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Emerging Therapies in Neurorehabilitation

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Introduction

Neurorehabilitation is entering a new exciting era. A wide range of new technologies is increasingly taking part of the clinical practice, enhancing the potential of therapists and clinicians to rehabilitate, diagnose, and generate knowledge. Wearable robotics, virtual reality, brain–machine interfaces, and neural prosthetics are playing a leading role in this innovating process.

In the last edition of the Summer School on Neurorehabilitation (SSNR2012,[1]), 60 Ph.D. students had the opportunity to meet an outstanding group of world-class professors and experts in the field of neurorehabilitation and neuroscience. During an intense week of lectures and workshops, they learned and experienced most of the methods and techniques that may constitute the future of clinical practice. Throughout the week, students and professors also met up in small working groups to write together what you can see here: a comprehensive book on the emerging therapies for neurorehabilitation.

This book is more than a conventional survey on the state of the art; it is the result of deep discussion and reflections arising from intense debating between wondering students and experienced professors. For this reason, we think that this book represents an essential guideline for any Ph.D. student, researcher, or professional interested in getting a multidisciplinary perspective on current and future neurorehabilitation scenario.

This volume is organized into four parts. The first part presents the major challenges and the latest advances in the rehabilitation of a selection of common impairments affecting the brain, i.e., Stroke, Cerebral Palsy (CP), and Parkinson's Disease (PD).

The second part is related to the plastic mechanisms of the spinal cord and brain. Specific attention has been devoted to the assessment of spasticity and to the technique of neuromodulation, mainly addressed (but not limited) to Spinal Cord Injury (SCI) patients.

The third part covers the most recent technological advances for rehabilitation and diagnostics, including robotics, neuroprostheses, brain–machine interfaces, and EMG systems. Rehabilitation potentials and engineering challenges are presented and discussed.

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[1] www.ssnr2012.org (3rd edition at www.ssnr2013.org)

The fourth and last part presents practical examples and case studies for the application of some of the latest techniques in realistic clinical scenarios. These chapters reflect the contents of the hands-on workshops held during the SSNR2012. Due to the presence of mathematical language, this part may be more suitable to a technical/engineering audience.

We hope that many students and young researchers will find in these pages inspiration and useful contacts for their current and future research.

Lastly, we would like to thank professors for their invaluable guidance in the writing process, and all the students for their motivation in participating in this educational and scientific experience.

The Editors

Part I
Central Neurological Impairments

Chapter 1
Emerging Perspectives in Stroke Rehabilitation

Guillermo Asín Prieto, Roberto Cano-de-la-Cuerda, Eduardo López-Larraz, Julien Metrot, Marco Molinari and Liesjet E. H. van Dokkum

Abstract Poststroke characteristics vary significantly between patients and over time, necessitating the introduction of individualized therapy. To provide the appropriate therapy to a patient at the correct time, several theoretical considerations must be taken into account—from a clear delineation of rehabilitation goals to an understanding of how a certain therapy can influence the underlying neuroplasticity. With regard to the differences between upper and lower limb motor recovery, both domains have experienced a change in perspective on rehabilitation.

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In gait training, assist-as-needed rehabilitation paradigms have become more pertinent, allowing each patient to find his/her individual walking rhythm and style within healthy boundaries. With the introduction of robotics in upper limb training (with or without virtual reality games that are attached), the amount of training and feedback that is provided to a patient can be increased without a rise in cost. The emerging consensus is to consider the various motor therapies and pharmacological interventions as part of a single, large toolbox instead of separate entities, guiding us toward a more patient-therapist-tailored approach, which is demonstrating tremendous efficacy.

Keywords Motor recovery · Patient-centered · Stroke rehabilitation · Technology-based interventions

1.1 Introduction

Stroke is not a uniform disease, affecting the motor, cognitive, sensorial, and somatosensory systems. How and to what extent it interferes with these systems depends on many characteristics, such as the nature (hemorrhagic vs. ischemic), location, and size (dominant side, cortical vs. subcortical, cerebral lobe) of the lesion; the condition of the patient before stroke onset; and the time poststroke.

Simply, poststroke characteristics vary between patients and over time. The high variability within and between patients has necessitated individualized rehabilitation. Regarding the current state of stroke rehabilitation, however, most therapies might fail to consider this significant heterogeneity.

Although recovery after stroke is seldom, if ever, complete (Sharma and Cohen 2012), stroke rehabilitation focuses primarily on restoring the exact patterns of movement that existed before the onset of stroke, paying little attention to compensatory strategies. Complicating this matter, the interactions between specific training and spontaneous recovery processes have not been examined extensively. In most rehabilitation centers, a general recovery pattern is projected onto each patient. Clinical studies then aim to evaluate the clinical and functional outcomes of a given therapy.

Given the high variability of stroke patients, however, it was not surprising that a recent large Cochrane review demonstrated that no rehabilitation therapy was superior, with the exception of constraint-induced movement therapy (CI) for the upper limbs (Boddice et al. 2010). Nevertheless, the highly specified inclusion and exclusion criteria of CI distinguish it from other upper limb rehabilitation methods. Thus, CI appears to have been adapted to a specific subgroup of stroke patients and can not be applied to all patients under various circumstances. Unfortunately, this therapy is seldom used in clinical settings, because the energy costs for the patient and therapist might be exorbitant.

Another important aspect that increases the variability between rehabilitation approaches is the interaction between the patient and his/her therapist. An empathic therapeutic relationship might support or interfere with the treatment, the mental state of the patient during rehabilitation, one's tendency to collaborate, and the general psychological reaction to the stroke (Scott et al. 2012).

Various rehabilitation procedures with disparate underlying neurophysiological assumptions are routinely applied in clinical settings, despite being based on little or no evidence of efficacy (Belda-Lois et al. 2011). In the past decade, several technology-based approaches to stroke rehabilitation have been proposed (Ifejika-Jones and Barrett 2011), but evidence of their efficacy is scarce (Mehrholz et al. 2007; Morone et al. 2012). Nevertheless, the number of novel methods for stroke rehabilitation continues to rise.

This ongoing development in poststroke rehabilitation increases stroke patients' expectations of recovery but complicates the selection of the appropriate therapy for therapists, due to a lack of treatment guidelines. Thus, a large toolbox must be developed, from pharmacological interventions to technology-based regimens, including guidelines and target specifications for each therapy. When evaluating new methods, one should focus on patient-related disabilities and the expectations and goals of the patient and his/her caregivers for rehabilitation (International Classification of Functioning, Disability and health www.who.int/classifications/icf/en/).

1.2 Current Tendencies in Poststroke Rehabilitation

1.2.1 Theoretical Considerations

After a stroke, no two patients share the same needs, which will likely change during recovery. To illustrate this concept, let us imagine two patients who are undergoing upper and lower limb rehabilitation. One might prefer to focus on the rehabilitation of walking, because the use of only the nonparetic upper limb is sufficient for his/her lifestyle. In contrast, the recovery of hand function might be more important for the other patient, if he is a potter, for example. The needs in motor recovery thus depend highly on the individual's life perspective and habits, previous lifestyle (e.g., sportsman vs. housewife), and cognitive and mental state.

Many therapists focus primarily on the motor aspect of poststroke rehabilitation, but the influence of cognition and mental state on the potential of motor recovery can not be ignored. Motivation and attention are considered key elements in the success of motor recovery (Cramer et al. 2011). A patient needs to understand why a certain exercise is proposed—specific exercises need to make sense, and goals must be clear to enhance motivation. If one lacks the capacity to understand how an exercise is executed correctly, little effect can be expected. Further, if one is depressed and unable to see the value in recovery of motor function, focusing on such a goal might not be the most appropriate at that time.

Considering the entire interaction of the motor recovery-cognition-mental state system in a patient, it is often claimed that therapeutic interventions should be functional. To ensure adherence and maximum effort by the patient toward rehabilitation, therapeutic exercises should focus on walking or picking up a glass instead of knee flexion and elbow extension. Consistent with this approach, the Institute of Medicine (IOM) defines patient-centered care as "health care that establishes a partnership among practitioners, patients, and their families (when appropriate) to ensure that decisions respect patients' wants, needs, and preferences and that patients have the education and support they need to make decisions and participate in their own care" (Institute of Medicine (US) 2001).

An important element of this definition is the 'establishment of a partnership' between the patient and caregivers to meet the needs of the former. As discussed, we would like to broaden this definition. This partnership comprises more than one individual, and all participants' needs should be met for it to be successful and for optimal therapeutic profit to be gained.

