during movement. This method allows the animals to voluntarily initiate bipedal locomotion from a resting position, to walk for extended periods of time, to pass obstacles, and to climb a staircase. These results inspire hope for future neuroprosthetic devices as well as for promoting recovery and motor function after severe lesions.

Electrical and pharmacological stimulation of spinal neural networks is still in an experimental stage. Despite promising results in animal models, further research is required before widespread application of these techniques in humans will be possible. Principal concerns are the selection of the appropriate neuromodulators to be used in humans [37] and the timed control of pharmacological and electrical stimulation. Moreover, in animals the techniques have been applied only targeting the hindlimbs. In the future, refinement of animal studies may contribute to greater translational success [32]. Thus, the combination of pharmacological and epidural stimulation to enhance motor function remains a promising research direction yet to be fully explored.

4.2 Descending Modulation

As noted previously, supraspinal inputs to the spinal cord provide a continual flow of activity in a variety of pathways [143]. This descending activity modulates the spinal cord behaviour contributing to motor development in childhood and to learning new motor skills later in life [85, 136]. Understanding the mechanisms of brain-modulated spinal cord plasticity and its interactions with activity-dependent plasticity elsewhere in the CNS is important for explaining normal behaviours as well as the complex disabilities produced by neurological disorders and for proposing new ways to induce spinal changes that will correct pathological motor behaviours. Over the past several decades, a number of studies have been proposed (using sensitization, classical conditioning and operant conditioning protocols among others) to induce plastic SC changes with supraspinal structures having a relevant modulatory role. In some cases, as in the paired associative stimulation paradigm initially proposed by [119] to facilitate cortico-muscular pathways (synchronously stimulating the motor cortex and the peripheral nerves), it was first assumed that the effects were circumscribed to cortical and subcortical regions. However, later studies demonstrated additional changes in spinal structures [93]. Other experimental protocols have been designed specifically to modify certain behaviours of the SC or alter the strength of corticospinal connections (while also acknowledging plastic changes in other spinal and supraspinal areas). This section summarizes two specifically relevant lines of research in which supraspinal modulatory activity is used to induce spinal cord plasticity to improve motor function in individuals with neurological damage such as that in SCI.

4.2.1 Operant Conditioning of Spinal Reflexes

Starting in the 1980s [139–141] and continuing to the present [122–124], Wolpaw and colleagues have shown that descending supraspinal activity may be used to modulate specific spinal behaviours. These studies involved the operant conditioning of spinal reflexes. In the first studies, in monkeys, an operant conditioning protocol was used to train the animals to up-or down-regulate their spinal stretch reflex or its electrical analogue, the H-reflex [139, 140]. The animals were rewarded if they changed the reflex amplitude in the correct direction over 50 days. Approximately 80–90 % of the test animals were able to successfully modulate the reflex in the desired direction [140]. Changes were observable immediately after onset of training and persisted even during inactive periods after cessation of the reward protocol. The protocol had three key features. First, it required maintenance of both a certain elbow angle and a certain level of biceps EMG activity as the animal opposed a constant extension torque in order to generate a stimulus producing the reflex. Second, it based reward on the size of the recorded reflex. Finally, the reward criterion (i.e., requiring successful up- or down-conditioning in the animals) remained constant over days and weeks. In sum, the protocol was designed to induce and maintain a long-term change in descending influence over the spinal arc of the reflex, and to thereby change the spinal cord. Subsequent studies in which the spinal stretch reflex or H-reflex was conditioned in rats [21, 22], mice [20], and humans [43, 112] confirmed the first results with monkeys and served to further elucidate the anatomical, physiological, and biochemical mechanisms of this conditioning (see [124] for review).

Interestingly, in rat studies [22], analysis of the effect of soleus H-reflex conditioning on locomotor kinematics showed that successful conditioning in the intended direction of the reflex produced changes not only in this reflex, but also in the kinematics of locomotion. However, the changes did not alter key aspects of locomotion (such as gait speed, gait symmetry or step length) but rather provoked compensatory changes in other pathways (i.e., the quadriceps reflex) [21]. These compensatory changes demonstrated the ubiquity of plastic changes in the SC and how newly acquired behaviours can cohabitate with existing ones, leaving the latter unaffected despite the change in the soleus reflex [21, 137]. In addition, [22] found that rats with partial SCI undergoing soleus H-reflex up-conditioning could improve locomotion parameters such as soleus burst and locomotion symmetry, providing the first evidence of the potential functional impact of this kind of intervention.

The experimental accessibility of the SC, the relative simplicity of the conditioned reflex (largely monosynaptic), the well-defined descending pathways from the brain, and the direct association to a specific observable behaviour, make H-reflex operant conditioning a unique tool for understanding the basic mechanisms of spinal cord plasticity and how it changes behavior. Moreover, by taking advantage of the targeted modulation of specific spinal pathways, it offers the possibility of new approaches to neurorehabilitative intervention.

An adaptation of the stretch-reflex and H-reflex conditioning paradigm was also tested in humans [44, 122]. Whereas the animal studies included several thousand trials per day, 7 days per week, over 50 days of conditioning [141], the humans performed only 225 trials per one-hour session three times per week [122]. For the human studies, the electrodes used for stimulation and recording were placed on the skin rather than implanted as in the animal studies. In the animal studies, the animals were rewarded with food for correct performance; in the human studies, the subjects received visual feedback showing performance on a computer display. In these human studies, a small number of trials at the beginning of each session were acquired as control trials: in these trials the subject was not asked to change the reflex and received no feedback [122]. These control trials served to check for intra- vs. inter-session H-reflex changes. These studies showed that 70–90 % of normal human subjects were able to modify the conditioned reflex in the correct direction. Over 24 conditioning sessions H-reflex size increased to an average of 140 % of initial value in up-conditioned subjects and decreased to an average of 69 % in down-conditioned subjects. Reflex changes occurred in two phases: they began (Phase 1) with a rapid small change, in the correct direction, that was attributable to rapid task-dependent adaptations, and then (Phase 2), over days and weeks, changed gradually further in the correct direction (long-term change) [122]. Phase 1 appears to reflect rapid mode-appropriate change in descending influence over the spinal arc of the reflex, while Phase 2 appears to reflect gradual spinal cord plasticity produced by the chronic continuation of the descending input responsible for Phase 1 [122]. These bi-phasic results were consistent with the animal studies previously performed by [142].

A more recent study was carried out in people with incomplete SCI [123]. The experimental procedure was similar to the one with healthy subjects. Success rate and magnitude of reflex change were comparable to those in people with intact SC. As in the previously cited studies of locomotion in rats, the comparison of functional capacities before and after the conditioning showed that appropriate H-reflex conditioning (i.e., down-conditioning in this human study) was associated with faster and more symmetrical locomotion. The improvement was evident both in quantitative testing and, most important, in subjective observations by the subjects themselves: they spontaneously reported improvements in walking speed and endurance, and in other aspects of motor function (e.g., balance). Interestingly, the subjects with SCI showed long-term H-reflex changes that were greater than the changes observed in healthy subjects (24 % vs. 16 %). In contrast, task-adaptation changes (i.e., reflex changes observed within sessions but not maintained between consecutive sessions) were smaller in subjects with SCI (7 % vs. 15 %). Another recent study [82] also found that appropriate H-reflex conditioning had beneficial effects on locomotion in people with incomplete SCI.

The smaller long-term changes in healthy subjects as compared to people with SCI suggests that, in healthy subjects, H-reflex changes are mainly occurring during the experimental sessions. That is, for healthy subjects, the H-reflex changes are unlikely to provide any beneficial effects in terms of functional outcomes outside the experimental sessions (in locomotion for example), and they may even interfere with the already well-functioning circuits for locomotion and other behaviours in the intact SC. Therefore, in these healthy subjects, over the conditioning sessions, additional plasticity may occur to maintain SC equilibrium that ensures that locomotion and other important behaviours are normal . On the other hand, as was the case with the SC injured rats [22], appropriate H-reflex conditioning in people with SCI led to improvements in lower-limb functions (such as locomotion). Since the H-reflex change was beneficial, the SC retained the neurophysiological change resulting from the experimental protocol. In other words, the injured SC was guided towards a new and more optimal equilibrium [124, 137].

Taken together, these animal and human experiments indicate that reflex conditioning protocols can improve recovery after chronic incomplete SCI, and possibly in other neurological and physical disorders. Mrachacz-Kersting and colleagues are currently exploring ways to up-condition the soleus stretch reflex in healthy people. The main goal in this work is to enhance ankle stiffness in athletes who are prone to suffer ankle sprain. Preliminary data indicate that up-regulating the reflex is possible that this reflex change is associated with enhancement of the intrinsic and total stiffness of the ankle joint and an improved stability after drop landings [96].

4.2.2 Electrical Stimulation of the Motor Cortex

As previously described, plasticity in corticospinal pathways occurs during development of mature motor function [85]. Corticospinal descending axons (mostly from the motor and somatosensory cortical areas) descend through the brainstem down to the spinal grey matter. Corticospinal axon outgrowth and organization during development or after an injury are guided by activity-dependent competition between descending axons [86, 87]. Based on this concept, J. H. Martin and colleagues proposed harnessing the activity-dependent plasticity induced by electrical stimulation of the brain to promote a competitive advantage of ipsilateral-spared corticospinal axons in the spinal cord after a neurological injury [15, 17]. This idea originates from the observations of neural reorganization occurring after injury, where spared corticospinal axons increase their synaptic connections with neighbouring cells but often to a degree insufficient to restore motor function [85].

In these studies animal models of a lesion affecting the pyramidal tract were used to analyse the effects of electrically stimulating spared corticospinal axons in the uninjured pyramidal tract [15, 17]. The analyses focused on: (1) the influence of activity and injury on the corticospinal plasticity, (2) whether continuous stimulation (6 hours/day over 10 days) can promote the outgrowth of descending projections into the spinal cord; and (3) whether activity-dependent plasticity combines with injury-driven sprouting of corticospinal axons to reinforce their connections in the SC.

In one of the first of these studies [15], the experimental rats were divided into four groups: (1) uninjured controls, (2) animals with transected pyramidal tract, (3) animals undergoing electrical stimulation and (4) animals with both pyramidal transection and electrical stimulation of the contralateral pyramidal tract. Results showed that an outgrowth of ipsilateral CS axons and stronger ipsilateral motor responses were observed in group-2 (reducing the competitive activity from the transected descending projection) and in group-3 (increasing the activity of ipsilateral corticospinal terminals). Moreover, it was shown that the combination of injury and stimulation (group-4) produced the strongest spinal connections and a shift of corticospinal terminations towards the ventral motor areas of the spinal cord. Importantly, connections in the animals with injury and stimulation were stronger than after injury alone. These results highlight the relevant interplay between injury and activity in the spinal cord, and suggests that electrical stimulation provides a competitive advantage of the ipsilateral spared axons, which increased their activity ultimately leading to the development of stronger connections [15]. Interestingly, ipsilateral motor responses generated by stimulating the pyramidal tract were comparable to those generated by contralateral stimulation, although the density of the contralateral axon terminations was much higher. These results therefore suggest that the increased ipsilateral response is mainly caused by an increase in the synaptic strength.

Subsequent studies along these lines further confirmed the robust outgrowth and strengthening of ipsilateral CST axon terminations to the impaired side of the spinal cord and demonstrated functional improvements in injured rats that were stimulated [18, 19]. Stimulated rats showed full recovery of the affected motor function, and the recovery was maintained beyond the intervention period [17]. Martin and colleagues also demonstrated that: (1) electrical stimulation can promote recovery of motor function even when applied long after injury; and (2) this recovery of motor control can be exerted from the ipsilateral motor cortex when the contralateral cortex becomes nonfunctional. Comparable studies in humans are still required in order to determine whether the uninjured motor cortex can be targeted for brain stimulation in people with large unilateral CST lesions and whether this stimulation can improve motor recovery.

5 Conclusion

Despite the historical reluctance to consider the SC a dynamic and learning entity in the nervous system, the last decades have witnessed a marked increase in interest in studying it as a key element in motor restoration of people with neurological damage. The SC has the ability to reorganize itself based on afferent and supraspinal input, and to learn new functions. Experiments with animal SCI models confirmed this by showing that the isolated SC is capable of adaptive motor plasticity and that it can support simple forms of motor learning, including stimulus learning (habituation/sensitization), stimulus association (classical conditioning), and response-outcome (instrumental/operant conditioning) learning. It has also been shown that localized changes in the SC can in turn result in a cascade of further distributed neurophysiological and functional changes that can improve the basic motor functions (such as locomotion) in subjects with SCI.

The active role of the SC in the processes of learning and memory is still not fully harnessed by currently available rehabilitation therapies. Novel targeted neuromodulation therapies aim to take advantage of this rehabilitation potential, in order to increase the functional output of rehabilitation. This is achieved by shaping the neural response of the SC to specific inputs in the direction of more functional behaviours.

An interesting model for the application of these therapies is rehabilitation after SCI. In fact, the effects of the lesion are twofold. On the one hand, the injury stimulates numerous neural changes within the spinal cord; on the other hand, the partial or complete interruption of ascending and descending pathways that occurs with the injury disrupts the close interaction between the supraspinal centres and the rest of the body, often leaving the plasticity of the SC uncontrolled and giving rise to a wide array of maladaptive plasticity-associated changes as for example neurological pain or spasticity.

This chapter presented a review of the evidence for SC plasticity, and of the rehabilitation potential of using it. Novel neuromodulation-based therapies taking advantage of this undisclosed potential for the recovery of locomotor function after SCI have also been described. These techniques have been divided in two main groups, to differentiate between two fundamental approaches to neuromodulation: (i) driving plasticity through the activation of peripheral pathways, either from afferent feedback or directly stimulating SC neural circuitries, and (ii) using supraspinal descending inputs to modulate the neural structures in the SC.

However, the impact and dissemination of these targeted neuromodulation interventions in the SC is still limited and further studies in this research field are therefore needed. In particular, many neural mechanisms in the SC are still unknown or not completely explained. The complex interactions between different spinal mechanisms at distributed SC levels should be modelled, as well as their function in daily activities. Deeper knowledge regarding the precise temporal and spatial properties of the changes occurring in the SC during acquisition of new behaviours will make it possible to improve and optimize current targeted modulation interventions. In the route towards this goal, an increasing number of novel protocols and therapies are expected to emerge, targeting a wider number of functions, that will likely support and increase the effects of more traditional rehabilitation strategies.

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BCI Applied to Neurorehabilitation

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Abstract Brain-computer interface (BCI) systems are novel and emerging technologies that allow a person to interact with the environment without any muscular activity using only his or her brain. Currently, there are various applications of neurorehabilitation, which have emerged from this technology. These are based mainly on the performance of motor imagery tasks and visualization of movement, which encourage a process of neuroplasticity. Virtual reality (VR) is an innovative approach that is used in numerous neurorehabilitation applications. Several studies have combined BCIs and VR to develop applications, which allow a person to navigate in virtual environments or to play video games, among others. Some studies have been focused on neurorehabilitation applications, such as applications that allow a person to control virtual limbs. However, nowadays neurorehabilitation has become essential to our society, and this resulted in a substantial increase in BCI research directed toward this field. This chapter will introduce the current state of the art in BCI systems developed for neurorehabiliation applications, among which are innovative studies that make use of VR.

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1 Brain-Computer Interface (BCI) Systems Developed for Neurorehabilitation Applications

Advances in medicine and technology have increased the life expectancy of people leading to an aging population. This has also increased the number of people with motor impairments who would not have survived without todays advanced technology in medicine. Even only the number of people who have suffered from a stroke among the numerous neurological disorders represents a significant global public health challenge. In 2012, stroke was the third cause of mortality in the world [108] without considering the number of people who live with motor impairments after suffering from a stroke. Only in the United States, the costs related to cardiovascular diseases and stroke in 2010 were estimated at USD315.4 billion. This total includes direct health care expenditures which are associated with the cost of physicians and other professionals, hospital services, prescribed medications, home health care, and other medical durables.

Enhancing the quality of life of patients who are severely disabled by disorders such as amyotrophic lateral sclerosis (ALS), cerebral palsy, brainstem stroke, spinal cord injuries, muscular dystrophies, or chronic peripheral neuropathies is the main goal of rehabilitation studies. According to the World Health Organization, the aim of rehabilitation is to enable people with disabilities "to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination" [107].

An important aspect related to rehabilitation is to avoid new damages associated with the condition of the patient, such as loss of body and space perception, or excessive bed rest, which is the main factor for the reduction of muscle function: 5 weeks produce a 26 % muscle strength reduction in the ankle plantiflexor muscle, while 12–16 weeks lead to a 30 % reduction of muscle strength over the same muscles. Therefore, early therapy is essential for the patient's recovery. One of the most beneficial treatments involves physical therapy in conjunction with pharmacological treatment. A variety of treatment options are available and clinical experience has shown that a multimodal approach has many benefits [58]. Therefore, researchers in the BCI field are also directing this technology in clinical applications such as neurorehabilitation.

BCIs used in neurorehabilitation applications could be used to treat a wide variety of neurological or neuropsychological disorders. However, this chapter will focus only on BCIs that aid in the recovery of motor functions. Ideally, the main goal of such a BCI in neurorehabiliation would be to totally restore the patient's motor function but this is not always possible. Yet a lot of BCI studies have been focused on developing applications for establishing communication channels, environmental control and control of devices that substitute motor function to improve life quality of people with disabilities [66].

The development of BCIs oriented to neurorehabilitation therapy should be focused on classifying the patients by the extent, rather than the etiology, of their disability [68]. This distributes potential BCI users into three reasonably distinct groups: (1) people who have no detectable remaining useful neuromuscular control and are thus totally locked-in; (2) people who retain only a very limited capacity for neuromuscular control, such as weak eye-movements or a slight muscle twitch; and (3) people who still retain substantial neuromuscular control and can readily use conventional muscle-based assistive communication technology.

In order to obtain successful results, it is important to know what occurs inside the brain after damage has occurred due to a traumatic brain injury. Experimental evidence has shown that the brain possesses cortical plasticity, which can be defined as the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function, and connections [29]. Several years of research have demonstrated that the neuroplasticitiy is stimulated by a learning process [24]. Moreover, this learning process can be encouraged in three different manners:

- *The user realizes the movement*. The most common effect after a cerebrovascular damage is motor disability contralateral to the brain lesion. The suggested physical therapy is a technique applied to recover motor function, and it is focused on task specific training that involves the affected limb [99]. The realization of a real movement is the most logical manner to stimulate the neuroplasticity process. Therefore, this technique has been widely applied in the rehabilitation process [50]. During rehabilitation therapy, the patient should be assisted by a therapist who helps him/her to realize the desired movement. However, recently different technologies have been developed in order to assist the patient in this rehabilitation process [19, 34]. The rehabilitation that implies real movement is directed not only to patients who retain a substantial neuromuscular control, but also for patients with limited control.
- *The user imagines the movement*. Motor imagery (MI) can be defined as a dynamic state during which a given action is mentally simulated by the patient. Considering the physiological bases, movement execution and motor imagery share common mechanisms. In both cases, event-related desynchronization of mu (or Rolandic) and beta rhythms over the contralateral side of the brain with respect to the movement are present. The region of the brain that is most activated during motor imagery is the prefrontal cortex, which is involved in the movement planning [32]. This kind of learning has demonstrated to activate the cerebellar and cerebral networks [56]. The patient could implement the imagination in two different manners: "first person perspective," or motor-kinesthetic, and "third person," or visuo-spatial perspective. For the purpose of obtaining results in neurorehabilitation, it is important that the patient carries out the first type of motor imagery because only motor-kinesthetic imagination modulates the corticomotor excitability [98]. This type of physical therapy is more effective for patients with severe motor disorders and impairments, when physical exercise is no longer possible.
- *The user observes the movement*. The idea that observation of movement is an alternative technique for neurorehabilitation was firstly studied in monkeys.

Excitability in a section of neurons was noticed when a monkey observed another individual (congener or the trainer) performing a movement [33, 93]. This behavior was also observed in healthy humans [38]. The results of this experiment demonstrate that excitability of the motor system increases when a subject observes an action performed by another individual. Furthermore, the pattern of muscle activation evoked by transcranial magnetic stimulation during action observation is very similar to the pattern of muscle contraction present during the execution of the same action. This activity is produced by mirror neurons which are a particular class of visuomotor neurons that fire when an individual visualizes another performing an action, and these have a particular role in action understanding. A more detailed study of mirror neurons in both monkeys and humans is presented in [94]. A study with patients revealed that recovery of motor functions after stroke is positively influenced by the observation of the action since such observation induces reactivation of the motor areas [37]. This type of physical therapy that encourages the learning process might be more useful to a patient who is locked-in or when a patient has spent some time without performing the movement and thus has problems to imagine the movement (as was described in the imagination of movement section, the kinesthetic part is very important). Also, this kind of learning can be combined with both, imaginary or real movement. In combination with imaginary movement, it is an additional approach to provide feedback to the patient. In combination with real movement, the patient can actually realize the movement and consequently this helps to obtain better results in the rehabilitation therapy.

Since the performance of a real movement was the most obvious answer to treat motor disorders, physical neurorehabilitation was the first technique that was studied and used in this field. The rehabilitation process was managed by a physiotherapist who made the patient perform several motor exercises to improve his/her condition [28]. With recent advances in technology, neurorehabilitation has become a multidisciplinary field. The medical field is its kernel but currently, neurorehabilitation can be supported by the use of devices and supplementary technologies in order to achieve a high level of performance and patient recovery. The use of the first rehabilitation devices, such as threadmills and other exercising machines [31], was followed by the appearance of more complex devices, such as exoskeletons. There are numerous researchers worldwide exploring this field of studies. In [34], a thorough review on lower limb rehabilitation is given among, in which several kinds of robotic lower limb devices and rehabilitation techniques are described. There are also a lot of studies focused on upper limb rehabilitation by robotic systems as exhibited in [19]. The neurorehabilitation improvement can also be achieved by other means, such as using different kinds of muscle stimulation (magnetic, electrical, and ultrasound) [100, 109] or using new emerging technologies.

With the current appearance of motor imagery and visual movement neurorehabilitation techniques, BCI technology has become applicable in the rehabilitation field. BCIs provide a means of recording electrical brain impulses related with motor imagery tasks. With a proper processing and classification algorithm, it is possible to detect several motor tasks from brain signals while a person is imagining the movement. In [90], the researchers could recognize between two mental tasks related with the imagination of left-hand movement and right-hand movement with an average classification accuracy of 94 % with three users. With this level of classification, a BCI system could provide visual feedback about the imagined movement or even to control a device according to the desired movement. It has been demonstrated that visual feedback related with a desired movement combined with imaginary movement provides improved results in rehabilitation over using only imaginary movement [80].

By combining a BCI with other rehabilitation systems, it is possible to considerably improve rehabilitation strategies. In [49], a hierarchical BCI system is used to control a planar robot in a 2-dimensional plane by the classification of 2 mental tasks related with right- and left-hand imagery movements. This system simultaneously provides motor imagery and visual neurorehabilitation to a patient. There are more complex studies, such as the Smart Wearable Robots with Bioinspired Sensory-Motor Skills (BioMot Project) [13] with the goal of developing an exoskeleton that receives data from several physiological factors such as electroencephalographical (EEG) and electromyographical (EMG) signals. In this project, EEG data is used to detect the intention of the initiation or termination of a movement, to measure changes in velocity and direction/orientation, and to evaluate the attention level of the patient and the possible appearance of obstacles during the rehabilitation process. In this case, the use of an exoskeleton allows physical rehabilitation and the use of a BCI includes the patient's desires and mental state in the rehabilitation process, which makes the patient take a more active part of his/her recovery. With these kind of systems, the same physical movements performed by patients and triggered by their desires are used as visual movement feedback. This combines the three types of neurorehabilitation strategies mentioned on this chapter.

2 Problems and Need on Neurorehabilitation

In the beginnings of rehabilitation, the obvious way to tackle a motor dysfunction was the first strategy mentioned in the last section, the performance of real movements guided by clinicians. For that reason, physiotherapists and other experts on the field have developed several works related with this strategy. In order to rehabilitate a patient, the method followed is not the only trouble to get over. Although it was well known that the origin of neurologic disabilities is placed at the central nervous system (CNS), conventional therapies used in neurorehabilitation two decades ago were mainly focused on providing sensory feedback [78] and performing real movements. Main problems found by clinicians on this matter are mentioned below.

Physical problems

- *Facilitating functional restitution.* The principal mechanisms implicated in motor recovery involve enhanced activity of the primary motor cortex induced by active motor training [22]. A simultaneous activation of sensory feedback circuits and primary motor cortex may reinforce cortical connections by Hebbian plasticity principles and support functional recovery [78]. Assuming that the connection between peripheral muscles and the sensorimotor cortex has been disrupted in a CNS lesion, it is necessary to develop new clinical approaches that encourage patients on paying closer attention to the motor tasks performed [7]. This may constitute neurofeedback interventions with the capability of inducing neural plasticity [44]. An emerging intellectual paradigm for neurological recovery that includes neural regeneration, repair, and dynamic reorganization of functional neural systems, as well as increasing awareness of behavioral principles that may support best return to function and freedom, has brought forward treatments based on experience-dependent learning, neurophysiologic stimulation, and a combination of these concepts [9]. BCI systems employ neurofeedback to enable operant conditioning to allow the user to learn using it. Neurofeedback strategies ranging from sensory feedback to direct brain stimulation are also being used [97]. There is not conclusive data in the literature about the superiority of one type of feedback. Some study suggests better results in patients who used a haptic feedback versus visual or auditory feedback [85]. Several studies in last years have been developed to demonstrate the clinical efficacy of BCI in neurorehabilitation, and they have had significant results and positive correlations with functional outcome measures as Fugl-Meyer Assessment [4–6, 25, 91]. Since the performance of physical movements by neurological patients is often not possible, alternative strategies are needed. Motor imagery combined with a BCI system represent a new approach to access the motor system that can be used for rehabilitation at all stages of stroke recovery [7, 95] avoiding the dependance on residual motor performance.
- *Maladaptative changes*. The neuroanatomical, neurochemical, and functional changes that occur during the plasticity reorganization facilitate the recovery of affected functions (adaptative plasticity) and may hinder the development of others (maladaptative plasticity). Usually it is difficult to avoid that patients develop compensatory movements in order to be functional, but these new skills are reflected in motor cortex like maladaptative changes, hindering the normal evolution of neural plasticity [72]. Several studies developed during BCI interventions have showed results in terms of clinical motor improvements correlated with neuroimaging techniques. [25] presented a case report of a BCI intervention using functional magnetic resonance (fMRI) showing evidence of recovery as a result of adaptative brain plasticity in the injured hemisphere of a stroke patient. [101] reported another fMRI trial in stroke patients compared with a robotic intervention, finding higher functional connectivity changes in the BCI control group. Also, [52] developed an intervention with transcranial direct current stimulation (tDCS), showing an increase in the activation of cerebral patterns in the affected hemisphere too.

- *Patient's motivation.* Plasticity of central nervous system conditions include the importance of motivation and attention [29]. Active participation of patients throughout the rehabilitation process is a prerequisite to facilitate recovery [87]. Still these processes are sometimes repetitive and last long periods of time, making difficult to maintain the patient's interest on recovery. BCI could be used to induce and guide activity-dependent brain plasticity by paying close attention to a motor task that requires the activation or deactivation of specific brain signal. [20] revealed an improvement in concentration and participation after a BCI intervention motivated by the recovery of skill lost after a neurological lesion. Entertainment-orientated BCI applications through motor imagery have typically had a lower priority in neurorehabilitation field, but it could be another future application [81].
- *Generalization of learning.* The development of new technologies to facilitate the performance of evaluation and intervention procedures has stimulated research on novel rehabilitation paradigms and more effective rehabilitation strategies. More realistic scenarios are necessary to support learning processes and their incorporation into daily living. In this sense, the VR-based rehabilitation has been validated in the treatment of acute and chronic stroke and has been proved to be more effective than existing methods [103]. For the generalization of learning with BCI interventions, some works [5, 6] have made a follow-up after BCI interventions, showing adherence to therapy, as well as conservation of several improvements and gains in motor outcomes.
- *Physical effort required by clinical personnel during manual therapy.* There is no clear evidence that better outcomes can be achieved using technology-assisted intervention modalities compared to conventional therapies, but an advantage of robotic devices is their possibility to provide intensive therapies. Cerebral plasticity is an individualized process limited in time, and there is enough data to conclude that repetitive, high intensity, task-orientated training is efficacious [73]. Still, these conditions are not possible with conventional therapies. Higher intensity of practice is proved to be an important aspect of effective physical therapy, and additional therapy time of 17 h over 10 weeks is necessary to find significant positive effects at body function level [102]. The current challenge for BCI technology in neurorehabilitation is to enable the effective clinical use of BCIs with minimal effort to install and manage the devices used to register EEG signals to solve several problems yet derived from comfort, signal-acquisition hardware, and usability [96].
- *Development of accurate assessment tools for the evaluation of neurological deficits.* The motor cortex recovery is one of the biggest enigmas in neuroscience. Motor recovery patterns are heterogeneous, and until the last decade, the only prognostic indicator used was the degree of motor deficit [72]. The severity of the initial deficit and the improvement in the first weeks are the strongest indicators for a favorable outcome. Neural plasticity is an individualized process limited in time, so therapy should be regularly adapted and stopped if the deficit remains stable [73]. Imaging techniques are used to confirm neuroplastic changes produced by rehabilitation, still these techniques have some limitations in their use, mainly

because of the costs, contraindications, and poor accessibility. Also, patients with an undesired evolution time are excluded from rehabilitation programs [111], so it is necessary to design new treatment strategies and sensitive measures of outcome predictions that facilitate the clinical decision-making process. Characterization of brain signals from electroencephalogram is feasible, and these signals can be analyzed in real-time, which is useful for control and self-regulation of brain function [97]. Another application of BCI interventions could be the analysis of the evolution of motor patterns activation during recovery.

Economical problems

Costs of equipments are another problem to solve. New rehabilitation devices like exoskeletons have high marketing costs. Currently, each exoskeleton costs around $100,000, which is why they are only being sold to rehabilitation centers and hospitals. Several individuals suffering from motor disorders have costs that sometimes exceed one million dollar over their life time due to their condition. Added to these costs, the acquirement of proper rehabilitation devices is a really hard task. Looking at the exoskeleton market, the cheapest offer seen on current days is the HAL equipment from Cyberdyne which rent you this exoskeleton for $1000 a month [30]. Even with these prices the complete acquisition of these systems becomes difficult for an average individual. It is necessary to develop new low-cost technologies. In a period of limited resources and continuous increase of health care expenditures, clinicians need to carefully evaluate the economic impact of their decisions. In the last decade, economists have been particularly productive in offering to the decision makers a set of tools able to compare costs and benefits of each single-medical procedure. Long-term therapies can also be considered a great effective learning environment for health professionals. Prolonged therapies can be considered an environment for experimenting "creative" solutions and approaches [17]. The characterization and management of electrophysiological signals from the central nervous system with EEG equipment have been reinforced by various characteristics that make the EEG optimal clinical evaluation tool. They are noninvasive, portable devices, and affordable. In this regard, different authors have used to assess the functional cortical reorganization after motor cortex lesion. The analysis revealed EEG characteristics and uses of different patterns of brain activation related to movement and neural mechanisms related to motor control. Furthermore, it has revealed that the activity-dependent plasticity occurs in the central nervous system throughout life and that, therefore, the study of their evolution can be a useful way to determine the functional consequences of neurological accident and its progression [72].

Logistic problems

Another drawback of new systems like exoskeletons is the limitation in their use. There is a large percentage of paraplegics who will not be able to benefit from this technology based upon their height, weight, and type of injury. As an example, ReWalk Robotics define that the individual using their exoskeleton ReWalk [110] must be between 157–193 cm in height, weight less than 100 kg, and must have strong upper body strength to use the device. Quadriplegics are individuals who cannot move their upper and lower body. Because of this, they will be a large category of people who cannot use this technology due to their physical limitations. Implementation of care activities into daily practice is essential to improve quality of care, but it is also challenging. There are people who need rehabilitation that due to the region they live or their physical limitations cannot move easily to the rehabilitation center. There is a branch of telemedicine called telerehabilitation focused on solving this problem by the use of the telecommunication technologies [42], but telerehabilitation based on the performance of real movements is still nearly impossible because the patient should have all the expensive equipments at home and the therapist will not be there if the patient health is in risk during some exercise.

3 Review of BCI Systems

A BCI, also referred to as a brain machine interface (BMI), gives a person the ability to communicate with and control a computer through his or her brain signals rather than using the peripheral nerves and muscles [105]. This technology is directed towards providing people with severely restricted mobility or suffering from motor neuron degenerative diseases the possibility of communicating through a software application or controlling a device without requiring continuous assistance. BCIs are also starting to be used by healthy individuals, in particular in gaming applications, and may be expected to become an alternative means of communication and control in the near future.

3.1 A General Process of a BCI System

Noninvasive BCIs use electroencephalography to acquire the electrophysiological signals produced by the neurons and synapses of the central nervous system, and translates them into commands or messages to external devices. A typical process

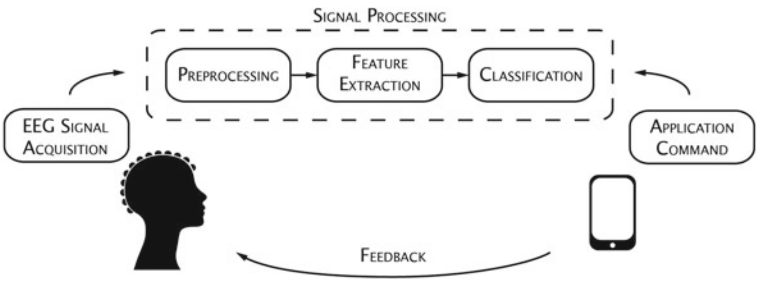

Fig. 1 General BCI process

of a BCI system is shown in Fig. 1. This consists essentially of the EEG signal-acquisition stage, the signal processing stage, and the application interface.

The signal-acquisition stage involves the recording of brain activity using EEG equipment while the user performs a predefined task. Electrical brain activity is recorded as voltage fluctuations resulting from ionic current flows within the neurons of the brain by electrodes placed on the scalp [82]. Each electrode reflects the summation of the synchronous activity of a large number of neurons in that particular area of the brain. The 10–20 international electrode placement system [69] is a standard method used for electrode placement. It is desirable to choose only the most relevant and necessary EEG channels while recording data. Minimizing the number of electrodes makes the BCI system more portable, practical, easier, and faster to set up. Moreover, reducing the number of EEG signals results in a possible smaller feature space and less computationally complex signal processing, which in turn reduces the classification time and hence improves the information transfer rate of the BCI system. Brain signals measured on the surface of the scalp have amplitudes in the order of hundreds of microvolts and thus must first be amplified. Preprocessing is carried out to improve the quality of the raw EEG data and filter unwanted noise and artifacts. The data is then passed through a feature extraction algorithm that obtains relevant and discriminative information from the EEG data that characterizes the distinctive neurophysiological phenomena. These features are fed into a classifier that predicts the brain activity of the user. This predicted class is translated in real time into a particular application command providing direct feedback to the user.

3.2 EEG Control Signals Used in BCI Systems

There are various brain signals evoking distinctive characteristics that have been adopted as control signals for BCIs. These include:

- *Sensorimotor Rhythms (SMRs)*. These are oscillatory patterns of cortical activation and inhibition that can be observed over the sensorimotor cortex during an imagination or actual execution of a movement [79]. Movement-related activation of the sensorimotor cortex is associated with two oscillatory patterns which are event-related desynchronization (ERD) and event-related synchronization (ERS). An ERD is an amplitude decrease of rhythmic activity occurring during motor preparation and execution, and is dominant in the alpha frequency band (around 8–12 Hz), while an ERS is an amplitude increase present after movement and is found in the beta frequency band (around 16–22 Hz). SMRs have the advantage of being well localized on the sensorimotor cortex; i.e., movement of a particular body part can be observed in the corresponding area of the cortex. This spatial information is used in motor imagery-based BCIs to distinguish between different motor imagery tasks [63, 88, 106]. The fact that motor imagery requires no actual muscular activity to modulate brain patterns is a great advantage for assistive BCIs.