We are faced with a necessity to develop and investigate treatment modalities that are oriented toward the specific needs of the patient-caregiver system. All developed exercises or technological interventions should be customizable and adaptable. Further, they should be accepted by the entire system. The incorporation of user criteria requires a method that implements user preferences into design specifications. User preferences, however, are related to various factors, from technical acceptance to usability and emotions that a product elicits in a patient. Thus, these complementary aspects require an integrated approach that takes them into consideration. Moreover, in the development of treatment modalities, one should reflect on the possible effect of the therapy and how the effect is established on a neurological level.

There are two chief approaches to the development of therapies for poststroke rehabilitation: BOTTOM-UP and TOP-DOWN. Whereas the former induces changes at the neural level (up) by acting on the periphery of the body (bottom), the latter focuses on neurological interventions that are based on the state of the brain after stroke to alter peripheral behavioral outcomes (Belda-Lois et al. 2011). Many exercise-based techniques are bottom-up approaches and constitute the benchmark in poststroke rehabilitation, per Bobath (Bobath and Bobath 1957), Brunnstrom (Stern et al. 1970), and Perfetti (Perfetti 2001).

However, a better understanding of the neurological physiopathology can facilitate the introduction of neuroplasticity-modulating therapies, integrating bottom-up and top-down approaches—such as pharmacological, biological, and electrophysiological techniques [e.g., transcranial magnetic stimulation (TMS), direct current stimulation (DCS), functional electric stimulation (FES), and computer-brain interfaces (CBIs)] (Dimyan and Cohen 2010).

In gaining such an understanding with regard to cortical functioning, a challenge lies in correlating brain activation patterns by electroencephalography (EEG), muscle force, electromyography (EMG), and executed movements that are sensed by motion capture (e.g., inertial measurement sensors). Further, new noninvasive brain imaging techniques, such as functional near-infrared spectroscopy (fNIRS), can be used to complement and, in some cases, overcome the technical and practical limitations of EEG as a brain-monitoring technique. Systems that are based on noninvasive methods for brain/neuronal-computer interaction (BNCI) are becoming more common in the development of robotics-based approaches to rehabilitation of motor disabilities (e.g., tremor, stroke, traumatic brain injury, cerebral palsy, multiple sclerosis, and spinal cord injuries) (Iosa et al. 2011; Pichiorri et al. 2012).

The only way to achieve this is by promoting a multidisciplinary approach, whereby researchers, therapists, and patients are challenged to look outside beyond themselves and use each other's specific knowledge to customize the poststroke rehabilitation toolbox.

Robotic-based systems are a good example of technological-based interventions. They are used and tested widely, but there is no consensus on their functional benefits, perhaps because many early-developed devices are considered 'rigid' systems that focus primarily on the strict restoration of healthy motor control to prestroke levels.

For instance, the Lokomat® was designed to treat gait, based on undamaged walking models. Stepping movements are controlled only in the sagittal plane, allowing for limited joint involvement. Considering the specificity of stroke in individuals, this general walking pattern might fail to improve walking capacity. The former physiological pattern can not be restored, because a part of brain function is lost. Instead, new connections should be established, allowing the therapy to vary and adapt to patient-specific walking patterns. As a consequence, several groups have developed walking devices that permit free exploration within boundaries, following the principle of guidance when needed (Wirz et al. 2005).

The upcoming challenge for researchers and clinicians will be to implement one optimal rehabilitation therapy to the right patient at the right time, because certain stroke patients are better responders to a specific therapy than others, solutions must be adapted to each patient. An interdisciplinary step-by-step approach begins with increasing our understanding of physiopathological mechanisms after stroke to favor training-induced plasticity by developing tools that promote functional recovery. Despite the efforts that are being made to develop rehabilitation techniques, there are no accurate guidelines or prescriptions to guide the optimal solution for each patient. One emerging concept likely relies on incorporating objective measurements into the clinical diagnosis before and during treatment to mold the therapy to a patient's individual needs (Backus et al. 2010).

1.2.2 Upper- Versus Lower Limb Motor Control

Although rehabilitation attempts to effect the maximal restoration of patient function as a whole, a distinction is usually made between upper limb and lower limb recovery. Thus, we will discuss the chief neurological processes that underlie upper and lower limb motor control. Although both extremities are involved in voluntary and automatic movements, the function of lower and upper limbs differs.

The upper limb is primarily involved in conscious goal-directed tasks, whereas the lower limb participates in semiautomatic functions, such as gait and postural control. Understanding these differences can mitigate the respective therapeutic challenges.

Movements in humans are controlled by cortical and spinal processes, the functions of which vary by task. Cortical involvement is often linked to conscious control and complex movements, whereas spinal control is generally considered 'lower control' for automatic processes and reflexes. For instance, spinal control primarily mediates rhythmic tasks, such as locomotion of the lower limb (Grillner and Rossignol 1978) and scratching for the upper limb (Berkowitz 2008). In contrast, voluntary movements are controlled by cortical processes (Sartori et al. 2012; Carpaneto et al. 2012).

Yet, this apparent dichotomy has been proven to be incorrect, and spinal and supraspinal mechanisms interact in both types of movement. Recent primate research has demonstrated that spinal control is involved in grasping and reaching (Alstermark and Isa 2012). Similarly, cortical processes regulate the monitoring of locomotor patterns, contain important information on the central pattern generation functioning (Cheron et al. 2012), and maintain postural stability, as observed in transcranial magnetic stimulation studies during walking (Rogers et al. 2011).

Taking into account the functional disparities above, it is not surprising that upper- and lower-limb motor control mechanisms differ. Regarding the lower limb and its primary function (gait), the reduced variability in motor pattern and the highly influential theory of central pattern generators (Grillner et al. 2005) support the proposal of locomotion-modeling algorithms (Umberger and Rubenson 2011). This theoretical framework is the foundation of various robotic tools that have been developed for the recovery of walking. Optimal trajectories have been calculated, minimizing energetic costs of the closed chain between hip, knee, ankle, and foot placement, and projected onto the system of the recovering patient.

The clinical picture of the upper limb and its main functions (reaching and grasping) is less clear, because modeling these movements is more complex. There are many effective ways and muscular activation patterns to execute a specific reaching movement successfully, particularly due to the many degrees of freedom in the upper limb. Nevertheless, various modeling approaches have been proposed (Archambault et al. 2009; d'Avella et al. 2011; Sartori et al. 2012), although there is little consensus on the matter. Further, existing models have been applied only to robotic rehabilitation devices with a motor repertoire and limited degrees of freedom (Schmidt et al. 2004).

The developing knowledge base of neurological mechanisms, plasticity, and theoretical models influences our understanding and application of therapies for each limb. Independent of the many therapeutic interventions that have been proposed, both branches of rehabilitation have been affected by the necessary change in perspective—individualizing therapy to the needs of the patient-care-givers system, based on time and severity after stroke. Thus, in the following sections, we will focus on the changing perspective from therapy-centered to client-caregiver system-centered approaches toward lower limb and upper limb rehabilitation.

1.3 Emerging Perspectives in Lower Limb Rehabilitation

1.3.1 Body Weight-Supported (BWS) Gait Rehabilitation

As discussed, lower limb rehabilitation focuses primarily on the recovery of gait. The introduction of electromechanical/robotic-assisted gait rehabilitation techniques in recent years has represented one of the main novelties in stroke rehabilitation. The two best-known robotic commercial devices that conduct ambulation training in hemiparetic patients are the Gait Trainer (GT), which controls endpoint trajectories (GT II, Rehastim, Berlin, Germany), and the Lokomat®, which integrates a robotic exoskeleton and a treadmill (Hocoma Medical Engineering Inc, Zurich, Switzerland) (Jezernik et al. 2003; Peurala et al. 2009). Both devices have been used for stroke and spinal cord injury rehabilitation. Their high cost and uncertain efficacy and the skepticism of certain clinicians have limited their use for inpatient care.

A recently updated Cochrane review (Mehrholz et al. 2007) concluded that electromechanical-assisted gait training (Lokomat® or GT) with physiotherapy raises the odds of recovery of independent walking, based on the functional ambulation category (FAC), compared with conventional therapy without significantly increasing walking velocity or walking capacity. This report included nonambulatory and ambulatory patients at various stages of stroke, from subacute to chronic. A multicenter study by Hidler et al. on Lokomat® demonstrated that conventional gait training interventions are more effective than robotic-assisted gait training in facilitating the recovery of walking ability in subacute stroke patients with moderate to severe gait impairments (Hidler et al. 2009).