Nevertheless, substantial amount of training to voluntarily modulate SMRs and gain control of a motor imagery-based BCI is required.

- *Slow Cortical Potentials (SCPs)*. These are slow-voltage shifts of the mean potential measured on the cortex. A negative shift of the cortical potentials correlates with increased neuronal activity, while a positive shift correlates with a decreased activity [26]. SCPs can be self-regulated through a *thought-translation device* (TTD) [15], which involves a training process that rewards the trainee for achieving the desired brain potential change [105]. SCP self-regulation training may take several months and depends on numerous factors such as the trainers psychological and physical state. The long-training period necessary for accurate control of SCP-based BCIs is their main disadvantage. BCIs based on SCPs also have a relatively low-information transfer rate since typically several seconds of recording are required to discriminate between a positive and negative SCP.
- *Visual Evoked Potentials (VEPs)*. These are electrical potentials recorded over the visual cortex and evoked by a visual stimulation. In [92], phase-locked occipital responses were studied by presenting a stimulus light modulated at a certain frequency. The EEG waves evoked by these stimuli produced a stable VEP response proportional to the stimulus frequency, thus were termed steady-state visual evoked potentials (SSVEPs). SSVEP-based BCIs consist of flickering stimuli that induce SSVEPs at different frequencies, each associated with a particular command of an application. The user focuses his/her attention on the target stimulus while the BCI system analyzes the ongoing EEG, extracts relevant SSVEP features to predict the target stimulus, and executes the command linked to that particular stimulus. Some of the advantages of SSVEP-based BCIs are that few electrodes over the occipital region are required since SSVEP is well localized; SSVEPs are less susceptible to EOG and EMG artifacts, and the user does not require training to evoke an SSVEP response. The disadvantage of SSVEP-based BCIs is that they require eye-gaze shifting.
- *P300 Potential*. This is a significant mid-central peak observed approximately 300ms after an infrequent stimulus is evoked among a series of routine stimuli. The Farwell–Donchin (oddball) paradigm [41] was developed to evoke P300 potentials during which subjects are presented with a random sequence of two types of stimuli: the target stimulus (or oddball) appearing rarely in the sequence and the nontarget stimulus appearing more often in the sequence. P300-based BCIs are limited to a low-information transfer rate [81]. In addition, the P300 potentials are not well localized on a specific region of the cortex [26] and thus require a larger number of electrodes than that necessary for a BCI system based on SSVEPs. The advantage of a P300-based BCI is that users do not need to train to control the EEG signals. However, offline training sessions are generally still required to train the BCI algorithm that detects P300 potentials which are known to vary between users [26].

3.3 Applications of BCI Systems

The BCI research is currently focused at developing clinical applications to serve as direct control to assistive technologies and as a form of rehabilitation [68]. BCI communication systems are vital applications for patients with strong disabilities. Various spellers using different EEG control signals have been developed [1, 27, 83, 104] although they are still limited by relatively low-information transfer rates. Restoration of movement control with BCI systems have also been studied by evaluating navigation systems through virtual environments [40, 63], control of mobile robots [71], and motorized wheelchairs [43, 62, 74]. BCI systems have also demonstrated potential use for controlling the movement of electrically driven prosthesis and orthosis [48, 75, 89]. The implementation of the discussed BCI applications would be personalized for locked-in patients or patients with severe motor impairments based on the patient's alertness, attention, visual and auditory capabilities, and higher cortical functions [68]. Novel hybrid BCI systems have been developed, which are either a combination of different types of BCIs [2, 89], or a combination of control channels including a BCI channel and any other biosignal, such as electromyographic (EMG) or other assistive technology input device [70]. The innovation of portable and relatively cheap EEG systems [61], although not reliable for critical applications as a medical-grade EEG system, have triggered great interest for healthy users, such as BCI computer gaming applications [55, 57, 84]. Furthermore, BCI technology is envisioned in the near future to be further developed in other fields such as robot control performing in dangerous or extreme environments, vehicles, as well as attention monitoring of aircraft pilots and drivers. Despite the fast-growing technology, many limitations such as the accuracy, speed, practicality, reliability, and cost of current BCIs must be overcome before these can be used outside the laboratory.

4 BCI and VR as a Tool for Neurorehabilitation

BCI technology was focused primarily on developing assistive devices for people with limited mobility. However, recent progress in this field shows the potential use of novel applications in neurorehabilitation. Thus, BCIs could also be beneficial for users with disorders such as stroke, autism, and attention deficit hyperactivity (ADHD) [14]. Such BCIs ensure the participation of the patient during rehabilitation to stimulate brain plasticity, thereby significantly enhance rehabilitation therapy. Similarly, VR could increase the participation of the patient during rehabilitation, thus strengthening the benefits of the treatment. Typical physical rehabilitation therapy is intensified with VR by providing the patient with useful stimuli related to the function that is being rehabilitated. VR also has the advantage of modifying the environment which the patient interacts with during rehabilitation, thus introducing motivating situations that promote the participation of the patient [51]. Considering the benefits of these two technologies, merging them in a BCI-VR system could enhance todays neurorehabilitation. This section provides an overview of recent studies related to BCI-VR systems, in particular for applications in neurorehabilitation. The benefits and limitations in current systems will also be discussed.

4.1 Current BCI-VR Systems

Lately, research groups have combined BCI technology and VR to create various BCI-VR prototype systems. These studies have demonstrated that VR is a useful tool for analyzing and developing BCIs, since it allows performing safe and controlled experiments. The interactions between BCIs and VR can be broken down into basic tasks [59, 66], such as navigating the position of a camera [67], selecting or manipulating virtual objects [3], and controlling an application [35]. The first task can be controlled typically with one to three commands by means of different BCI paradigms, such as SSVEP [39] and motor imagery (MI) [3, 67], while the other tasks are based mostly on the P300 and SSVEP paradigms [35]. The selection of paradigms affects the intuitive and natural control of the BCI, while aiming to avoid fatigue to the user. A recent review [66] presented different BCI-VR application studies. This review discussed the impact of VR and its future applications in the BCI field context. However, there is lack of information on current BCI-VR systems developed for neurorehabilitation applications. Hence, state of the art in BCI-VR systems for neurorehabilitation will be discussed in the following subsection. An overview on current BCI-VR studies is first given.

One of the most important application for people with motor impairments that BCI-VR research has been focused on is mobility. Presently, the wheelchair is the most important technology that provides individuals who suffer from limited motor function such as spinal cord injury (SCI) mobility [16] because of the simplicity of its movement patterns. It has already been demonstrated in [62] that a tetraplegic can use a self-paced BCI to control a wheelchair in a virtual street using feet MI. A wheelchair displacement was produced in proportion to the duration of MI detected from the user's EEG signals. The subject's task was to reach the end of the street and stop at each one of the fifteen avatars found for 1 s and encouraged to communicate with them. In two days, the subject was able to stop at 90 % of the avatars, achieving in some runs a performance of 100 %. This BCI-VR application is appealing for wheelchair-bound people, as they can try a prototype system in a safe environment before it is actually developed. Eventually the goal is to control an actual wheelchair outside the lab in real circumstances. In [23] a similar system was further developed to increase the degrees of freedom in both direction and speed of the wheelchair to provide a more realistic mobility application for the user. Currently, efforts are being made in implementing augmented reality in a telerehabilitation environment for the training of wheelchair use [21].

Other studies have focused on mainly on the design of the VR using different BCI paradigms. For example, in [39] an SSVEP-based BCI system was developed in which the flickering stimuli that evoked SSVEPs were embedded in a virtual environment. This study proposed 3D SSVEP stimuli within the 3D graphics of VR or augmented reality (AR) [39]. In a first study with seven healthy subjects, the application was one among three VR scenarios, while in a second study with three healthy people the application was an AR scenario. The first VR scenario showed an avatar on a first-person perspective that had to push correctly one of two buttons that had at their side-squared stimuli that flickered at different frequencies. During this task, the user had to focus on the stimulus associated with pushing the correct button and to achieve as many correct activations as possible in a fixed time. The other VR scenarios had an avatar which the user had to navigate through a slalom or an apartment scenario. Three stimuli where placed at the left, top, and right of the scene associated with turning to the left, walking straight, and turning to the right avatar control commands. The slalom had a fourth stimulus for stopping the motion. The goal of these tasks was to follow a predetermined path in a fixed time. The average positive predictive value (PPV) for the VR scenarios was above 93 %, while for the AR scenario, two of the three subjects could complete the task on time. These results suggest that this 3D virtual environment could elicit SSVEP, and therefore further BCI-VR realistic applications could be developed.

More recently, 3D stereoscopic feedback has been evaluated [12, 76], resulting in contradictory effects that could be caused by user vulnerability to stereoscopic 3D. For this reason, [76] investigated the differences in SSVEP BCI performance between 2D and 3D displays depending on such susceptibility. In this study, twenty-one healthy subjects navigated an avatar through a fixed pathway in a 2D or 3D virtual home. Prior and after the experiment with 3D stereoscopic feedback, the subjects were questioned on their visual stress, eye strain, physical strain, and difficulty to focus, such that they could be divided into fatigued and not fatigued groups. Results indicate that it took longer for the fatigued group to complete the task in the 2D view compared to the 3D view. Contrary results were obtained with the group of subjects who were not fatigued. Interestingly, mean PPV only increased significantly in the 3D mode compared the 2D mode for the not fatigued group. These findings show that personalized BCI-VR systems could improve their performance. In another SSVEP-based BCI study [12], the system developed was evaluated by four healthy subjects in a realistic virtual city using stereoscopic 3D. The users were able to accomplish the task of navigating through a fixed path with a mean accuracy (0.875 ± 0.076 %). This accuracy rate shows that further BCI-VR mobility applications in virtual environments could be developed and used not only for entertainment purposes but also for neurorehabilitation and training for actual mobility devices.

BCI-VR applications that allow interaction and communication with other people via Internet have also been considered. For example, in [45] a tetraplegic with muscular dystrophy operated a self-paced BCI-VR system that classified between motor imagery of three different limb movements each associated with a movement control of an avatar in an internet-based VR. The motor imagery of feet, left hand, and right hand where translated into the avatar moving forward, rotating left, and rotating right, respectively. The hands and feet classifiers ran in parallel to allow the avatar to move forward while turning. While the user navigated through the virtual environment, he/she could also communicate via voice-chat with other users who logged in to the application. The tasks given to the subject were to enter virtual buildings or walk in a defined path with other avatars. The training with this system lasted about 5 months, during which the user trained twice a month at his home for 1 h. After this period, the subject decreased the error rate of classification from 40 to 28 %. This kind of system demonstrates the possibility of developing further BCI-VR applications using the Internet.

Despite the promising results of these and other BCI studies, some people cannot operate BCIs with specific neuromechanisms. Consequently, hybrid BCIs that combine different neuromechanisms have been introduced to improve BCI control and their usability. One example of this type of BCI [35] assesses an interface using P300 to control a smart home environment. This interface consists of a rectangular matrix with different icons and characters, representing the different devices that could be controlled in the smart home, flashing randomly fifteen times for each command. When the speller is on, the user has to concentrate on the icon related to the command of interest, such that each time it flashes a P300 is elicited and detected by the BCI. Three healthy people were asked to switch on the BCI, select five predetermined commands, turn off the application, and wait for approximately 1 min for the next trial. Results showed that 4.5–5 s were required to switch on the system and 5.8–7.9 s to switch it off, and the P300 matrix accuracy was 100 %. This system is currently being adapted for its use in an actual smart home to be used by people with restricted mobility.

Most BCIs use low-level commands to operate, which means that each mental state is associated to a simple command such as turning left in a virtual environment. This limits the number of BCI commands especially for MI-based BCIs. Hence, a new approach was proposed in [67] for exploring a virtual museum using a BCI based on MI high-level commands. This approach uses three MI classes (left hand, right hand, and foot MI) as commands in a binary decision tree. Left hand and right-hand MI are used for selecting tasks within the tree, and foot MI is assigned for canceling the last choice. Based on this concept, two navigation modes are provided at the top of the tree: free navigation and assisted navigation. The former allows the user to modify the camera's view, while the latter allows the user to select between different points of interest (artwork or navigation points) that are at the right or left side of the current position. Feedback is also provided to the user while operating the system by icons of a left hand, a right hand, and feet, which increase in size when their mental state is detected by the BCI. A state has to be detected several times to reassure the correct command before it is activated. Three users performed different navigation tasks, and the system's performance was compared with a state of the art BCI low-level command museum interface. Results showed that users navigated through the virtual environment almost twice as fast using the high-level command approach. This approach demonstrates that such practical BCIs could be developed for more realistic applications.

Unfortunately, in most BCI applications mental constrains and cognitive workload to the user are often ignored, especially in BCIs with a large number of low-level commands. For this reason, in [3] the researchers propose easing user adaptation in demanding scenarios, particularly for a synchronous MI-based BCI system to control a simulated living-environment platform (SLEP). User-system adaptation was evaluated by BCI accuracy and user's heart rate (HR). The system was designed to satisfy four aspects: necessities and desires, mobility, environment control, and communication. These activities were organized in a user-friendly interface that had four different categories divided in submenus. Right MI was used for navigating through the top-level menu, while left MI was used for command selection. Navigation through submenus was automatic to avoid fatigue. The task was to accomplish defined sequences of instructions with four increasing in demand levels: familiarization with the assistive software, user-system adaptation, cue-driven system, and target-driven system. The first two levels were designed to help the users get familiar with the menu and the assistive software, and the last two levels had a virtual environment with visual and aural stimuli related to the performed activities. In the third level, if the target option was not selected, the system did not execute the action. In the fourth level, the users had to plan their own sequence of activities, and if they failed at selecting their planned activities, they had to deal with unexpected activities and their interfering aural and visual stimuli. Results showed that performance improved for increasingly challenging learning scenarios, while there was an apparent HR reduction in more demanding scenarios, which is associated to intake tasks. Such approach could be implemented to ease the subject adaptation in BCI-VR systems or to increase the tasks that the system can accomplish. However, these studies have to still be validated with physically impaired users.

King [54] faced the problem of actual technology for substituting lost motor functions, including robotic devices or electrical stimulators. For patients with paraplegia, such technology is not intuitive and these devices could be controlled manually. Therefore, the feasibility of BCI implementation in such systems was assessed with five participants having spinal cord injury. A self-paced BCI was used for 5 sessions of 10 min by the users who alternated MI of idling and walking for controlling the ambulation of an avatar and making 10 stops at determined points in the virtual environment. The participants could finish the tasks given within the assigned time, achieving an average performance of 7.4 ± 2.5 out of 10. In addition, BCI control was maintained during the study and performance continued improving in 4 of 5 participants. These results suggest that a BCI controlled lower extremity prosthesis for ambulation or gait rehabilitation may be feasible.

Within recent work on BCI-VR systems a passive EEG BCI approach has also been developed [59]. This refers to an interaction that is not voluntarily controlled, which in this case is the mental workload. This BCI computes in real time a mental workload index of the user. If the index indicates high workload, then haptic assistance is activated. Eight healthy people participated in this study where a cursor was moved through a 2D virtual maze while trying to avoid collisions with the maze walls. The cursor was controlled by a haptic device that exerted a force that was inversely proportional to the distance from the closest wall. A condition in which there was no haptic assistance was evaluated together with two other conditions that included either continuous guidance or guidance only when a high workload was detected. Results showed that performance improved with the assistance compared to when there was no guidance at all. There were no significant performance differences between workload-based and continual guidance. Correspondingly, there was a reduction in the workload index if assistance was provided. This index was also correlated with the subjective mental workload of the users. These results indicate that passive systems could be employed when assistance is required, such as providing complimentary assistance during therapy or easing the use of other devices.

All the studies mentioned in this subsection are summarized on Table 1. Unfortunately, very few studies related to BCI-VR systems conducted during the last 5 years evaluated the systems with physically impaired users.

4.2 BCI-VR Systems for Neurorehabilitation

As mentioned in Sect. 1, BCIs applied to neurorehabilitation applications and concerned with motor dysfunction are not intended to replace lost motor function, but to improve motor functions in patients by means of brain signal regulation that produce cortical reorganization and compensatory cerebral activation [14].

Current BCI applications for neurorehabilitation are considerable in quantity, but still only a few are validated. In [8], researchers developed a BCI with a combined approach of movement imagination and observation while also evaluating the risk of stroke. Its prediction is based on the Stroke Risk Self-Assessment Chart from Brain foundation, and its result comes as one out of four levels of risk [18]. This evaluation is calculated from a self-report that also includes factors as hand grip force and waist circumference. The application for neurorehabilitation consists of a 2D game in which, a left- and right-hand MI are associated with movement of hands of an avatar to the left and right, respectively. MI is performed to catch a ball that falls from the left or the right side. Twelve healthy users participated in the study, and after 5 times of performing 100 trials, the highest accuracy achieved was 70 %. Additional experiments were performed with three trained subjects and one stroke patient, whose highest accuracy was 70.67 % and 77 % respectively. Another system that includes a combined approach developed in [11] is an EEG BCI-VR system that combines a personalized motor training and a modified rehabilitation gaming system (RGS). RGS combines movement performance and movement observation to recover motion functionality, such that only patients who have enough motor control are candidates for its training. Thus, the RGS was extended to a BCI that includes MI training, making it available for patients with more limited mobility. However, the goal of the study was to evaluate the feasibility of the BCI-VR system, therefore the virtual environment was controlled only by MI. The task was to control the upper extremities of an avatar in first-person perspective through MI in order to catch incoming spheres. Thus, the task did not require precision but functional control. The amount of time that an arm movement was detected controlled the level of the arm extension of the avatar. Additionally, the difficulty of the training varied dynamically depending on the skills of the user in order to personalize the training and to keep the user motivated. In this experiment, the nine healthy subjects who participated were able to control the virtual arms above chance level, and their self-report questionnaires indicated enjoyment and acceptance of the system. In a future

Table 1 Recent BCI-VR studies that are not about neurorehabilitation

References	BCI	Signal	Timing	Application	Subjects	Year
[62]	MI	EEG	Self-paced	Wheelchair control in virtual environment	1(tetraplegia)	2007
[39]	SSVEP	EEG	Self-paced	First study (VR):	7(healthy)	2010
				Pushing a button	First study	
				Navigation in slalom	3(healthy)	
				Navigation in apartment	Second study	
				Second study (AR):		
				Navigation slalom		
[67]	MI	EEG	Self-paced	Navigation in a virtual museum	3(not specified)	2010
[45]	Motor intention	EEG	Self-paced	Avatar ambulation and e-communication	1 (tetraplegia with muscular dystrophy)	2010
[35]	SSVEP, P300	EEG	Synchronous	Controlling a smart home environment	3(healthy)	2011[a]
[3]	MI	EEG	Synchronous	Navigation and interaction in SLEP	11(healthy)	2013
[54]	MI	EEG	Self-paced	Avatar ambulation	4(paraplegia)	2013[a]
					1(tetraplegia)	
[60]	Workload	EEG	–	Navigation through a virtual maze	8(healthy)	2013[a]
[76]	SSVEP	EEG	Synchronous	Navigation in a home environment	21(healthy)	2013[a]
[12]	SSVEP	EEG	Self-paced	Navigation in a virtual city	4(healthy)	2014

[a]Ongoing study

work, authors will incorporate a motor plus neurofeedback paradigm in order to evaluate the suitability for patients.

Another EEG system for upper limb neurorehabilitation is a BCI that can control either a VR system or an upper limb rehabilitation robot [86]. The BCI-VR system was evaluated with eleven post-stroke patients and eleven healthy people as a control group. Also, preliminary results from four healthy users with the BCI-robot system were presented. In the experiment based on robotic rehabilitation, the robot gave a discrete delayed feedback of the dominant hand MI by flexion and extension of the five fingers. A cue was given by an arrow on a screen pointing to the left or to the right, and if the instruction was not used for controlling the robot, then the user had to execute the movement. In the VR experiment, real-time feedback was presented for both hands in first-perspective as the flexion or extension of a left or right hand, depending on which hand movement was detected. The cue was presented by flexion and extension of one of the virtual hands. This denoted to imagine the execution of the movement displayed during the cue. It is important to state that for the robot test, user personalized classifiers were used, while for the VR test, a generic classifier was used. The results achieved were a mean accuracy of $86.55 \pm 13.97\,\%$ for the four healthy subjects using the robotic feedback paradigm in four sessions, while with the VR paradigm mean accuracies were $63.77 \pm 16.52\,\%$ and $59.7 \pm 6.08\,\%$ for the eleven healthy participants and five post-stroke participants in the first session, respectively. The five stroke patients performed further sessions and by the fourth session they reached a mean accuracy of $72.48 \pm 8.45\,\%$. This improvement is important considering that the motivation and, in consequence, the advance in the rehabilitation therapy depends on BCI accuracy. The results with VR are lower than with the robot mainly due to the different classifiers that were used. The difference in control between the accuracy of healthy and stroke users was about $3\,\%$. In future studies, the authors plan to adapt the robotic feedback such that it is in real time, to combine the robotic and the VR rehabilitation strategies, and also to evaluate a functional electrical stimulation (FES) approach.

Muñoz [77] presented a multimodal interface called Brain Kinect Interface (BKI), which combines BCI-VR videogames and exergames (exercise games) with inexpensive RGB-D cameras such that the rehabilitation process is improved by sensing the movements of the patient with a camera. With this approach, technology used for therapy could be cheap and implemented at home. Different games have been designed for different disorders. Although this is an ongoing study, the system is currently being used in a rehabilitation center. The BCI game (that is still being validated) is a BCI duck hunt, based on the popular Nintendo game, however, controlled through hands MI. This game is oriented particularly with patients for spatial neglect, Parkinson, and monoparetic stroke patients.

Movement restoration studies are not only focused on upper limbs, but also in gait restoration. For example, in [53], an individual with paraplegia used an EEG BCI system that had FES for gait restoration. Before using the gait restoration system, a walking simulator training system [54] was calibrated for the subject. This was then used to control the walking of an avatar within a virtual environment while making ten stops at designated points. In addition, the subject was prepared by a physical therapist and also with a FES system in order to recondition his muscles before gait training. The user then endured suspended walking tests and BCI-parastep overground walking tests. The performance achieved for the overground walking tests was purposeful according to Montecarlo simulations ($p < 0.0001$). There were no absence of walking response for intended walking condition and few initiations of walking response of the system for idling epochs. As the number of walking responses for idling time lapses increased when changing the user from suspended tests to overground tests, it was reported that there might have been issues with the postural stability and the participants balance, so there is a need for FES to compensate weight loading in gait restoration systems in the future, as well as testing the system with a larger population with SCI.

Within resent BCI-VR for neurorehabilitation studies, there is also a proposal based on wireless functional near infrared spectroscopy (fNIRS) for assessing cortical activation by determining the changes over time of both the concentration of oxyhemoglobin and deoxyhemoglobin [46, 47]. Since this is new for MI neurorehabilitation, the objective was to test if the so called simulation hypothesis holds for a fNIRS system. Right-handed healthy subjects participated in the study either in the bilateral or in the unilateral (contralateral to the movement involved in the task) group of brain activity recording. The virtual environment contained virtual representations of the upper limbs. The subjects performed a catching-a-ball VR task with each virtual arm under different conditions: passive observation, observation plus MI, MI without visual feedback, and observation plus imitation of a virtual arm. Comparisons between these conditions revealed that oxygenation changes could be found over the same secondary areas during observation, motor imagery, and motor execution, such that the simulation hypothesis was met, although not all differences were statistically significant. For the unilateral group, there was a significant difference in the oxyhemoglobin concentration of the rest and the stimulus states for the MI and the imitation conditions, but not for the observation and the observation plus MI conditions. On contrast, for the bilateral group, there were statistical significant differences in the oxyhemoglobin concentration of the rest and the stimulus states at the left hemisphere when observing or imitating the movement of either the left or the right arm, while at the right hemisphere the differences were only found for movement imitation of the left or the right hand. It was suggested that differences between the results of the two hemispheres are attributed to handedness. In the future, the authors aim to develop a VR-fNIRS BCI that provides real-time neurofeedback of cortical oxygenation changes. In this design, handedness and intersubject variability (larger for oxyhemoglobin) should be considered.

Even though not discussed in this chapter, it is important to remark that new BCIs in neurorehabilitation studies that are not used for motor neurorehabilitation are being conducted. Among these, is a BCI using a 3D virtual environment for helping people with autism spectrum disorder to interact with social situations without real-world pressures [36]. There is also interest to develop BCI-VR systems for assessing chronic pain with help of the illusion of ownership of a virtual body [65], as well as using BCI technology for attention disorders [10]. A summary of the systems discussed in this subsection can be found in Table 2.

Table 2 Recent neurorehabilitation BCI-VR studies

Reference	BCI	Signal	Timing	Application	Subjects	Year
[46, 47]	MI	fNIRS	Synchronous	Upper limb control of an avatar	23(healthy)	2010[a]
[8]	MI	EEG	Synchronous	Control of a virtual hand	12(healthy)	2013
					1(post-stroke)	
[11]	MI	EEG	Synchronous	Upper limbs control of an avatar	9(healthy)	2013[a]
[86]	MI	EEG	Synchronous	Hands control of an avatar	11(healthy)	2013
				Control of an upper limb rehabilitation robot	11(post-stroke)	
[65]	Concentration	EEG	–	Control of virtual body	5(healthy)	2013[a]
					1(idiopathic fixed dystonia)	
[36]	Facial emotion	fMRI model, EEG	–	Interaction in a class social VE	–	2013[a]
[53]	MI	EEG	Self-paced	Avatar ambulation and gait restoration	1 (paraplegia)	2014[a]
[77]	MI	EEG	–	BCI Duck Hunt	Recruiting patients for valitation	2014[a]
[10]	Movement recalling	EEG	Synchronous	Reward based-environment	1(frontal syndrome)	2014[a]

[a]Ongoing study

In conclusion, using BCI-VR systems for neurorehabilitation a controlled environment can be designed to target individual needs of each patient through specific tasks. The VR can promote motivation by means of the performed tasks, reward, and augmented feedback that stimulate cortico-spinal tracts in an extended way by including in the latter paradigms such as the ones described in Sect. 3. In addition, BCI-VR systems may help patients to participate more in rehabilitation therapy and lets the patients self-monitor their improvements. Depending on the system design, these may also allow decreasing the therapy cost since BCI-VR systems do not necessarily require the use of expensive devices such as rehabilitation robots. In addition, the use of BCI-VR systems in therapy that uses MI could increase the accessibility of neurorehabilitation treatment by allowing patients with little or no motor control to benefit from these novel technologies. However, further research on the design of BCI-VR systems is needed for enhancing motor learning during the neurorehabilitation process. This technology for neurorehabilitation applications is new, thus most of the studies are still being evaluated or still designed for users in clinical trials.

5 Conclusions and Discussion

BCI research and development have been focused on developing applications projected to have significant social impact. BCIs were primarily directed toward developing applications that provide people with motor impairments the possibility to communicate or control a device. This technology is now directed toward other novel applications, including applications for neurorehbilitation. As described in this chapter, neurorehabilitation has become essential in today's society, and as a consequence the number of scientific research studies in this field has also increased. Currently BCIs still encounter various limitations; however, the fast-growing research will lead to applications that would significantly improve the quality of life for several people. BCIs developed for applications in neurorehabilitation are useful not only for people who have suffered traumatic disorders such as spinal cord injuries but also for people who have limited motor capabilities due to, for example, muscular dystrophy. Due to the nature of BCI technology, applications in neurorehabilitation are mostly based on motor imagery. This has been widely proved in the literature to be a useful approach to restore neural paths in the brain. The use of VR in this field provides a novel technique in neurorehabilitation, apart from the patient actually moving or imagining the movement as physical therapy, with VR the patient can also observe the movement. The combination of these techniques enhances the patient's motivation in the rehabilitation as the patient can observe the movement in VR he/she is imagining or trying to perform.

As it was discussed in this chapter, the use of an exoskeleton for neurorehabilitation brings several challenges. Apart from the economical aspect, regulatory of exoskeletons to meet the needs of a wide range of patients is a major challenge since each patient has unique conditions and needs. In addition, generating an artificial movement of a limb either by an exoskeleton or a physiotherapist could lead to several derived motor diseases. These could be avoided by combining VR with BCIs to develop neurorehabilitation applications that encourage natural movement.

Currently there are numerous studies that use VR for BCI applications; however, only a small number of these studies are focused on neurorehabilitition applications. The field for BCI-VR neurorehabiliation systems is novel and has great potential with further research and development. This technology could provide an efficient and safe way to neurorehabilitate people who suffer from different kinds of motor diseases. The variables that influence motor learning and VR for this technology are: practice, augmented feedback, motivation, and observational learning [64]. Thus, this along with new knowledge about the related pathways and therapeutical benefits of motor observation, imagery, etc., may be considered broadly in BCI-VR designs for neurorehabilitation process in the future.

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Robot-Assisted Rehabilitation Therapy: Recovery Mechanisms and Their Implications for Machine Design

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Abstract Robot-assisted rehabilitation therapy interventions are emerging as a new technique to help individuals with motor impairment recover lost motor control. While initial clinical studies indicate the devices can reduce impairment, the mechanisms of recovery behind their effectiveness are not well understood. Thus, there is still uncertainty on how best to design robotic therapy devices. Ideally at the onset of designing a robotic therapy device, the designer would fully understand the physiological mechanisms of recovery, then shape the machine design to target those mechanisms. This chapter reviews key potential mechanisms by which robotic therapy devices may promote motor recovery. We discuss the evidence for each

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mechanism, how initial devices have targeted these mechanisms, and the implications of this evidence for optimal design of robotic therapy machines.

1 Introduction

Robot-assisted rehabilitation therapy is an emerging form of rehabilitation treatment for motor recovery after neurologic injuries such as stroke and spinal cord injury. Robotic devices can help patients achieve the intensive, repetitive practice needed to stimulate neural recovery, reducing the need for supervision and improving cost-benefit profiles [1]. They can also provide quantitative parameters to characterize the therapy. Initial clinical studies have found that training with robotic therapy devices typically matches or exceeds the therapeutic benefits possible with conventional therapy approaches [2–4].

With these promising results, there has been a proliferation of device designs. For example, a recent review of robotic therapy devices for the upper extremity found over 150 devices in the literature [5]. However, even if numerous robot-assisted devices have been proposed, the rationale for the design of each device is still largely improvised, because there is limited scientific knowledge of why robotic therapy is effective.

The objective of any neurorehabilitation system is to exploit neuroplasticity and motor learning, involving the patient in an intervention that recreates the favorable conditions that can induce the modification of the residual neural networks of the brain. However, despite progress, a full understanding of the neuroplasticity and motor learning mechanisms that are involved in beneficially modifying brain networks is not currently available. The objective of this chapter is to review current state of knowledge of the mechanisms that might cause robotic therapy to improve motor recovery. To organize this chapter, we identify three categories of mechanisms:

- Parameters of the therapeutic experience: therapy dosage, task specificity, and challenge level.
- Types of motor learning: learning from augmented feedback, Hebbian learning, and reinforcement learning
- Approaches to human-machine interaction: haptic guidance, error augmentation, and machine-enhanced motivation

We discuss experimental evidence for each mechanism. We also interpret this evidence with respect to its implications for current and future robotic therapy device design. We primarily focus the discussion on stroke rehabilitation, which is the largest potential user group of robotic therapy. Many of the results likely can be extended to other patient populations, including people with spinal cord injury and cerebral palsy.

2 Quality of the Therapeutic Experience and Robotic Therapy Design

2.1 Dosage

2.1.1 Evidence for a Dose-Response Effect

Perhaps the primary rationale for using robots in rehabilitation therapy has been to increase the dosage of therapy that can be delivered. Dosage in rehabilitation therapy can be defined in different ways, including the amount of therapy in minutes per day, the number of exercise repetitions achieved during therapy, or the number of therapeutic sessions in the rehabilitation process. The term "dosage" can also include the concept of therapy "intensity", such as the amount of external work and/or power the patient produces during training [6].

What is the evidence that a dose-response mechanism exists in rehabilitation movement therapy? At least in the case of stroke, evidence is relatively strong that there is an overall effect of dose, as summarized in a recent review [7]. Improved dose can improve activities of daily living (ADL) performance [8–12], strength [9, 13, 14], and shorten the length of stay in a rehabilitation center [15]. However, there are some questions about the persistence of the dose-response effect, as well as its specificity. For example, in one key study, an increase in therapy dose was achieved by giving longer therapeutic sessions (usually 1.5-2 times than what the control group is receiving) [8]. This increased dose improved the ADL scores in the beginning of the therapy (at 4 months), but this effect was transient, since, after 12 months of therapy the increased dose group had similar ADL scores as the control group. A similar trend was observed in other studies [9–12]. This suggests that an increase in rehabilitation dose in the first six months may not be mandatory for long-term rehabilitation outcomes but allows the patient to regain earlier a better performance in activities of daily living, thus justifying the use of robotics to increase dose early in therapy.

Other studies have suggested that increasing dose affects different activities of daily living differently. For example, the correlation between repetition and improvement has been suggested to be stronger for occupational therapy than for physical therapy activities [12], or for discipline-specific therapy than for combined therapy across disciplines [16]. In another study, increasing dosage improved stair climbing and 6-minutes of walking in a sustained way, but not timed up-and-go test [13].

2.1.2 Implication of Dose for the Design of Rehabilitation Robotics

The dose-response mechanism is likely a key reason that robotic rehabilitation therapy has been successful. For example, a recent review stated that, when robotic therapy and conventional therapy were applied with the same duration and intensity, there were similar improvements in outcome [4]. This has also been confirmed in other studies, where the patients with the highest robotic therapy dose (here expressed as hours of therapy per week) had the best improvement in motor function [17, 18]. Therefore, a key consideration in the design of robotic therapy devices is how to make therapy (1) less demanding for the rehabilitation therapist, and/or (2) possible for patients to complete without continuous one-on-one supervision from the therapist. Thus, ideally, devices must be designed to allow the patient to exercise as independently as possible, so that rehabilitation dosage can be increased. This has strong implications that robotic therapy devices must be designed for ease of use, and must include engaging rehabilitation games or other motivation strategies that facilitate extended, semi-autonomous practice. Designing devices that can provide gradable amounts of work or power, and adjustable number of repetitions per second, also appears to be important due to the dose-response recovery mechanism.

2.2 Task Specificity

2.2.1 Evidence for Importance of Task Specificity

The development of new robotic therapy devices in the last ten years has been driven by the finding in rehabilitation research that task-related, functional training leads to better outcomes than non-functional training [19, 20]. Indeed, rehabilitation after stroke has evolved during the last 20 years from mostly analytical rehabilitation methods to task-oriented training approaches [21]. By "analytical methods" we mean methods that address single-joint movements that are not directly linked to skills. These are usually movements without a goal and in one plane. In contrast, task-oriented approaches involve training of skills and activities aimed at increasing the subject's participation. Task-oriented training consists of either multi-joint simple movements not directly related to activities of daily life (e.g. moving blocks from one location to the other) or movements with a clear functional goal (e.g. washing dishes or dressing) [21].

A key rationale for task-specific training is that transfer of motor learning has often been found to be limited [22]. Therefore, practicing the tasks that one wishes to be able to participate in during daily life ensures the greatest learning on those tasks. With regards to upper-extremity training, it has also been shown that practicing tasks that are meaningful for the person increases cortical reorganization. Moreover, the effects of task-related training were found to be long-lasting compared to the effects of traditional therapies [23].

Regarding lower-extremity training, there has also been a strong preference in rehabilitation practice for task-specific training, particularly training focused on walking. Thus, both manual body-weight support treadmill therapy and robot-aided treadmill training have received great attention in the rehabilitation world. One of the main reasons is that task-specific training provides locomotion-relevant afferent input to spinal central circuitries that generate rhythmic stepping behavior [24].