The poor performance of robotic approaches might be attributed to the control algorithms that are used. In particular, control systems that are more flexible or adjustable to patients' needs appear to provide better results (Ziegler et al. 2010). This assist-as-needed (AAN) rehabilitation paradigm states that robotic interventions must be tailored to the requirements of each subject and their use minimized only to situations for which the subject truly requires them.

Regarding current assistance strategies for robotic systems, the AAN control concept encourages the active motion of a patient, wherein the robotic device intervenes only when the subject is unable to complete the movement on his/her own. AAN has thus become the benchmark for controlling robotic assistance in stroke rehabilitation. In summary, the first robotic systems used a direct approach, applying a predefined fixed pattern, whereby a patient's singularities were not taken into account; conversely, novel approaches apply the AAN concept.

AAN is assumed to stimulate activation of the efferent motor pathways and afferent sensory pathways simultaneously during training. Current AAN strategies face the significant challenge of providing an adequate definition of the desired assistance to the user during the exercise. To this end, control algorithms that are based on predetermined reference trajectories, mechanical impedance of a patient's effort, or various degrees of body weight support have been proposed (Lunenburger et al. 2004; Hesse and Werner 2009; Gizzi et al. 2012).

Robotic exoskeletons measure the force interactions at several or all joints and support the movement of the patient by reinforcing the 'correct' pattern and impeding the 'incorrect' one (Banala et al. 2009). The crucial step, however, is to define the 'correct' pattern—i.e., to define the trajectory that the robot generates while assisting the patient during the exercise. It has been proposed to return to predefined (recorded from healthy subjects) gait patterns and adapt to them, based on the mechanical impedance that is measured by the robotic device (Abdullah et al. 2007; Pei et al. 2011). An alternative method is to base on the zero-force mode, whereby the device moves compliantly to the movement of the patient (Belda-Lois et al. 2011).

Most popular available robotic devices are position-controlled or impedance-controlled, exerting lower-limb control that varies between "robot-in-charge" and "patient-in-charge." Examples of such approaches are the robot-driven gait orthosis Lokomat® and the LOPES gait rehabilitation robot (Veneman et al. 2007). Another gait trainer, the LokoHelp (Woodway, USA), has been developed to guide the feet of the patient automatically, using harnesses for various applications (Freivogel et al. 2008). The KineAssist™ was developed to increase the challenge in maintaining balance during gait training (Patton et al. 2008). The outcome of rehabilitation with these devices can be enhanced by increasing active participation of the patient in the therapy. Motivation strategies, such as biofeedback measures and virtual reality (presented below), can also improve the outcomes of these therapies.

In addition to control algorithms, other aspects should be considered in refining robotic approaches to gait rehabilitation—the nature of the stroke (hemorrhagic or ischemic), severity of symptoms, poststroke delay, frequency and duration of training, and interactions with other therapies are important elements that should be taken into account. Recent studies have highlighted the significance of this multifactorial approach, demonstrating that only a subpopulation of stroke patients might benefit from electromechanical gait training (Morone et al. 2011, 2012). Moreover, future research should also include cost estimates of the therapy. Dickstein (Dickstein 2008) noted that simple "low technology" and conventional exercises are at least as effective as more complex strategies, such as treadmill- and robotic-based interventions (Dickstein 2008).

1.3.2 Ambulatory Exoskeleton for Gait Rehabilitation

BWS-based robotic systems must be permanently installed in a room and require a treadmill. Overground gait differs substantially from treadmill gait. Further, BWS-based systems do not allow balance training or training that is focused on single joints.

To overcome these limitations, ambulatory exoskeletons are being developed. The WalkTrainer™ is intended for a patient to relearn gait by combining a hybrid orthosis with functional electrical stimulation (Stauffer et al. 2009). It also supports a body weight support system. Alternatively, there is a large group of exoskeletons that support indoor over ground and treadmill walking, such as the IHMC (Institute for Human and Machine Cognition) Mobility Assist Exoskeleton (Kwa et al. 2009), the externally powered lower limb orthosis (Saito et al. 2005), and the Lower Body Exoskeleton (Costa and Caldwell 2006).

Exoskeletons can also target single joints. Thus, instead of actuating the entire lower limb, a single joint or a pair of joints, such as the knee-ankle joint with a knee-ankle–foot orthosis (KAFO) or the ankle joint with an ankle foot orthosis (AFO), is addressed. The powered KAFO is a unilateral KAFO that actuates joints by measuring surface electromyography signals from the patient (Sawicki and Ferris 2009). GAIT is a quasipassive KAFO that was developed as a low-power device (Moreno et al. 2008). The variable impedance AFO (Blaya and Herr 2004), an ambulatory version of AnkleBot (Krebs and Hogan 2006; Wheeler et al. 2004), is an AFO that impedes foot drop.

The BETTER (BNCI-Driven Robotic Physical Therapies in Stroke Rehabilitation of Gait Disorders http://www.car.upm-csic.es/bioingenieria/better/index.htm) project is attempting to develop an exoskeleton that supports entire lower limb movement and single joint approaches. BETTER comprises full and partial approaches in a single exoskeleton that is designed as a modular frame.

1.3.3 Virtual Reality and Games: A User-Centered Approach

Virtual reality is a relatively new approach in neurorehabilitation that can improve scenarios for rehabilitation. It has been defined as the "use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments that appear and feel similar to real-world objects and events" (Weiss et al. 2006).

Virtual reality might be advantageous, offering several features, such as goal-oriented tasks and the possibility for repetition, that are important in neurological rehabilitation (Dobkin 2004) and has the potential to provide an enriched environment in which stroke patients benefit from specific problem solving and master new skills. This approach has been used with a neurological rehabilitation bent to improve upper (Henderson et al. 2007) and lower extremity function and gait

(Deutsch et al. 2004), cognition, perception, and functional tasks for daily living (Rose et al. 2005). Although it is uncommon as a rehabilitation method, virtual reality is becoming more accessible and affordable (Burdea and Coiffet 2003). Further, commercial video games are a low-cost alternative (Deutsch 2011; Rand et al. 2008), and interactive video games that are geared specifically toward rehabilitation of stroke patients are being developed (Lange et al. 2010) (for a comprehensive description on virtual reality see also Chap. 13).

Recent studies indicate that robotic-assisted rehabilitation is improved by providing feedback to the patient about his/her performance during training. Virtual reality might be a useful and entertaining means with which to do so and can compensate for diminished proprioceptive capacity. To this end, new metrics that are based on kinematic, kinetic, and physiological measures are being designed and tested (Collantes et al. 2012a, b) that do not rely exclusively on the robot's sensors and can be combined with brain activity (EEG), muscular activity (EMG), and limb motion (inertial measurement units), effecting a more accurate analysis and characterization of the patient's activity, because the biofeedback does not depend on a single source of information. This feedback, based on biological signals, or biofeedback, monitors the patient's degree of activity, involvement, and compliance rendering it a valuable tool in assessing a rehabilitation therapy.

1.4 Emerging Perspectives in Upper Limb Rehabilitation

1.4.1 Examining Upper Limb Recovery

One-third to two-thirds of poststroke patients recover useful upper limb function. Clinical predictors [age, gender, lesion location, stroke volume, time to reassessment, initial Fugl-Meyer (FM) score] explain less than 50 % of the variance in recovery at 3 months poststroke (Prabhakaran et al. 2008). The best predictor of recovery over 6 months remains the initial severity of the impairment (Heller et al. 1987; Sunderland et al. 1989). Up to 86 % of the variance in impairment at 6 months (expressed as the FM) is attributed to the level of impairment at 1 month poststroke, suggesting that subacute rehabilitation has little impact on the impairment in the subsequent 5 months (Duncan et al. 1992).

Arm function at 6 months (expressed as the Barthel Index), however, is best predicted by the functional improvements in the first several weeks poststroke. Notably, only 56 % of variance is explained, which indicates that current rehabilitation strategies target the recovery of function than healing of the impairment. These findings call into question the value of compensatory strategies (Huang and Krakauer 2009) and the therapist in determining whether recovery of function or the impairment should be prioritized.

Nevertheless, the wide variability and poor predictability of recovery over the first 3 months underscore the necessity for developing individualized therapies.