2.2.2 Implication of Task-Specificity for the Design of Rehabilitation Robotics

Because of the importance of functional training, robotic therapy devices have become increasingly complex, with the inclusion of more degrees of freedom (DOF) [5]. With these devices, task-oriented exercises that resemble activities of daily life are possible and they are usually combined with virtual-reality software that mimics activities of daily living [25, 26]. This increasing complexity has typically meant a trend to build exoskeletal devices, rather than end-effector based devices, to more closely mimic the structure of the limbs, for safety and comfort during the complex movements required for ADLs (e.g. ARMin [27], BONES [28]). Recently, hand modules have also been increasingly integrated into exoskeletal devices, allowing the integrated use of the arm and hand [5]. Among the lower-extremity robots, we can find that the robotic gait trainers that allow functional training of walking are usually the exoskeletal devices that have actuated hip and knee joints (Lokomat [29], LOPES [30], ALEX [31]), which are increasingly incorporating pelvic movement for balance training (PAM [32], LokomatPro FreeD). There has also been rapid development of legged exoskeletons that allow practice of overground walking, with several commercial products now available (Ekso, HAL [33], ReWalk [34], Indego [35]).

It is unclear however, at least for the upper extremity, if the increased complexity has been necessary. For example, a recent study with an upper-limb robotic device (BONES) showed that multi-joint, task-related training was not superior to single-joint training in a group of 20 chronic stroke patients. It seems that better learning of the movement occurred when the task was decomposed in simpler parts as opposed to practicing only the whole [25]. Likewise, a recent clinical study with a more complex exoskeletons seemingly did not produce better results than previous studies with less complex robotic devices [26]. Indeed, it has been hypothesized previously that more severely impaired patients would benefit more from impairment-based training than from functional training [36]. It may be the case that, until patients have developed the whole repertoire of movements required to complete a task, they might not fully benefit from functionally-based robotic rehabilitation approaches.

For the lower extremity, while functional robotic gait therapy is effective in stroke patients [37], there is also evidence that home-exercise programs, with the aim of enhancing flexibility, strength, coordination or balance, are equivalent to locomotor training (LEAPS trial [38]). In the case of walking, it has been clearly shown that the locomotor capacity correlates well with strength of leg muscles, like hip flexors or extensors [39, 40]. In this case, therefore, training aimed at improving the strength of some target muscles of the lower limbs could be more beneficial than walking with a robotic gait trainer alone [41]. Another interesting example is the single-joint training provided by an ankle robot that trained dorsi/plantarflexion and inversion/eversion movements, where patients improved velocity and distance walked [42]. No comparison with functional training was made in this study.

In summary, it is currently difficult to draw a definitive conclusion on how mechanically complex it is to make robotic therapy devices for the purposes of retraining function. At present, then, robotic-therapy designers must rely on clinical wisdom.

One clinical framework that may be useful is the concept that sensory-motor training should present a total package, consisting of several stages [43]:

- training of basic physical capabilities that are prerequisites for skilled movement (e.g. muscle force, range of motion, tonus, coordination)
- skill training (cognitive, associative and autonomous phase)
- improvement of endurance on muscular and/or cardiovascular level.

In this framework, task-related training and analytical training are complementary, and different robots can be designed to account for the different needs of the patients: from very complex multi-DOF exoskeletons to more simple, but as important, single-joint devices.

2.3 *Optimal Level of Challenge*

2.3.1 Evidence for the Importance of Optimal Challenge

A key aspect of the recovery of motor function is to challenge patients during training according to their skill level [44]. Too low a level of challenge can make a treatment boring, and not encourage motor learning. On the other hand, too high a level of challenge can be frustrating or overwhelming, and also make it difficult for a patient to garner new information needed to learn. In motor-learning research, these ideas have been captured in the Challenge Point Theory, which posits an optimal challenge level for learning based on the skill level of the trainee [45].
The idea of optimal challenge can also be related to studies of the role of guidance in motor learning. In one seminal study, always guiding a person during movements reduced motor learning in a task where participants had to learn to position the elbow at a desired location without vision [46]. In contrast, faded guidance, which is a time-scheduled reduction of guidance, was found to be approximately as effective as no assistance, and significantly better than a fixed amount of assistance. Reducing guidance therefore seems to promote optimal levels of challenge.
Regarding neurorehabilitation, the upper-limb function of stroke subjects has been reported to improve after robot-mediated treatments that require the patient's effort during the entire movement and assist only to complete the task [47]. Patients seem to benefit from a progressive reduction of the assistance, although definitive conclusions cannot be drawn yet [47]. Results in robotic gait training also seem to suggest that devices that "over-assist" patients produce lower therapeutic benefits [48–50].

2.3.2 Implication of Challenge for the Design of Rehabilitation Robotics

A key advantage of robotic therapy devices is that they can provide varying degrees of assistance, balancing the difficulty of training, theoretically maximizing the rehabilitation outcome because of the challenge-dependence of motor learning.

However, how best to manage the trade-off between training variables, and how to determine the level of optimal assistance that the robot must provide to help the patient without replacing his volitional movement, are still open issues [51]. What is clear is that robotics technology allows for a range of approaches, from a passive robot that follows the patient [52], to an active device that carries the patient and assumes the control [47, 53].

One strategy for providing challenge is the assistance-as-needed paradigm, which lets the patient execute the movement and tracks the performance error to provide support only when required. This is similar to faded guidance in motor-learning research, except the guidance is adjusted based on real-time measurement of performance, rather than based on a fixed-time schedule of reduction. In this paradigm, the participant's effort is encouraged, and only self-initiated movements can be performed. This can be done, for example, by allowing some error variability around the desired movement using a deadband (an area around the trajectory in which no assistance is provided), and triggering the assistance only when the participant achieves a force or velocity threshold [53]. As another example, Emken et al. developed in 2007 a mathematical algorithm for fading robotic guidance based on a measure of ongoing error [54]. This "guidance-as-needed" robotic assistance helped people learn to form an internal model of a novel force field that was applied to the leg while walking. This strategy reduced performance errors while it allowed participants to progressively experience more of the actual task to be learned. Nevertheless, the main challenge that the assistance-as-needed controllers still need to face is the optimal choice of the measured process variable, as well as the algorithm for adapting the system parameters to align to the requirements of the patient.

Several robotic neurorehabilitation systems have been developed based on the assistance-as-needed paradigm. The first robotic system to be clinically tested was the MIT-Manus, which allows a free movement of the arm in the horizontal plane with low friction. The impedance selection allowed the treatment to change according to the performance of the patient and it has provided positive results on its repeated tests with stroke patients [55–57]. Wolbrecht et al. developed in 2008 a controller to learn the patient's abilities and complement them with the robot, by reducing the force exerted on the upper limb when the errors in the task execution were small [58]. GENTLE/A, a robot designed to rehabilitate the upper-limb function in point-to-point and single-axis movements, also estimates the contribution of the participant during the treatment and adapts its assistance/resistance accordingly, automatically tuning the difficulty of the task to challenge the patient [59].

In summary, the trend of the robotic controllers in recent years is to continue to improve the human-robot interaction, adapting the robot behavior and cooperation in an attempt to make the communication more natural and the challenge level optimal [44]. For example, the robot can even be made to anticipate to the user's actions, to provide more effective assistance-as-needed [60].

3 Learning Mechanisms and Robotic Therapy Design

3.1 Learning from Augmented Feedback

3.1.1 Evidence for the Importance of Augmented Feedback

Augmented feedback refers to providing artificial feedback of movement parameters [61], given in addition to intrinsic feedback, defined as the natural information from internal sensory processes like vision, proprioception and hearing [62]. Training with augmented feedback in rehabilitation is generally recognized to be more effective than training without [42, 62, 63], but the neurological mechanisms underlying its effects still remain to be clarified. It could be that either new pathways are developed, or old persisting cerebral and spinal pathways are mobilized by introducing the auxiliary feedback loop [64]. In this model, visual and auditory feedback activate unused or underused synapses in executing motor commands. As such, continued training could establish new sensory motor memories that help patients perform tasks without feedback [65]. Biofeedback may also enhance neural plasticity by engaging auxiliary sensory inputs [63]. This could be the case for patients with injuries of the central or peripheral nervous system where perception is often disturbed or missing due to lack of appropriate afferent input from the receptors. In this case, artificial sensors can be used for recording the signals to be fed back to the subject [66]. Moreover, it is known that an effective rehabilitation training should be intensive, repetitive, task-oriented and of long duration [67] and feedback can potentially enhance these aspects by increasing the level of attention, reducing the mental fatigue of executing the task [42, 63, 68, 69].

Augmented feedback can be conveyed in two paradigms: knowledge of performance feedback delivers information about the whole performed action, whereas knowledge of results feedback informs only about the final outcome [62]. Augmented feedback can be further classified according to the display modality: visual, auditory, haptic or a combination of these [42, 63, 67, 69, 70]. Visual feedback is the most used display modality [71, 72] and it can span from a very simple display using lines or colors to convey information [61], to more complex representations, such as an avatar displayed on a screen [66, 67] in a Virtual-Reality (VR) environment. Auditory feedback can also be played back in response to an action or an internal state of a robotic therapy system [73]. Auditory tones can be used with a rewarding function ("positive tone") or continuously to map a particular characteristic of a movement (e.g. smoothness or distance to the target in a reaching task) [63]. Sounds can be also used to augment realism in a VR environment [73]. Haptic information feeds back kinaesthetic sensations that are important for task performance and it highly enhances the immersiveness of VR environments [63]. A trend in rehabilitation robotics is to combine the three modalities in VR applications that provide a more immersive feedback for task-related training [63, 74].

The optimal feedback modality is thought to be dependent on the information to convey and on the characteristics of the population involved in the training.

Visual feedback seems to be more effective for information related to spatial aspects of the task, while haptic cues are thought more suitable for conveying timing information [75, 76]. Auditory feedback can be employed to emphasize small kinematic errors, which are not visible due to limited resolution of video feedback. Also, sound is very suitable to display velocity-related information [73]. It has been hypothesized that the optimal feedback is different for upper limb (visual) and lower limb (haptic) motor tasks [66]. Variables such as the site or size of the brain lesion, the patient's motivation during therapy, and his/her cognitive ability may also influence the effectiveness of biofeedback or any therapy [63]. It is important that the feedback is neither overloading nor distracting, since distraction reduces effort [71]. Moreover, it is important to consider the transfer from exercise to real life, and not only the short-term effects of feedback training. Patients are capable of learning motor tasks in a virtual environment and the acquired skills can be transferred to real life [42, 70], but it may be important to fade the feedback or to provide it more intermittently to prevent the subjects to rely on it [71]. Healthy subjects performing motor-learning tasks showed improved retention if the feedback was given at the end of the task or if no-feedback trials were included during the learning phase [72].

3.1.2 Implications of Biofeedback for Rehabilitation Robotic Therapy Design

Robotic therapy devices are particularly suitable to deliver augmented feedback since they are equipped with sensors, as well as visual, audio, and haptic display capabilities. Further, augmented feedback is highly recommended in robotic therapy because, unlike in traditional therapy, the psychological, relational, verbal, and touch contact between therapist and patient is missing. This lack creates the need for additional channels to provide feedback on the performance and to improve the patient's motivation. However, although many interesting studies have paved the way for a more systematic use of biofeedback in robotic rehabilitation as summarized above, evidence on the best paradigm remains to be established.

Feedback training for the upper limbs has in general an added value to conventional therapy in stroke rehabilitation but its optimal characteristics have not been determined yet [62, 77]. VR exercises with a robotic device could engage the participants for a longer period leading to potentially better therapeutic outcomes [78]. Several studies showed the benefits of robotic devices for upper-limb training that make use of VR and feedback [26] but further studies are needed to prove the benefits attributed to augmented feedback itself.

In lower-limb training, augmented feedback was found superior both to conventional therapy and to therapist's feedback, and these benefits were maintained also long term [79]. Visual feedback enhanced active participation in robotic therapy [42, 69, 80]. Positive effects on gait parameters were found after feedback training [42, 81] but the lack of systematic studies prevents drawing definitive conclusions.

In summary, then, augmented feedback during robotic therapy appears at minimum to increase motivation, thus leading potentially to better therapeutic outcomes. Nevertheless, evidence on short- and long-term effects of training with augmented feedback and on the optimal feedback modality for different patient populations is incomplete.

3.2 Hebbian Learning

3.2.1 Evidence for the Importance of Hebbian Learning

As stated in the Introduction, the objective of any neurorehabilitation system is to exploit neuroplasticity and motor learning, involving the patient in an intervention that recreates the favorable conditions that can induce the modification of the residual neural networks of the brain. Donald Hebb introduced in 1949 a fundamental concept of how residual networks are modified, which is that *cells that fire together, wire together*. This statement summarizes the increase of synaptic connection between neurons that is produced by their simultaneous activation [82]. Further research has shown that this important mechanism of neuroplasticity involves not only synaptic potentiation, but also structural changes, like axon sprouting and the formation and stabilization of new dendritic spines [83].

Recent work has shown that Hebb's rule can be used to artificially induce neuroplasticity, modifying a neural network by imposing coactivation firing patterns on target neurons that an experimenter wishes to wire together [83, 84]. It has been suggested that this paradigm could be used as a treatment to shift the function of a destroyed area of the brain to another area that can adapt to perform the new function [85]. A similar idea can be applied to the most common robotic therapy paradigm, which is to have the robotic device assist patients in completing target movements. In this paradigm, the patient attempts to move, causing efferent activity. Then, the robot assists, causing time-correlated afferent activity. The convergence of the afferent activity with the efferent activity in residual sensory motor centers would then be expected to cause plasticity in those centers via Hebbian learning. Note that in this scenario, the robot actually enhances afferent activity, since the patient is weak and impaired and cannot move well without the robot. This robot-enhanced afferent activity may in turn enhance Hebbian learning. To our knowledge, however, this rationale has not yet been experimentally verified in robotic therapy.

Hebbian learning is also the underlying rationale of two widely-used neurorehabilitation paradigms: motor imagery and movement observation. These paradigms have direct relevance for robotic therapy, and so we summarize them briefly here.

Motor imagery is a key application of Hebb's rule to neurorehabilitation, and consists of activating with imaginary movements the areas of the brain that are involved in movement preparation and execution. The effects of motor imagery have been widely stablished as a training method for athletes, and its impact on neurological patients has been studied for the past decades [86], including studies with stroke patients [87], incomplete spinal-cord patients [88], and children with cerebral palsy [89].

The studies that are centered in neurophysiology suggest that the brain responses to movement imagination and execution seem to have the same duration; however, the amplitude of the responses suggests that imaginary movements produce a weaker degree of activation of the central nervous system [90, 91]. Furthermore, not all subjects (particularly stroke subjects) are able to focus intensively and for long periods when imagining a movement; this inability has been termed chaotic motor imagery [90, 91]. Recent studies are also proposing ways of quantitatively assessing the degree of effective motor imagery performance, measured as a suppression of the sensorimotor rhythm [92].

Finally, the application of movement observation to robotics has primarily been in the use of mechanical guidance to teach patients how to perform a movement. We refer the reader to the section on haptic guidance for further discussion.

3.2.2 Implications of Hebbian Learning for Rehabilitation Robotic Therapy Design

If robotic assistance indeed stimulates afferent activity that in turn promotes Hebbian learning, this would provide a rational framework for the design of robotic therapy devices, since the devices could then be explicitly designed to promote activity parameters optimal for Hebbian learning. Thus, a major research direction for robotic therapy research should be to determine the role of Hebbian learning in the therapeutic effects seen with active assistive robotic therapy.

The design of robotic therapy devices could also potentially benefit from incorporating ideas from other rehabilitation techniques inspired by Hebbian learning. For example, the mental imagery of a motor task can be the input of a Brain-Computer Interface (BCI) that commands the robot, fully integrating the patient into his rehabilitation [87]. This goal-oriented setup guarantees that the patient focuses on producing the motor task, which presumably will increase neuroplasticity and enhance motor recovery [87]. Many studies have already shown the feasibility of BCI in the control of external devices [93]. BCI techniques have also been shown capable of classifying imaged grasping movements of the paralyzed hand of stroke subjects [94]. With respect to incorporation of BCI into robotic therapy, Ang et al. recently conducted a randomized controlled trial with 21 hemiplegic stroke patients that commanded hand opening and closing actions to a haptic knob robot for arm rehabilitation [95]. Before the study, the patients who underwent the robot-assisted rehabilitation were screened for their ability to operate the BCI, and after 6 weeks, they significantly improved motor recovery with respect to control subjects. Likewise, priming brain activity with a BCI-controlled robotic therapy device before rehabilitation therapy improved the patient outcomes, for individuals with severe impairment after stroke [96].

Another approach to exploit Hebbian learning in robotic therapy is through Neuromuscular Electrical Stimulation (NMES), which has already been shown to reinforce neuron synapses and enhance motor relearning when combined with simultaneous voluntary effort [97]. NMES and robots have been traditionally used separately for rehabilitation of neurological patients, but the disadvantages of each might be mitigated by combining them [98, 99]. For instance, the robot normally uses an externally applied torque to produce movement on the limb, whereas NMES activates the muscle to generate the force; on the other hand, NMES applications usually have difficulties at controlling the speed, trajectory and smoothness of the movement, which could be mitigated with a robotic device [98]. An EMG-driven robot system combined with NMES was recently proposed for wrist training after stroke [98], and was tested on five subjects. Results showed that the robot assistance improved movement accuracy, whereas NMES reduced the excessive muscular activations of the elbow joint.

3.3 Reinforcement Learning

3.3.1 Evidence for Importance of Reinforcement Learning

Reinforcement learning is a type of biological learning [100], which has also inspired extensive work in machine learning approaches [101]. The key idea is that the learning agent measures a parameter associated with reward that results from its actions, then changes its actions in order to find the optimal policy that maximizes the estimates of future cumulative rewards. A reinforcement-learning system must therefore solve a credit-assignment problem, which is to determine how to adjust many internal parameters (e.g. neural connection strengths in a biological system) based on a scalar measure of reward produced by its actions. It must also balance *exploitation* of what it already knows with the *exploration* of new actions that might improve the policy in the future. Reinforcement learning in biological movement control has been strongly tied to the dopaminergic system [100].

Reinforcement learning has recently been used in computational neuroscience as a way to model the mechanisms of rehabilitation therapy. Han et al. used reinforcement learning to model the learned non-use typical of stroke subjects, suggesting from this model that upper-limb rehabilitation must aim not only at improving motor control of the paretic limb, but also at reaching the point where the patient spontaneously uses the weakened limb on his daily life. Otherwise, it is just a matter of time until the paretic limb goes back to the initial deteriorated point [102]. Reinforcement learning was also recently used to model the recovery of movement strength in stroke patients, obtaining results that mimic the strength-recovery curve, residual capacity, and the influence of therapy timing and impairment level on the recovered strength [103].

3.3.2 Implications of Reinforcement Learning for Rehabilitation Robotic Therapy Design

Reinforcement learning is important for rehabilitation robotic design in two key ways. First, a full understanding of how the motor system uses reward-based teaching signals will open new ways to improve the design of robotic therapy after stroke.

For example, the study by Han et al. suggests that robotic exoskeletons that are worn throughout the day might help a patient by encouraging spontaneous use of the weakened limb, resulting in a self-training, therapeutic effect. At the minimum, a recent study highlights the importance of considering reward in robotic therapy design. Ten chronic stroke patients underwent a clinical pilot study of nine sessions, where they trained ankle plantar- and dorsi-flexion with an impedance-controlled ankle robot [104]. The subjects were divided in two groups, receiving either high or low reward. The enhanced rewards were in the form of game scores, positive social interaction, and monetary rewards. The group with high reward had significantly faster learning curves, smoother movements, reduced contralesional-frontoparietal coherence, and reduced left-temporal spectral power, with respect to the low-reward group. Additionally, only the high-reward group increased the non-paretic step length.

In targeting reinforcement during robotic therapy, there are some factors to consider. Reward can be considered to be a scalar biofeedback that assists the patient in improving his performance, and increases motivation. However, use of a scalar reward might lead to negative compensatory movements that undermine motor relearning [105]. Indeed, as proposed by Kitago et al., a stroke patient who wants to reach an object will obtain the same reward whether he does it with his arm or by leaning with his trunk [105]. Therefore, the robot-enhanced reinforcement learning protocol must be carefully defined if compensation is not the goal. Another factor is that a scalar reward might discourage subjects when they cannot achieve the target on the first trials. To solve this problem, Sans-Muntadas et al. developed a system that measured the subjects' execution with respect to their best performance, adapting the reward levels to the real abilities of the subject [106]. This algorithm was tested on 21 healthy subjects that simulated impairment, and was reported to provide a motivating workspace where virtually-impaired subjects could relearn how to move an impaired limb without feeling discouraged by the process. However, the a reward also reduced the subject's willingness to explore other motor tasks, which would over time slow the learning process.

A second way that reinforcement learning is relevant to robotic therapy devices is that such devices can use reinforcement learning approaches for their control systems, to create adaptive controllers that change according to the users' needs. The use of reinforcement learning is particularly useful when the policy must be learned from maximizing a simple reward signal, which in robotic therapy could be the amount of patient learning from trial to trial or a measure of effort, for example. A controller based on reinforcement-learning algorithms successfully controlled a robotic arm during a double-target reaching task with two monkeys using a body-machine interface [107], which has the potential to become an upper-limb rehabilitation treatment. The controller used binary feedback with information about the previous robot performance (good/bad) to quickly learn to control the robot, providing a stable control through several sessions and robustly adapting to perturbations of the neural inputs. Tamei et al. also used a reinforcement learning algorithm to guarantee stable control of a robot that based its decisions on EMG signals, modelling the scenario as a Markov decision process where the learning agent and the human shared the same goal [108].

4 Human-Machine Interaction and Robotic Therapy Design

4.1 Haptic Guidance

4.1.1 Evidence of the Importance of Haptic Guidance

In motor rehabilitation, the demonstration of the correct movement trajectory is often addressed by manually moving the patient's limbs as the patient attempts to move. This "active-assist" technique is thought to support motor learning by means of demonstrating the task and providing a feeling of the correct movement [22], and perhaps by stimulating Hebbian learning (see section above). In human-robot interaction, this strategy is termed "haptic guidance". In this context, a robot moves the user's limbs through a correct kinematic pattern in order to reduce errors and, in some applications such as gait training or surgery, to enhance safety during practice. Furthermore, haptic guidance has the capacity to deliver more movement repetitions than conventional training protocols [109].

With healthy subjects, several studies have studied learning a novel arm movement with and without haptic guidance (e.g. [76, 110]). Haptic guidance increased especially timing accuracy of the learned movement. Recently, a study showed that haptic guidance in combination with interspersed free trials was able to shape the movement pattern of a novel complex sport-specific motor task, and these changes persisted after seven days without any further training [111]. Therefore, there is potential for the use of haptic guidance in teaching generic movement trajectories.

However, a number of studies have found that physically guiding a movement may actually decrease motor learning for some tasks. This phenomenon relates to the "guidance hypothesis" [53], which is that guiding a movement may reduce the burden on the learner's motor system to discover the principles necessary to perform the task successfully. The dynamics of movement are also fundamentally different when a human or machine trainer guides limbs. Thus, training with haptic guidance is paradoxical: it may be helpful for reducing performance errors during training, but the experienced task is dynamically different from the actual one to be learned, and this may impair learning [112].

4.1.2 Implications of Haptic Guidance for Rehabilitation Robot Therapy Design

Haptic guidance in robotic therapy may be beneficial for the reasons outlined above – providing a feel for the movement, especially timing, increasing safety, and perhaps stimulating Hebbian learning. However, there is also some evidence in rehabilitation robotics that haptic guidance can be less effective than conventional training. For instance, patients with motor incomplete spinal cord injury who walked in a gait training robot that was controlled with an impedance-based assistive controller consumed 60 % less energy than in traditional manually-assisted therapy [48].

Likewise, stroke patients who were assisted by an adaptively-controlled, compliant robot that had the potential to "take over" a reaching task for them decreased their own force output, letting the robot do more of the work of lifting their arm [113].
In summary, the benefits and pitfalls of haptic guidance for rehabilitation robotic therapy are still under debate [53, 112, 114]. Most robotic therapy systems that have undergone clinical testing have used robotic guidance, and have shown benefits for improving motor recovery of the arm following acute and chronic stroke [2, 3]. However, it is not clear whether haptic guidance in rehabilitation is better than conventional rehabilitation treatments or just provides an alternative treatment possibility [72]. It will be desirable in this area to achieve consensus about appropriate outcome measures in order to quantify the motor re-learning benefits of haptic guidance [115].

4.2 Error Augmentation

4.2.1 Evidence for Importance of Error Augmentation

Another strategy used to enhance motor learning with robotic devices is error augmentation, which derives from the fact that many forms of learning are error-driven processes. By artificially increasing performance error in the course of learning, it has been hypothesized that the motor system could be driven in a way that makes it adapt more completely [114, 116]. This section briefly discusses error augmentation strategies, including resistive exercise, error amplification, and noise force disturbance.
Resistive exercise refers to the therapeutic strategy of providing resistance to the participant's hemiparetic limb movements during exercise. There is a reasonable amount of evidence now from multiple non-robotic studies stating that resistive exercises that require higher effort from the impaired limb can indeed help stroke subjects improve motor function [53]. An alternative control strategy is to apply a performance-based resistance that amplifies error, based on subjects' online performance.
A recent study assessed whether amplification of error or haptic guidance induced more motor learning, during a timing-based task with health subjects [117]. Both training conditions promoted learning. However, when dividing subjects based on their skill level, error-amplification training benefited learning more for the skilled subjects while it seemed that haptic-guidance training was more effective for the less skilled subjects. It appears that this result supports the challenge point theory, proposed by Guadagnoli et al. [45], which speculated that greater learning is achieved when an optimal challenge is provided to the individuals based on their skill level. The optimal level of challenge can determined from the ability of the performer, the complexity of the task, and the conditions of practice.
Kao et al. recently investigated whether performance-based robotic training using an error-augmentation algorithm better facilitated short-term changes of a typical gait pattern in healthy individuals compared to robotic training employing an error-reduction algorithm [118]. In the results, neurologically intact subjects were able to

walk with stepping patterns closer to a prescribed template that required a higher than normal step height. Matching the target template was substantially better in persons receiving error-augmenting forces compared to error-reducing forces.

Another approach to error amplification is noise disturbance, i.e., randomly-varying feedforward forces that disturb subjects' movements during training. A published study reported that training with noise disturbance resulted in better tracking than unassisted training and than training with a more conventional error-amplification strategy (repulsive forces proportional to tracking errors) [119]. In a more recent study, experiments under different training modes were performed, including exercises with haptic guidance, without guidance, with error amplification (repulsive forces proportional to errors), and in noise-force disturbance mode (with a randomly varying force disturbance added to the no haptic guidance mode) [120]. Moreover, adding random force disturbances during training appeared to increase attention, and therefore improve motor learning. Another recent study with robotic training of virtual golf putting found that error augmentation can decrease motivation for training, in a way that persists days after the experience of the error augmentation [121].

4.2.2 Implications of Error Augmentation for Rehabilitation Robot Therapy Design

Patton et al. explored the features of motor adaptation in chronic stroke survivors during the execution of planar multi-joint movements that are disturbed by a force field (forces as a function of hand position and/or hand velocity) [114]. They found that enhancing trajectory errors by the use of force fields induced better learning compared to reducing trajectory errors (haptic guidance) or providing no force field, in individuals with stroke. Using a similar paradigm, another study also suggested that a two-week training program of error enhancing trajectory seemed to provide the most benefit to the least impaired individuals, whereas active assistance during target reaching tended to be more helpful for the most impaired individuals [122]. Training with error augmentation was recently shown in a randomized controlled trial to produce better motor outcomes in chronic stroke patients than training without error augmentation [123].

In summary, error augmentation is a promising strategy for inducing a therapeutic response in robotic therapy. More research is needed to determine under what conditions error augmentation is appropriate, and for what kind of patients.

4.3 Motivation

4.3.1 Evidence for Importance of Motivation

Motivation can be defined as the "forces acting on or within a person to initiate a behavior" [124]. Patient "engagement" is a construct that is driven by a patient's motivation; in motor rehabilitation it is the effort to regain movement capabilities executed through active, effortful participation during therapy [125] resulting in increased physical activation. Motivation can be regarded as intrinsic if it comes from doing an activity for its inherent satisfactions rather than for some separable consequence, or as extrinsic if, on the contrary, the activity is done in order to attain some separable outcome [126]. In motor rehabilitation, patients already have a personal, extrinsic motivation to regain their movement capabilities. This motivation could, however, further be increased by turning boring, repetitive training into enjoyable and entertaining therapy sessions [127].

Motivation is a multifaceted concept, which has been shown to be linked to features inherent to the prescribed regimen, personality traits of the patient, physician, and therapist, and characteristics of the broader social environment [128]. Important factors that have a role in improving motivation are: setting rehabilitation goals that are perceived as relevant by the patient, providing information about rehabilitation, and accessing and using the patient's cultural norms [128].

Rehabilitation professionals have long suspected that a patient's motivation plays an important role in determining the outcome of a therapy. Indeed, motivation is recognized to be one of the critical modulators of neuroplasticity, together with salience and attention [129]. In particular, dopamine production favors plasticity of the brain and it is enhanced by performing enjoyable training, such as game-like exercises [130]. Furthermore, a high degree of motivation leads to an active behavior during the training. Active training is more effective than passive training, leading to better motor outcomes and higher degrees of activation at the cortical level [131, 132]. Motivating exercises potentially also allow patients to perform longer training with more repetitions, therefore increasing therapy dosage. Thus, motivation, acts on three different levels: it can modulate neuroplasticity, it can elicit more intense motor effort (e.g. development of higher muscular forces during training) and it potentially results in longer training time.

4.3.2 Implications of Motivation in Rehabilitation Robotics Therapy Design

Enhancing motivation is particularly relevant in rehabilitation robotics, where there is a possibility that the patient might "slack" due to the assistance provided by the device [53]. In order to prevent this behavior different strategies have been proposed. One consists in the use of an assist-as-needed controller with a forgetting term that constantly tries to reduce the assistance provided by the device in order to challenge the patient [53]. In this way the patient is "forced" to be active because he cannot rely on the guidance of the device. Another essential approach to enhancing motivation is the use of game-like feedback and virtual reality to provide a more entertaining environment for the therapy.

Making sure robotic therapy devices are motivating is particularly important for children involved in robotic rehabilitation programs: diversification, fun and motivation are essential because children are generally not able to find enough "extrinsic" motivation in a boring and repetive training task [69, 133]. As also discussed in Sect. 3.1, studies that compared conditions with virtual-reality feedback or game-like exercises found better outcomes when the subjects were actively involved in the training and motivated by the additional feedback [42, 62, 78].

Interestingly, patients seem to enjoy particularly training with robotic devices and this high acceptance can enhance even more the efficacy of robot-based training strategies. In particular, it must be considered that robots allow patients with very severe impairments to perform movements that otherwise would be unattainable, leading to a strong positive feeling that could potentially affect the therapy outcomes. Finally, the development of sensitive and valid assessment tools for motor recovery that can be implemented in robots [134] are important to promote motivation in patients, so that they can be more aware of the effects of a therapy and increase their motivation.

5 Conclusions

Robot-assisted rehabilitation is a relatively new type of intervention for motor recovery, introducing benefits such as the possibility of the patient working semi-autonomously during training, and giving the patient and the therapist quantitative measurements of performance improvements. The first generation of robots has already provided hints of the potential benefits these devices can generate in the rehabilitation of movement after neurological impairment. Optimizing these benefits will require a thorough consideration of the mechanisms of motor recovery triggered by robotic therapy, as we have argued in this chapter.

We reviewed nine recovery mechanisms related to the parameters of the therapeutic experience (therapy dosage, task specificity, and challenge level); types of motor learning (learning from augmented feedback, Hebbian learning, and reinforcement learning); and approaches to human-machine interaction (haptic guidance, error augmentation, and machine-enhanced motivation). Based on this evidence, it seems clear that robotic-therapy devices will be most effective if they are designed to promote high levels of therapy dosage, optimal challenge, and high levels of motivation. For example, a positive loop can be established in which biofeedback from biomechanical data recorded through the robot sensors is used to enhance the motivation and involvement of the patient, therefore increasing the intensity of the training and the number of repetitions. Robot-aided rehabilitation has great potential for increasing patient's motivation: virtual-reality games can be easily implemented in a robotic setting, sensors can be used to assess the patient's performance, and the games can feed back the information to them. At the same time, robots can guarantee an intensive training since they are able to take over the physical demand required to the therapists in conventional physical rehabilitation. The level of challenge can be automatically adapted by the control algorithm of the robotic device to constantly match the patient's status.

On the other hand, the role of task specificity in robotic therapy training is less clear. Recent studies have challenged the hypothesis that task-related training is undoubtedly superior to other kinds of training [25, 41] and further research will lead to the formation and consolidation of a stronger rationale behind the concept and design of future rehabilitation robots. Either way, in rehabilitation robotics there is the possibility to combine single and multi-joint or task-related training.
With respect to learning mechanisms, reinforcement-learning techniques are a promising direction for further research, either by providing faithful mathematical models that prescribe how to enhance motor recovery using new rehabilitation paradigms, or by customizing human-machine interfaces based on key outcome measures that can be sensed in real time. Understanding the role of Hebbian learning in robotic therapy is also a key direction for further investigation.
Finally, with respect to human-machine interaction, haptic guidance is a promising technique, but with some caveats, such as the potential to produce slacking by the patient. At the least, it can be used to enhance safety of tasks such as walking; it may also enhance motivation. Error-augmentation techniques are an exciting direction for future research, as they could be incorporated into a wide variety of robotic therapeutic exercises by exploiting the robot's ability to sense a variable of interest and then to provide an action that augments the error under consideration.
Further research should provide a quantitative assessment of the relative importance of these recovery mechanisms in a short- and long-term time span and. an evaluation of the outcomes that might come from their combination. Such evidence will promote the optimal design for novel rehabilitation robots.

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Motor Control and Learning Theories

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1 Introduction

Patients who have suffered impairment of their neuromotor abilities due to a disease or accident have to relearn to control their bodies. For example, after stroke the ability to coordinate the movements of the upper limb in order to reach and grasp an object could be severely damaged. Or in the case of amputees, the functional ability is completely lost. Early rehabilitation interventions are aimed to help patients reduce the impairment's impact on their lives, and help them recover in a way that allows them to regain some ability and independence during activities of daily living. It is highly recognized that a rehabilitation intervention should be well-guided, well-focused, and repetitive. This is in a way the same kind of strategy used when learning a new skill, such as playing an instrument or a sport.

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This is why it is important for people working in rehabilitation to study and understand the mechanisms of human motor control and learning. This knowledge have helped to shape current rehabilitation methods, as well as to develop technologies and machines that assist impaired people to improve their quality of life and integrate faster into society.

Understanding motor control and learning even for a simple movement (e.g., reaching for a glass) is a very big endeavor due to the many variables that comes into play. David Marr [80] identified three levels of abstraction that could be used for the study of motor control [97]. Certainly, these levels are not independent from each other, but they could used to organize all the vast amount of details that have to be taken into account in motor control and learning.

The first level is the *computational theory level*, which relates to an abstract description of what the systems is supposed to achieve and why, and that results in operations defined only by the constrains that need to be satisfied. Therefore, this level could be regarded as a mathematical formulation of the movement plan, and it should take into account the different variables, restrictions, difficulties, and outcomes that would arise when the movement has started. The second level is the *algorithmic level*, which describes the behavioral and cognitive states that are used in real time during the movement. In order words, it specifies how the first level would be accomplished. There are often several possible algorithms that can be used to achieve a desired movement and the choice will depend on the characteristics of each algorithm. For example, a person could decide to grasp a cup from different angles (e.g., from the top or from the side) depending on his initial posture or the state of the cup (e.g., fill or empty). The algorithm could even change once the movement has started due to novel states (e.g., external perturbation or obstacles). The final level is the *implementation level*, which describes how algorithms are physically implemented (e.g., by contracting muscles or using a prosthetic hand).

In this chapter, we would like to present a general overview of the computation and the algorithmic levels by discussing the most relevant motor control and learning theories that have been put forward in recent years. Furthermore, we would like to discuss how these theories are currently being applied on rehabilitation technologies.

The chapter is divided into two different parts. The first will provide a general overview of relevant and recent theories of motor control and learning. On the second part of the chapter, we will describe two practical applications that make use of this theories in order to improve the control and development of neuroprostheses and hand prostheses rehabilitation.

2 Theories of Motor Control

Imagine that in a sunny day you are thirsty, and you decide to drink a glass of water. Although you are able to perform this action relatively easily, a variety of challenges have to be takled in order to accomplish the required task. Which muscle contractions will allow you to reach the glass, grasp it and bring it to the mouth, eventually satisfying your thirst? How does your central nervous system (CNS) compute this solution? These and other similar questions have been arousing scientists' curiosity for centuries, who have proposed several theories to explain the control of coordinated movements. This section provides a general overview of these works.

There are several issues that make the generation of movements a very difficult problem. First of all, the musculoskeletal system is inherently redundant. Each point in space can be reached with many different joint configurations. Similarly, joint torques can be obtained by an infinity of muscle forces, which in turn can be generated by several muscle activation patterns. Redundancy allows us to perform motor tasks flexibly and robustly; however, it rises the question on how motor commands are selected. The question of how the CNS "chooses" among all the possible solutions to a motor task is a long standing riddle in motor neuroscience, referred to as the "redundancy problem" or "Bernstein problem" [11]. Second, our sensing and motor systems are corrupted by noise [30]. This feature, along with the unpredictability of the environment, add uncertainty to our perception of the world and to the result of our actions. Moreover, neural pathways introduce delays. Hence, sensory information carries past information, and motor command will be executed in the future. How does the CNS account for these delays in order to, for example, react to a sudden change of the world? Finally, the nonlinearities of the neuromusculoskeletal system have to be taken into account for effective motor planing and execution.

2.1 Optimal Control

Theoretically, redundancy enables to perform the same action in very different ways. Yet experimental observations have shown that individuals seem to employ the same strategy to solve a given task, i.e., movement features are shared across subjects. As an example, during simple point-to-point reaching movements hand trajectories appear consistently straight and characterized by bell-shaped velocity profiles, independently of movement direction and amplitude [84]. The fundamental principle underlying this phenomenon is unknown; however, a largely accepted idea in the scientific community is that movements are selected because they optimize certain aspects of behavior [115]. This view allows scientists to explain similarity across subjects in terms of fundamental principles, but it poses the challenge of identifying the behavioral aspect that is actually optimized. The main criticism to this approach is indeed that it might always be possible to find an optimization criteria that explains the behavior at hand.

To interpret motor skills in terms of optimization principles, it is necessary to model the body, and to propose a cost function to be minimized. The model represents the evolution of the body variables (e.g., joint angles, end-effector position, muscle kinematic) as a function of the state and the motor commands (e.g., joint torques, muscle force, muscle activation); the cost function formalizes the behavioral aspect that is hypothetically minimized. The idea is to find the *control policy* (i.e., a mapping between time or state of the body to motor commands) that leads to a successful completion of a desired motor task, and that minimizes the cost function. If simulations of the model under the computed control policy approximate the movements experimentally observed, then it is suggested that the CNS selects such movements because they minimize the proposed cost.

A variety of cost functions have been proposed as models of movements selection processes. Initially, to explain the kinematic regularities observed by Morasso [84], Flash and Hogan [38] theorized the so-called *minimum jerk model*, where the square of the third derivative of the end-effector position (i.e., jerk) is minimized, obtaining straight trajectories and bell-shaped velocity profiles. Later, scientists have started to focus on dynamical aspects of the motor system. Uno et al. [119] proposed that the rate of change (with respect to time) of joint torque was minimized instead of the third derivative of end-effector position. Since these variables are related by an nonlinear mapping, these cost functions render different solutions. More recently different research groups formalized a model based on minimizing the squared motor commands [25, 60, 116]. This measure does not reflect energy consumption, instead it should be viewed as an abstract notion of "effort" [50]. One of the criticisms to all these models has been that they do not include the inherent noise of the sensory-motor systems. A fundamental characteristic of motor noise is that its standard deviation scales with the amplitude of motor commands, i.e., signal-dependent noise [62]. To take this observation into account, Harris and Wolpert [53] proposed that the process of motor planning minimizes endpoint variance, hence maximizing movement accuracy. The minimum endpoint variance model was able to predict eye and arm movements [53, 54]; however, it was less accurate than the minimum effort model in predicting the distribution of forces generated by each finger to produce a total desired force goal [89].

2.2 Optimal Feedback Control

The optimality models described so far provide control policies that do not react to execution errors. In mathematical terms, they are functions of time only (i.e., feedforward). On the other hands, we are able to adjust our movements at the occurrence of unexpected events. One possibility to address this limitation could be to introduce a fast feedback loop that, upon disturbances, tries to push the state of the system to a previously planned desired trajectory. However, this strategy is very inflexible (as it assumes a single strategy to solve a motor task, i.e., the planned trajectory), and it might lead to suboptimal solutions (for example, it could increase the effort to solve a task). A less trivial possibility is provided by the framework of optimal feedback control [12, 103, 116]. An optimal feedback control law is a policy that minimizes a given cost function, and specifies the optimal motor command for each state of the body and time of execution. In the field of motor neuroscience, many researchers have proposed a cost function that takes into account task accuracy and effort [116]. As a results, the controller reacts to perturbations that are task-relevant and ignores deviations of task-unrelated variables, as opposed to following a preplanned trajectory.

This strategy is also referred to as minimum intervention principle [75]. These predictions are confirmed by several experimental observations [25, 40, 49]. However, optimal control theories have recently been challenged by novel results that suggest a habitual rather than optimal execution of motor tasks [24, 77].

2.3 Internal Models

One of the assumptions of optimal feedback control models is that precise sensory information is instantly available. This assumption is unrealistic, because noise as well as delays affect the sensory-motor system. To overcome this issue, it has been proposed that the CNS computes online estimates of the current sensory information by taking into account previous motor commands and (out-of-date) sensory readings. This is hypothetically achieved by means of two mechanisms: forward models and sensory integration.

Forward models are computational entities that instantiate models of the neuromuscular system and the environment, and predict the sensory consequences of motor commands. The brain could then take decisions based on such predictions (hence used as fast feedback loops) without having to wait for the actual delayed sensory readings. The idea that the CNS employs such a mechanism has been initially proposed to explain how the brain corrects movements that are executed so quickly that sensory feedback cannot be used, i.e., saccadic eye movements [106]. Recently, Xu-Wilson et al. [126] have shown that, unlike healthy subjects, patients with cerebellar damages cannot compensate the variability of motor commands in saccades. Since there is an evidence that forward models are implemented in the cerebellum [90], this results suggest that healthy people employ forward models to predict the consequences of saccadic motor commands and readily correct predicted errors.

Internal models have been investigated also in movements affected by long-latency sensory feedback. To this end, the classical experimental paradigm consisted in applying force disturbances by means of a robotic device [105]. The authors of these studies observed that after an adaptation period, subjects were able to compensate for the applied disturbance, and concluded that internal models were continuously updated in order to predict the sensory consequences of the motor commands in the altered environment (see Sect. 3). Flanagan et al. [36] arrived to similar conclusions by showing that subjects were able to predict grip forces during object manipulation [35, 37]. Ariff et al. [5] observed that saccades anticipated the final position of the hand during reaching movements without visual feedback in healthy people. If the arm movement was perturbed by an external force field (i.e., changing the dynamics of the environment), subjects were initially not able to predict the final hand location, but they regained this capability after learning. The authors of this work concluded that saccades rely on predictions, and that the internal forward model can be adapted to account for changes in the environment [88]. Miall et al. [83] showed that perturbations on the cerebellum by transcranial magnetic stimulation (TMS) pulses during arm movements led to delayed estimate of the position of the limb.

The elements required by the CNS to compute forward sensory predictions are the motor commands and an estimate of the current body state. It is hypothesized that the CNS keeps a copy of the descending motor signals, called efference copy. Estimating the current body state involves the integration of various sensory modalities, which might carry different noisy information. This process has been explained with the framework of Bayesian integration. In this context, previous sensory predictions are used to compute a *prior* probability of the current state, which is then combined to the actual sensory information, obtaining a *posterior* probability. The latter represents the current belief about state of the body and the environment. These ideas have been tested experimentally by assessing the capability of human subjects to estimate positions [67], forces [66], and velocities [112] using sensory information currupted by noise.

Optimal feedback control, internal models, and Bayesian integration can been assembled in a unified computational framework, depicted in Fig. 1, that arguably represents the most comprehensive view of motor control [104].

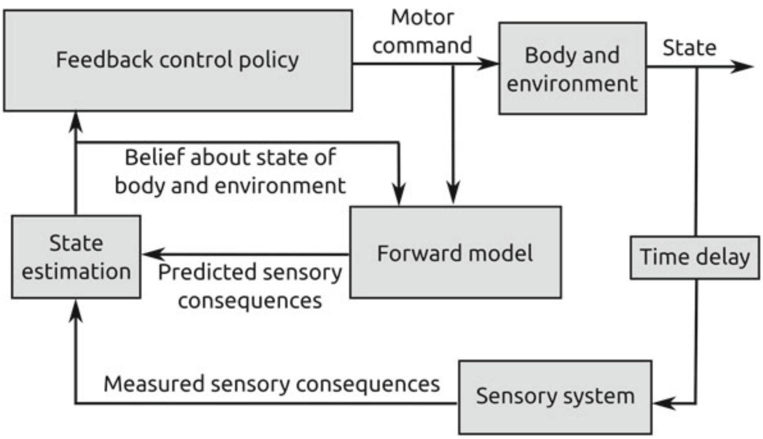

Fig. 1 A *unified view* of motor control theories. Motor commands are generated according to an optimal feedback control policy, which embeds the requirements of the task. Body and environment react to these commands, and move to a different state. The sensory system measures the new state but, due to time delays in the neural pathways, it provides "out-of-date" measurements. Optimal feedback control, however, needs updated, rather than delayed, feedback information in order to generate optimal motor commands. Such an updated information is provided by a fast-state estimator, which integrates the sensory measurements (that possibly arrive from a variety of sensory streams) with a prediction of the sensory consequences of motor commands; hypothetically, this integration is performed according to the Bayessian framework. Predicted sensory consequences are generated by a forward model. This scheme has been adapted with permission from Shadmehr and Krakauer [104]

2.4 Equilibrium Point Hypothesis

An alternative to the models discussed so far is the so-called equilibrium point hypothesis (EPH) [32, 33]. This hypothesis assumes that the CNS controls body parameters rather than variables directly related to the task, and that movements emerge from the physical interaction between the appropriately tuned body dynamics and the environment. In particular, it is hypothesized that descending motor commands adjust parameters of the tonic stretch reflex in order to produce a desired equilibrium point of the limb [31]. Thus, the EPH exemplifies the main idea of the dynamical pattern theory of motor control, i.e., movements are emergent properties [102, 114].

To understand the EPH it is necessary to spend a few words on its key ingredient, the tonic stretch reflex. This is defined as a sustained muscle contraction in response to slow stretching [72]. When a muscle is slowly stretched by an external load, initially it produces an opposing force due to its passive elastic properties. If the muscle length overcomes a certain threshold, the subsequent activity of muscle spindles leads to the recruitment of a group of motor neurons, which causes the muscle to contract producing an active force that opposes the stretch. This force increases nonlinearly with the amount of stretch. For a given constant load, the muscle stabilizes at a given length called equilibrium point.

In the context of the EPH, the position of a limb results from the equilibrium points of the muscles around its joints. In order to generate voluntary movements, the brain sends descending commands that modify the threshold of the tonic stretch reflex arcs. As a result, new equilibrium positions are defined, and the limb moves accordingly. This idea has a few implications that are worth discussing. First, muscle activation is not directly controlled by descending motor commands, rather it results from the tonic stretch reflex. In other words, for a constant motor command (which defines the threshold of the reflex), different muscle activations as well as limb positions can be obtained depending on the external load. Second, there is no need to estimate the body state to compute appropriate motor commands. Indeed under an assumption of stability, the body will move toward the equilibrium point independently on its initial condition.

The problem of motor coordination is not solved by the EPH. A great number of variables, in this case the parameters of the stretch reflexes across muscles, should be coordinated in order to accomplish the desired task. How does the CNS solve such a redundancy? To this end, the uncontrolled manifold hypothesis (UMH) has been suggested as a general principle of coordination that could be applied at any level of details of the CNS. The idea is that the controller tries to keep the values of a group of task-related "elemental variables" (e.g., joint angles, muscles forces, muscle activations, thresholds of tonic stretch reflexes), named structural unit or synergy, within a subspace corresponding to successful task achievement (the uncontrolled manifold). Thus, the controller does not specify a single task solution (as in the case of optimal control), rather it facilitate variability within the uncontrolled manifold. In principle, this is the same behavior of an optimal feedback controller, which only reacts to deviations on task-related dimensions (see Sect. 2.2). The UMH and the notion of structural units have been used to explain postural control [42, 71, 74, 123] and manipulation [22, 73, 108, 127].

Usually, scientists who support the EPH are rather skeptical about the idea that the CNS learns and use internal models. Instead, they are more inclined to think that no heavy computations are performed, and that movements emerge from the interaction between body and environment. As a matter of fact, however, there is the need for the CNS to compute how to modify the parameters of the tonic stretch reflex in order to accomplish a desired task. Thus, a mapping between motor commands (i.e., reflex thresholds) and output variables (i.e., an internal model) might still be needed.

3 Motor Learning

Humans show a remarkable capacity to learn a variety of motor skills, whether it is adapting to changes in our environment, acquiring new skills, or improving existing skills. A lot of progress has been made on motor learning over the last few decades; however, researchers have a fair understanding of motor learning only of a narrow range of tasks, including simple reaching task in which different types of perturbations are applied. One of the exciting challenges ahead includes bridging the knowledge on simple movements to 'real-world' motor learning, and translating this knowledge to neurorehabilitation paradigms.

Motor learning is a broadly defined term referring to improvement in motor performance through practice [69]. It is believed that motor learning consists of multiple processes, of which motor adaptation and skill acquisition are considered to be the main processes in the literature [64, 69]. Motor adaptation is commonly defined as the response of the motor system to perturbations, such as changes in the environment, to regain a former level of performance in the new, changed environment [106]. Skill acquisition is considered to be a process in which task performance is improved beyond the baseline, mostly in the absence of perturbations. Researchers posit that skill acquisition is manifested by reduced motor variability and achieving higher levels of performance without a reduction of speed [69, 94, 109].

The goal of this section is to provide an overview on motor learning. Note that excellent reviews are already available describing the substantial progress of our understanding of the mechanisms of motor learning over the last decades (e.g., see Refs. [69, 106, 125]). Here, we give a short overview of the most important aspects of these mechanisms as a background for the other sections and chapters of this book.

3.1 Motor Adaptation

Motor adaptation has been investigated extensively using error-based learning paradigms, such as visuomotor rotations or force fields [105, 106]. In these paradigms, participants experience a perturbation resulting in a discrepancy between the predicted

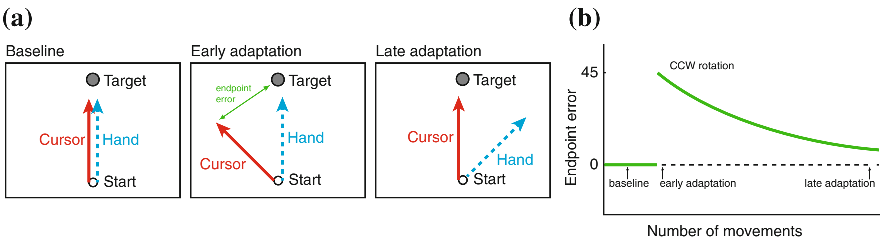

Fig. 2 A visuomotor rotation is a commonly used error-based learning paradigm. **a** Participants are asked to make movements with their hand so that a cursor moved from a starting position to a target. In the baseline condition, hand and cursor movement are congruent. In the adaptation phase, a visual rotation is imposed (45 degrees counterclockwise in this case) on the cursor movement; e.g., when moving the hand straight forward, the cursor would move at an angle. Studies have shown that participants gradually learn to move their hand in a way that compensates for the rotation, such that the cursor moves to the target again. **b** This figures shows a typical adaptation *curve*. When the rotation is introduced, the error at the end of the reaching movement initially is large, followed by a gradual decline of endpoint errors with increasing number of movements. At some point, the movement error is similar to the baseline, indicating that the participant is adapted to the visual rotation. Adapted from [82, 106]

and executed hand trajectories; for instance, due to a perturbation in visual information (visuomotor rotations), or to perturbing forces (force field paradigms) [69, 106], see Fig. 2 for an short description of a visuomotor learning paradigm. Adaptation is the process that reduces the systematic error induced by the perturbation, and it is believed to occur through trial-by-trial adjustments of an internal model (the forward model) that maps motor commands onto predicted sensory outcomes. By doing so, error-based learning keeps movements well calibrated and correct for systematic biases [106].

3.1.1 Error as a Learning Signal

The learning signal driving adaptation in error-based learning is, as the name implies, the error signal between a desired and actual action, as well as the particular way the desired action was missed [106, 125]. The error signal is believed to adapt the motor commands, such that the error decreases in consecutive movements [106]. Wolpert and colleagues reported that in order to adapt to perturbations, the nervous system also estimates the gradient of the error with respect to each motor command component [125]. This means that the motor system needs to have an idea of how components of the motor command attribute to the error, and subsequently how the motor system can reduce the error. Wei and Körding posited that the sensorimotor system might adapt to errors in a nonlinear fashion [124]. They suggested that the sensorimotor system must weigh the information, in this case the error, provided by the uncertainty the information has in the signal. The ideal strategy, they argue, is therefore nonlinear, where small errors are compensated in a linear fashion and large errors would be disregarded. Errors that fall within the expected variance will be adapted for in a fairly linear way, whereas participants showed nonlinear and non-specific adaptation to single trials containing error signals that exceeded expectation [41, 124].

3.1.2 Different Processes of Motor Adaptation

Temporal processes Smith and colleagues [111] proposed a model in which two parallel temporal processes drive motor adaptation: (1) a fast-acting process that learns and forgets quickly and (2) a slow-acting processes that learns and forgets more slowly. This model is able to explain complex features of motor learning such as spontaneous recovery of learning, savings (relearning of a perturbation or skill is faster than the initial learning), anterograde learning (the ability of a previously learned force field task to reduce the learning rate of a different subsequent task) and even patterns of 24-hour retention [61, 110]. More recent studies suggested that additional learning processes also need to be present to fully explain the temporal evolution of motor adaptation. Lee and Schweighofer [76] proposed a model with a single fast process combined with multiple slow processes, that could explain different types of adaptation tasks. An advantage of such a multi-rate learning model is that it can account for different temporal changes of the sensorimotor system, such as fatigue or injury [76, 125].

Model-based and model-free processes It is likely that multiple processes occur during motor learning, which are often classified as model-based learning processes (e.g., adaptation of the internal model) or model-free learning processes (e.g., use-dependent plasticity and reinforcement learning). For instance, studies have shown that several (model-free) processes occur besides error-based learning (adaptation): use-dependent plasticity [28, 56, 121] and reinforcement learning [56].

It has been shown that repeating a movement in a particular direction does not only reduce movement variability, but also creates a bias toward that direction in future movements [121]. This repetition-induced bias has been termed as use-dependent plasticity [69]. A couple of studies showed that when performing a reaching task in a perturbed environment, adaptation and use-dependent plasticity occur simultaneously [28, 56]. Huang and colleagues used a modified visuomotor rotation paradigm to show that participants, when adapting to the visuomotor rotation, create a bias toward the adapted movement direction [56].

In addition, Huang and colleagues [56] hypothesized that, during a visuomotor rotation adaptation task, hitting a target is a form of implicit reward driving a reinforcement process whereby successful error reduction is associated with the motor commands. They also showed that the model-free reinforcement learning process is independent of model-based learning (adaptation). Combining the model-based adaptation process with the reinforcement process leads to faster relearning (i.e., savings).

3.1.3 Structural Learning

Structural learning is a framework to explain the learning-to-learn phenomenom [14, 15]. Structural learning can be considered as learning certain features of a learning task, such that learning of similar tasks is facilitated. Braun and colleagues found support for structural learning by having participants perform reaching movements, during which random visuomotor rotations were imposed. The participants then adapted to a constant visuomotor rotation. They found that being exposed to the random visuomotor rotations facilitated learning in the constant rotation [14]. Braun et al. suggested that training with the random rotations allowed the participants to extract relevant features, or structures, of the task; all tasks were rotations. Structural learning is also consistent within the Bayesian framework, in that it would correspond to learning new prior distributions on the parameters of the perturbation [9, 10, 34].

3.1.4 Neural Correlates of Adaptation

Although the notions of different learning processes are intriguing, it is still not completely known how the brain performs all these hypothesized actions. Evidence suggests that the cerebellum plays an important role in trial-by-trial error-based learning [8, 26, 29, 117]. More specifically, some studies posit that the cerebellum computes the prediction error-driving adaptation [99, 113]. Patients with cerebellar lesions showed substantial impairment in fast adaptation across different tasks [26, 117]. Brain stimulation studies found that enhanced cerebral activity using transcranial direct current stimulation resulted in faster adaptation [44, 47, 100]. Where different types of adaptation are neurally stored remains an open question [125].

3.2 Skill Learning

Whereas in error-based learning, the motor system aims to reduce the error to zero, it does not systematically improve performance beyond baseline, a feature that is considered to be crucial in skill acquisition [82, 94, 109, 125]. Unlike adaptation, skill acquisition is studied for tasks where often no perturbation is present. Although different learning processes, such as reinforcement learning, are likely to play important roles in skill acquisition, they are not as well understood compared to the mechanisms underlying error-based learning.

3.2.1 Reinforcement Learning

To achieve an increase in performance, such as a reduction in error variability, reinforcement learning can help to find a solution to a movement problem. Reinforcement learning is driven by a reward signal; for instance, the information about the relative success and failure of a movement [41, 125]. In contrast to the error signal in error-based learning, a reward signal does not give information about the direction of required behavioral change [125]. Therefore, reinforcement learning tends to be slower than error-based adaptation. However, when a complex sequence of actions is necessary to achieve a goal, reinforcement learning can be used to explain what actions led to success and which led to failure, whereas error-based learning might be less successful.

3.2.2 Speed-Accuracy Trade-Off

Recent research has defined skill acquisition as a shift in the speed-accuracy trade-off function (SAF) [94, 109]. Reis and colleagues argue that defining skill acquisition as a shift in SAF is necessary, otherwise it is not clear how to relate changes in speed and accuracy to a change in skill. For instance, one could reduce execution speed and obtain a higher accuracy by "moving" along the same SAF, which would not reflect a change in skill.

Furthermore, Shmuelof et al. posit that a crucial concept regarding skilled performance is that successful execution and the trajectory kinematics associated with this execution are distinct. This is the case because only the task success is explicitly required, whereas there may be multiple kinematics that reach the desired goal [109]. In an experiment where subjects were instructed to follow a curved path without perturbation using wrist motions, the authors examined changes in the SAF and trajectory kinematics during learning. They found that practicing in restricted speeds led to a global shift of the SAF. Improved performance largely resulted from reduced trial-to-trial variability and increased movement smoothness. The authors propose that motor skill acquisition can be characterized as a slow reduction in movement variability, which is consistent with previous studies [85, 86] but distinct from faster model-based learning, which reduces error in adaptation paradigms.

3.2.3 Skill Learning and Optimality

Optimal feedback control (OFC), as described in Sect. 2.2, could be used to study skill learning [27, 69]. Although OFC has not been used to describe the learning process itself yet, it has been used to explain how we learn to control complex objects with internal degrees of freedom [87], see Fig. 3. For these tasks, there is no simple one-to-one mapping from the hand state to the state of the object (i.e., there are uncontrolled degrees of freedom). During training, participants interacted with the objects and showed improvements in meeting an accuracy criterion even though they had to move faster (i.e., shift in SAF, which is considered to be an improvement in skill). The hand kinematics after training could be described by OFC using a relatively simple cost function. The authors assumed that during training, the participants adapted to the complex dynamics in accordance with a model-based optimization of the cost function [87]. One could speculate that only the model-based

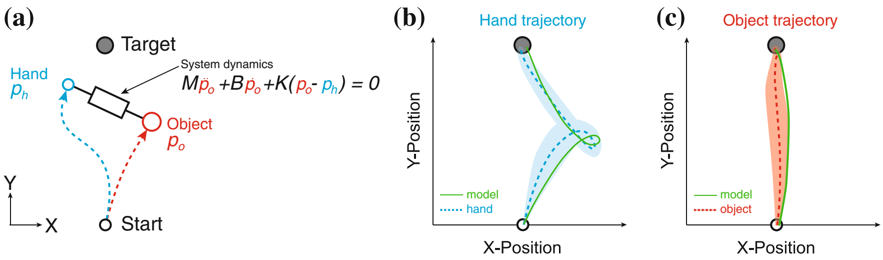

Fig. 3 Optimal feedback control could be used to study motor skill learning. **a**s Schematic representation of the task. Participants were asked to move both their hand and and the object from a start position to a target within a prescribed time window. The hand and object were connected through the complex dynamics of a mass-damper-spring system. **b** The recorded hand trajectory (*blue dashed line*) and simulated hand trajectory (using OFC) are shown for a particular mass-damper-spring system. Note that a relatively complex hand trajectory was necessary to move the hand and object to the target. Nagengast et al. concluded that the simulated hand trajectory fits the measured hand trajectory well. **c** The measured object trajectory and simulated object trajectory describe a relatively *straight line* from the start to the target. As mentioned before, the simulated object trajectory described the measured object trajectory well. Adapted from [87]

optimization part would lead to skill acquisition; however, since the training was not the focus of Nagengast's study, insufficient data were available. Krakauer and Mazzoni suggested that two processes could occur during training, leading to better performance: convergence to the optimal policy, or improved execution of the control itself. Either of these processes could lead to a shift in SAF [69] and to reductions in movement variability [85, 86].

4 Application to Upper Limb Prosthesis Users

"Neurorehabilitation is based on the assumption that motor learning principles can be applied to motor recovery after injury, and that training can lead to permanent improvements in motor function in patients with motor deficits". Considering this statement of [63], the reconstruction of upper limb prosthesis user joint functions appears as a special case of neurorehabilitation.

Amputees have quite different medical history than, for example, stroke survivors. This is because prosthesis users have either lost one or more joints due to an accident, or they have already had received a surgery for reconstruction that unfortunately ended up in an amputation. Besides pain and physiological problems, prosthesis users become substantially influenced by psychological factors, such as (i) *learning ability*, (ii) *cognitive skills*, (iii) *motor skills*, and (iv) *mental status* (e.g., motivation, will, stress), which are situated in their mental–body. Thus, a prosthesis user needs time for adaptation and reorganization of the neuronal network to the new setup. It seems that they feel and imagine their original joints and they can also move them, a phenomenon called phantom limb [91], and that they can even feel phantom-limb pain [39, 101].

Reasons for amputation can be different; however, all amputees have to struggle with the new situation: some structure of their limbs is no longer present, but their synaptic input connections to the brain, say the neural network, is still present. Some afferent connections are lost, where the synapses are then somehow floating, say they are simply left open; and some efferent connections (i.e., axons from neurons that formerly have had controlled muscles of the lost joints) also end up. Patients have been able to perform mental finger motions right after amputation and after several years they are still capable of controlling their forearm muscles. This has been attributed as evidence to brain plasticity and reorganization [91].

Hence, exploiting the phantom-limb phenomenon could enable more intuitive prosthesis control to users. They may simply try to move the phantom-limb joints as if they used their original joints. In particular, contractions of residual muscles of the stump can be captured by means of surface EMG electrodes, and they can be used for the control of the prosthesis.

4.1 Prostheses of Today

Standard applications of prosthesis control use two EMG electrodes, one on the flexors' side and one on the extensors' side of the residual part of an amputated upper limb, either on the forearm or the upper-arm. Such a setup enables the control of at least one degree of freedom (DOF). In order to support more DOF, a switching mechanism is used to switch between available DOF. This switching mechanism can be implemented by co-contractions or other muscle activation sequences. Although this works in principle and it is relatively simple, the downside is that the full prosthesis control has a low chance to be integrated over time into dedicated motor programs by the user brain, because of the required switching actions.

In the last years, more dexterous prosthesis components and systems emerged on the market providing more DOF, e.g., the Michelangelo®-Hand Advanced Prosthesis System (Otto Bock Healthcare Products GmbH, D), the iLimb Hand (Touch Bionics, UK), the be-bionics-Hand (RSLSteeper, UK), or the Vincent Hand (Vincent Systems GmbH, D), to name a few. An EMG controlled prosthesis consists of an inner shaft and an outer shaft. The inner shaft carries the EMG-electrodes and fits the prosthesis user stump very tightly in order to provide a vacuum in the socket for fixation. The outer shaft is made of carbon or other material for protecting the prosthesis equipment and providing the carrier for the hand component. Fitting the prosthesis to its user is a mandatory step toward a successful prosthesis utilization.

For the control of advanced devices, more signals are required, and can be obtained using additional electrodes. However, muscles do not work independently, because of synergies that include groups of two or more muscles. Therefore, separability between single muscle contractions is not naturally given and can be achieved only approximately by intense training.

4.2 Prosthesis Control, Machine and Human Learning

It is assumed that a prosthesis user has at least residual understanding of doing phantom movements [91]. In addition, motor programs are assumed to work also for voluntary controlled joint movements [43] as they work for continuously repeated movements. The more degrees of freedom a multifunctional prosthesis provides, the more factors of user performance become important. These factors originate from users' motor abilities, such as the discriminability of their EMG signal pattern vectors between different phantom-like and the precision of repeating them always in the same manner.

During assessments, psychometric measures of user ability and classification performance for rating user performance in laboratory [45] and real-life scenarios [4] have been applied. When a novice prosthesis user tries to perform repetitions of the same movement, using a certain joint and using the same contraction, it can happen that the resulting outcomes are not always the same. This observation can be attributed to variability in motor control.

In order to face the variability of motor control, statistics and machine leraning are often used to control robotic prostheses. To this end, it is crucial that the collected training set provides sufficient information on the realtionship between EMG signals and desired movements. Figure 4 shows three exemplary training sets: (i) a small training set (pictured in red), which can be obtained with minimal training effort; (ii) a huge training set (black), which is robust to variability but it requires a very high training effort; and (iii) a medium training set (blue), which represents a trade-off between variability and learnability. In Fig. 4, a mean-shift[1] between training and test data D is depicted. It is possible to notice that, while there is no overlapping between the small training set and the test set, the medium training set comprises the test set, thus it can lead to satisfactory performances.

In conclusion, different phantom movements should result in differentiable muscle contractions with no overlapping EMG patterns. This can only be achieved by repeated training, perhaps with visual feedback to speed up the learning process.

4.3 Optimization of Training

Training amputees to use robotic prostheses should be divided in two components: (i) *training for machine learning*, which identifies a mapping between EMG readings and prosthesis joint control signals; and (ii) *training for human learning*, which should train amputees to perform stable and repeatable phantom movements..

While literature focuses mainly on machine learning techniques for prosthesis control, in practice, the variability of user behavior is more crucial and may degrade completely the performance of a sophisticated machine learning solution. Additionally, the more functionalities a prosthesis provides to the user, the more

[1] In practice, also covariance shift changes are possible, changing also the shape of the data [46] .

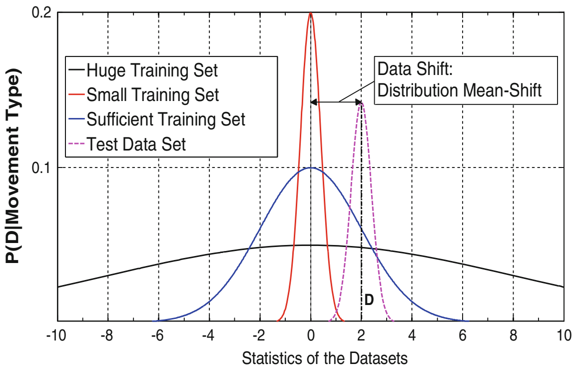

Fig. 4 Toy example of the statistics of three training sets with different data sizes and one test set D. The *small* set is out of only few *training* trials and a *small* mean-shift of the *test* set D distribution leads to nonfunctional behavior. The *huge* set is robust against mean-shift, but needs too much training effort. Thus, the *sufficient* set uses an optimized trial set and is more robust to slightly changed distributions

precisely the user must perform required muscle contractions, in order to provide direct control. Recall about the assumption of benefit that users should get able to simply forget about operating a prosthesis, because direct control handling, on the long run, should seamlessly integrate directly into the motor cortex.

Applying learning methods to yet untrained subjects might cause the following problem. When the user tries to minimize their signal variability, the resulting EMG pattern may overlap those associated to other phantom movements. This would require to retrain the prosthesis user to employ different patterns across movements, which is cumbersome and should be avoided. Information on these EMG overlaps could be exploited by a physioterapist to guide the amputee to perform distinctive phantom movements [52].

The co-optimization of machine learning and human learning seems to be a promising approach to solve this issue. Interested readers should refer to [4, 45].

5 Motor Learning in Rehabilitation

This section describes some rehabilitation techniques based on motor-learning principles, given special attention on those supported by novel technologies as robots and electrical stimulation. These rehabilitation techniques rely on the assumption that patients with neurological lesions are able to learn by means of the plasticity of the CNS [43]. The plasticity capacity of the CNS has been demonstrated in literature [51], and it is currently exploited for rehabilitation after neurological injuries. In this regard, rehabilitation techniques attempt to exploit plasticity to achieve recovery through different motor learning concept. Patients can be exposed to combinations of sequences of different techniques based on their needs and their performance history [70].

5.1 Constraint-Induced Movement Therapy

Constraint-induced movement therapy (CIMT) is a rehabilitation therapy based on the theory of "*learned nonuse*." The learned nonuse phenomenon is developed during the early stages after stroke, as the patient begins to compensate their motor function due to difficulty and inability to successfully carry out motor tasks using their impaired limb [48]. This compensation increases reliance on the intact limb hindering recovery of the impaired limb.

This rehabilitation technique has two main components and is usually given over 2 weeks [70]. The first one is to restraint the less-affected extremity, the second one is to practice with the affected limb for 6 hours a day using shaping. Although it has been demonstrated that chronic stroke patient can show significant motor improvements, the use of CIMT remain controversial [70, 120]. The main arguments arise by the facts that the restrain stage can be very frustrating and that the inclusion criteria may lead to excluding many patients. In literature, there is not a clear position regarding inclusion criteria about the patient stage after stroke, despite it has been used in acute, subacute and chronic stages [120]. The generally accepted condition is that patients must have capability of perform at least 10 degrees of finger and wrist extension.

Massive practice is the main principle behind this rehabilitation technique, in which patients are required to use their affected arm to carry out motor activities. At the beginning, this therapy could be frustrating specially in patient with high motor impairment [79]. It has been also mentioned that since the restriction the movement of the nonaffected arm yields to explore command space with the affected arm, this technique encourages the exploration of a global optimum [58].

5.2 Robotics Rehabilitation

The development of robotic therapy was driven by the evidence that the injured motor system can reorganize in the setting of motor practice (plasticity). Also, that robotics devices provide the ability to automate intensive training techniques, increasing safety for both patient and therapists, and improve user-therapy accessibility [92]. High intensity and repetitive training are the key features to promote motor learning, reduce motor impairment and enhance motor function [58, 64]. In this regard, robotics provide a great opportunity to deliver a much higher dosage of training and intensity [92].

It is worth noting that these devices allow scientists to carry out a rigorous validation and application of motor learning principles in neurorehabilitation [58]. Furthermore, robotic platforms provide the possibility to test different motor learning principles through variations of control algorithms, to create many dynamic environments, and to investigate the human ability to adapt to them [93].

It is important to note that as Reinkensmeyer and Patton introduced, guidance can impair learning because it changes the dynamics of the task to be learned [93]. They also mentioned that guidance could be very helpful to teach skilled movements that require coordinated motions of multiple joints while the vision must be kept on the target object. So the usefulness of guidance for trajectory learning may depend on the task to be learned.