The course of recovery varies tremendously between patients and clinical measurement tools (Kwakkel et al. 2006). Therapists have access to many clinical evaluation scales and tests, ranging from measurements of impairment (Fugl-Meyer, action research arm test, Jebsen-Taylor function test, box and block test, 9-hole peg test) to those of functional performance in activities of daily living (ADL) (functional independence measure, Barthel index). Due to this broad choice of scales, selecting the appropriate therapy at the right time is difficult if the therapist is unaware of the exact state of the deficit. Thus, defining the optimal rehabilitation strategy for a patient within standard therapeutic settings appears to be an impossible task.

The current challenge is to define the clinical predictors of recovery and implement the appropriate rehabilitation strategy to the correct patient at the right time. To do so, one needs to address many questions: What is the main goal of rehabilitation? On what criterion of recovery should the therapist focus? Should we focus on endpoint movements, as they are modeled, or are smooth muscle synergies more important? Is it the time course of recovery that determines the choice of therapy or the severity of the impairment? Since there are many ways to execute the same reaching movement, how do we determine which approach is correct, and what is the value of compensation?

Thus, although we lack well-established theories, a change in therapeutic attitudes has already occurred. In the following section, we will discuss two examples of shifting from the application of a fixed therapy toward a patient-system-centered approach.

1.4.2 Nontechnology-Based Interventions to Restore Interhemispheric Balance

Restoring interhemispheric balance after stroke has an important function in upper limb rehabilitation. Generally, the undamaged hemisphere inhibits the damaged counterpart, further exacerbating the functional limitations of the paretic upper limb. There are several theories on how this negative influence can be overcome: stimulating the damaged hemisphere, inhibiting the undamaged hemisphere, and forcing the 2 hemispheres to interact through bilateral training.

In the early 1990s, Dr. Edward Taub developed the constraint-induced movement therapy, a neurorehabilitation technique that improves use of the paretic upper limb after stroke by inducing plasticity in the damaged hemisphere. Essentially, the nonparetic limb is constrained, forcing the poststroke patient to use his/her paretic limb. The underlying concept behind this technique is the 'learned nonuse' theory: discouraged by the difficulties that are faced when using his/her paretic limb, a patient learns to use the nonparetic limb.

Learned nonuse is a type of negative feedback, and CI seeks to reverse this process (Taub and Morris 2001). Overcoming nonuse in the initial phase might be critical—Schweighofer et al. noted the existence of a threshold in recovery, predicting spontaneous use of the paretic upper limb (Schweighofer et al. 2009). When this threshold is not reached during therapy, the function is lost, rendering all therapeutic efforts vain.

In 2006, the first CI placebo-controlled trial demonstrated that after 2 weeks of intensive, treatment spontaneous paretic arm use in a real-world environment increased, as evidence by large effect sizes on the Motor Activity Log (MAL). This change did not occur in the control group, which spent as many contact-hours with the therapist but did not have their nonparetic limb constrained (Taub et al. 2006). This result was later confirmed, singling CI as the only evidence-based therapeutic intervention (Boddice et al. 2010).

The success of CI is often linked to its restrictive inclusion criteria, such as 20° active wrist extension and 10° active extension of each finger that is involved in paretic UL (Taub et al. 1998). These standards render the therapy accessible to a small percentage of stroke patients. Thus, CI is a good example of a clearly targeted therapy for a well-defined subpopulation.

Yet, the entire training program is highly intensive for the patient and therapist, and it often fails to suit the needs of the patient and his/her caregivers, resulting in limited use of CI in clinical practice. The need to overcome nonuse and increase spontaneous use, however, remains for all patients. As CI has remained a promising intervention, adaptive versions of CI have been developed, constraining the use of the less-affected limb only during specific tasks that were determined by the patient and therapist to be 'crucial' to activity of daily life (ADL) function.

Another example of a therapy that restores interhemispheric balance is bilateral arm training (BAT). BAT facilitates cortical neural plasticity by treating both arms simultaneously or cooperatively. Bimanual movements activate the primary motor corticospinal tract and are assumed to stimulate ipsilateral uncrossed fibers and facilitate neural plasticity (Cauraugh et al. 2005; de NAP Shelton and Reding 2001). Whereas overcoming nonuse is important during the initial phase of recovery (although the effects of CI have been shown primarily in chronic stroke patients), bimanual therapy is more effective when the plateau phase of motor recovery develops—i.e., when initial spontaneous recovery processes level off (Metrot et al. 2013).

Notably, Stinear et al. suggested an advantage of BAT for patients with low functional potential and poor recovery of upper limb function (Stinear et al. 2007), who are already more likely to engage the contralesional hemisphere during paretic upper limb use. By being forced to use both hands, patients might experience involvement of the contralesional hemisphere in controlling the nonparetic limb simultaneously, facilitating recruitment of the damaged hemisphere.

Thus, CI and BAT restore hemispheric balance, albeit through disparate means and on different time scales. Both therapies have similar benefits on movement smoothness but differential effects on force and functional performance. BAT might be preferred if improvement of force is the provisioned goal. Conversely, CI might be more appropriate for enhancing functional ability and use of the affected arm in daily life in stroke patients (Wu et al. 2011). The ultimate selection of optimal therapy for each patient, however, might depend on goals or preferences with regard to unimanual or bimanual training and follow a logical sequence, wherein various therapies stimulate the correct neuronal process at the right moment.

1.4.3 Technology-Based Interventions that Improve Existing Therapies

Technological tools have been developed gradually to increase the number of possible interventions at the various stages of poststroke. Many technological fields have attempted to improve existing rehabilitation therapies, proposing interventions that are based on robotics (Kwakkel et al. 2008), functional electrical stimulation (Pomeroy et al. 2006), virtual reality (Henderson et al. 2007), and brain-machine interfaces (Buch et al. 2008) and their various combinations (Daly et al. 2009; Fluet et al. 2012; Meadmore et al. 2012).

However, technology experts often design technological interventions without accounting for clinician experience or patient needs, which can unfortunately result in the development of efficient technology that never enters daily practice, because potential users do not understand or agree with its purpose.

One such example is the MIT-Manus robotic system, a robotic device that is designed for upper limb rehabilitation that allows the execution of repetitive movements on planar trajectories. To use this device, the patient sits at a table and attaches his/her arm to the robotic arm. The therapist first guides the arm though a given exercise that is stored by the robotic system so that it repeats the trajectory autonomously during a training session in active (in which the participant moves his/her arm but is corrected when the movement is wrong) or passive mode (the participant's arm is moved by the system) (Krebs et al. 1998).

Possibly due to the range of movements that are used and the low variability and rigidity of the system, it increased spasticity in certain patients. Updated versions of MIT-Manus allow for various modalities, offering assistance as needed, whereby the therapist is free to define the outer boundaries of a certain trajectory at which the robot influences the natural movement of the hand (Lo et al. 2010). With these adaptations, similar improvements were achieved by patients who used robotic rehabilitation as those who underwent intensive human-assisted therapy (Lo et al. 2010)—the lack of intensive human guidance, however, led to reduced therapeutic costs.

Another innovative tool that has improved therapies is the brain-computer interface (BCI). Pichiorri and colleagues (Pichiorri et al. 2011a) used BCI to improve motor imagery (MI) on the patient and therapeutic levels. MI has been used for many years in stroke rehabilitation, enhancing the therapeutic effects of physical therapy alone (Nilsen et al. 2010). However, the chief drawback of MI interventions was that the therapist lacked an objective measurement of how well the patient was performing an imaginary task or whether the patient was trying to perform it at all.

To overcome this omission, BCI was implemented to monitor the electroencephalography (EEG) of a patient, providing the therapist with feedback of brain activity during task performance (Pichiorri et al. 2011b). With this information, the therapist can guide a patient during the MI exercise and encourage him/her when brain activation drops below a threshold. Using this type of new technology allows the therapist to become part of MI interventions, contributing to the application of such interventions to a larger population of stroke patients and extending their use to clinical environments (Mattia et al. 2012).

These two examples demonstrate how technology improves existing rehabilitation therapies, but technology developers must bear in mind clinicians' attitudes toward elaborate optimal interventions. A new patient-based paradigm must be established, considering that technological tools do not always have to be centered around the patient but the patient-therapist-doctor triad. Thus, a technological intervention is successful if it effects better rehabilitative outcomes results or if similar results are reached faster and more inexpensively, or if it eases the therapist's work in evaluating and selecting patients. Overall it must be possible to tailor to patients characteristics, and within the selected group of patients it should allow standardization

1.5 Conclusion

It is an exciting time for stroke rehabilitation. The longlasting gap between neuroscience data and clinical application is closing rapidly, and many concepts from experimental evidence are guiding everyday activity in stroke rehabilitation centers. This new knowledge is also accelerating the development of new neuromechanical and robotic tools to support and improve the efficacy of rehabilitation. Although the evidence that supports the efficacy of such approaches remains scarce, the knowledge of the causal relationships between rehabilitation approaches and cerebral plasticity with regard to functional outcome is directing us in creating more specific apparatuses and more effective control systems.