Another trend widely explored regarding motor learning and robotic devices is motor adaptation. Huang and Shadmehr [58] describe motor adaptation as a learner's reaction to a change in the environment. An example of a study that induced motor adaptation consisted in performing reaching movements under perturbations introduced by a planar robot (perturbation force field). These perturbations were perpendicular to movement directions and proportional to movement velocity [105]. After some movements under the perturbation force field, the learner modified its motor response during reaching movements. This modified response is called motor *after-effect*, and it has been demonstrated that the subject's adapted response temporarily persist as if the perturbation force was still present. This after-effect technique is opposite to robotic guidance because it increases trajectory errors during movement, and thus it could be also called as an error-augmentation strategy [93].

Many studies were presented that deal with motor after-effect for both upper and lower limbs. Scheidt and Stoeckmann used the MIT-Manus to compare force field adaptation in post-stroke and healthy subjects [98]. They found that both groups utilize the same compensatory strategies evidencing that post-stroke patients have the capability to adapt their motor responses as healthy subjects do, although it may take more training. For lower limb case, Reisman et. al. carried out a study in a split-belt treadmill with chronic hemiparesis that showed asymmetry in inter-limb coordination during walking [95]. In the experiment, one belt sped up and the other slowed down. Similarly to the upper limb study, patients presented after-effects responses that improved the symmetry of their gait patterns. The last remark concerning the after-effect is that the learner does not solely adapt to environmental dynamics changes, but he/she is also able to anticipates the expected dynamics of the new environment and moves according to a new set of expectations. Huang and Shadmehr [58] mentioned that motor adaptation appears to rely on an update in the internal representation (internal model) of the external environment, and that internal model learned in the robotics force field paradigm could be retained over time.

Rehabilitation training must be executed to achieve lasting and generalizable gain of motor capabilities. The main idea behind generalization is that training task X must lead to improved performance in task Y and Z. Baraduc and Wolpert [6] performed experiments of reaching and point to a target from the same starting point using index fingers but with different initial arm configurations, and concluded that in robotic neurorehabilitation is important to train patients across different movement directions to learn a task . Wang and Sainburg [122] discovered that training under clockwise force dynamic perturbations in one arm can generalize to the other arm with counter clockwise perturbations. Hemminger et al. [21] concluded that adaptation to force dynamics can transfer only from the dominant to the nondominant arm . Regarding force field rate variation, gradual user adaptation to a force field promotes larger and longer lasting after-effects than sudden changes in the force field [65].

It is also important to remember that a variable training schedule is better than a continuous schedule as it promotes retention and generalization [68]. In the work presented by Aboukhalil et al., they conclude that motor retention is higher when training sessions are temporally distributed over a period of time [2]. Huang and Krakauer also affirmed that minutes or even hours between training sessions may facilitate consolidation of motor memories [57]. Addressing these principles, robotic therapies must be programed to combine two or more tasks in one session rather than training only one task.

Robotic rehabilitation is an ideal tool to both test and eventually implement rehabilitation paradigms to aid motor recovery after stroke and other central nervous system diseases [58]. Furthermore, it enables to deliver automated and predefined training session. However, in order to promote motor skill acquisition and retain it beyond the training session, motor control principles should be taken into account.

5.3 Triggered-Based Functional Electrical Stimulation on Rehabilitation

Instead of using a robot to drive the limb of a patient by applying external mechanical forces, neuromuscular electrical stimulation (NMES) therapy facilitates exercise execution leaded by the participant's own muscles. NMES relies on short electrical pulses with the aim of recruiting motor neurons that generate muscle activations and hence produce movements. The intensity of the electrical pulses sets the total charge transferred to the muscle. The amount of charge driven to muscles depends on pulse shape, amplitude, width and the frequency [78]. The use of NMES has arisen as a research cooperation between disciplines like neurophysiology, engineering, and rehabilitation and others, that have promoted their development and use for rehabilitation purposes [16].

In literature, two applications based on electrical stimulations for motor relearning can be distinguished: cyclic NMES and neuroprosthetics. Cyclic NMES was defined as continuous or periodic muscle stimulation through electrical pulses. While the term neuroprosthetics involve an artificial system bypassing the neural system to restore lost body functions by providing functional movement patterns using electrical stimulation [59]. During cyclic NMES patients are passive, and they are not required to perform any cognitive effort, in the form of either initiation of muscle contraction, interpretation of afferent signals, or functionality of motor task [107]. Whereas in neuroprosthetics applications, alternative motor pathways are recruited and activated to assist the damaged efferent pathways of the central nervous system [19]. In this second strategy, repetitive movement training is performed in the context of functional behavioral tasks [16, 107].

The most popular way to perform user-triggered NMES is based on electromyography (EMG) signals. EMG-triggered stimulation consists in monitoring the activities of one or more muscles, and triggering NMES when the corresponding EMG signals overcome a predefined threshold. This technique is usually used in patients with residual motor function, where motor neural connections are still working, in a way that voluntary commands generate strong enough EMG signals that can be distinguished from its baseline activity. A step forward to this approach was presented in [1], where the stimulation was modulated in proportion to the voluntary EMG, so that a closed-loop EMG-controlled system resulted in both clinical improvement of the paretic upper extremity and cortical modulation in patients after stroke. When neural connections are too weak and the muscle baseline signal is indistinguishable from the activation stage, electroencephalography (EEG) signal could be used [55]. In this case, patients' intentions can be detected by monitoring cortical brain activities, which then trigger the electrical stimulation to assist the movement. Two motor learning principles are coupled during voluntary NMES-triggered therapies: repetition and sensorimotor integration [70]. Furthermore, triggered NMES has also been coupled with randomized practice schedule, testing the hypothesis that contextual interference will aid recovery [19], and with bilateral coordination training [18].

Controversial results were found in literature regarding the benefits of cyclic NMES compared with a neuroprosthetics. On the one hand, De Kroon and IJzerman have not detected significant differences regarding the functional outcome [23]. On the other hand, Bolton et al. have mentioned that neuroprosthetics generated higher improvements compared with cyclic NMES [13]. Despite this discrepancy, it is globally accepted that functional improvement is enhanced when stimulation is associated with voluntary attempts [16]. Cauraugh et al. explained that improvements obtained in stroke patients after neuroprosthetic therapy can be explained in terms of the sensorimotor integration theory. In particular, neuroprosthetics movements produce proprioceptive feedback, an afferent signal that returns to the somatosensory cortex, completing the sensorimotor cycle. The voluntary efferent output as well as the afferent input may assist in organizing the distorted signals arising from the damaged brain area [17]. Indeed, proprioceptive feedback has a critical role in motor planning by updating an internal model of the state [70]. For additional details on triggered NMES studies, the reader can refer to [16, 18, 59, 107].

In order to enhance patients' recovery, some motor learning principles must be taken into account during the use of neuroprosthetics devices. These considerations include task repetition, novelty of activity, concurrent volitional effort, and high functional content [107].

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Muscle Synergies in Clinical Practice: Theoretical and Practical Implications

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Abstract Understanding how the CNS copes with the redundancy of the musculoskeletal system is a central aim in motor neuroscience and has important implications in the clinical scenario. A long-standing idea hypothesis is that motor control may be simplified by a modular organization, in which several a few muscle synergies are used to organize muscles in functional groups. In this chapter, we present the theory hypothesis of muscle synergies under from a simplified point of view and we describe its practical implications in the context of neurological pathologies. This chapter wants to be an intuitive and practical guide to those practitioners, new to the concept of muscle synergies, willing to understand how to perform such an analysis in typical clinical settings.

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1 Introduction

Consider a movement, even a simple one that we perform effortlessly many times in a day, such as reaching for an object, or walking on a sidewalk. The apparent simplicity of movement execution may hide the complexity of its control. To perform any movement, the central nervous system (CNS) must modulate and coordinate the contraction of a large number of muscles. In each muscle, the generation of contractile force is regulated by the recruitment of a large number of motor units, which modulate the complex internal dynamics of muscle fibers. The forces generated by all motor units in all muscles must sum up to produce the appropriate amount of torque in each joint. As, in most cases, there are more muscles than joints, a wide range of combinations of muscle patterns can produce the same movement, i.e. the system is redundant. Understanding how the CNS copes with the redundancy of musculoskeletal system is a central aim in motor neuroscience and has important implications in the clinical scenario, as it appears evident observing the profound motor impairments caused by even a small lesion of the CNS.

A long-standing idea is that motor control may be simplified by a modular organization. Under this hypothesis, the control problem is reduced to modulating an appropriate selection of an adequate number of motor modules, also called *muscle synergies*, resulting in a simplified control of movement. In the last fifteen years, several experimental studies have provided evidence of such modular organization in humans and animals. Other studies have shown that this modular control may be disrupted due to neural injuries, resulting in poor intermuscular coordination and consequent pathologic behavior. Due to these evidences, we believe that the analysis of muscle synergies has strong potential for the assessment and rehabilitation of neuromotor diseases. Nevertheless, most of the experimental studies in literature are confined on the neurophysiologic scenario. In order to facilitate the introduction of muscle synergy analysis in the clinical setting, this chapter aims to be a practical 'hands-on' guide to any clinical researcher and/or professional willing to explore the potentialities of this new methodology.

In the first section, we will present the basic concept of muscle synergies, and its implications to the neurological pathologies, i.e., stroke and spinal cord injury. In the second section, we present an experimental case study in which we describe, step by step, the experimental and mathematical procedures necessary to extract meaningful synergies from electromyographic recordings and avoid common experimental and interpretational pitfalls. In the third section, we will briefly discuss about the sensible parameters that can affect the results, to which the practitioners or researcher should pay particular attention. In the conclusion section, we give an overview of the current and future challenge of synergy analysis, focusing in particular on the clinical applications.

1.1 State of the Art

1.2 Muscle Synergies as a Simplified Control Strategy

The concept of muscle synergy has been used with different meanings in different contexts. The term ‘synergy’ means ‘working together,’ and it generally indicates the existence of some coupling among functional elements. In neurorehabilitation, it refers to stereotypical muscle activation observed after lesions due to a loss of independent control. In contrast, in motor neuroscience, it indicates a strategy to simplify motor control by grouping multiple degrees-of-freedoms together. In the last fifteen years, the neuroscientific perspective has gained more and more relevance. The key hypothesis is that the CNS controls muscle activations using a set of basic control elements, called synergies. Each synergy defines a ‘group’ of muscles that are coactivated, thus working as a single functional unit.

Making an analogy, let us consider muscles as musicians in an orchestra (Fig. 1). The overall symphony normally results from several melodies combined together, each of them played by a different group of musicians (e.g., violins, trumpets, and cellos). From the point of view of the director (corresponding to the brain),

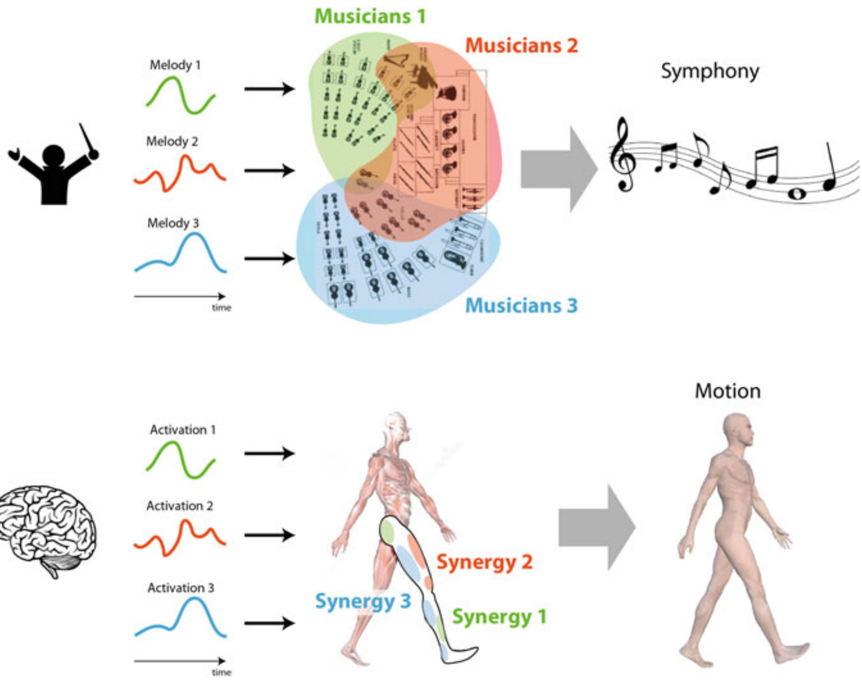

Fig. 1 Analogy between the coordination of muscles by means of muscle synergies driven by the CNS and the coordination of an orchestra by a director

the apparently complex task of coordinating all music players is turned into the simpler task of modulating a limited set of basic melodies, each of them associated to a defined group of musicians. We call 'synergies' the groups of musicians playing each melody. In conclusion, the appropriate 'activations' of 'synergies' produce the coordinated activity of body muscles, which results in functional movements (the 'symphony').

If the CNS combines a small number of muscle synergies to generate motor commands, we expect to recognize regular patterns in the motor output. In particular, we expect to recognize a number of synergies (muscle groups) smaller than the number of muscles (back to the analogy: having a number of basic melodies smaller than the total number of instruments). Conversely, in the absence of any synergistic control, we expect to find as many synergies as the number of muscles, meaning that muscles are not grouped together, but rather they are activated independently. In this extreme case, the term 'synergy' will lose meaning, because each synergy would drive just one muscle and not a group of muscles. Mathematically, this concept can be modeled in different ways, whose description goes beyond the goal of this chapter. For those readers interested in these mathematical formalizations, please read [45, 65].

Muscle synergies not only describe which muscles work in coordination, but also "how" they work together. As shown in Fig. 2, each synergy describes the extent to which each muscle contributes to the synergy it belongs to. Under the proposed analogy, the synergy would specify the intensity of each instrument within the same group of musicians (e.g., 3 out of 6 violins should play louder than the others). This concept is expressed mathematically as *weights*. Synergies represent the ensemble of weighted connections between activations and muscles, resembling the role of spinal interneurons that translate supraspinal commands into α-motoneurons recruitment.

A growing number of studies have provided evidence for the synergistic hypothesis, showing that the muscle patterns can be reconstructed by a number of synergies much smaller than the number of muscles, in a variety of species, behaviors, and tasks. In particular, studies have been conducted with frogs [12, 17, 21, 30, 58, 66], cats [61, 62] , monkeys [50, 51], and healthy human subjects while walking [15, 25, 38, 42], running [11], reaching [18, 20, 47], fingerspelling [43, 69], standing during postural perturbations [63, 64], cycling [4, 23, 35, 37, 68], catching [1], and generating isometric force [6, 9, 26, 54]. Moreover, s few studies have provided theoretical interpretations of the synergy hypothesis ffff. A number of reviews on muscle synergy decomposition have been published recently [2, 8, 19, 27, 44].

1.3 Muscle Synergies as a Novel Assessment Tool of Neurologic Pathologies

Disorders of the CNS such as stroke and spinal cord injuries (SCI) are characterized by several motor deficits resulting from inappropriate muscle activity and coordination.

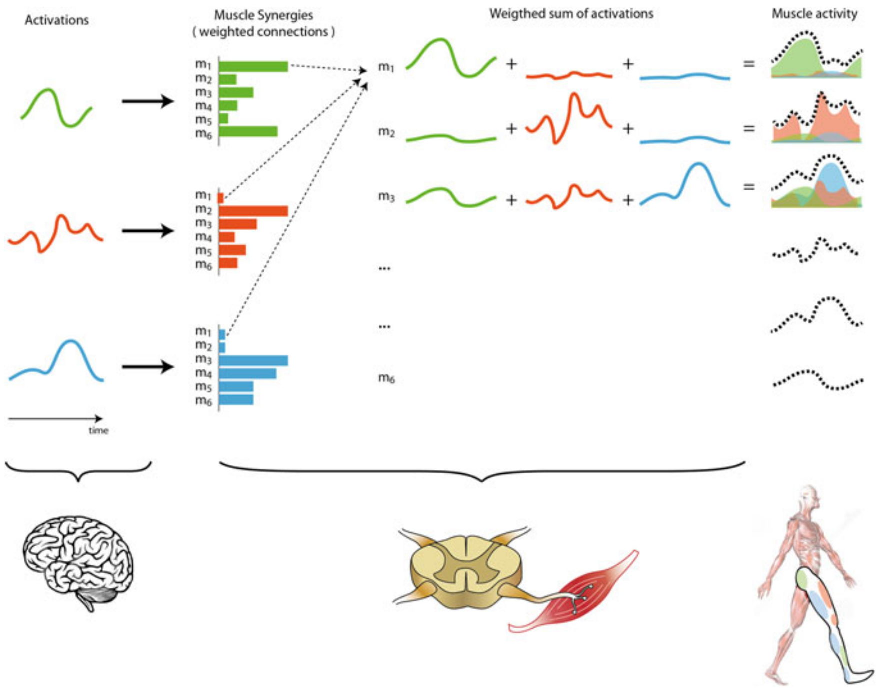

Fig. 2 Under the muscle synergies hypothesis, muscle activities result from a combination of a few activation signals mediated by muscle synergies. Functionally, muscle synergies assume a similar role of spinal interneurons, which translate supraspinal commands into α-motoneurons recruitment, by means of appropriate-weighted connections

Among these deficits, patients with stroke show stereotyped muscle activation patterns due to the loss of independent control. The analysis of muscle synergies, combined with behavioral and biomechanical measures, is expected to highlight these modifications and provide a better understanding of the deficits that result from the impaired nervous system [57]. Since the design of present and future motor interventions strongly relies on the scientific understanding of the neural function and plasticity, muscle synergy analysis could be exploited to improve our understanding of the motor recovery process and to design new effective therapeutic approaches [59]. For these reasons, some groups have recently started looking at muscle synergies organization in upper and lower extremities of patients with SCI and stroke.

1.3.1 Muscle Synergies in SCI Subjects

So far, just few studies have been conducted to investigate the effect of SCI on muscle synergies [41]. Ivanenko and colleagues [40] studied lower limb muscle synergies extracted in 11 SCI subjects with a thoracic lesion around T8, characterized by different sensory and motor impairments, during treadmill walking at different speeds

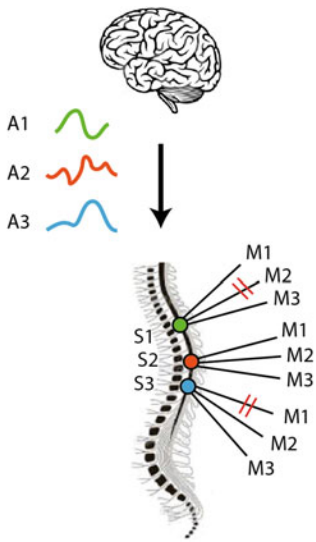

Fig. 3 SCI may disrupt the weighted connection constituted activations and the α-motoneurons connecting each muscle. Despite activations may be preserved and controlled by supraspinal circuits, the synergy vectors will be different (different weights because of the disruption of some interneurons)
A: Activation; S: Sinergy; M: Muscle

and different levels of body weight support. Results showed that with respect to the healthy people, temporal activations were preserved, while the structure of muscle synergies was altered (see Fig. 3): in particular, the synergies of the less impaired subjects were more similar to the healthy ones than those of the most affected subjects.

Another study extended these findings investigating a population of 8 SCI patients presenting incomplete lesions at different levels of the spinal cord (from C4 to T10), during overground walking [31]. The number, composition, and activation of muscle synergies were altered with respect to healthy controls. In particular, the patients showed fewer muscle synergies and altered activations. Remarkably, the alteration of muscle synergies reflected an altered muscle coordination, which could limit safe and effective walking.

A further study showed how the organization of muscle synergies was also altered in upper limb, during different grasping movements [70].

In summary, the few investigations of muscle synergies in SCI subjects suggest that the plasticity induced by the lesion and by the training after the lesion leads to a reorganization of the connections of the interneuronal networks in order to modify and create new muscle synergies while the temporal organization of the activation coefficients remains preserved [40, 41]. The reorganization of muscle synergies occurs both in upper and lower extremities [40, 70], while in some cases, it is also possible to observe alteration of their number and activations [31].

1.3.2 Muscle Synergies in Post-stroke Subjects

Few more studies investigated muscle synergies in post-stroke subjects. Concerning locomotion, Clark and colleagues [16] analyzed 57 chronic post-stroke subjects, characterized by different levels of impairment, during treadmill walking at different speeds. They found that muscle synergies were generally preserved, but the ability to differentially activate the synergies was compromised in many of the paretic legs. They also observed that fewer synergies were needed to account for the whole muscle activity in the paretic leg relative to non-paretic and healthy control leg. This decrease in the number of synergies was also correlated with degradation of clinical and biomechanical walking performance variables, such as the preferred walking speed, speed modulation, step length asymmetry, and propulsive asymmetry [10, 16]. The fewer number of muscle synergies in the affected limb has been hypothesized to result from the merging of more synergies normally observed in healthy subjects (this 'merging' phenomenon will be explained afterward).

Gizzi et al. [28] extended these results by investigating muscle synergies from 32 muscles on 10 patients recently affected by stroke (maximum 20 weeks), while they were walking overground at comfortable speed. Focusing only on lower leg muscles, they observed a preservation of the temporal organization of the synergy activations. By considering lower limb, trunk and upper limb muscles, the synergies, but not the activations, of the affected side were different from those in the unaffected side and of the healthy controls. The results induced the authors to speculate that these changes in muscle synergies could be due to compensatory strategies mainly carried out by the upper and trunk musculature.

Cheung et al. [13, 14] evaluated upper limb muscle synergies in a population upto 31 patients affected by (moderate to severe) stroke, while they were executing 3D reaching movements. In case of less impaired subjects, the muscle synergies of the

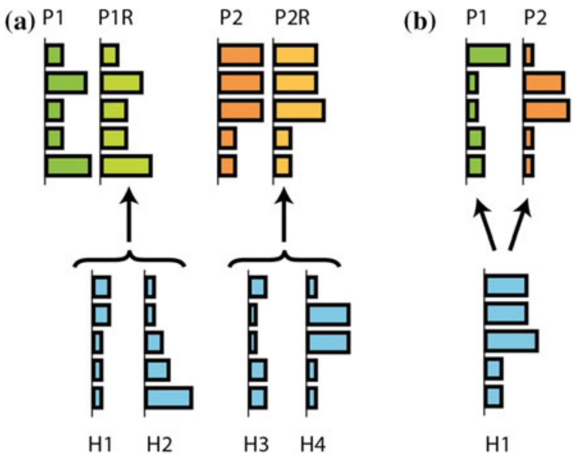

Fig. 4 Merging and fractionation of muscle synergies. **a** Merging of muscle synergies. Paretic side synergies may be explained as the merging of healthy synergies. For instance, healthy synergies H1 and H2 can merge and form P1R (paretic synergy reconstructed), which is very similar to the original paretic synergy 1 (P1). **b** Paretic synergies P1 and P2 may be explained as fractions of healthy synergy H1

unaffected and affected arm were similar even though the muscle activation patterns were different [13]. However, severe impaired subjects (Fugl-Meyer score $\leq$ 30) showed three distinct behaviors: the preservation, merging, or fractionation of the affected muscle synergies of the affected arm with respect to those of the unaffected (or healthy) arm [14] (see Fig. 4). The merging of muscle synergies (Fig. 4) is the process by which two groups of muscles that are normally independent to each other, become grouped. Under the synergy analogy, we may see this phenomenon as two independent groups of musicians that, at a certain moment (following a certain re-organization process), start to follow the same melody. The fractionation of muscle synergies appears when a group of muscles belonging to one synergy is divided in two groups, each following a different modulation signal.

Roh et al. [55] investigated upper limb muscle synergies in 10 chronic and severe (Fugl-Meyer score $\leq$ 25) stroke survivors, using a submaximal isometric force matching protocol. The activations were modulated in a task-dependent manner in healthy and stroke subjects, while an alteration in synergy composition was observed only in the stroke-affected arm. In particular, the altered recruitment was correlated with the abnormal task performances. In this case, no merging or fractionation was observed.

Finally, Tropea et al. [67] investigated the effects of the conjunction between natural recovery and intense robot-mediated treatment on muscle synergies in subacute patients (one week to four months after the lesion). Patients underwent 6-week rehabilitative training, performing planar robot-assisted reaching movements. The results suggested that (i) muscle synergies underlying shoulder control can reflect the functional deficit induced by the pathology, (ii) muscle synergies can be modified by the rehabilitative treatment, and (iii) the improvement of motor performance was achieved in conjunction with a slight, even though not statistically significant, restoring of the coordination of the activity of shoulder muscle groups.

Overall, all observational studies of muscle synergies in stroke subjects showed that the organization of muscle synergies depends on the level of impairment and maybe on the onset of the cerebrovascular accident. In particular, in severe impaired chronic stroke subjects, in the lower and upper limb, it is possible to observe the preservation, merging or fractionation of muscle synergies. In subacute or mildly impaired stroke subjects, it is possible to observe the preservation of muscle synergies. In both lower and upper limb, the activation coefficients of muscle synergies are generally preserved, and, in the upper limb, the synergies dominated by the activation of shoulder muscles are generally altered.

The merging and fractionation may be interpreted as a possible compensatory or adaptive reorganization of brainstem and spinal control [14], and the degree of merging seems to be related to the degree of motor and functional deficit. The merging of upper limb muscle synergies can be ascribable to the higher muscle co-contraction in the affected side, analogously to what was found in the lower limb [16]. While the merging was related to the severity of the impairment, the fractionation emerged only after years from the initial stroke lesion, but whether it is an adaptive process triggered in response to the motor impairment following stroke remains an open issue [14].

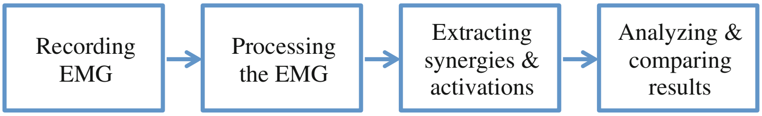

Fig. 5 General experimental procedure to analyze muscle synergies

Muscle synergies can be modified by the motor reorganization following a rehabilitative process [67]. In particular, modifications involving a reorganization of muscles within the same muscle synergy seem to occur in a short-time period, while the fractionation process of merged synergies seems to require more time [14].

1.4 Muscle Synergy Analysis in the Clinical Setting

In this section, we will provide a step-by-step guide to those practitioners willing to understand how to perform synergy analysis in a typical clinical setting. We will give examples based on previous experiments during cycling movements. Most of the information included in this section can be found in [4], from which data are extracted and adapted.

The basic experimental data that a researchers or clinician needs in order to perform synergy analysis is muscle activity. This is usually done by non-invasive electromyography (EMG) analysis which is, the technique of recording the superficial electrical muscle activity by means of electrodes placed on the skin surface. The recorded EMG signals should be consequently processed and then used as input to special algorithms responsible for extracting the synergies and their corresponding activations. The analysis of synergies ends with the interpretation of results. Each of these four steps (shown in Fig. 5) entails several aspects that should be taken into account to extract meaningful information. In the following subsection, we will bring the reader throughout this process.

STEP 1. Recording EMG

The first step in the experimental design is defining which muscles should be recorded. As the analysis of muscle synergies intends to unveil the coordination strategies over a large set of muscles, it is important to record the muscular activity of as many muscles as possible. It is recommended to at least record those that play an important role in the motor task or behavior. Participants should be instructed to refrain from intense physical activities for at least 2 days before testing [4], to avoid biasing the results due to fatigue.

The positioning of the electrodes on the skin strongly influences the quality of the EMG signal: badly positioned or oriented electrodes can produce significant variations in the signal quality and/or reliability. The SENIAM project [32] developed a set of recommendations about the placement of sEMG electrodes on the different muscle groups. After selecting the muscles, the researchers should therefore follow these recommendations for sEMG recording procedures: shave the places where the electrodes are placed; clean the skin with alcohol to minimize impedance; allow the alcohol to vaporize in order to dry the skin before placing the electrodes. After that, the bipolar electrodes (with a 2-cm interelectrode distance) should be fastened to the specific locations, according to the respective sensor placement procedure in SENIAM. In the case of electrodes connected by cable to the EMG acquisition system, it is recommended to wrap the electrodes with bandages to ensure that the wires do not impede the subject's movement and also to avoid movement-induced artifacts. Finally, care should be taken to ensure that the reference electrode is placed as far away as possible from the recorded muscles and on electrically neutral tissue (say over a bony prominence) and that it makes very good electrical contact with the skin.

To ensure the correct placement of the electrodes, some preliminary tests to check for cross talk and cable-induced noise should be performed. If needed, electrodes should be repositioned [4].

Depending on the motor behavior or task recorded, some additional events could be detected to segment the data into individual cycles. For instance, in the case of cycling, the crank angle should be also measured, and synchronized with the EMG recordings.

Finally, at the end of each trial, data have to be stored to allow for further offline processing.

STEP 2. Processing the EMG

A correct placement of the electrodes does not imply that the recorded EMG signals are appropriate for synergy extraction. Many disturbances may affect such signals. Thus, the investigator should inspect and preprocess the dataset in order to minimize their influence on the analysis. The idea is to remove all the features of the raw data that do not relate to muscle activation. Although it is impossible to guarantee a perfect removal of all these undesired features without affecting the signal, a series of methodologies can be adopted to minimize them.

The typical disturbances that affect EMG signals can be classified as follows [53]:

1. **Inherent noise in the electronics equipment**. This source of noise is originated from the electronics equipment used for detecting, amplifying, and recording the signals. The usage of high-quality electronics can reduce this disturbance.
2. **Ambient noise**. This noise component arises from the electromagnetic radiations in the ambient where the recordings are conducted. In particular, its main cause is the radiation from the electrical power line, which can be 50 or 60 Hz, depending on the country.
3. **Motion artifacts**. These disturbances derive either from movements of the cables connecting the electrodes and the amplifier, or from the interface between the electrode and the skin. Thus, they result in low-frequency fluctuations in the EMG signals.
4. **Inherent randomness of the signal**. Motor units are characterized by a quasi-random firing rate in the range between 0–20 Hz. This behavior affects the

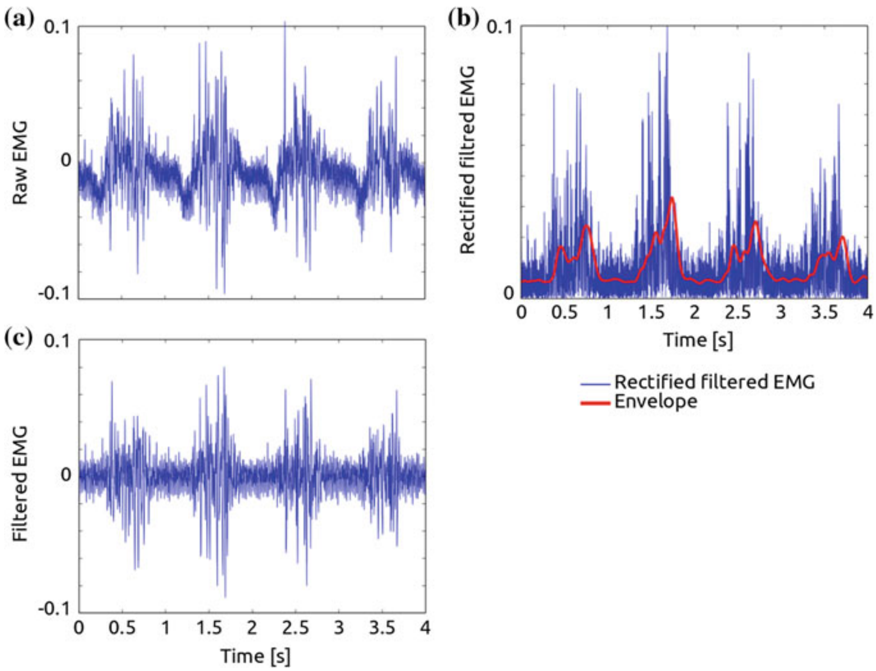

Fig. 6 Processing of a surface EMG signal acquired during a cycling task from the vastus lateralis muscle of a healthy subject. The raw signal (**a**) is corrupted by motion artifacts (low-frequency fluctuations) and high-frequency noise (not clearly visible in figure). By applying a low-pass and high-pass filters at, respectively, 400 and 20 Hz, these disturbances are removed (**b**). The signal is then rectified (**c**, *blue line*), and the envelope is extracted by applying a low-pass filter with cut-off frequency of 5 Hz (**c**, *red line*)

amplitude of the EMG signal, which in this frequency region can be considered unrelated to the task at hand, and therefore unwanted.

Filtering is the process of removing the disturbances described above by applying appropriate mathematical techniques, generically called *filters*. While a detailed description of these techniques is out of the scope of this chapter, it is worth spending some words on the frequency ranges that should be particularly taken care of.

In order to facilitate the explanation of the filtering process, we will refer to Fig. 6, which depicts the step-by-step processing on a real EMG signal acquired during a cycling task from the vastus lateralis muscle of a healthy subject.

The bandwidth of EMG signals is 0-400 Hz, indicating that the main information of muscle activity is included in this range of frequencies. Thus all the frequencies above 400 Hz should be eliminated by the so-called *low-pass* filter. Motion artifacts, characterized by slow fluctuations in the raw original signal (see Fig. 6a), can be eliminated by filtering the low frequencies of the signal, typically setting a *high-pass* filter with cut-off frequency around 10 Hz [22].

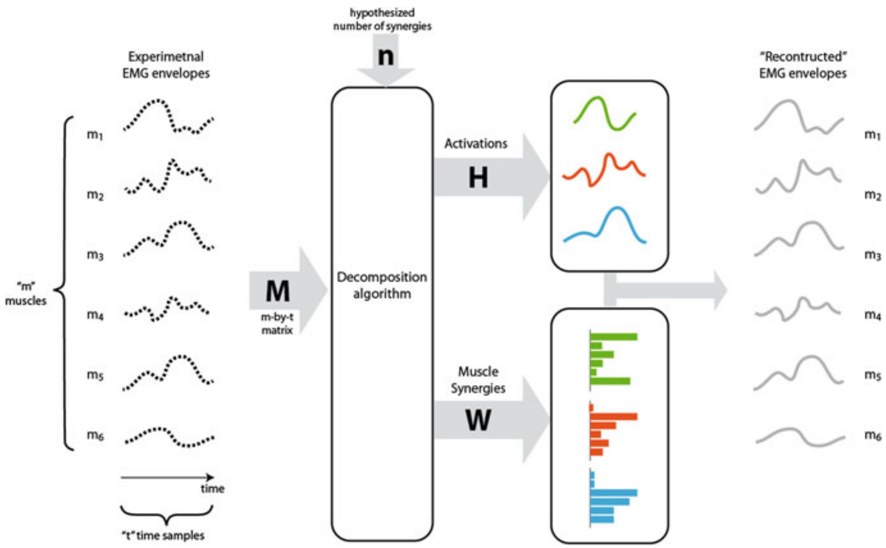

Fig. 7 The process of estimating the activation and synergy matrices (H and W) from six experimental EMG envelopes

Ambient noise can be almost totally eliminated with modern electronics technology. If required, although not suggested [53], a "notch" filter could be applied to eliminate selectively the frequency of the power line (50 or 60 Hz). Figure 6b shows an example of filtered EMG signal.

In order to obtain clean estimates of the neural drives to muscles, two processes should be then applied to the filtered EMG signals: rectification and envelope extraction. *Rectification* consists on translating the EMG signal, which has both positive and negative values, to a new signal that has only positive values. This is typically done by simply taking the absolute value of the filtered EMG signal, *i.e.*, a process called full-wave rectification (see Fig. 6c, blue signal). The purpose of the full-wave rectification is to ensure that signals do not average to zero. In addition, it has been discussed that this process enhances the firing-rate information of the data [48]. Finally, *envelope extraction* consists in extracting a smooth curve that outlines the trend of the rectified EMG signal (see Fig. 6c, red line). This can be achieved by applying either a low-pass filter to the rectified signals or a convolution. A cut-off frequency of 4–10 Hz is often used [4, 16, 28, 29, 35, 37, 56].