The pioneering approaches in robotic rehabilitation, such as the Lokomat® and MIT-Manus, are paradigmatic. After an initial wave of excitement, clinical studies were somehow disappointing and forced to reconsider the mechanical structure and control systems. Further, the possibility of operating in controlled environments and the scientific interest in determining the pathophysiology of poststroke plasticity have effected a surge of data on the specificity of every method, propelling us toward a more patient-therapist-tailored approach that is demonstrating tremendous efficacy. We have highlighted the critical points that are limiting the full implementation of technology-based approaches in clinical neurorehabilitation. Nevertheless, we conclude that such approaches are shaping the present, rather than future, of stroke rehabilitation.

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Chapter 2
Emerging Rehabilitation in Cerebral Palsy

Stefan Lambrecht, Oiane Urra, Svetlana Grosu and Soraya Pérez Nombela

Abstract Cerebral Palsy (CP) is the most frequent disability affecting children. Although the effects of CP are diverse this chapter focuses on the impaired motor control of children suffering from spastic diplegia, particularly in the lower limb. The chapter collects the most relevant techniques that are used or might be useful to overcome the current limitations existing in the diagnosis and rehabilitation of CP. Special emphasis is placed on the role that emerging technologies can play in this field. Knowing in advance the type and site of brain injury could assist the clinician in selecting the appropriate therapy. In this context, neuroimaging techniques are being recommended as an evaluation tool in children with CP; we describe a variety of imaging technologies such as Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI), etc. But creating new knowledge in itself is not enough; there must be a transfer from progress through research to advances in the clinical field. The classic therapeutic approach of CP thus hampers the optimal rehabilitation of the targeted component. Traditional therapies may be optimized if complemented with treatments. We try to collect a wide range of emerging technologies and provide some criteria to select the adequate technology based on the characteristics of the neurological injury. For example, exoskeleton based over-ground

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gait training is suggested to be more effective than treadmill-based gait training. So, we suggest a new point of view combining different technologies in order to provide the foundations of a rational design of the individual rehabilitation strategy.

Keywords Cerebral palsy · Robotics · Neurostimulation · Neuroimaging · Myoelectric signals

2.1 Introduction

The general objective of rehabilitation interventions is to restore previous functional levels or abilities. However, when children are involved, the target level cannot be limited to re-establish a prior-value. Pediatric rehabilitation implicitly involves a moving target, the maturing child with transitory emotional, behavioral, cognitive and motor abilities. Therefore the objective in pediatric rehabilitation is twofold, restore prior levels and facilitate the further development of these abilities (Alexander and Matthews 2009).

Among all disabilities affecting children, Cerebral Palsy (CP) is the most frequent and its incidence rate keeps rising, partly due to greater numbers of premature infants who are surviving and longer overall survival (Wilson-Costello et al. 2005). Despite the lack of consensus on a definition of CP, three elements are recurring: (i) brain lesion, (ii) onset at birth or early child years, and (iii) impaired motor control. A well-cited definition of CP defines CP as: "a group of disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, by epilepsy and by secondary musculoskeletal problems" (Bax et al. 2005). Currently there is no specific diagnostic protocol, nor is there a clear singular etiology and pathology. There is a need for knowledge and tools to facilitate a reliable and accurate prognosis of CP outcome.

CP results in different movement patterns including spastic, dyskinetic, hypotonic, ataxic, and mixed forms. The most common movement pattern is spastic, with a minority of cases being primarily dyskinetic, ataxic or hypotonic (Yeargin-Allsopp et al. 2008). The primary means of classifying in CP is done according to the anatomical distribution of motor complications. There are three categories, each occurring with fairly equal frequency: hemiparesis, diparesis, and quadriparesis. *Hemiparetic CP* affects only one side of the body and typically demonstrates greater impairments in the upper extremity. *Diparetic CP* primarily affects the lower limbs with very little or no impairment in the upper extremities. Spastic *quadriparetic CP* affects the entire body, including the axial as well as appendicular skeleton (Alexander and Matthews 2009). Given the wide variety of impairments related to CP we have decided to put the emphasis on the impaired motor control of children suffering from spastic diplegia, and gait rehabilitation in particular.

Advances in neuroscience, neurophysiology and neuroimaging techniques offer an important contribution to neurorehabilitation by generating knowledge on impaired motor control and providing guidance to set future clinical and research pathways. In CP the most common neurological abnormality is found in the white matter near the lateral ventricles, often termed periventricular leukomalacia (PVL). PVL abnormalities are present in up to 56 % of all CP patients, occurring mostly in premature infants (90 %) rather than in term infants (20 %), and arise as a result of intraventricular hemorrhage. Because the corticospinal tract fibers to the lower extremities are medial to those of the upper extremities in the periventricular white matter, children with PVL abnormalities typically have spastic diparesis (Korzeniewski et al. 2008).

In this chapter we will focus on the diagnosis and rehabilitation of the impaired gait and motor control of children with CP, and the role emerging technologies can play herein (Fig. 2.1). The main body of the chapter consists of a section highlighting the clinical needs in CP (Sect. 2.2), and a section dedicated to how technologies that are emerging in research or other clinical fields can alleviate (some of) those clinical needs (Sect. 2.3). The technologies discussed in this chapter were selected based on their promising potential in CP treatment, or demonstrated impact and effect in other neurorehabilitation areas, such as stroke management. The section on emerging technologies is further divided into four parts: Myoelectric signals (Sect. 2.3.1), Neuroimaging (Sect. 2.3.2), Neuro-stimulation (Sect. 2.3.3), and Rehabilitation robotics (Sect. 2.3.4).

2.2 Clinical Needs in Cerebral Palsy

Little is understood about the causes and mechanisms underlying CP. The few well established fundaments have yet to find their way into clinical practice. As a consequence, the diagnosis and treatment of CP is largely based on empirical criteria. However, specialists in the field claim that children with CP may benefit from emerging technologies, both for diagnosis and rehabilitation. Their claim is supported by the positive impact demonstrated in an increasing number of studies. Furthermore, advances done in fields such as neuroimaging may help to shed light in the physiopathology of CP or enable a more accurate diagnosis. Similarly, novel neuro-stimulation techniques or rehabilitation robotic devices are expected to significantly improve the outcome of rehabilitation. Despite the potential of emerging technologies to solve important clinical issues in CP, the technological transfer in this area is almost blocked. In this section we list some of the most relevant limitations found in the field of CP that could be mitigated with the use of appropriate technologies.

The research on CP is still far from giving a clear picture on the physiopathology of the disease. The development of the human brain and how it is affected by different injury conditions such as hypoxia, trauma or encephalitis remains poorly understood. There are still manifestations of CP with a non-identifiable