STEP 3. Extracting synergies

In order to extract muscle synergies, first the EMG envelopes previously obtained have to be arranged appropriately. Let us imagine the EMG envelopes recorded from m muscles (Fig. 7). Each of these EMG signals is constituted by a number of "time-samples," depending on the frequency of acquisition of the EMG system and the duration of the recording (*e.g.*, a 1000 Hz system recording during 5 s will produce 5000 time samples). Let us call "t" the number of time samples of the recorded EMG signals. We can organize these data into an "EMG matrix," called **M,** of dimensions m-by-t, where each row contains the t time samples of the EMG signal recorded from one muscle (Fig. 7). This EMG matrix is then decomposed in the product of two matrices, **W** and **H** (mathematically: $\mathbf{M} = \mathbf{WH}$, Fig. 7), by means of appropriate decomposition algorithms. Matrix **W,** namely the "synergy matrix," or "matrix containing the synergy vectors," expresses the contribution of each of the m muscles within the n synergies. Matrix **H**, namely the "activation coefficients matrix" contains information on how each synergy is modulated over time.

Based on assumptions on noise and on the constraints involved in the muscle pattern generation, different factorization algorithms can be used. The most frequently used algorithm is nonnegative matrix factorization (NMF) [45], which assumes that both synergy vectors and activation coefficients are nonnegative. For more extensive description on the algorithm, see [45] or [65]. To assess the quality of the extracted synergies, two metrics have been commonly used in literature: the variance accounted for (VAF), and R^2. These metrics indicate to what extent the "reconstructed" EMG, as obtained by multiplying the matrices W and H (see Fig. 7), is similar to the recorded EMG signals. Both metrics quantify the fraction of data variation (a generalization of variance to the case of many EMG signals) accounted by the synergy reconstruction, but they differ in how they quantify the data variation. In one metric, sometimes referred to as R^2 [20] or centered-VAF, the data variation is computed with respect to the mean. In the other metric, sometimes referred to as Variance Accounted For (VAF), the mean is not subtracted to compute the data variation. High values of VAF and R^2 indicate that the resulting synergies (W) and activations (H) represent a basis of the recorded-muscle patterns. Low-VAF values (i.e., close to 0) cast doubt on the extracted synergies, indicating that they do not explain a large part of the EMG variance. The mathematical description of VAF and R^2 can be taken from [20, 62], respectively.

None of the decomposition methods proposed in the literature can calculate automatically the optimal number of synergies. They can only approximate EMG signals based on a predefined number of synergies "n," introduced by the user (in Fig. 7, $n = 3$). A common method to define the optimal number of synergies is to perform different iterations, each with a different n, and then choose the lowest n that produces sufficient quality of the result. In practical terms, this can be done by representing the VAF and/or R^2 as a function of the number of synergies (as shown in Fig. 8) and applying on it a number of decisional criteria.

A commonly used criterion is the point where the graph reaches a threshold level (e.g., 90 %) [62]. A second criterion is to identify the flattening point, i.e., the point where a clear decrease of slope is observed (e.g., smaller than 5 %), also called the elbow point, interpreted as the point that separates "structured" and "noise-dependent" variability, and therefore it can be used to define the minimum number of synergies that capture the task-related features [20, 65]. The VAF/R^2 can be also calculated for each muscle (actually the VAF/R^2 total is a mean of the VAF/R^2 of each muscle). An additional criterion can be also established at the level of the individual muscle, which should be higher than a predefined threshold (typically 75–80 %).

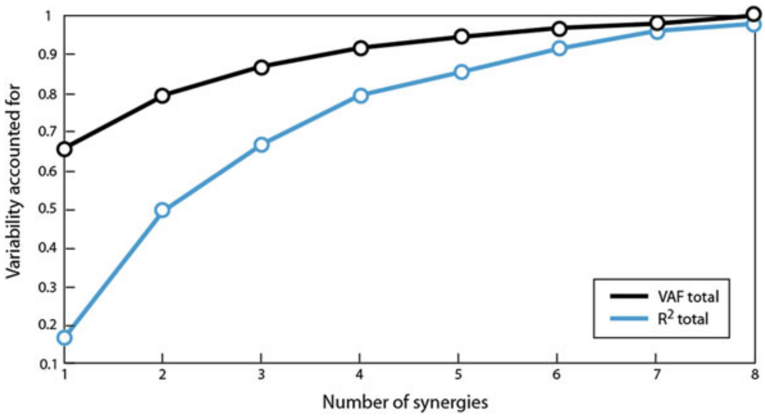

Fig. 8 Reconstruction quality: variance accounted for (VAF) and R^2

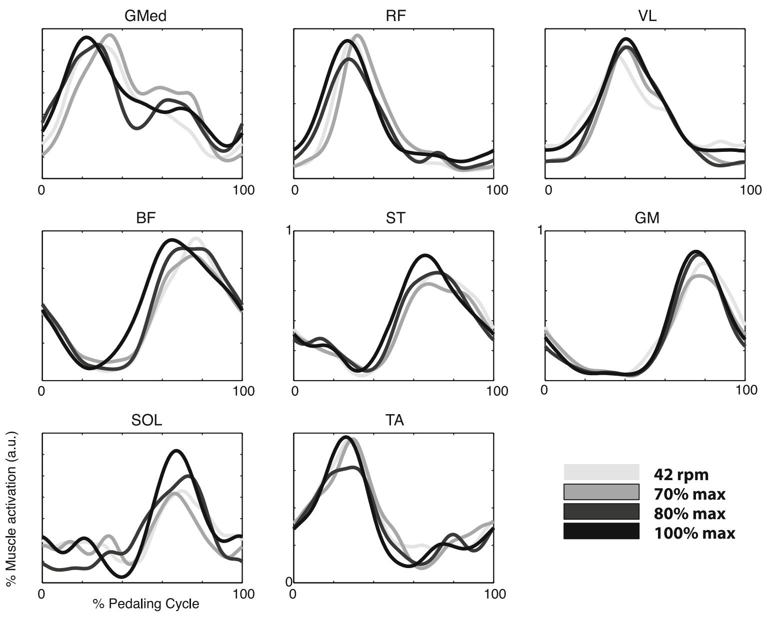

Fig. 9 EMG envelopes during cycling at different speeds. Muscle abbreviation: gluteus medius (GMe), rectus femoris (RF), vastus lateralis (VL), biceps femoris (BF), semitendinosus (ST), gastrocnemius medialis (GM), soleus (SOL), tibialis anterior (TA). Adapted from [4]

STEP 4. Analyzing and comparing results

When analyzing muscles synergies, it is a good practice to first take a look at the EMG envelopes from which synergies have been extracted. For each individual subject, we should verify whether the shapes of the EMG envelopes change across subjects or

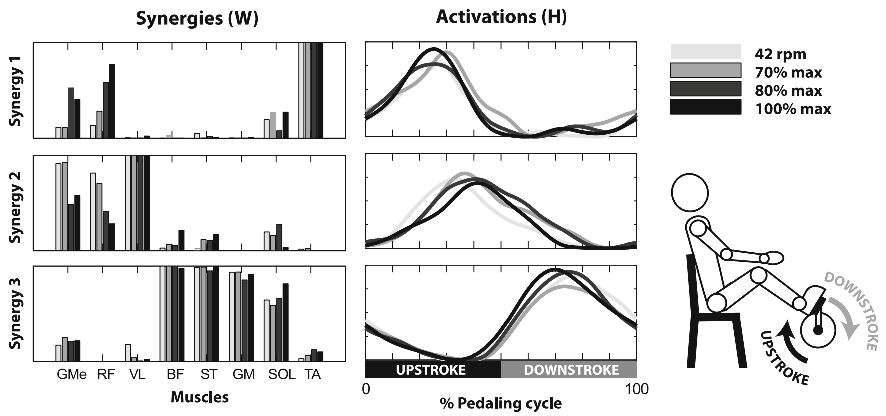

Fig. 10 Synergies (W) and activations (H) during cycling movements, at four different speeds. Modified from [4]. Muscle abbreviation: gluteus medius (GMe), rectus femoris (RF), vastus lateralis (VL), biceps femoris (BF), semitendinosus (ST), gastrocnemius medialis (GM), soleus (SOL), tibialis anterior (TA)

conditions. This is particularly relevant to interpret synergies in the case of pathologic conditions, when one or a few muscles can greatly affect the overall results. When comparing EMG envelopes, the main interesting features to be considered are: the presence of clear peaks of activations (see Fig. 9), the number of peaks, the presence of irregularities, and the deviation from the mean profile. Some of these features can be easily observed by visual inspection. Others need mathematical and statistical methods, such as the *correlation* between signals, which give information on the similarity of the shapes of the profiles in time [5, 46, 68]. One feature that is normally analyzed is whether the EMG envelopes are shifted in time across conditions. This analysis is particular useful when a clear peak of activation can be established (see e.g., the RF muscle in Fig. 9). In this respect, previous studies [33, 42] showed how the peaks of activation tend to occur slightly earlier in the cycle as the speed increases.

Once we have checked the EMG envelopes, we can move to the core of the analysis, which is to analyze the muscle synergy vectors and the corresponding activation coefficients profiles. To carry out a good and detailed analysis, for each synergy extracted, we should focus on two main questions: (1) which are the muscles that mainly contribute to a specific synergy (and their physiological role, with a particular attention to the motor task examined)?; and (2) in which phase of the cycle was the synergy mainly activated?. To answer the first question, we should take a look at the elements of the matrix W that present the highest values in each column (each column is formed by the weights of the muscles within each synergy). To answer the second point, we should instead focus on the time-varying activations (matrix H) and examine where the time profile of the activation coefficients presents a peak, and whether this peak is shifted in time across different speed conditions. Both kinds of information can be usually determined by visual inspection. For instance, by observing the data from cycling experiments (see Fig. 10), the following conclusion can be drawn:

- Synergy 1 primarily involves hip flexor (GMed), knee extensor (RF), and ankle dorsiflexor (TA). It is mainly active in the first part of the cycle, responsible for providing the force to start the upstroke phase of the cycle.
- Synergy 2 primarily involves hip abductor (VL), hip flexor (GMed), knee extensors (RF and VL), and ankle plantarflexor (SOL). It is mainly active in the central part of the cycle, contributing to the final part of the upstroke stage and to the initial part of the downstroke phase.
- Synergy 3 primarily involves hip extensor (ST and BF), knee flexors (ST and BF), and ankle plantarflexors (SOL and GM). It is mainly active in the final part of the cycle, therefore responsible for providing power during the downstroke phase of cycling.

When studying several subjects, if the protocol imposes fixed speeds across subjects, one important thing is to check is whether all subjects performed the corresponding movement at the same speed.

When analysing the muscle synergy vectors and the activation profiles, we can first visually check the similarity across subjects at each matched speed. In addition to visual inspection, it is reasonable to quantify possible difference across subjects. In order to assess similarity between two synergy vectors, we can use the mathematical operator called *normalized scalar product* (for details see [66]). This index ranges between 0 and 1, with 0 representing vectors with no similarity, and 1 meaning maximum similarity between the two vectors. To investigate similarity between the activation coefficients, it is possible to use another mathematical operation, called *cross-correlation* [34], between the two time profiles of the coefficients. The cross-correlation is a measure of similarity of the two profiles, and at the same time, it gives information on the possible shift in time between them.

In pathologic conditions, additional observations should be considered. In particular, one should pay attention to differences between pathologic and normal conditions, and in the case of hemiparesis (e.g., in stroke patients) paretic and the non-paretic side. This investigation should take into account three level of analysis, namely the EMG, synergy weights, and activations. Clark et al. [16] reported that when comparing healthy and post-stroke subjects during walking, synergies with similar muscle weightings are present, whereas a difference is observed for the activation coefficients. Indeed, as the severity of the pathology increases, the activation timing profiles become progressively more similar across the different synergies, suggesting that the ability to differentially activate the synergies is compromised in neurological patients.

In addition, the parameters that typically reflect the quality of the motor performance should be also analyzed. For instance, when analyzing a cycling task, we should take a look at the pedaling asymmetries in force or kinematics between the paretic and the unaffected leg.

In pathologic conditions, one parameter that is central when comparing different patients to each other or with controls is the VAF/R^2. Literature [14, 16] usually reports a lower number of synergies required to reconstruct the original EMG activations of patients, compared to healthy subjects. A lower number of synergies are usually ascribed to a lower complexity in the patterned EMG activity, characterized by increased levels of coactivation between muscles. In case this difference between healthy and pathological condition is observed in our data, we could perform a "VAF-based" analysis in two possible ways. A first option is to extract a number of synergies that fit the VAF criterion independently for each patient, and check whether patients need a different number of synergies with respect to healthy subjects. A second option is to fix a number of synergy (e.g., three in cycling, or four in walking) for all the subjects, and compare the resulting value of the VAF/R^2, expecting that patients will obtain a higher values with respect to healthy subject (meaning that a lower number of synergies is sufficient to reconstruct the pathologic muscle activity compared to the healthy one).

1.5 Discussion: Sensitive Parameters in Synergy Analysis

Muscle synergies have so far been proposed as expressions of a hypothetical modular organization of the neuromuscular system. While such a hypothesis has been difficult to test directly and the experimental evidence provided by the decomposition of muscle pattern has been debated [6], the analysis of muscle synergies can indeed be used as a compact representation of an EMG dataset. However, care has to be taken in defining the sensible parameters that could affect the entire investigation, potentially leading to erroneous conclusions.

First of all the investigator should choose the muscle groups to be recorded. Ideally, one should consider all the muscles involved in the task at hand. Clearly this might result very difficult, if not impossible, due to practical limitations such as the number of available EMG channels or the locations of the muscles of interest. Recently, Steele and collaborators [60] have shown in a simulated study that a wrong choice of muscles could lead to results that are different from ground truth. This problem can be ameliorated by taking into consideration at least the dominant muscles involved in the task.

Surface electromyography captures the electrical charge underneath the electrodes. In order to estimate the underlying neural drives, EMG signals should be processed as described in the previous sections. Particular attention should be paid to the cut-off frequency of the low-pass filter used to extract the EMG envelopes. If this frequency is lower than the frequency contents of the neural drives, the number of synergies might be underestimated [36].

The number of synergies to be extracted is always controversial and often prone to subjective choices. By analyzing the trend of the quality measure (VAF or R^2) as a function of the number of synergies, the investigator/clinician could either set a threshold or consider the elbow of the VAF graph. One strategy that might ameliorate this problem is to test the generalization capabilities of the extracted synergies: If they actually underlie the recorded data, they should be able to reconstruct part of the dataset that has not been used for the extraction (i.e., cross-validation). To the best of our knowledge, this method has never been tested in the context of muscle synergies. Moreover, measures based on the reconstruction quality of the EMG dataset are inherently confined to the input-space of the musculoskeletal system, and therefore they do not guarantee the observed task performance. A complementary metric based on single-trial task-decoding techniques has been recently proposed [24]. However, this method requires a very large amount of task repetitions that might not be available or feasible to acquire.

1.6 Conclusions and Future Trends

Muscle synergies analysis represents an interesting tool for clinical investigations thanks to its potential to infer neural functions from the noninvasive and relatively simple measure of the muscle activity. Differently from the traditional assessment methods describing overall motor behaviors, the analysis of muscle activity reflects the output of the nervous system, and muscle synergies analysis may help interpreting the difficult functional implications of muscle activity during motor tasks [57].

The application of muscle synergies in the rehabilitative clinical practice has been recently proposed, and their possible use in this field is suggested only by some observational studies. Results of muscle synergies analysis on SCI and stroke patients showed that they provide a compact description of changes in the activations of many muscles [13], and in case of stroke, the modifications of muscle synergies seems to be correlated to the motor and functional impairment [14, 16]. Moreover, it was also observed that muscle synergies change after therapy [67]. Therefore, muscle synergies analysis showed a diagnostic potential that can be used for quantitatively assessing the motor abilities of patients with motor deficits and the efficacy of any existing or new rehabilitative therapy. Besides, the observation of different patterns (such as preservation, merging, and fractionation) of muscle synergies across individuals suggested that muscle synergies analysis could drive patients classification and prompt the development of different customized therapeutic approaches [14]. According to the observation that some muscle synergies would be preserved and other modified by the pathology, it is possible to hypothesize that at the base of customized neurorehabilitative treatments there would be the choice to primarily target the abnormal muscle synergy structure and/or recruitment patterns [13, 14, 55]. In this sense, in addition to the motor therapy, other assistive approaches, such as electrical stimulation and cortically driven prosthetics, could favor the restoring of muscle synergy structure and recruitment [39].

However, given the poor availability of studies relating muscle synergies and rehabilitative treatments, the question of how muscle synergies can guide rehabilitation remains open. In particular, there are no evidences that motor impairments could be due to the dysfunctional synergy recruitment, or to the merging or disruption of the synergy structure, and if the neuromotor recovery may be achieved with the recovery of the correct recruitment, the reorganization of the original synergies or the creation of new adaptive and compensatory synergies.

To put more insights into this issue, more investigational and clinical studies should be performed not only on SCI and stroke, but also in other neurological diseases [39] such as multiple sclerosis, cerebral palsy, and Parkinson's disease. These studies not only should characterize muscle synergies in different populations, but they also should also focus on single subjects, follow the evolution of muscle synergies during the rehabilitative treatment, focus on the relation between rehabilitative treatment and neuromuscular organization, and compare different rehabilitative strategies.

Finally, it is evident that among the different studies, the methodological procedure for the analysis of muscle synergies is largely variable. The variability includes the task selected for the lower (such as walking overground or on a treadmill, with or without support, or at different walking speeds) and upper (such as planar or space reaching or isometric force generation) extremities, the kind and the number of muscles included in the analysis [52, 60], and the processing of EMG signals [34] (such as the low-pass filtering frequency, the factorization algorithms, the criteria to detect the number of muscle synergies). Such an incoherency could be one of the causes underlying the different and sometime discrepant results in literature, and consequently it increases the difficulty in comparing different studies.

This chapter aimed at deepening some issues of muscle synergies analysis, in order to favor the comparison of results across different studies, and to suggest the definition of a standard procedure for the acquisition and extraction of muscle synergies in human subjects that would further help the application of muscle synergies analysis in clinics.

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Workshop on Transcutaneous Functional Electrical Stimulation

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Abstract This chapter aims to give a general description of basic concepts related to transcutaneous FES. It offers examples of simple exercises to introduce the reader into the practical aspects of the application of transcutaneous FES. Different influencing aspects such as stimulation waveform, stimulation parameters, electrode type, placement, and size are analyzed. Available models related to FES that represent the electrical properties of the skin, current distribution on the skin, or either nerve excitability are presented as well, highlighting those factors that affect most transcutaneous FES applications. A practical guide on upper and lower limb is also presented, where different exercises are proposed to experience previously described theoretical aspects in practical application of FES. Finally, conclusions of the chapter and challenges observed during the exercises are described and novel techniques and technology used to overcome some of these challenges are mentioned.

1 Introduction

Functional electrical stimulation (FES) is a technique that applies electrical impulses to the peripheral nerves in order to elicit an artificially induced contraction of a muscle. The current is applied through at least a pair of electrodes that can be placed over the skin (transcutaneous or superficial stimulation), or inside the body (percutaneous

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or implantable stimulation depending on the degree of invasiveness). In any of these cases, an electric field is created between the two electrodes, producing current that propagates through the tissue and depolarizes muscle nerve fibers, generating an action potential. This action potential propagates along the nerve to the innervated muscle, where it creates a muscle contraction [23].

Neurological disorders such as brain injury or spinal cord injury can often lead to motor dysfunctions, which affect negatively to their quality of life. This inability of performing many ADL tasks can be overcome with the application of FES either by including it in rehabilitation programs or using it as an assistive device. Although its use in assistive applications is still limited, results of the application of FES in therapy have shown significant benefits [5, 18, 19].

2 Functional Electrical Stimulation (FES) Basics

2.1 Principle of Electrical Stimulation

When a muscle is physiologically contracted, the alpha motor neurons that are first activated are those innervating slow-twitch and fatigue-resistant muscle fibers. This recruitment order minimizes fatigue and guarantees that the less fatigue-resistant fibers are activated only when a higher force needs to be produced. However, when the muscle contraction is electrically induced through the skin, the recruitment order is typically inverted, because the motor neurons that are excited more easily are those with axons that have larger diameters, which usually innervate the less fatigue-resistant muscle fibers. The reality in transcutaneous FES applications is a bit more complex, since the activation of motor neurons depends not only on the size of their axons, but also on the stimulation parameters (frequency, amplitude, pulse-width) and on the distance between the motor neuron and the electrodes. Electrically-induced muscle contractions are in general more fatiguing compared to the natural activation of the muscle, because the muscle contraction is generated by continuously activating the same set of nerve and muscle fibers.

These differences between physiologically- and artificially-induced muscle contractions represent some of the challenges that have been overcome to some degree with novel devices and techniques. The choice of the appropriate electrodes and stimulation parameters is critical to produce a muscle response as natural as possible. The following sections will shed some light on this topic, giving special attention to transcutaneous stimulation.

2.2 Electrodes and Devices

The electrodes used for functional electrical stimulation can be classified into three categories, according to their invasiveness: transcutaneous, percutaneous, and implantable. Transcutaneous electrodes are the most used in practical applications, probably due to their versatility and minimum invasiveness. Percutaneous electrodes have been used in the past for better selectivity, specifically for the activation of deeper muscles that are difficult to activate from the surface. However, in chronic applications there is always a risk of infection. Nowadays percutaneous electrodes are mostly used for experimentation and neurophysiologic measurements that require high selectivity for a short period of time. Implantable electrodes are preferred as a permanent solution that minimizes the discomfort of the user since afferent skin receptors and nerves are not necessarily activated, as it is the case with transcutaneous electrodes.

Transcutaneous or surface electrodes stimulate the nerve fibers through the skin, making them the least invasive type of electrodes, but also the least selective for the activation of deeper neuronal structures. They must be carefully placed over the muscle belly or the nerve trunk, using the anatomical landmarks as guidelines. However, in most cases some readjustments are needed to obtain the desired elicited response, especially if the aim is to produce a pure movement that rotates the joint only around one axis. The muscle response depends on multiple factors, such as the properties of the muscle (muscle type, hydration, etc.), the thickness of the skin and the underlying fat tissue, and the position and exact orientation of the nerve fibers with respect to the electrodes. In fact, the high inter-subject variability constitutes one of the main drawbacks of transcutaneous electrodes, coupled with the difficulty to stimulate deep muscles, a poor cosmetic appearance, and the risk of the electrodes to come off the skin and alter the impedance during wear. Additionally, transcutaneous stimulation activates the sensory fibers and pain receptors of the skin, producing sometimes discomfort or pain to the subjects. On the other hand, transcutaneous electrodes have the clear advantage of being non-invasive and flexible to repositioning. This makes them the preferable solution in applications where the electrodes must be often relocated (e.g., when the paralysis after an injury changes over time, or when the muscle volume increases because of the training), in spasticity treatments where the antagonistic muscles must be strengthened, or in simple applications where only a few electrodes are needed to elicit a response [23]. As a consequence, main design criteria for these electrodes affect their comfort and performance; sufficient electrical surface area to prevent skin irritation, flexibility to adapt to the body surface, easy donning and doffing without being prone to come off the skin, reliable connection to the stimulator, electrical properties (stable electrical resistivity), material properties (made of hypoallergenic materials, resistant to biomedical chemicals), and convenience (reusability, low cost) [2].

Percutaneous electrodes, also called needle electrodes, are in between transcutaneous and implantable electrodes, and therefore share some of their advantages and drawbacks. They can be applied with minimal invasive procedures, since the electrodes are inserted in the body through a puncture on the skin. Only the wire tip is conductive, so, being subcutaneous, the discomfort caused to the subject is lower than with transcutaneous electrodes. However, the skin interface needs to be carefully maintained in order to reduce the risk of infection, although it has been reported only a few times in literature during application. The main risk of infection occurs through extraction and related electrode fractures that leave parts of the electrode inside the body. An infection rate of 16 % has been reported in subjects with long treatments [8]. Percutaneous electrodes are positioned with an epidermal needle next to the nerve and allow the stimulation of deep muscles. In case percutaneous electrodes move or break, the subjects do not have to undergo a surgery, since wires can be easily replaced. However, remaining artifacts are left in the body. Nevertheless, percutaneous electrodes have not been used in literature as much as transcutaneous or implantable electrodes.

Implantable electrodes are the most invasive solution, and therefore the choices of materials that are biocompatible and resistant to mechanical stress are critical in their design. They consist of two main parts: the electrode wire, often made of stainless steel, and either an electrode cuff including multiple contacts that is wrapped around the targeted nerve or a silicon embedded platinum plate (in case of epimysial electrodes) that is sewn on the epineurium [23]. The short distance between the electrode and the nerve fiber guarantees the highest sensitivity and good selectivity when properly placed. Their placement requires a surgery, which must be repeated if the electrodes break or move. Implantable electrodes are indicated for long-term applications that want to free the patient from continuous placement or repositioning of the electrodes, for systems that minimize the skin sensation (or discomfort) caused by surface electrodes, or for applications where surface electrodes cannot be applied, such as the stimulation of deep muscles [23].

Implantable electrodes have also been used in the past for high-density stimulation involving many muscles, e.g. in hand and finger movements where muscles are spatially close. Conventional surface electrodes are difficult to use for this type of applications; however, in the last few years transcutaneous electrode arrays have arisen as an alternative solution to implants. An electrode array is a matrix that contains many small electrodes that can be activated independently, and it is very useful when placed over a skin area with several motor points, allowing the simultaneous stimulation of a few muscles using only one matrix. Additionally, the high density of electrodes opens the way to new control techniques that can achieve personalized transcutaneous stimulation. In fact, several algorithms have been recently proposed to automatically calibrate the single electrode or cluster of electrodes that must be active to elicit a specific response, and this has drastically reduced the set-up times and has eliminated the need to reposition the matrix. Some other novel techniques have been proposed to change the distribution of active electrodes with time, switching between fibers and reducing muscle fatigue.

2.2.1 Influence of Stimulation Parameters

The human musculoskeletal system is highly complex, and its response to external stimuli varies between subjects, over time, muscle and fiber locations, among others. Therefore, even if some general guidelines can be established, most FES applications have an initial phase of calibration, in which several parameters are tested in order to choose the best solution. The most important parameters are the stimulation waveform, frequency, amplitude and pulse-width, and the electrode size and position. These are going to be analyzed in the following pages, providing some practical hints to the reader.

Stimulation waveform

The stimulation waveform used for FES applications is generally a train of rectangular pulses, either monophasic or biphasic (see Fig. 1). Monophasic pulses are often used for research purposes, as they do not contain a hyperpolarization pulse (anodic pulse) that balances the electrical charge applied to the muscle. Most FES applications use biphasic pulses, with a depolarization pulse (cathodic current pulse) that in most cases is rectangular, and an hyperpolarization pulse (anodic current pulse) that can have a symmetric shape, or has a longer width and a smaller amplitude (which can be useful if the amplitude is below the motor threshold) or in some cases has an exponential decreasing shape. Generally, symmetric biphasic waveforms are used to generate force in bigger muscles, whereas asymmetric waveforms are preferred for smaller muscles where higher selectivity is needed.

Stimulation frequency

A stimulation pulse produces in the muscle a twitch that fades out after 200 ms (see Fig. 2). When the stimulation signal is a train of pulses, the ratio between this muscle relaxation time and the period between pulses is crucial to understand the response of the muscle, which is highly dependent on the stimulation frequency.

When the stimulation frequency is below 10 pulses per second (10 Hz), the muscle twitches can still be differentiated from each other, and the muscle response can be characterized as a sort of tremor. This effect gradually decreases when the stimulation frequency increases, usually around the band of 10–30 Hz, until it reaches a point where it evokes a smoother muscle response known as tetanic contraction (see Fig. 2). The frequency when this happens is called the fusion frequency, and its exact value varies between subjects and fibers.

However, this does not mean that functional electrical stimulation should always use high frequencies. In fact, when the stimulation frequency keeps increasing toward the fusion frequency and above, the muscles start to fatigue very fast. The main reason is that with FES the excited fibers are all firing synchronously and not asynchronously and distributed among several hundreds to thousand fibers as it is the case in the

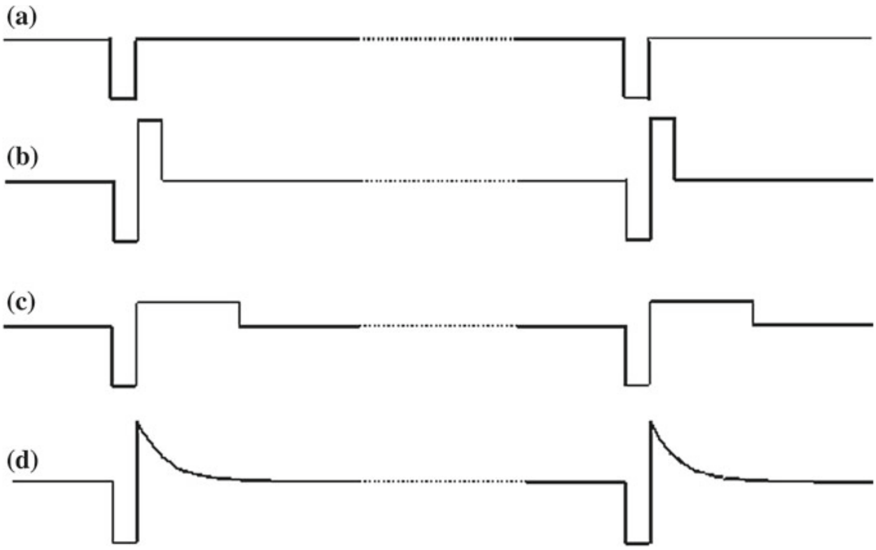

Fig. 1 **a** Commonly used pulse forms. The depolarization pulse is for all pulse forms rectangular with a pulse-width up to 300 μs and the hyperpolarization pulse is (**a**) not existent = *monophasic pulse*; **b** the same as depolarization pulse = *symmetric biphasic pulse*; **c** longer than the depolarization pulse, with a subthreshold amplitude = *asymmetric rectangular biphasic pulse*; or **d** shorter than the depolarization pulse, with a subthreshold pulse duration = *asymmetric exponentially decreasing biphasic pulse*

natural activation. In the natural case each single fiber is only activated 0.3–5 times per second allowing sufficient recovery time for recovery and energy uptake. In FES the stimulation frequencies that are normally used are in the range from 20 to 100 Hz, depending on the application.

Stimulation amplitude

Changes in the stimulation amplitude or pulse duration cause similar effects on the elicited muscle response. Higher stimulus intensities produce higher contractions through activation of more fibers, which can be measured as higher joint torques. However, there is a lower threshold under which the stimulus produces no response, and also an upper threshold of saturation where no additional fibers can be recruited. Additionally, the muscle response between the two thresholds is not linear; as it has been described before, the electrically-induced response of the muscle is created by the activation of several muscle fibers whose activation threshold depends on their diameter. Smaller myelinated nerves have closer nodes of Ranvier, which means that to elicit an action potential using FES we would need a higher voltage gradient (thus, a higher electric field and a higher current). Finally, the distance between the

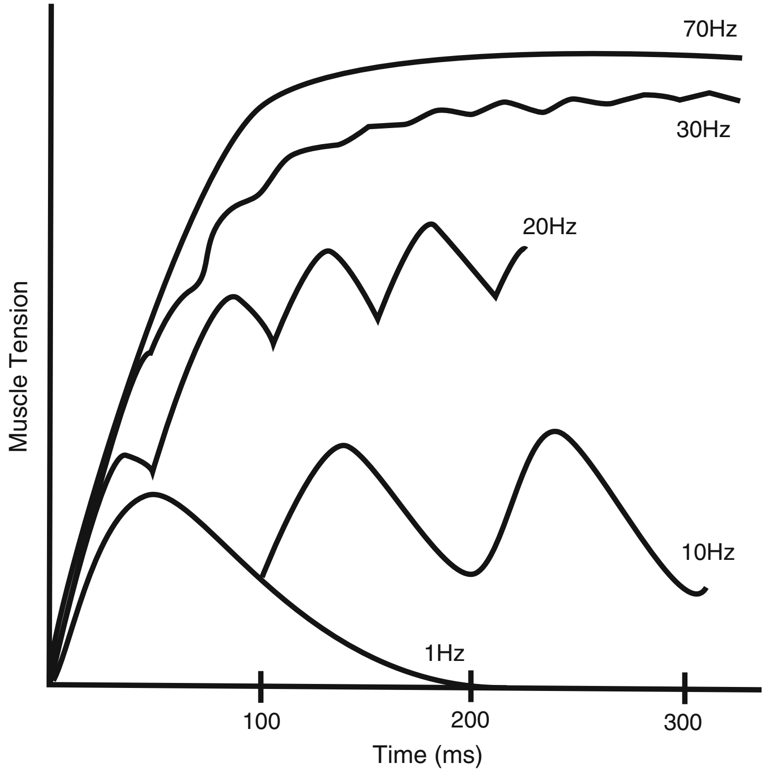

Fig. 2 Effects of stimulation frequency on muscle tension (Adapted from [3])

muscle fibers and the skin also plays a fundamental role, since the fibers closer to the electrode are reached by a stronger electric field.

It could be shown in [3] that due to afferent feedback in stroke subjects higher torques in triceps muscles could only be generated with shorter pulses, as a longer pulse duration caused antagonistic muscle responses of the biceps muscles. The curves in Fig. 3 represent the pairs of intensity current and pulse-width that elicit the same motor response in a subject, and as a rule of thumb, larger pulse-widths need to be paired with lower currents in order to obtain the same motor responses. However, there is a saturation for the pulse-width that prevents the muscle from producing a stronger contraction, even when the current amplitude is maintained and the pulse width is increased. The stimulated motor response in healthy subjects is in between the innervated motor threshold and the maximum motor response; therefore, the dotted rectangle represents the range that is normally used in FES applications. For example, for wrist extension the typical pulse widths vary from 40 to 300 μs, whereas the current amplitude is usually set up between 10 and 40 mA. However, it is very dependent on the subject pain threshold and the muscle that has to be activated. The other extreme is completely denervated muscles, e.g., in spinal cord injured patients.

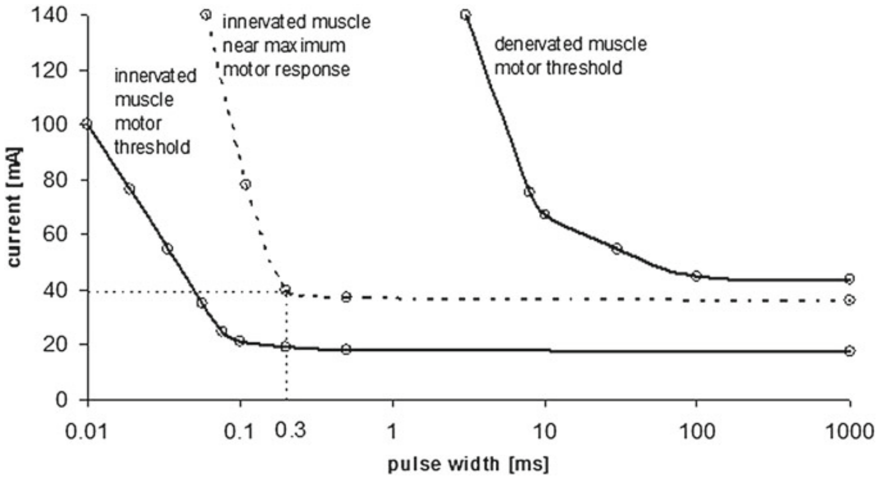

Fig. 3 Curves of equal motor response for different pulse widths and pulse amplitudes. For intact motor neurons stimulation pulses longer than 300 μs do not increase the motor response if the stimulation amplitudes are higher than 40 mA. Denervated muscles require a 100–1000 times longer stimulation pulse-widths than innervated muscles (Data from wrist extensor, surface stimulation, stimulation frequency 35 Hz). Adapted from [3]

Those muscles are no longer connected to the spinal cord (e.g., a cauda equina lesion) and get completely denervated. In such cases, it is possible to produce, after a long training period of weeks to months, muscle contractions by direct stimulation of the motor end plate instead of the nerve. However, the pulse-widths that must be used have to be 100 times larger. Here, one cannot increase the amplitude instead, as the high currents would heat the tissue to unaccepted levels.

Electrode placement

Two main aspects must be considered for the electrodes placement: the position and the distance between anode and cathode.