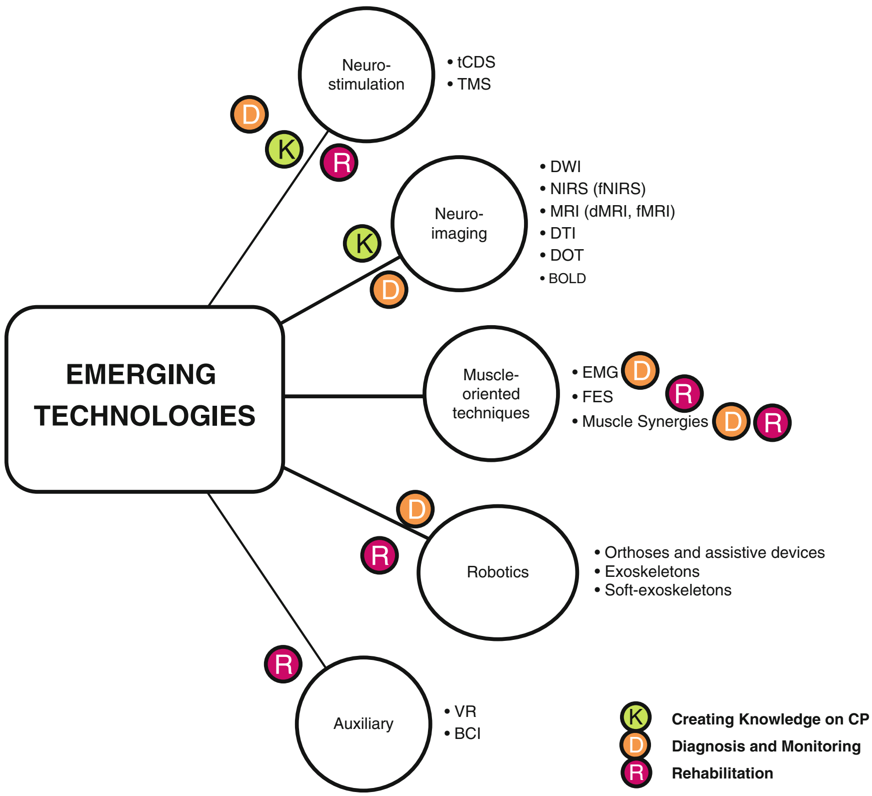

Fig. 2.1 The array of emerging technologies and their potential fields of impact related to cerebral palsy: rehabilitation, diagnosis, basic knowledge on physiopathology and motor control. *tDCS* transcranial direct current stimulation, *TMS* transcranial magnetic stimulation, *DWI* diffusion weighted imaging, *(f)NIRS* (functional)near-infrared spectroscopy, *MRI* magnetic resonance imaging, *DTI* diffusion tensor imaging, *DOT* diffusive optical imaging, *BOLD* blood oxygenation level dependent MRI, *EMG* electromyography, *FES* functional electrical stimulation, *VR* virtual reality, *BCI* brain-computer interface

neural cause. As a consequence, it is difficult to detect CP before motor symptoms appear. Therefore, in most cases rehabilitation starts relatively late (up to several years) after onset of injury. Interpreting the neural damage from the observable motor dysfunction alone is an almost impossible task. Some authors suggest that muscle synergy analysis may offer the clinician a better view of the neural structure underlying motor behaviors and how they change in motor deficits and rehabilitation (Safavynia et al. 2011). Such information could inform diagnostic tools and evidence based interventions specifically targeted to a patient's deficits.

Unfortunately, unlike in stroke, it is usually hard to detect the brain area that is affected in a patient with CP. Recent advances in neuroimaging could be of great value not only for delving into the physiopathology of CP but also for allowing the exact identification of the neural damage, beyond the symptomatic level

(Cioni et al. 1999). Emergent techniques such as Diffuse Tensor Imaging (DTI) are being used to shed light on the mechanisms underlying the disorder. This and related techniques may allow early diagnosis of CP, before motor dysfunctions can be observed. Given that during the first eight years of life the developing brain holds the capacity of rerouting and reorganizing damaged signal paths and neural patterns, prompt diagnosis offers tremendous potential in the treatment of CP. Therefore, the earlier the disorder can be diagnosed, the higher the potential success rate and more advanced the outcome of the therapy.

Different neurological injuries can lead to similar functional disabilities. Diagnosis based on the observable functional disability could thus result in patients with similar symptoms to be prescribed the same therapy. Furthermore, there are plenty of aspects of motor control, lower limb control in particular, that remain unsolved. The therapeutic possibilities of the rehabilitation depend to a great extent on the underlying causes of the disability, rather than on the disability itself. For example, an injury on the pyramidal system prevents the learning of new patterned movements. In this case, therapies promoting new movements are likely to fail. Thus, knowing in advance the type and site of injury could assist the clinician in selecting the appropriate therapy.

Enhanced knowledge and understanding of CP not only offers potential improved diagnosis and treatment, but would also assist in making more accurate predictions. A complete picture on the condition, including functional outcomes and the dysfunctions in the motor control generating those disabilities, would enable the creation of a theoretical framework. This framework can then be used to predict progress of functional impairment, impact of different therapies and their final outcome, and assist in the development of a specific therapy on a case-by-case basis to target the observed motor dysfunction.

Creating new knowledge in itself is not enough; there must be a transfer from progress through research to progress in the clinical field. Current knowledge about CP is not being used to its full potential in rehabilitation. For instance, it is known that injuries to the CNS cause three different types of motor impairment, each requiring a different therapy: (1) spasticity, (2) muscle weakness and (3) impaired motor coordination. Nevertheless, CP rehabilitation generally focuses on regaining motor coordination, whilst ignoring the other two. Based on this knowledge, a new therapy design could combine strategies to treat the three types of interacting motor impairments, in order to improve the overall motor function. The individual rehabilitation of each motor component could significantly improve the others. The classic therapeutic approach of CP thus hampers the optimal rehabilitation of the targeted component. Traditional therapies may be optimized if complemented with treatments for reducing spasticity or muscular weakness, by means of classical stretching exercises or more advanced techniques such as FES (Functional Electrical Stimulation). Of course, to do so more accurate measures of these conditions are desirable.

Functions of damaged brain areas can be taken over by other, non-affected, regions of the brain. This process is known as cortical reorganization and is based on the principle of brain plasticity (Merzenich et al. 1984; Calautti and Baron 2003).

This implies that motor control functions targeted by rehabilitation interventions can be affected by brain areas other than the primary site of injury.

Traditional therapeutic interventions follow a bottom-up paradigm. In gait retraining, the patient's limbs are moved along a fixed reference trajectory by the therapist, under the hypothesis that the generated movement pattern will be restored. Despite the relatively modest improvements obtained through this form of therapy it has been copied and adapted for use in combination with modern technology, such as exoskeletons and robotics. Hypothesizing that better effects could be achieved by increasing therapy intensity (movement repetition and movement time), and by canceling out imperfections in the execution of the reference pattern. However, this repetitive approach has not been found to stimulate cortical reorganization, nor is it in line with the current understanding of neurological mechanisms (Kollen et al. 2009).

Brain plasticity and cortical reorganization are thought to be strongly correlated with movement intention (efferent pathway) and appropriate proprioceptive feedback (afferent feedback). Therefore, it is important to target both pathways simultaneously during rehabilitation (Emken et al. 2009). By strictly focusing on the execution of the movement pattern, traditional approaches fail to meet these criteria. Recently an alternative approach is surging, based on the idea that the execution of the movement pattern should agree with the motion as intended or developed by the patient. This top-down approach is believed to result in the correct proprioception feedback for the brain, and is thus more closely linked with our current understanding from clinical and neuroscientific research.

In healthy populations EMG signals are an adequate measure to represent motion intention. However, in CP patients clinicians or researchers cannot rely solely on myoelectric control in order to describe intention. Incoherent, non-voluntary, rapidly changing, weak signals or spasms impede the reliable application of this metric. Therefore other techniques have to be used to measure intention in this population, such as: BCI, fNIRS, DTI, MRI and EEG

The amount of available technologies that have a potential positive impact on the rehabilitation of CP is continuously increasing. However, little of this potential is being realized. Clinicians lack clear guidelines on how to select and combine these technologies in order to increase the efficacy and efficiency of the treatment. Absence of these guidelines has rendered the inclusion of technology into rehabilitation strategies to not always be beneficial. Interference due to interaction between technologies can deteriorate the outcome of the therapy to the extent that the patient was better off prior to the introduction of one or several technologies. Incorporating technology into therapy does not automatically generate advantages or improvements or the patient. For instance, the introduction of virtual reality to enhance motivation in many cases did not result in an improved outcome of the therapy provided. It was not until coupled with a functional objective, such as a visual motor integration task, that inclusion of virtual reality resulted in superior outcomes. Selection of the adequate technology to be implemented into the therapy design should be based on the characteristics of the neurological injury, the observed functional impairments, and framed within a motor control improvement strategy. For instance, exoskeleton-based over-ground gait training is suggested to be more effective than treadmill-based gait training. It is thought that afferent feedback is more naturally provided during the former, resulting in significant balance improvements. The choice of technology should be directed to create new motor skills, prompt specific muscle capabilities or activate specific physiological modules. Given the wide variety in underlying conditions and functional manifestations, personalized interventions are desirable.

Currently there is a wide range of treatments and therapies applied to patients with CP disability. This variety represents the diversity of clinical conditions that can be found despite similar functional disabilities. All therapies should accomplish a minimum set of care requirements and physical therapy goals: (1) to maximize level of independence, (2) to optimize mobility, (3) to prevent deformity, (4) to keep the pain under control, (5) to stimulate peer and social interactions.