In order to elicit muscle responses, the active electrode (cathode) must be placed on the muscle belly, close to the innervating nerve or anywhere else where the innervating nerve is close to the surface. Placing them on the muscle belly is easier, especially in the case of the lower limbs, where the muscles are bigger and the electrodes must simply be placed along the fiber. Alternatively, the stimulation of the innervating nerve at some other location (where this nerve is close to surface) has the advantages that stimulating deeper lying muscles can be reached. Often smaller electrodes are used in this case, which sometimes can have the drawback of making the subject feel discomfort. The area that can be found to stimulate a specific muscle is called the motor point of this muscle. Some regions of the body have several motor points very close, like the arm or the hand. For such regions, the best option is to use multiple small electrodes as proposed with electrode arrays.

The second aspect that plays an important role is the distance between the anode and cathode. Considering the tissue to be homogeneous, the same electrical potential difference between the electrodes will create a stronger and more superficial electrical field if the electrodes are closer. This electrical field will activate only the superficial fibers, and with a very high intensity, which can be useful for small muscles (like the arm muscles). On the other hand, bigger muscles (like for instance the rectus femoris) require a higher distance between electrodes, where the electrical field will reach more fibers with a lower intensity. However, there is a drawback for increasing the distance between electrodes: as the electrical field spreads out over the tissue, it can activate other muscles, including the antagonists if the distance is high enough.

Electrode size

The choice of the size of the electrode (i.e., the size of their active area) depends on the dimension of the muscle or nerve that wants to be activated. As a rule of thumb, larger electrodes will reach deeper nerves, thus achieve overall stronger contractions but have a lower muscle selectivity. Small electrodes can result in very high current densities, which can lead to skin irritations or burns. Generally, small electrodes provide a better selectivity, however limit the penetration depth. The size of the electrodes that are normally used ranges between 2 and 50 cm^2; the smallest ones are used for stimulating superficial nerves, those of 6–10 cm^2 are indicated for smaller muscles, whereas electrodes bigger than 25 cm^2 or more are designed for larger muscles or dermatomes [1].

2.3 Modeling FES

The recent development of more selective FES technologies has created the need to better understand the properties of the nerve, bone, muscle, fat, and skin, and how they react when external electrical stimuli are applied. In this scope, simulations of body segment volume conductor models have been used to determine which structures are important to be considered and how stimulation parameters need to be optimized for more efficient stimulation of neural structures. This second aspect requires a two-step model, the volume conductor with all relevant physical properties and a nerve model that determines when the neuronal structure is activated. Simpler, more classical modeling of effects of electrical stimulation to tissues can be done with electrical circuit models, in case the physical structures and anatomical properties are not important.

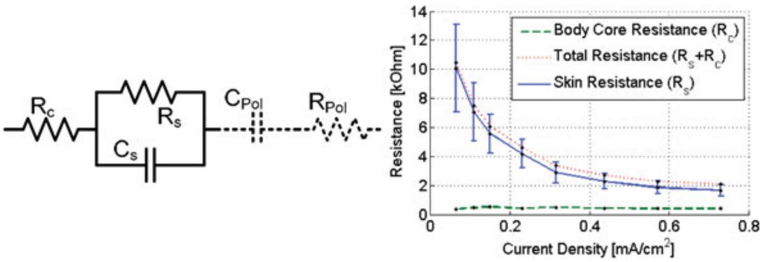

Fig. 4 Equivalent electrical model for the biological tissues (Reproduced from [11])

2.3.1 Models Used for Describing the Electrical Effects of Electrical Stimulation

Both modeling approaches characterize the full dynamics that connects the stimulation current to the nerve recruitment. In this section we first describe simplified one-dimensional electrical models and then the combination of volume conductor models with nerve activation models.

Simplified electrical models

The simplest way of modeling the skin and underlying tissues is by assuming their permittivity and resistivity is homogeneous and hypothesizing the propagation of the current impulse to occur only along one axis. This leads to the equivalent electrical model that is shown in Fig. 4, consisting on a resistor representing the fat and the muscle (Rc) in series with a RC parallel circuit representing the skin (Cs, Rs), and an additional capacitor and resistance that model the electrode polarization effects, which can be neglected for surface FES. The values of the body-core resistance, and the skin resistance and capacitance can be experimentally determined by current–voltage responses measured on the skin and with needle electrodes within the muscle tissue. Results show that the value of the body-core resistance is independent of the current density, whereas the skin resistance decreases when the stimulation amplitude increases using a specific stimulation electrode size (see Fig. 4). Hence, the skin impedance is a non-linear function of the current density [6].

Volume conductor models

A full characterization of the three-dimensional propagation of the stimulation current and the induced voltage gradients requires a more advanced model that includes more complex volumetric models, where current and voltage can have arbitrary directions. Recent studies have used a finite element (FE) model to simulate the distribution of the potential inside the biological tissues, i.e., the skin, fat, muscle and bone layers

[9]. These types of models can work with detailed geometries (reconstructed from MRI scans), are able to deal with inhomogeneities (such as sweat ducts and glands), and can simulate specific stimulation pulse waveforms, electrode positions and sizes. The equations that are used to model the propagation of the electrical field can be static or quasi-static or transient (including the inductive effects and the times of wave propagation). Additionally, each tissue layer can be defined in terms of geometry and structure, and its electrical properties can also be accurately specified (permittivity, conductivity). The inclusion of the dielectric properties of the tissues was introduced by Kuhn and colleagues [9], proving that the differences in the dielectric properties between tissue layers create capacitive effects that are not negligible for the skin. Their method obtained very good comparisons with experimental measurements on healthy volunteers.

Nerve models

The second step of modeling tissue excitability focuses on the transmembrane potentials of the nerve axons, which depend on the extracellular potentials that are calculated using the FE model of the conductor volume. The nerve model contains thousands of myelinated axons that can be activated using electrical current pulses, generating action potentials that activate the muscle fibers [12]. The main information that can be extracted from the nerve models is which factors are important in the design of the optimal transcutaneous electrical stimulation.

2.3.2 Important Factors for Nerve Activation

The analysis and simulations with these two-step models can be used to extract quantitative relations between the several factors and the stimulation outcome. The main factors that have been investigated with respect to the volume geometry were thicknesses, nerve depth, inhomogeneities, electrode position, electrode size, properties of the different layers (permittivity, resistivity), modeling equations (transient or quasi-static, including the pulse amplitude and duration), and the type of nerve model (axon diameter and diameter distribution) [9, 11, 12]. The parameters that have a stronger influence in transcutaneous electrical stimulation are the nerve depth, the resistive properties of the muscles, the axon diameters, and the axon diameter distribution. In addition, the stimulation parameters (electrode position and size, pulse-width, and amplitude) must be carefully considered when designing a FES application.

2.3.3 Selectivity and Comfort of Electrodes

The combination of the volume conductor and the nerve models is leading to a full understanding of the dynamics that connect the transcutaneous stimulation parameters with the response of the nerves and fibers. This has opened a research line that

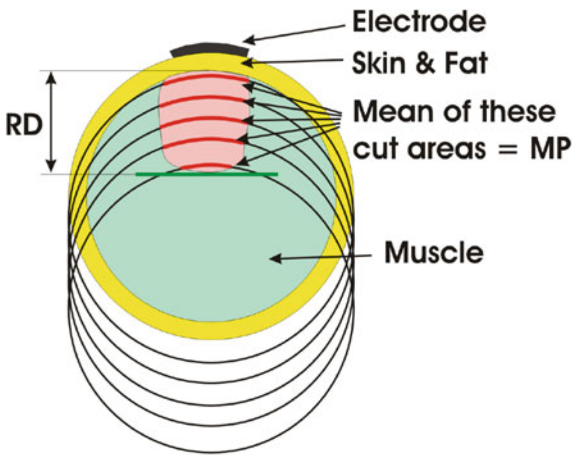

Fig. 5 Definition of the Recruitment Depth (*RD*) and Mean Profile (*MP*) (Reproduced from [10])

aims at optimizing the FES applications, which is translated into stimulating muscles with the highest selectivity, while causing the lowest discomfort to the subject. However, reaching both goals simultaneously is not simple. The two main factors that influence selectivity and comfort are the electrode size and the electrode materials. The electrode is usually built by stacking two layers of conductive hydrogel, a conductive substrate (made of fabric or carbon film) and a substrate. This construction provides a distributed current density over the electrode surface, prevents the skin from burning and guarantees a low electrode-substrate-skin impedance in order to excite the minimum number of afferent nerves [7]. Therefore, when designing a FES application, it is much easier to reach the selectivity and comfort specifications by changing the electrode size. The size of the electrodes is usually chosen in function of the stimulation site, depending on the size of the muscle that wants to be contracted and the proximity of the adjacent muscles that want to be avoided. Smaller electrodes produce more selective activations; however, it might be difficult to activate deep muscles as they generate high current densities that could cause discomfort to the subject [13]. The optimal electrode size can be assessed by combining transcutaneous stimulation FE models (that will establish the selectivity) and experiments in subjects (who will characterize the perceived comfort). The electrical field that is created by the electrodes will penetrate the skin with a certain recruitment depth and width, shaped as a lobe in a cross-sectional view of the muscle (See Fig. 5).

Therefore, the selectivity can be defined as proportionally dependent on the Recruitment Depth (RD) and inversely related to the area that is affected by the lobe, i.e., the Mean Profile (MP) [10, 13]:

$$\text{Selectivity} = \text{RD/MP}$$

On the other hand, the estimated comfort can be assessed as a combination of the pain threshold (ThePain) and the current density of the electrode (CD). None of these

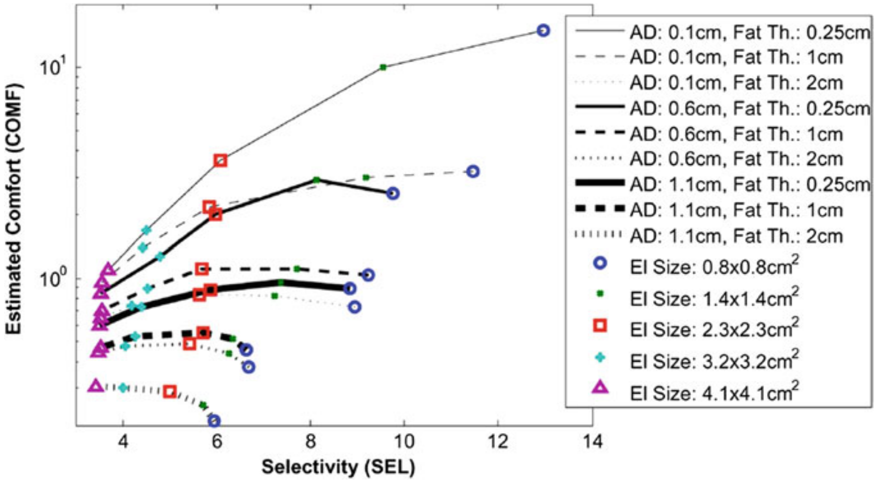

Fig. 6 Comfort versus selectivity, for a various set of Activation Depths (*AD*), Fat Thicknesses (*Fat Th*), and Electrode Sizes (*El Size*) (Reproduced from [11])

parameters can be measured directly; therefore, it has been suggested in literature to measure the perceived pain threshold as the average on ten healthy subjects, and to calculate the current density by dividing the amplitude of the stimulation by the area of the electrode [13]:

$$\text{Comfort} = \text{ThePain/CD}$$

A recent study in literature [13] simulated the selectivity and comfort for a set of electrode sizes, activation depths, and fat thicknesses (Fig. 6). Results show that both selectivity and estimated comfort are strongly influenced by the three factors, and they all play a role in the muscle response. This study also indicates that smaller electrodes produce more selective muscle activations and tend to cause less discomfort in the subject when the current density is kept constant. However, the estimated comfort reaches a maximum that does not always correspond to the smaller electrode. In fact, for high activation depths and thick fat layers, smaller electrodes can be less comfortable than larger electrodes. The reason for all this is twofold: electrical stimulation is more tolerable when it is felt on a smaller portion of the skin (less receptors are activated), and the current with smaller electrodes (at a specific current density) penetrates less deep into the tissues than with a larger electrode.

3 Upper Limbs—Practical Guide

Upper limbs are involved in a countless amount of activities of daily living (ADL) that include reaching, grasping, and manipulating objects.

This section aims to be a practical introduction to transcutaneous FES on upper limbs, where practical exercises are suggested in order to experimentally prove the basic concepts described in the previous section and check at first hand the main challenges related to transcutaneous FES application in upper limbs.

General notes In order to use transcutaneous functional electrical stimulation in efficient and safe manner it is necessary to obey certain elementary rules.

As explained in the introduction, FES is achieved by applying electrical current to the muscle or nerve fibers through electrodes placed on the skin surface. It is important that the surface of the electrode is conductive, adhesive, and has good contact with skin along the entire surface. Most commercial electrodes used today have a layer of conductive gel which ensures these properties. In any case, before placing the electrodes one should check if the gel is moist and adhesive, as dried up electrode can cause discomfort or pain during stimulation.

When starting the stimulation it is advised to start with the lowest recommended amplitude and gradually increase it until the required response is achieved.

3.1 Upper Arm

Upper arm muscles act mainly at shoulder and elbow joints; therefore, the main functional task carried out by these muscles is the reaching task.

3.1.1 Anatomy

Anterior and posterior views of arm muscles are shown in Fig. 7. However, for the following exercises we will briefly describe the prime movers and those muscles located distally starting at the shoulder.

Deltoid is one of the most important muscles involved in shoulder motion. When its lateral or all fibers are active, deltoid causes abduction of the arm, but it is also responsible for flexion/extension of the arm when its anterior/posterior fibers are activated isolatedly. This muscle is innervated by the axillary nerve. Biceps and brachialis are prime movers of elbow flexion, and are innervated by the musculocutaneous nerve. Finally, triceps muscle is the prime mover of elbow extension and is innervated by the radial nerve. In Fig. 8 we can see an scheme of the peripheral nervous system relevant to the arm.

3.1.2 Exercises

The aim of the following exercises is to experiment basic application of FES on the upper arm and see the effects of location of electrodes and parameters regarding motor outcome and discomfort. As the aim is to generate a contraction of a big

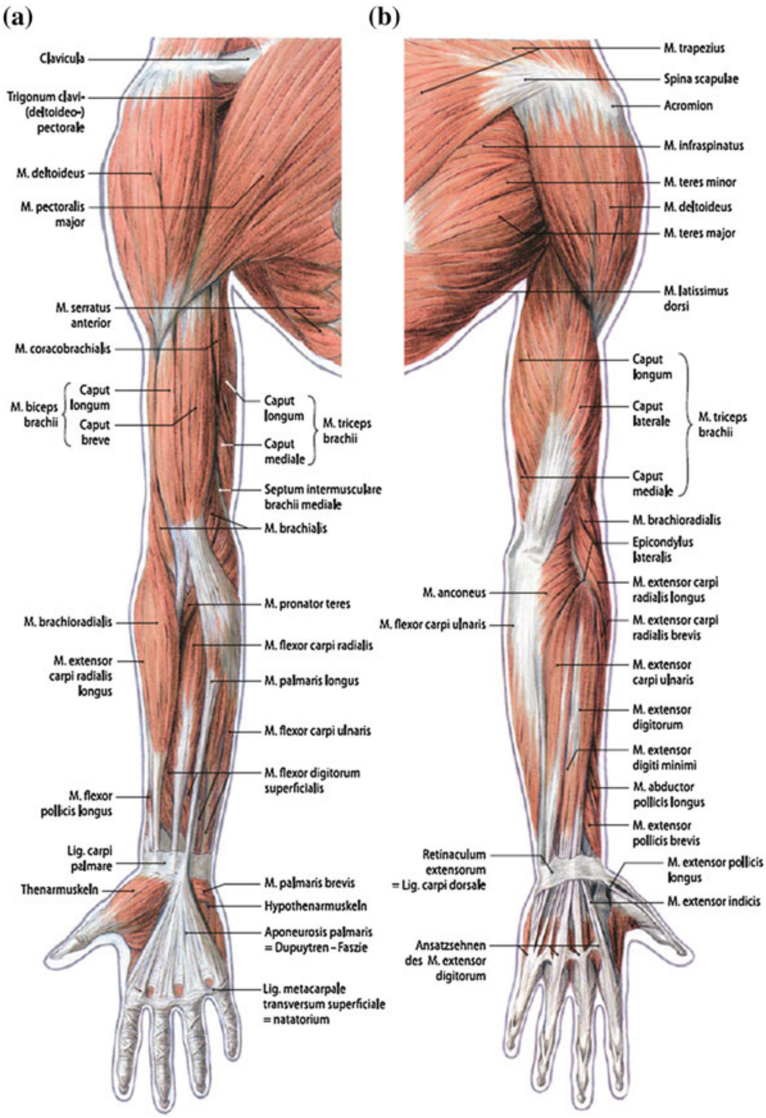

Fig. 7 **a** Anterior view of arm muscles. **b** Posterior view of arm muscles [17]

muscle, in these exercises electrodes are placed over the top and bottom sides of the targeted muscle belly (along the muscle) with enough distance between them to ensure that the current goes deep enough to reach the motor nerve fibers and generate an action potential [3].

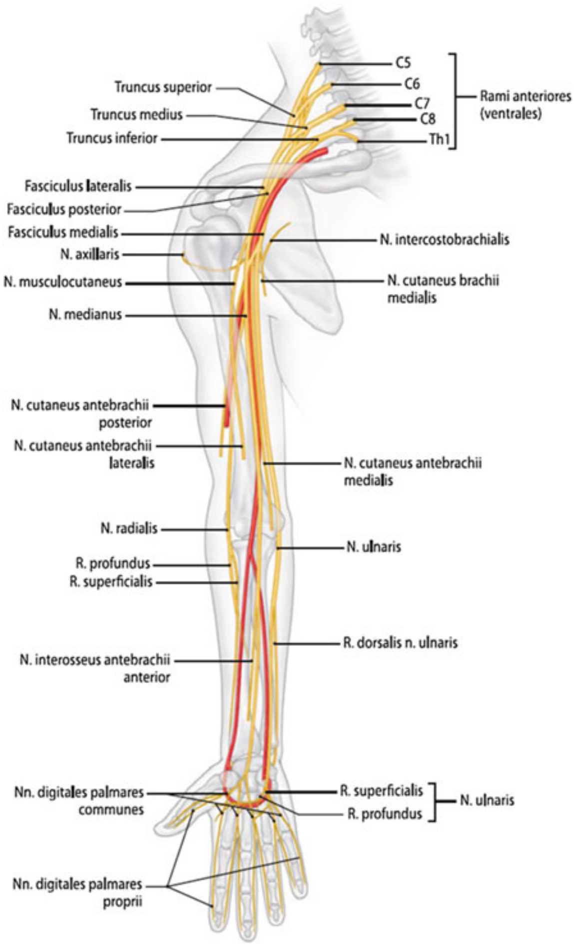

Fig. 8 Scheme of upper arm nerves [17]

If the exercises are carried out in group, the high inter-subject variability in terms of sensation (amplitude tolerance) and motor response to FES application will be observed.

Arm movements at the shoulder are primarily performed by the deltoid muscle, as previously described. In this exercise we will see that flexion, extension, and abduction of the arm at the shoulder can be achieved by acting in the different fibers that form the deltoid. Figure 9 shows some examples of electrode placement for different movements of the arm. Parameters used during the the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 25 Hz
- Pulse-width: 200 μs
- Amplitude: upon tolerance

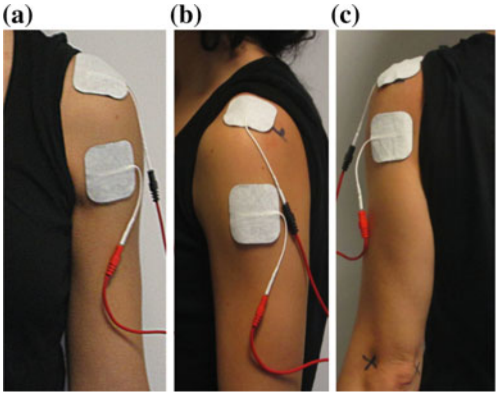

Fig. 9 **a** Example of electrode position for shoulder flexion. **b** Example of electrode position for shoulder abduction. **c** Example of electrode position for shoulder extension

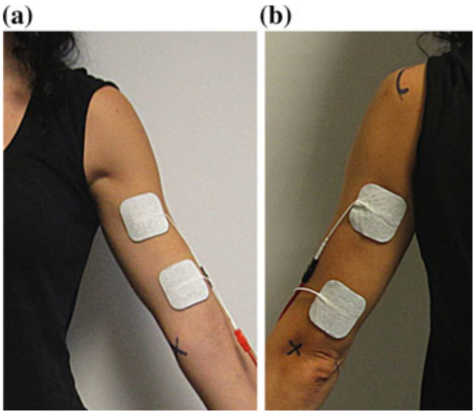

Fig. 10 **a** Example of electrode position for elbow flexion. **b** Example of electrode position for elbow extension

After performing stimulation of the deltoid muscle with different electrode placements, we should be able to see the different arm movements generated when applying FES to motor nerves that innervate different muscle fibers.

Elbow flexion is mainly operated by the muscles located in the anterior part of the upper arm. The objective of this exercise is to get an elbow flexion and observe the effects of changes in pulse-width on outcome and discomfort. An example of electrode placement for elbow flexion is shown in Fig. 10. Parameters used during the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 25 Hz
- Pulse-width: 100–300 μs
- Amplitude: upon tolerance

After applying FES to the anterior part of the arm with different pulse-width values, we should be able to see that muscle contractions are stronger when higher pulse-width values are used and, on the contrary, higher amplitudes are needed to

achieve a motor response when lower pulse-width values are used. This fact proves the concept shown in Fig. 3 and explained in Sect. 2. Regarding discomfort, in general the longer the pulse-width is, the more uncomfortable the stimulation becomes.
Elbow extension is performed by the triceps muscle, located on the posterior part of the upper arm. The objective of this exercise is to get an elbow extension and observe the effects of changes in frequency on outcome and discomfort. An example of electrode placement for elbow extension is shown in Fig. 10. Parameters used during the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 5–50 Hz
- Pulse-width: 200 μs
- Amplitude: upon tolerance

After applying FES to the posterior part of the arm with different frequency values, we should be able to see that the outcome to low frequencies are short muscle twitches or fasciculations, whereas we get tetanic muscle contractions as we go higher in frequency values. This fact proves the concept shown in Fig. 2 and explained in Sect. 2. Regarding superficial discomfort, in general, high frequencies (35–50 Hz) are more comfortable than middle frequencies (20–35 Hz), although they carry a big disadvantage in terms of fatigue that will be discussed more in detail in Sect. 4.

3.2 Forearm and Hand

Forearm and hand muscles are mainly involved in wrist, finger, and thumb movements. Therefore, the main functional tasks carried out by these muscles are the grasp and manipulation of objects.

Although a healthy human is able to grasp precisely different types of objects in a great variety of manners without a special effort, it is an extremely complex task that is the result of a combination of perfectly synchronized muscle contractions. The objective of these exercises is to explore the effects of the application of transcutaneous FES onto the forearm while trying to achieve a functional grasp by combining different wrist, finger, and thumb movements.

3.2.1 Anatomy

Most forearm muscles act at wrist, finger, or thumb joints. The forearm muscles that generate finger and thumb movements are known as the extrinsic muscles of the hand, which arise in the forearm and insert into the digits via long tendons crossing the wrist. The intrinsic muscles of the hand, which arise and insert within the hand, are involved in finer finger and thumb movements where thumb is controlled by the thenar muscles. However, for practical reasons, in most applications transcutaneous FES is limited to stimulation of the extrinsic muscles of the hand. Figure 7 shows anterior and posterior superficial views of arm muscles.

Most muscles located on the anterior part of the forearm generate flexion movements at the wrist and fingers and are mainly innervated by median or ulnar nerve. Conversely, muscles located on the posterior part of the forearm generate extension movements at the wrist and fingers and are innervated by the radial nerve and its branches. Although there are forearm muscles that act on the thumb, thenar muscles are the prime movers of thumb abduction and opposition, which are innervated by median or ulnar nerves. In Fig. 8 we can see an scheme of the peripheral nervous system relevant to the arm.

3.2.2 Exercises

The objective of the following exercises is to explore the effects of the application of transcutaneous FES onto the forearm and try to achieve selective movements by finding different motor points.

It is important to point out that the neuromuscular system that controls hand movements is extremely complex, with numerous muscles located at different depths from the skin surface and innervated by branches of the same nerve. Therefore, small electrodes are suggested for finding independent motor points. We call motor points to those skin surface points where, when transcutaneous FES is applied, a determined and, if possible, isolated muscle contraction is obtained. When muscles are deep or are located under other muscles, it can be very difficult or impossible to activate them without activating neighboring motor nerve fibers as well.

For compensating this selectivity issue, a system with multi-field electrodes was used for these exercises [21, 26]. Two regular electrode matrices of 16 small fields each were used, one of them was placed covering the extensor muscles and the other one was placed covering the flexor muscles. One big common anode was used for each electrode matrix, which was located over the tendinous area of the wrist in its respective side. Electrode configuration is shown in Fig. 11. This approach of small cathode matrix and big common anode is used in order to generate an action potential in a precise location of the forearm without generating any at the wrist.

It can be that certain movements are not achieved in the following exercises in some subjects and it is due to inter-subject physiological variations. Relative position of muscles, nerves, and skin changes slightly among individuals, which can make it difficult to find some motor points in some subjects. If the exercises are carried out in a group, the high intersubject variability in terms of sensation (amplitude tolerance) and motor response to FES application will be observed once more.

Parameters used in the following exercises should be:

- Waveform: biphasic symmetrical
- Frequency: 25 Hz
- Pulse-width: 200 μs
- Amplitude: upon tolerance

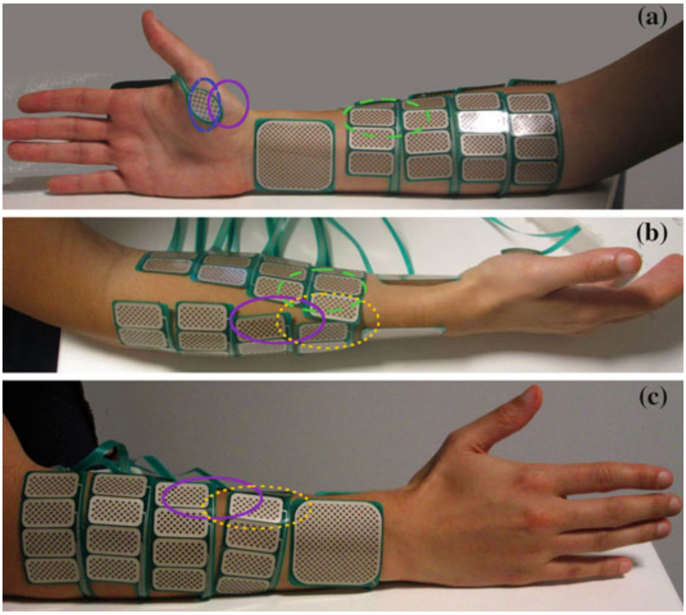

Fig. 11 Approximated areas where motor points are expected to be found. Each color aims at a different thumb movement. *Orange dotted*—extension, *purple solid*—abduction, *blue dash-dotted*—opposition, *green dashed*—flexion. **a** Anterior view of thumb motor points. **b** Radial view of thumb motor points. **c** Posterior view of thumb motor points

Thumb movements are controlled by muscles located both on the forearm and on the palm. In this exercise, we will try to find motor points that generate thumb extension, flexion, abduction, adduction, and opposition. Figure 11 shows areas where the corresponding motor points are usually found.

After applying FES on forearm and palm with different electrode placements, we should be able to see the different thumb movements generated when applying FES to the different motor points.

Wrist and finger flexors are located in the anterior part of the forearm. In this exercise, we will try to find motor points that generate combined wrist and finger flexion as well as isolated wrist flexion and finger flexion. Figure 12 shows areas where the corresponding motor points are usually found.

After applying FES on the anterior forearm with different electrode placements, we should be able to see the different wrist and finger movements generated when applying FES to the different motor points.

Wrist and finger extension is controlled by the muscles located in the posterior part of the forearm. In this exercise, we will try to find motor points that generate combined wrist and finger extension as well as isolated wrist extension, index extension, and finger extension. Figure 13 shows areas were the corresponding motor points are usually found.

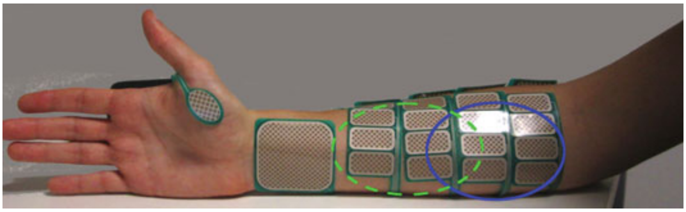

Fig. 12 Approximated areas where motor points are expected to be found. Each color aims at a different flexion. *Blue solid*—wrist flexion, *green dashed*—finger flexion

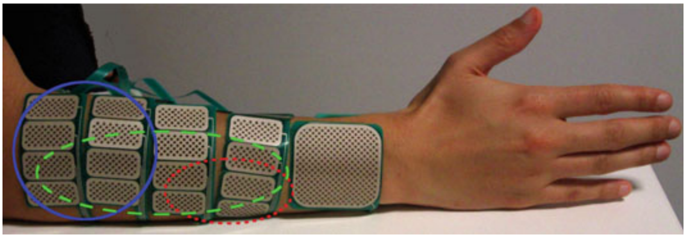

Fig. 13 Approximated areas where motor points are expected to be found. Each color aims at a different extension. *Blue solid*—wrist extension, *green dashed*—finger extension, *red dotted*—index extension

After applying FES on the posterior forearm with different electrode placements, we should be able to see the different wrist and finger movements generated when applying FES to the different motor points.

Grasp sequences Many grasp classifications have been suggested in literature, but most taxonomies distinguish at least three main grasping postures, which are palmar or power grasp, pitch or precision grasp, and lateral grasp [14]. In these exercises we play around to find sequences of activations in order to achieve different grasps. The objective is to achieve a palmar grasp (bottle), a lateral grasp (credit card), and a precision grasp (very small object). Quick design of simple sequences is suggested to be designed by a trial-and-error method, where motor points are manually activated and deactivated. An example of a simple sequence for the palmar grasp is presented as follows:

Palmar grasp sequence *Activate wrist extensors⟶Activate finger extensors⟶ Activate thumb abductor⟶Deactivate finger extensors⟶Activate finger flexors⟶Deactivate thumb abductor*

4 Lower Limbs—Practical Guide

In this section, we will describe practical guidelines for applying functional electrical stimulation for activation of various muscles in lower limbs in order to actuate different joints. Through these exercises we will get familiar with the challenges present in this field, such as muscle fatigue and electrode placement. These challenges, as well as techniques for overcoming them will be discussed.

General notes In order to use transcutaneous functional electrical stimulation in efficient and safe manner it is necessary to obey certain elementary rules.

As explained in the introduction, FES is achieved by applying electrical current to the muscle or nerve fibers through electrodes placed on the skin surface. It is important that the surface of the electrode is conductive, adhesive, and has good contact with skin along the entire surface. Most commercial electrodes used today have a layer of conductive gel which ensures these properties. In any case, before placing the electrodes one should check if the gel is moist and adhesive, as dried up electrode can cause discomfort or pain during stimulation.

When starting the stimulation it is advised to start with the lowest recommended amplitude and gradually increase it until the required response is achieved.

4.1 Upper Leg

Upper leg muscles are the actuators of knee joint, and they participate in the actuation of the hip. In this section we will focus on the functionality of the knee.

Knee flexion is actuated by hamstring muscles; semimembranosus, biceps femoris and semitendinosus, all innervated by the sciatic nerve. In order to activate these muscles, large electrodes are placed on the posterior side of the thigh, as shown in Fig. 14.

Parameters used during the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 50 Hz
- Pulse-width: 300 μs
- Amplitude: 20–45 mA (upon tolerance)

Fig. 14 Approximated areas where motor points for knee flexion are expected to be found

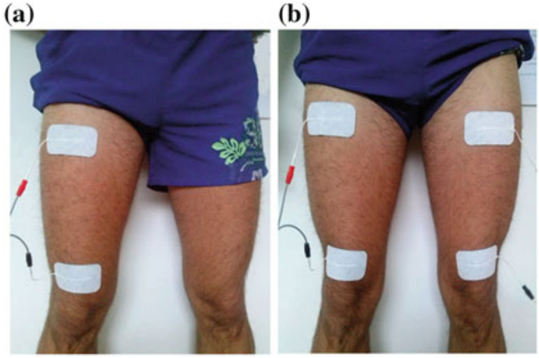

Fig. 15 Approximate electrode placement for **a** knee extension and **b** fatigue exercise

The subject should lie on the belly with his legs laid freely. When the stimulation starts, and the activation threshold is reached, the knee of the stimulated leg should start to flex, lifting the foot and the lower leg.

Knee extension is actuated by the quadriceps muscles; rectus femoris, vastus medialis, vastus intermedius, and vastus lateralis. These are innervated by the femoral nerve. In order to activate these muscles, large electrodes are placed on the anterior side of the thigh, as shown in Fig. 15a.

Parameters used during the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 50 Hz
- Pulse-width: 300 μs
- Amplitude: 20–45 mA (upon tolerance)

The subject should sit on a high chair with his legs hanging freely. When the stimulation starts, and the activation threshold is reached, the knee of the stimulated leg should start to extend, lifting the foot and the lower leg.

Influence of stimulation frequency on muscle fatigue can be easily demonstrated in a setup similar to the one in the previous exercise, but with both legs stimulated at the same time. Electrodes should be placed on each leg, as described in the knee extension exercise and shown in Fig. 15b. Two stimulators should be used, each connected to the electrode pair on one leg. Parameters used during the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 25 Hz left leg, 80 Hz right leg
- Pulse-width: 300 μs
- Amplitude: 20–45 mA (upon tolerance). It should be set individually to produce the same response as in the previous exercise.

When the parameters are set, both stimulators should be activated at the same time. Initially both legs should rise, the same way as in the previous exercise.

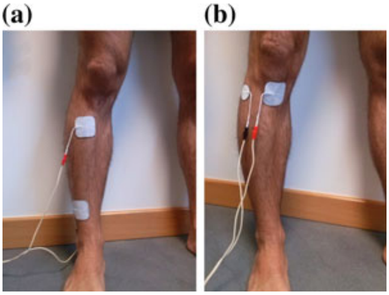

Fig. 16 Approximate electrode placement for **a** muscle belly stimulation and **b** peroneal nerve stimulation

After a short time, the fatigue in the right leg will become noticeable. First it will start to oscillate and then it will drop, while the other leg will remain lifted.

After a few minutes of rest, the stimulators should be switched to perform a control measurement. The effects should be the same, just mirrored.

This effect represents one of the main challenges in this field, and is discussed in more detail in further text.

4.2 Lower Leg

Lower leg muscles are the actuators of the ankle joint.

Ankle dorsal flexion is actuated by the tibialis anterior muscle, which is innervated by the deep peroneal nerve. Two methods for ankle dorsiflexion are described: direct stimulation of the muscle and stimulation of the peroneal nerve.

Stimulation at the belly of the muscle In order to activate this muscle, medium-size electrodes are placed laterally on the anterior part of the leg. Anode is placed distally, closest to the ankle, while the cathode is placed on the belly of the muscle, as shown in Fig. 16a. The belly of the muscle is located by palpation during several voluntary contractions. Parameters used during the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 50 Hz
- Pulse-width: 300 µs
- Amplitude: 15–35 mA (upon tolerance)

Stimulation of the peroneal nerve The biggest challenge in achieving dorsal flexion by stimulation of the peroneal nerve is cathode placement. The cathode should be a small size electrode placed near the head of the fibula, where peroneal nerve is superficially located. Anode should be a medium-size electrode, placed over or under the knee, as shown in Fig. 16b. It might be necessary to perform several adjustments of cathode position, in order to achieve good flexion. Parameters used during the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 50 Hz

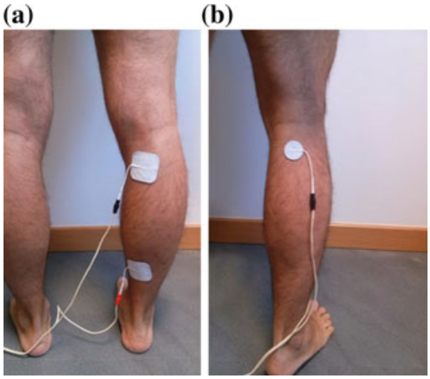

Fig. 17 Approximate electrode placement for **a** muscle belly stimulation and **b** peroneal nerve stimulation

- Pulse-width: 300 μs
- Amplitude: 7–15 mA (upon tolerance)

Even though this type of stimulation is more complicated from the electrode placement perspective, it is preferable because the muscle is excited in a more physiological manner, which postpones fatigue and requires less external energy (lower pulse amplitudes).

Ankle plantar flexion is mostly actuated by the gastrocnemius and soleus muscles, which are both innervated by the tibial nerve. Two methods for ankle plantar flexion are described: stimulation at the belly of the muscles and stimulation of the tibial nerve.

Stimulation at the belly of the muscle In order to activate this muscle, medium-size electrodes are placed medially on the posterior part of the leg. Anode is placed distally, closest to the Achilles tendon, while the cathode is placed on the belly of the gastrocnemius muscle, as shown in Fig. 17a. The belly of the muscle is located by palpation during several voluntary contractions. Parameters used during exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 50 Hz
- Pulse-width: 300 μs
- Amplitude: 15–35 mA (upon tolerance)

Stimulation of the tibial nerve The cathode should be a small size electrode placed on the posterior part of the leg, near the kneepit (popliteal fossa), where tibial nerve is superficially located, as shown in Fig. 17b. Anode should be a medium-size electrode, placed over or under the knee (as shown in Fig. 16b). It might be necessary to perform several adjustments of cathode position, in order to achieve good plantarflexion. Parameters used during the exercise should be:

- Waveform: biphasic symmetrical
- Frequency: 50 Hz

- Pulse-width: 300 μs
- Amplitude: 7–15 mA (upon tolerance)

Even though this type of stimulation is more complicated from the electrode placement perspective, it is preferable because the muscle is excited in a more physiological manner, which postpones fatigue and requires less external energy (lower pulse amplitudes).

5 Conclusions

Transcutaneous FES applications have been developed over more than 50 years with some success, however, limited to a few applications. In the clinical and sports environment, the technique is in wide use for non-selective muscle training, muscle endurance and relaxation and the treatment of pain complementary to TENS. One of the few successful applications of FES is the drop-foot stimulator, a device that helps to improve foot clearance during swing phase. In recent years, a new approach to address the main disadvantage of FES, the need to place the electrodes precisely by a skilled and experienced user has brought new attention to the field. A new multichannel stimulation electrode technology using arrays of electrode pads within a single physical electrode required new investigations of electrode properties, current pathways in human tissues, and the resulting activations of neural tissues. Models with physiological properties have been developed and used to simulate the current pathways and related nerve activations in inhomogeneous and realistic tissue configurations.

5.1 Modeling

Modeling of transcutaneous electrical stimulation that combines volume conductor and nerve models has proven to be a very useful tool to provide a full understanding on the activation dynamics of the musculoskeletal system, and a valuable information source to be considered when designing transcutaneous electrical stimulation applications. The simulation results obtained with such models could estimate the dominant parameters in the transcutaneous stimulation; these are the muscle resistivity, the electrode–axon distance, and the axon diameter. Additional factors mainly concerning the stimulation waveform (frequency, pulse-width, amplitude) nevertheless are also crucial and should be carefully selected depending on the application. The size of the electrodes has a strong influence on the selectivity and the comfort. The stimulation of superficial nerves has proven to be more comfortable when using small electrodes of about $1 \times 1\,\text{cm}^2$, however, larger electrodes are the better option as the activation depth increases. Finally, the relation between selectivity and electrode size is purely monotonic; the smaller the electrodes, the better the performance at targeting single and small superficial muscles.

5.2 Precision and Selectivity

As described before, one of the main challenges that affects mainly to upper limb applications is the selectivity issue. Simply analyzing an anatomy book we can realize how complex the upper limb system is, composed by around 50 muscles innervated by different branches of different motor nerves corresponding to the peripheral nervous system [17]. This redundant system allows us to reach, grasp, or manipulate objects in a wide variety of ways for the same task. Although unconsciously humans optimize the muscle activation patterns in order to perform the task successfully minimizing the needed energy, controlling this complex system with transcutaneous FES is challenging and we could point out three main reasons. First of them is the difficulty of achieving precise control of joints. Taking the reaching task, as an example, biomechanical models show that the human arm has 7 degrees of freedom (DOF) used to reach objects on the 3D space [24]. Although there could be ways of controlling 7 DOF for reaching precisely certain points in space by means of transcutaneous FES, it is extremely difficult to control each of these joints precisely enough to expand this success to any point in space. This is due to the reverse recruiting order of muscles [4, 25], where we activate big strong muscle fibers before smaller muscles responsible for precise movements, causing difficulties when fine-tuning control of reaching is needed. The second reason why controlling upper limbs for functional tasks is challenging is the issue of selectivity. Hand movements are a result of complex contraction patterns of muscles located both at the forearm and hand. As transcutaneous FES is applied over the skin surface, current is spread over different tissues before reaching the targeted motor nerve fiber, which becomes a problem when we pretend to apply it in a structure of small muscles, located at different depths, one on top of the other, and innervated by branches of the same nerve, like forearm muscle structure. As explained in Sect. 2, several factors affect the current distribution when FES is applied on the body surface and it is difficult to find isolated motor points or to generate action potentials in certain motor nerve fibers without acting in the neighboring nerve fibers as well [12]. Finally, another big challenge related to the application of transcutaneous FES on upper limbs is the high inter-subject and intra-subject variability in terms of motor response to FES, which makes it unlikely to find a unique solution for every user. At present, selectivity issues related to surface FES are being slightly overcome with the use of multifield electrodes, which bring diverse benefits like reduction of number of cables, improving selectivity or possibility of automatically determining customized stimulation patterns for each user, among others. [16, 20, 21].

5.3 Fatigue

As mentioned before, functional electrical stimulation can quickly lead to metabolic muscle fatigue. In normal conditions, muscle fatigue appears after prolonged intensive muscle activity, and is essentially a state in which the ability of muscle to generate force deteriorates. This can be caused either by inability of the nerve to produce excitation signals (neural) or by the inability of muscle fibers to contract (metabolic).

Electrical stimulation leads to metabolic muscle fatigue. Particularly when trying to achieve functions which require high force output from large muscle groups, such as standing and walking. The reason for this is the unnatural regulation order of muscle fibers.

Physiologically, the muscle fiber regulation follows the Henneman's size principle. This means that small, slow-twitch muscle fibers are activated first. These fibers are fatigue resistant, but generate low force. When additional force is required, large fast-twitch, muscle fibers are recruited. These generate high force, but they are less fatigue resistant.

On the other hand, when muscles are activated by electrical stimulation, first fibers to be recruited are those with biggest voltage gradient, i.e., the largest fibers. Therefore, the recruitment order is opposite from the physiological, which leads to faster fatigue.

One way to postpone muscle fatigue is to stimulate the nerve which innervates the muscle we want to activate. There the recruitment is performed by the nerve, i.e., it is performed in the physiological order. Even though this is the optimal method, it is not always achievable with transcutaneous stimulations. It can be achieved only if the nerve is close to the surface, and even then electrode placement is a nontrivial problem.

When nerve stimulation is not possible, alternative solution is distributed low-frequency stimulation, performed with multipad electrodes [15, 22]. Here, instead of using one large electrode to activate large muscle group, e.g., quadriceps, many smaller electrodes are used asynchronously so that while some of the fibers are contracting, the others have time to recover.

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Virtual Rehabilitation

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Abstract This chapter addresses the current state of the art of virtual rehabilitation by summarizing recent research results that focus on the assessment and remediation of motor impairments using virtual rehabilitation technology. Moreover, strengths and weaknesses of the virtual rehabilitation approach and its technical and clinical implications will be discussed. This overview is an update and extension of a previous virtual rehabilitation chapter with a similar focus. Despite tremendous advancements in virtual reality hardware in the past few years, clinical evidence for the efficacy of virtual rehabilitation methods is still sparse. All recent meta-analyses agree that the potential of virtual reality systems for motor rehabilitation in stroke and traumatic brain injury populations is evident, but that larger clinical trials are needed that address the contribution of individual aspects of virtual rehabilitation systems on different patient populations in acute and chronic stages of neurorehabilitation.

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1 Introduction

The world population is expected to grow to 9.68 billion people by 2050 [25]. More importantly, the proportion of people aged 60 or older is expected to increase in the so-called "more developed countries" from currently 23 to 32 % of the total population by 2050 [32]. With neurological disorders such as stroke, Parkinson's disease, or multiple sclerosis being more prevalent in older adults [1, 8, 30], our healthcare systems desperately need cost-efficient, widely available interventions that can address the cognitive and motor impairments of the aforementioned disorders and help reintegrate affected individuals in society.

Virtual rehabilitation technologies and interactive off-the-shelf games have seen increasing popularity in clinical settings over the past two decades [10, 14]. Virtual rehabilitation includes a wide array of applications that use virtual scenarios and environments for the purpose of clinical assessment and remediation. Available systems range from complex motion platforms, projection systems, tracking systems, and head-mounted displays to low-cost gaming consoles and motion-tracking sensors. Distinguishing factors of such systems are the use of fully virtual environments (i.e., virtual reality), real environments with an overlay of virtual information (i.e., augmented reality), or a mixture of both (i.e., mixed reality). Further, virtual rehabilitation setups can be immersive or non-immersive where immersive denotes systems in which three-dimensional scenarios are displayed and the user can change visual perspective through head movements (e.g., head-mounted displays or cave projection setups). On the contrary, non-immersive systems present virtual scenarios on a two-dimensional display (e.g., on a TV, laptop, or computer screen) with or without interface devices such as keyboard, computer mouse, or a joystick. Regardless of the actual hardware and software configuration, these approaches are often considered viable alternative or adjunct treatments to existing therapies, because of their motivational nature and precise control over feedback and task parameters.

This chapter focuses on the use of virtual rehabilitation systems for the treatment of motor deficits after stroke and traumatic brain injury. Recent advances of virtual reality hardware are being discussed and their potential for new rehabilitation systems along with strengths and weakness are being outlined. Moreover, relevant clinical trials and meta-analyses since the writing of the previous version of this chapter are summarized and their results discussed.

2 Advances in Virtual Reality Technology

Virtual reality systems are often a heterogeneous set of input/output devices that can consist of a wide range of displays, tracking devices, controllers, and computer systems. Historically, such systems were almost exclusively associated with high costs, cumbersome, wired equipment, and a lack of compatibility between different devices and device drivers [27]. However, within the past two years virtual reality technology has seen a transformation toward low-cost components that are being developed and marketed for the rapidly growing video and computer game industry. Much of that growth is also driven by the rise of mobile computing and the availability of high-resolution mobile displays. Modern head-mounted displays have evolved from cumbersome, tethered devices to goggles that simply allow the user to attach an off-the-shelf smartphone and leverage the inbuilt motion sensors and cameras of the phone. Consequently, prices for head-mounted displays have dropped from tens of thousands to merely hundreds of dollars while image quality and tracking latency have improved tremendously. Examples of such new display solutions are the Oculus Rift,[1] Samsung Gear VR,[2] Avegant Glyph,[3] Durovis Dive,[4] Google Cardboard,[5], or the Zeiss VR One.[6] Most of these are still in alpha or beta prototype stage, but new innovative products are announced on a regular basis and should invigorate the competition further. A similar trend is evident for video game peripherals and 3D interaction devices which are mostly developed for console and computer game markets. New tracking devices such as the Microsoft Kinect 1 and 2,[7] Leap Motion controller,[8] Razer Hydra,[9] Nimble Sense[10], and treadmills such as the Virtuix Omni[11] and Cyberith Virtualizer[12] provide an affordable entry to naturalistic 3D interaction in virtual scenarios. All of these new competitors are of high importance to developers and researchers in the virtual rehabilitation field, as for the first time in the history of virtual reality technology, therapeutic systems have become affordable and accessible for use in the wider clinical setting, outside of the research laboratory. In addition, the development of virtual rehabilitation software has become much more accessible

[1] https://www.oculusvr.com

[2] http://www.samsung.com/gearvr/

[3] https://www.avegant.com

[4] https://www.durovis.com

[5] https://www.cardboard.withgoogle.com

[6] https://www.zeissvrone.tumblr.com

[7] http://www.microsoft.com/en-us/kinectforwindows/develop/

[8] https://www.leapmotion.com/

[9] http://www.sixense.com/razerhydra

[10] http://www.nimblevr.com/

[11] http://www.virtuix.com/

[12] http://www.cyberith.com/

as game engines such as Unity,[13] Unreal Engine 4[14], and CryEngine 3[15] are widely available for low monthly subscriptions or even for free. Each development tool comes with large communities of enthusiastic game developers who provide free assets, tutorials, and help on online forums and discussion groups. Virtual reality hardware companies have realized the potential of these large communities and provide free integrations of their devices and drivers for the most common game engines. All of these factors taken together provide an excellent ecosystem for the development of low-cost virtual rehabilitation systems that would have cost hundreds of thousands of dollars three to five years ago.

3 Advantages of Virtual Rehabilitation

Innovative technologies such as virtual rehabilitation tools are being applied by using motor learning principles and taking advantage of neuroplasticity in order to compensate, restore, and recover loss of sensorimotor function occurring in stroke and traumatic brain injury patients. This section will outline the different factors that make virtual rehabilitation systems a suitable option for the treatment of sensorimotor deficits in neurorehabilitation and add value beyond traditional forms of treatment.

(a) Comprehensive data collection

Data is at the core of most other aspects of virtual rehabilitation systems mentioned in this section. Comprehensive collection of performance data enables the patient and therapist to track rehabilitation progress and adjust training parameters for optimal recovery. Performance data is also necessary to track the efficacy of each rehabilitation system and can help the clinician decide which intervention is best used for different patient populations or individual patients. Data collection can encompass usage patterns, task completions, task difficulty adaptations, and task outcomes on a macro level and reaction times, responses to task stimuli, movement quality, and logging of feedback or distractions on a micro (behavioral) level. Furthermore, each variable can be tracked and summarized over longer timespans across multiple sessions or even across patients and patient populations. This allows researchers and clinicians to track the efficacy of combinations of tasks and feedback for patients with different deficits, lesion locations, and demographics. Moreover, summary data of task usage gives deeper insights into the success and habits of clinicians and how their experience or background influence therapy outcomes with virtual rehabilitation tools.

Large datasets can be collected when using sensors and motion tracking systems. Oftentimes, datasets can be too complex for unprocessed use by clinicians and must be condensed before they can aid clinicians in their decision-making

[13] http://www.unity3d.com/

[14] https://www.unrealengine.com/

[15] http://www.cryengine.com/

process. Compared to clinical observation using rating scales, automated data collection of virtual rehabilitation systems can capture many high-resolution variables simultaneously. Exemplarily, a tracking system can capture movement of all tracked joints at millisecond and millimeter accuracy and combine this information with the system's presentation of task stimuli, distractions, and the user's responses and errors. Manually observing the same scenario and assessing all variables in a reliable and valid manner is simply impossible. Additionally, automating data collection frees the therapist's resources and allows for unhindered interaction between patient and therapist.

(b) Multisensory feedback

Feedback is an integral part to rehabilitation exercises as it allows patients to monitor their performance, promote errorless learning, and avoid compensatory movements. Virtual rehabilitation systems often have a multitude of opportunities for feedback delivery. Most systems include components for visual and auditory presentation of information which can be utilized for feedback delivery. Even tactile input through the use of pressure sensors, electrotactile stimuli, or puffs of air are potential feedback mechanisms.

Feedback can target individual performance parameters such as movement speed, trajectory, precision, and smoothness as well as more holistic parameters such as task completion or completion time. Feedback delivery can occur in real-time or as a summary after the movement or even the training session have been completed. With the proper use of feedback, the patient's attention can either be focused on individual task parameters or the movement as a whole, depending on the goal of the training session. Real-time feedback requires additional attentional resources and has to be used carefully in order to not distract from the actual task. The choice of feedback modality and presentation can facilitate the processing of feedback without too much task interference. For example, visual feedback can lend itself to outline an optimal movement trajectory while auditory feedback can indicate information about movement speed [16]. Moreover, feedback modalities should be adapted to accommodate the strengths and weaknesses of different patient populations. Exemplarily, patients with deficits in visual attention might benefit more from auditory feedback and aphasic patients might benefit most from non-written visual and non-spoken auditory feedback. Lastly and most importantly, all aforementioned feedback mechanisms can be applied dynamically and adaptively when a system's collected data is being utilized. Choice of feedback modality, frequency, and task parameters to give feedback on should be adjustable to the unique situation of each patient. Either the therapist, patient, or the virtual rehabilitation system itself should be able to change feedback parameters throughout the course of a patient's rehabilitation. As the patient's performance increases, different feedback mechanisms, frequencies, or increasingly implicit feedback might become more relevant for an optimal recovery.

(c) Precise control over scenarios

Developers of virtual rehabilitation scenarios usually have full control over all aspects of the simulation. That is, events, distractions, animations, task stimuli, and feedback can be precisely controlled to guarantee a consistent experience for each patient. Ideally, most of these parameters are then exposed in the application's interface to give the therapist control over the content of each training session. Alternatively, the aforementioned data collection capabilities allow the simulation to tweak task parameters automatically based on the user's performance and therapeutic goals. Exemplarily, error reduction or error augmentation can be adjusted dynamically to balance motivational aspects and therapeutic success over the course of therapy sessions. However, control over virtual scenarios extends much beyond the configuration of task parameters. Displaying environments and avatar movement are two key components that can have a large impact on the training scenario. Environments can range from game-like or abstract environments to more realistic simulations to suit the patient's preferences and enhance motivation. In fact, simulating environments that are otherwise inaccessible or too dangerous for patients is one of the key advantages of virtual rehabilitation tools. For example, patients can safely practice reaching for targets in a virtual supermarket which would otherwise be an inaccessible location for patients undergoing inpatient rehabilitation. The representation of the patient's movement on screen can heavily influence task performance. Moreover, it allows patients to assess their own movement and actively learn how their body movement is connected to the visual feedback they receive on the screen. The patient and his/her movements can be represented realistically or in a more metaphorical way in order to increase or take away focus from affected limbs and relevant movements. Characters, if displayed at all, can be realistic avatars, neutral mannequins, cartoon characters, or even real-time camera images of the patient (e.g., Microsoft Kinect or Playstation 2 Eyetoy[16]).

In sum, each and every aspect of a virtual scenario must be carefully considered by the developers and therapists and in best case should be highly flexible to adapt to each patient's unique circumstances.

(d) Enhanced motivation

Adherence to therapy programs is one of the most critical aspects of neurorehabilitation as high-frequency repetition of movements has been shown to be key for recovery [3, 18, 19]. Unfortunately, current therapy practices are not able to encourage patients to perform the number of repetitions required for neuroplastic changes to occur [12]. Furthermore, within the home setting, patients often lose their motivation over time as tasks become repetitive and feedback about progress is lacking or non-obvious. Virtual rehabilitation scenarios have become a popular choice for therapy, largely for their ability to motivate patients to continue their exercise regimes over extended periods of time. Game-based mechanics and features such as high scores, achievements, virtual reward items, diverse landscapes, and interesting characters are excellent ways to engage patients during their rehabilitation and clearly communicate progress over time. The implementation of game mechanics also takes away the focus from affected limbs and shifts attention to achievable goals within the game environment, thus potentially reducing

[16] http://de.playstation.com/ps2/accessories/detail/item51693/EyeToy-USB-Kamera/

anxiety. Repeating similar tasks in different game-like contexts even promotes generalization of learned behaviors which has been shown to be important for transfer to activities of daily life.

However, not each virtual rehabilitation tool needs to look and feel like a computer game. Enjoyment of game-like content or even graphics style often depend on personal preference and graphical fidelity. In some cases, a realistic simulation of a relevant real-life environment can be the most motivating scenario as long as it aligns with the patient's goals. Yet, even simple task rewards or a scoring system can go a long way to motivate the patient over extended periods of time and provide an easy-to-understand feedback system.

Increased patient motivation continues to be one of the most powerful aspects of virtual rehabilitation systems. Virtual scenarios and tasks need to be designed with a variety of content to engage patients beyond the novelty effect of the first few training sessions. After all, repetitive task practice is still thought to be the most effective means to regain motor function after neurological injuries, despite the frequent lack of patient motivation.

(e) Flexible use cases

Due to their flexible nature, virtual rehabilitation tools can be useful in a wide range of therapeutic scenarios. Virtual rehabilitation systems can be used as standalone setups for direct therapeutic interventions with any combination of the aforementioned hardware components. Such systems can be used statically in clinics and homes or as mobile setups utilizing tablets, laptops, smartphones, and head-mounted displays. Virtual rehabilitation systems can also be used as a visualization or extension for robotic rehabilitation systems or brain computer interface systems. Virtual scenarios can even be coupled to traditional exercise tools such as treadmills and cycling trainers. In each case, virtual scenarios can enhance the original therapy by adding feedback, tasks and other motivating aspects.

Lastly, the flexibility of use cases will only increase as new gaming hardware such as fully-tracked omnidirectional treadmills are becoming more mature and affordable (e.g., Virtuix Omni and Cyberith Virtualizer) and markerless tracking will support more unencumbered, natural full-body, or fine-motor movements (e.g., Microsoft Kinect 2, Nimble Sense).

Virtual rehabilitation is a very young discipline and many challenges and threats to its widespread use still have to be addressed. However, each of the advantages outlined in this section present a strong case for the adoption of virtual rehabilitation tools in clinical practice and should be encouraging for researchers and clinicians to strongly support the clinical implementation and evaluation of the outlined technologies. Many of the past threats and disadvantages of virtual reality technology that were described in 2005 [27] have already been overcome by recent technological advances. Some of the remaining challenges and threats to virtual rehabilitation tools and technologies are still existent and will be summarized and discussed in the next section of this chapter.

4 Challenges and Threats to Virtual Rehabilitation

While virtual rehabilitation has been demonstrated to have great potential to improve upon existing rehabilitation interventions and protocols, many of the proposed advantages of virtual reality systems within the clinical setting require more supporting evidence and exploration. The number of articles reporting development, usability, and feasibility of virtual rehabilitation tools has increased exponentially over the past five years. However, the research is published in a wide variety of journals and conference proceedings with a range of different keywords making it difficult to find. Many researchers and developers have published papers outlining the development process and intervention description (e.g., [4–6, 13, 26, 31]). These papers describe the underlying theories and processes used in the development of virtual reality systems for use in the clinical setting. Some of these papers are purely descriptive, however, other papers provide feedback and findings from initial assessment of patients or clinicians.

Usability and feasibility studies provide initial support for the concept for virtual rehabilitation tools and interventions. Usability and feasibility studies explore user feedback and likeability of virtual reality interventions and evaluate the potential of the intervention for clinical use prior to evaluating the system in a larger randomized comparison trial (for example [11, 21, 22, 29]).

A number of reviews of randomized controlled trials have been published recently exploring the efficacy of upper and lower limb virtual reality training for people following stroke [10, 14, 15, 20]. Overall, limited evidence exists for the use of virtual rehabilitation interventions for people with stroke. Virtual rehabilitation has been shown to be at least as good as existing therapies. While the review papers provide some support for the use of virtual rehabilitation for people with stroke, the existing research studies are variable in terms of patient population, outcome measures, intervention type, intervention dose, and intervention duration and frequency. Importantly, interventions used in existing trials range from high-end robotic devices to tailored low-cost systems and off-the-shelf video game consoles. There is little agreement and standardization across the research studies, making it difficult to compare the research and provide strong conclusions.

The following section provides an overview of the challenges and threats that the field of virtual rehabilitation is facing.

(a) Lack of standardization

Virtual rehabilitation is a very heterogeneous field with different types of technologies, design approaches, and many research groups and companies that work on the development and validation of novel technologies. With such a large and varied number of entities involved, standardization becomes a key factor in each step along the path from conceptualizing to implementing a virtual rehabilitation system. Many technologies applied in this field are new and innovative, thus lacking clear design standards. This is especially detrimental for interaction design where sensors and tracking devices enable users to interact with virtual objects in 3D space. Combining these sensors with unique display solutions

leaves developers with trial and error to arrive at design decisions. Only recently have companies behind new virtual reality hardware started to distribute design guidelines for their products that form a common basis for developing interactive systems (For example: LeapMotion,[17] Microsoft,[18] OculusVR[19]).
However, most of these guidelines are centered on specific technologies and often address the consumer market without any view for research or clinical use of these new technologies. This leaves many researchers and rehabilitation-focused companies on their own to address the problems of:

- interaction with virtual 3D objects,
- judging distances in virtual space,
- creating appropriate feedback,
- collecting and interpreting complex dataset,
- developing technology-agnostic applications,
- developing user-friendly interfaces that are intuitive for patients, caregivers, and clinicians.

Clinical data are critical to establish the feasibility, usability (ISO IEC 62366: 2007[20]), and efficacy of new rehabilitation interventions and are required according to the medical device directive [7] as long as they are intended and marketed as rehabilitation tools. It is important to show that improvements in motor function are existent, large enough to be clinically relevant, stable over time, and transfer to the patients' activities of daily life. In order to compare different interventions and decide which might be the most appropriate therapy for any given patient, it is helpful to be able to compare the outcomes of different evaluation trials by using similar outcome measures and reporting effect sizes. This is especially important for conducting meta-analyses. Unfortunately, each evaluation approach of research to date, differs substantially regarding outcome measures, patient inclusion and exclusion criteria, intervention time, and statistical analyses [10, 14, 20]. A standardization of study designs and comparability between studies, including replication studies, would greatly benefit the field of virtual rehabilitation.
Once these evaluation, development, and design standards have been agreed upon, sufficiently-powered, well-controlled clinical trials and usability evaluations must be conducted. The outcomes of the usability trials can inform the system design and implementation of future virtual rehabilitation tools. The results of clinical trials allow researchers and companies to draw conclusions about the clinical efficacy of different system components and parameters. Further, conclusions can be drawn about which system and technology is best suited for which patient population, demographic- or lesion location. A last step towards

[17] http://www.blog.leapmotion.com/inside-leap-motion-5-hands-on-tips-for-developing-in-virtual-reality/

[18] http://www.msdn.microsoft.com/en-us/library/jj663791.aspx

[19] http://www.static.oculusvr.com/sdk-downloads/documents/OculusBestPractices.pdf

[20] http://www.iso.org/iso/catalogue_detail.htm?csnumber=38594

widespread use of virtual rehabilitation tools is to use data gathered from the aforementioned trials and use them as a basis for cost–benefit analyses which pave the way for cost reimbursement and clinical adoption.

(b) Heterogeneity of evaluation trials
Three meta reviews have been published since the previous version of this chapter was written in 2012 and published in 2013. Pietrzak et al. [24] reviewed 18 studies that evaluated virtual reality and video game-based rehabilitation in patients with traumatic brain injury. Fluet and Deutsch (2013) included eight upper limb rehabilitation and two lower limb rehabilitation studies in their stroke-focused virtual reality meta review. Lastly, Lohse et al. [20] reviewed a total of 26 virtual rehabilitation studies that targeted patients with stroke. The conclusions of all three reviews are in agreement that there is much potential in the virtual rehabilitation approach, there are many open questions that remain to be answered, and, most importantly, that the reviewed studies differ substantially in fundamental aspects of patient characteristics, study design, intervention design, outcome measures and tested virtual rehabilitation systems and how each of these aspects is being reported by the studies' authors. It is this heterogeneity of conducted studies and their documentation and dissemination of results that make it almost impossible to draw much needed conclusions that could move the field of virtual rehabilitation forward. Looking at the different study characteristics the following discrepancies between studies were found:

(1) Patient population and characteristics
A detailed description that goes beyond demographics of the recruited sample is a basic requirement for researchers to draw sound conclusions across different studies and interventions. Unfortunately, all reported studies in each of the meta reviews differ substantially in describing their recruited patients and their interaction with study personnel, therapists, and caregivers. Patients with different deficit severity were tested with a wide range of reported standardized measures. While sensory and cognitive abilities were often reported as required inclusion criteria, no actual measurement of these domains were quantified in most studies. This is a critical point, as there is only very limited knowledge about how sensory and cognitive deficits impact the utility of virtual rehabilitation systems for treatment of stroke and traumatic brain injury patients. A more detailed description of motor, cognitive, and sensory abilities of the recruited samples was demanded by Fluet and Deutsch (2013), who also suggested sample stratification whenever appropriate sample size and range of deficit severity were given. Overall, sample sizes were rather small in most reported studies (e.g., 5–40 in Lohse et al.'s review) and mostly not justified by power analyses. Inclusion of acute, subacute, and chronic patients differed between studies, but was consistent within each study that was being reviewed.

(2) Study design
There were large differences in the design and characteristics of the reviewed studies. Studies often differed in their administration and comparison of

experimental treatment and control treatment. Exemplarily, Lohse et al. describe that only 61.5 % of their reviewed studies reported blinded experimenters, 61.5 % reported similar groups based on comparisons of baseline performance. Blinding participants and therapists to treatment allocation or study hypotheses were only reported in 19.2 and 3.8 % of all studies respectively.

(3) Intervention characteristics
Intervention intensity, frequency, and overall duration differed substantially between the reviewed studies. Lohse et al. reported virtual reality interventions ranging from 180 to 1800 min in total training duration. Pietrzak et al. mention a more consistent intervention schedule for the studies they reviewed, ranging from eight to twelve sessions, three times per week. Training sessions ranged from 30 to 90 min per session. Fluet and Deutsch report study durations between four and twelve weeks and on average 10.5 h of upper limb training and 7.5 h of gait training. Almost none of the reviewed studies in each of the three reviews control for the number of repetitions completed by the participants, which provides no basis for establishing a dose–response relationship between training time and outcome measures.
Treatment progression can either be achieved automatically through algorithms or manually through observation of the clinician or user. Both options are reported frequently, but descriptions of criteria for each progression mode are often lacking. Different variables underlying the progression algorithms further complicate the comparability of learning curves and outcomes of different virtual rehabilitation interventions. Lastly, difficulty parameters which are changed as the patient progresses through the intervention differ between each study and no clear relationship between these variables and intervention efficacy has been established yet.

(4) Virtual rehabilitation systems
Arguably the largest variability between all conducted studies comes from the tested rehabilitation systems themselves. Stark differences in input and output modalities, provided feedback, system components such as tracking systems, robotic devices, or brain computer interfaces were all reported in the three assessed reviews. System complexity and cost ranged from off-the-shelf gaming systems for a few hundred dollars (e.g., Nintendo Wii,[21] Microsoft Kinect) to custom-built, one-off rehabilitation devices to large immersive rehabilitation systems for several hundred thousand dollars (e.g., Motek Medical's CAREN system[22]). Comparing outcomes between these different systems can potentially outline the different options that are available for therapists. However, drawing conclusions about the efficacy of different system components for various subgroups of stroke and traumatic brain injury populations remains a large challenge which can only be

[21] https://www.nintendo.de/Wii/Wii-94559.html
[22] http://www.motekmedical.com/products/caren/

overcome if common frameworks for system design, task delivery and feedback mechanisms are considered.

(5) Patient Motivation

While patient motivation is expected to play a large role in the success of virtual rehabilitation systems, motivation is rarely ever mentioned or measured in any of the reviewed studies. Only few studies attempted to use entertaining or motivating tasks such as card games or video games for their control groups [20]. Most evidence to support the increased motivation of virtual rehabilitation tools seems to stem from anecdotal reports or unstructured interviews during debriefing sessions. Clearly, more evidence and stricter controls for the motivating factors of experimental and control interventions are needed to clearly establish the motivating advantage of virtual training scenarios.

(6) Outcome measures

All three reviews report outcome measures at all levels of the International Classification of Functioning, Disability and Health (ICF). Utilized measures differ substantially and include variables produced by each virtual rehabilitation systems and standardized measures of motor function, activity, and participation.

In conclusion, all reviewed studies differed dramatically in all aspects that are relevant for drawing conclusions about the overall efficacy of the virtual rehabilitation approach. In order to establish the merit of different system components and intervention methodologies for different patient characteristics, it is necessary to find common ground for the design and evaluation of these new technologies.

(c) Assumes ability to move

Tracking systems and sensors usually require the patient to have at least a minimal amount of movement or range of motion. This can be problematic with heavily impaired patients who might require assistive devices such as robotic systems, exoskeletons, or braces to interact with virtual rehabilitation systems. Symptoms such as tremor or spastic paresis can also interfere with accurate tracking as small hand movements and self-occlusion for clenched fists and spastic movements can be problematic for visual tracking systems. Moreover, many tracking devices are designed for healthy users and support use in standing or seated positions and might not work properly with patients who cannot leave their bed. Consequently, feasibility and usability trials need to shed light on the correct choice of technology for patients with varying range of movement capabilities and symptoms which might interfere with the proper use of virtual rehabilitation systems.

The majority of patients with upper limb paresis are treated predominantly during the subacute or chronic phases post-stroke or traumatic brain injury (greater than 3–6 months). Treatment during acute phases frequently becomes impractical due to medical instability or severe paresis of patients. However, some evidence supports the view that corticospinal connections and neuroplastic changes can be facilitated by upper limb motor training in acute phases post injury [28]). Consequently, virtual rehabilitation training could also be feasible and beneficial, even in early stages after neurological injuries for improving motor tasks execution and motor hand function [2, 33].

(d) Perception of technology
New technologies can be daunting to therapists and patients alike, especially if they have the label "virtual reality" or "virtual rehabilitation" attached. Therapists may perceive new technologies as threats which are taking over their responsibilities and ultimately their jobs. Conversely, patients may not have any experience with computers or video games and can be intimidated by large virtual rehabilitation systems or the prospect of wearing a head-mounted display. While new systems can be wireless and much less complex than traditional virtual reality setups, the preconception of large, uncomfortable systems that cause nausea and eyestrains while also taking diagnostic and therapeutic decisions away from the therapist still exists.

Many challenges of the past decade have been addressed with recent advances of mobile computing, low-cost HD-displays and virtual reality gaming hardware. What remains are threats that technology cannot solve on its own. Companies and researchers need to agree on design and evaluation standards to start a comprehensive effort toward validating virtual rehabilitation tools as viable alternatives to traditional therapy. Such potential success stories and increased market uptake of virtual rehabilitation tools might also change the perception of these technologies as niche products and scary visions of the future.

5 Conclusions

This chapter aimed to provide an update to the current state of the field of virtual rehabilitation regarding technological and clinical advances since the previous version of this chapter was published in 2013 [23]. Most recent progress in virtual rehabilitation seems to come from technological innovations in mobile computing, low-cost motion-tracking and sensing devices, the appearance of low-cost HD displays, and affordable virtual reality gaming hardware. Research and clinical validation of virtual rehabilitation tools seems to focus on small feasibility trials and validation of customized tools that do not allow to draw conclusions about the generalization of efficacy across technologies and tools. Moreover, transfer of gained abilities to the patients' activities of daily life is still sparse and often not addressed in recent published research.

In conclusion, there seems to be a large gap between the technological possibilities that virtual reality hardware and software provide and the transfer of this potential into actual clinical use via the design, development, and implementation of standardized virtual rehabilitation tools and protocols. It is of utmost importance that systematic evaluations of optimal task design, interaction design, feedback delivery, and technology selection for each individual patient or patient population are conducted. Such studies should then be leveraged for the dissemination of guidelines, common platforms, frameworks, and, ultimately, cost–benefit analyses that provide a strong argument for the implementation and reimbursement of virtual rehabilitation tools. First steps toward development and evaluation guidelines have already been undertaken through recent meta-analyses and publications that bring together principles of motor learning and virtual reality technology [17]. However, a more coordinated effort between researchers, companies, and policy makers is required to push the field of virtual rehabilitation toward widespread clinical adoption.

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