In conclusion, emergent technologies may be of great value to solve important limitations present in the field of CP diagnosis and treatment. A solid framework is needed for the design of personalized interventions and to guide the clinician to select the most adequate technology on a case-by-case basis. This framework could provide the foundations of a rational design of the rehabilitation strategy. Thus, it should be continuously supported by the latest discoveries about the physiopathology of CP and allow tailoring of the rehabilitation strategy according to both, the motor impairment and neural damage of each patient.

2.3 Emergent Technologies

2.3.1 Muscle Oriented Techniques

From a clinical point of view, myoelectric signals provide valuable information to assess the neurophysiological state of the muscle. Such information can be very useful in a number of scenarios. The most obvious application is to use myoelectric signals as a tool to assist in making an accurate clinical diagnosis. But also, techniques such as electromyography (EMG) or muscle synergies may serve to monitor treatment outcome, or even to aid rehabilitation, as in the case of Functional Electrical Stimulation (FES) (see Fig. 2.1). The following sub-sections are dedicated to illustrate briefly each of these techniques.

2.3.1.1 Electromyography

Electromyography (EMG) records the electrical potential fired by skeletal muscles. As such, EMG allows a direct evaluation of muscle activity. EMG can be performed noninvasively, by placing the electrodes over the skin (surface, sEMG), or invasively, by introducing needle electrodes or a needle containing two fine-wire electrodes straight into the muscle tissue (intramuscular EMG, iEMG). iEMG provides means to assess the activity of a few muscle fibers and their innervation. However, for certain applications, iEMG is considered to be too invasive. In contrast, despite its lower specificity, sEMG provides simple means to construct a general picture of the muscle activity. So, given its convenience of use, in the clinical practice surface EMG is preferred.

The electrode placement criteria are standardized by the recommendations of the Surface Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) protocol (van den Noort et al. 2010). It is remarkable that although sEMG represents one of the most accessible electrophysiological recordings, paradoxically, its interpretation is very complex and relies on advanced decomposition methods and the experience of the clinician. In addition, EMG signals can be large and highly variable, which precludes their clinical utility. However, in the last years intense work has been done in advanced signal processing techniques, so that nowadays it is possible to infer how muscles are neurally controlled or the state of the neuromuscular system from the decomposition of the EMG signal (Jiang et al. 2010). In this context EMG has been applied as a control signal in several devices and applications in neurorehabiliation (for more in-depth information on EMG, see Chap. 14).

The application of EMG in children with CP offers a great range of possibilities. The most straightforward is the use of EMG to record the specific muscle activity during contraction. This procedure allows the accurate assessment of the motor dysfunction during diagnosis or along diverse therapy sessions to directly follow up the muscular outcome of the intervention. On the other side, EMG also provides means to evaluate the spasticity of the patient. Before any rehabilitation procedure is designed, it is crucial to determine the degree of muscle spasticity of the patient. Spasticity restricts the way in which motor rehabilitation is carried out to the point that in some cases Botulinum A toxin (BOTOX) injections are prescribed in order to decrease spasticity and improve motor function (see also Chaps. 7 and 8. BOTOX injections also decrease the pain produced by spasticity. In this scenario, EMG may facilitate the localization of the injection site. In more advanced designs, EMG may be used to record muscle response following, for example, stimulation of the motor cortex (For further details see Neurostimulation section).

2.3.1.2 Muscle Synergies

The production of voluntary movements relies critically on the functional integration of several motor cortical areas, such as the primary motor cortex, and the spinal circuitries. Muscle synergies are defined as the pattern of muscles co-activated to obey a given motor command. Each synergy involves different muscles, and different muscles can participate in more than one synergy. Increasing number of experimental demonstrations suggest that the motor system may coordinate muscle activations through a linear combination of muscle synergies (Cheung et al. 2009). Therefore, muscle synergies appear to play a key role to understand the motor control orchestrated by the brain.

Muscle synergies are identified by measuring with EMG the activity of all (or at least the main) muscles involved in a given movement. In a synergy, each muscle contributes in a different proportion to the overall activation pattern. On the fine motor control level, motor coordination and the performance of complex movements is achieved by combining different synergies (Ajiboye and Weir 2009). The use of muscle synergies, thus, may be of a great value to design motor control strategies for prosthetics, Functional Electrical Stimulation (FES) application or any other EMG-based technology by means of synergy pattern recognition and decoding. Most of these applications have been tested in stroke patients. Further studies are needed to establish and validate the clinical use of muscle synergies in children with CP.

In addition, the analysis of muscle synergies may offer the clinician a better view of the neural structure underlying motor behaviors and how this structure changes due to motor deficits or after rehabilitation. Consequently, muscle synergies are powerful candidates to inform diagnostic tools and design evidence-based interventions specifically targeted to patients' deficits (Safavynia et al. 2011).

2.3.1.3 Functional Electrical Stimulation

Functional Electrical Stimulation (FES) delivers small electrical currents on intact peripheral motor nerves innervating the muscle tissue to improve or restore the overall muscle activity. Electrically primed muscle contractions are coordinated to produce functionally useful movements such as writing, walking, standing or grasping. Different FES-based devices are commercially available for use on upper limbs, lower limbs, the bladder and bowel system, and the respiratory system (for an in-depth analysis on bladder and bowel neurorehabilitation, see Chap. 4). During gait rehabilitation, direct orthotic effect is achieved by applying FES on tibialis anterior (TA) either with or without gastrocnemius stimulation. On upper limb function, FES has been shown to increase muscle strength, extend the range of motion and improve the motor function in children with CP (Wright et al. 2012; van der Linden 2012). In the future, the optimized design of hybrid neuroprosthesis is postulated by combining FES-based muscle stimulations with the analysis of muscle synergies. The idea behind this design is to fire FES with the motor intention of the user and coordinate the electrical delivery patterns according to the activation of identified synergies. However, further studies are needed including randomized controlled trials to validate the use of FES in children with CP. An extensive description on FES-based applications can be found in Chap. 11.

2.3.2 Neuroimaging

Current measurements of motor deficits in individuals with CP are largely based on empirical criteria. This is partly due to the absence of techniques to assess the

CNS functions. Testing novel techniques for CP rehabilitation faces a major obstacle as the principal population to be targeted is constituted of developing children (Wittenberg 2009). Neuroimaging is an imaging technology that enables us to visualize neural activity and pathways in the brain. Recently, neuroimaging is being recommended as an evaluation tool in children with CP (Towsley et al. 2011). The patterns in the neuroimaging data of CP patients are correlated to neurological subtype, CP severity and other categorical variables such as functional motor scales (Towsley et al. 2011). Neurological subtype has been shown to be a powerful predictor of ambulatory functional status, both prior and post treatment (Shevell et al. 2009). Neuroimaging technology thus offers us a view to understanding the relationship between brain activity and motor function, as well as the pattern and severity of the brain injury underlying cerebral palsy (Shimony et al. 2008). Innovations in imaging enable early identification of injury, before motor deficits and other abnormalities are present. These advances have the potential to drive therapies to re-establish the cortical input to spinal motor centers, facilitate normal development, and avoid secondary injuries such as bone deformities (Kułak et al. 2006). A variety of imaging technologies exists, each with its own strengths and weaknesses. Here we will specifically focus on neuroimaging technologies that, to the best of our knowledge, are or can be of value in CP rehabilitation or research: MRI, dMRI, DTI, DWI, BOLD fMRI, NIRS, fNIR (see Fig. 2.1).

A first distinction between the various technologies can be made with regard to their resolution. Current technologies suffer from a trade-off between temporal resolution (identify when an event occurs) and spatial resolution (where in the brain an event takes place). Technologies based on measuring electrical currents or magnetic fields provide high temporal resolution. On the other hand, techniques were blood flow is tracked offer great spatial resolution but are relatively slow.

Several technologies measure local changes in cerebral blood flow, often referred to as activations, which are related to neural activity (e.g. fMRI, NIRS) and enclosed in the term "neurovascular coupling" (Cabeza and Kingstone 2006; Leff et al. 2011). These methods result in high spatial accuracy. Within this group of technologies, there are methods that are more suited for focusing on specific areas (fNIRS,fMRI) and methods that enable the clinician to create a map of a bigger area (DOT,NIRI).

2.3.2.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has a high contrast resolution and is used to distinguish pathological from normal tissue. Strong magnetic fields and non-ionizing electromagnetic fields in the radio frequency range form the base of this technology. A typical MRI-examination consists of several sequences (up to 20), each providing a particular type of information about the patient's tissues. A multitude of specialized MRI applications exist, each with their own strength. Compared to computed tomography (CT) MRI: offers a better tissue contrast resolution, is capable of generating images in multiple planes, and does not require ionizing radiation

(Accardo et al. 2004). Several advances have been made to improve the MRI image quality and the data subtracted from these images, for specific purposes. Standard MRIs are often applied in pediatric neurological examinations. However, the evaluation of conventional MRI sequences is relatively subjective when compared to other techniques such as Diffusion Tensor Imaging (DTI). The improvements in sensitivity and objectivity with DTI may present it as a more useful technique to detect small changes in developmental status in the future.

2.3.2.2 Diffusion Tensor Imaging

Diffusion MRI (dMRI) has become the standard for white matter disorders. Diffusion tensor imaging (DTI) is an MRI application that measures the diffusion of water molecules in biological tissues (Le Bihan et al. 1986). When applied to CP patients, DTI allows us to better understand the connectivity of white matter axons in the central nervous system. The models of brain connectivity created from this data can further be used to examine the connectivity of different regions in the brain (i.e. tractography), or to identify and study areas of neural degeneration (Miller et al. 2003). For example, current DTI applications are able to distinguish between acute ischemic changes and chronic ischemic changes in stroke patients; this may influence both the prognosis and design of rehabilitation interventions (Yang et al. 1999; Sotak 2002). DTI values have also been suggested to have a predictive value for evaluating hand function outcome in chronic stroke patients (Song et al. 2012). The relation between DTI results and clinical outcomes in stroke patients underlines the potential for DTI applications in CP (Mulcahey et al. 2012; Barakat et al. 2012; Rha et al. 2012). DTI metrics have also been shown to be sensitive to regional changes in the contralateral hemisphere, the role of which is still largely unknown in CP (Granziera et al. 2012). Furthermore, DTI results of the pyramidal tract in chronic stroke patients appear to be related to the residual motor function. Radlinska et al. reported that parameters of the pyramidal tract integrity obtained within the first weeks are highly correlated with residual motor function in the acute as well as in the chronic stage (Radlinska et al. 2010). DTI thus presents itself as a promising technique to improve diagnosis of CP and prediction of its outcome (Mulcahey et al. 2012).

2.3.2.3 Diffusion Weighted Imaging

Diffusion weighted imaging (DWI) is capable of detecting early changes in cellular function occurring in the lesion (Moseley et al. 1990; Utsunomiya 2011). DWI values are able to identify the extent of brain parenchymal injury. The severity of which has been reported to correlate with the patient's outcome (Utsunomiya 2011).

DWI currently is the most important diagnostic tool for evaluating pediatric stroke scenarios and has become an essential part of the diagnosis of the majority of pediatric central nervous system disorders (Utsunomiya 2011). Its ability to make predictions about the patient's outcome, and the ability to rapidly diagnose acute neurological disorders result in an added value for the pediatric neurologist and neuroradiologist (Utsunomiya 2011).

2.3.2.4 Blood Oxygenation Level Dependent Functional MRI

Techniques such as DTI and Blood Oxygenation Level Dependent functional MRI (BOLD fMRI) can offer a view on the functional reorganization of the brain after injury. fMRI measures the signal changes in the cortical motor system that are due to changes in neural activity. However, it has been argued that DTI is more useful to evaluate white matter integrity with regard to interpreting motor deficits than fMRI (Qiu et al. 2011). The BOLD effect is based on the knowledge that increased neural activity creates a higher demand for oxygen in the active part of the brain. The vascular response to increase local oxygenation leads to a signal, detected by BOLD fMRI, which is thus related to neural activity. However, in the future cerebral blood volume (CBV) might prove to be a more useful metric due to an increased sensitivity when compared to BOLD fMRI or DTI. A limitation of CBV is the fact that a contrast agent has to be injected. The potential of CBV thusfar been demonstrated in pre-clinical trials and awaits confirmation in clinical trials.

2.3.2.5 Near-Infrared Spectroscopy

A more portable solution to assess similar data is near-infrared spectroscopy (NIRS). NIR light is transmitted and absorbed differently depending on the underlying body tissue. NIRS uses this information to extract hemoglobin concentration changes. As stated earlier, increased neural activity is paired with an increase in oxygen demand. Similar to BOLD fMRI, NIRS tracks these changes in localized blood volume. Unlike fMRI which can be used to examine neural activation throughout the brain, NIRS activation radius does not reach beyond the cortical tissues. NIRS can thus not fully replace fMRI. However, the motor regions of the human cortex, the primary sensorimotor cortex (PSMC) and the premotor cortex (PMC) are proximal to scalp tissues and thus accessible by NIRS. The main advantage of NIRS is that it is portable, with wireless versions being available. NIRS can thus be used for data collection or research on freely moving subjects in a more realistic setting. This is especially useful in pediatric populations where the laboratory setting can be quite startling for the young patients. Current fNIR applications have managed to investigate cortical contributions during complex tasks such as walking (Miyai et al. 2001). Little is known on cortical recovery mechanisms, the large majority of suggestions reflect recruitment of pathways outside of the normal adult pattern of contralateral dominance in the projection to lower motor neurons from the PMC (Wittenberg 2009; Rossini et al. 1998).

Neuroimaging and other emerging fields present a huge potential but also come at a cost, they generate large and complex datasets that are seldom easy to interpret. In addition, the metrics deduced, what we are capable to measure, does not always fully agree with the knowledge that is sought after by the clinician. Models are capable of resolving both those issues, using the elaborate and complex data as an input and providing new clinically relevant data streams as output. These data streams consist in a prediction of measured and unmeasured variables (Smith 2011). To make future technological advances useful in the clinical field, attention should be paid to the representation and interpretation of technical data in a clinical format.

2.3.3 Neurostimulation

Neurostimulation intends to modulate the cortical activity by delivering electrical currents that are able to prime neurons. Similar to neuroimaging techniques, non-invasive neurostimulation methods provide means to track the cortical reorganization taking place during recovery. Stimulation has been shown to modulate the cortical excitability favorably when applied moments before starting the therapy session. Increased cortical excitement correlates to greater plasticity, while enhanced inhibition is associated with impaired plasticity (Johnston 2009). As a consequence, the advent of non-invasive neurostimulation tools have rocketed the interest in modifying cortical excitability to improve recovery from brain injuries. In hemi-paretic stroke patients, somato-sensory cortex stimulation has been shown to enhance the effects of training for functional hand tasks (Johnston 2009). Similarly, Eyre et al. evidenced the potential benefit of brain stimulation techniques such as Transcranial Magnetic Stimulation (TMS) or Deep Brain Stimulation (DBS) to correct the postnatal imbalance in cortical activity and thus reduce functional disability in children with CP (Eyre 2007). Although little work has been done in the field of CP, studies in other motor disorders such as stroke highlight the promising potential of neurostimulation as a rehabilitation instrument. Furthermore, the developing child's brain exhibits a greater intrinsic plasticity. Activity-dependent neuronal plasticity appears to play a role in the evolution of clinical signs of motor dysfunction in children with CP. So it is likely that children with CP may receive a greater therapeutic benefit from these emergent strategies than the effect observed in stroke patients. To achieve therapeutic success, taking full advantage of the brain's intrinsic plasticity mechanisms, a purposeful design of the intervention in required. In this section we highlight the most important stimulation techniques: TMS, DBS and transcranial Direct Current Stimulation (tDCS) (see Fig. 2.1).

2.3.3.1 Transcranial Magnetic Stimulation and Deep Brain Stimulation

Transcranial magnetic stimulation (TMS) is one of the principal non-invasive techniques used to investigate functionality and interconnections of the brain. TMS is claimed to be complementary to fMRI. The use of TMS in children with CP is well spread (Heinen et al. 1999; Pilato et al. 2009; Kesar et al. 2012). TMS is a comfortable and safe technique with well-established standard protocols (Rossini et al. 1994). TMS has been approved for pediatric application but is not recommended for children younger than 6-7 years, due to the high neural activation by evoking motor-evoked potentials (MEPs) (Wittenberg 2009). In fact, the number of studies assessing the safety and efficacy of TMS in children is reduced (D'Agati et al. 2010).

TMS generates rapidly changing magnetic field pulses to induce a weak electrical activity in focal brain areas (Hoyer and Celnik 2011). When the motor cortex receives sufficient current to produce the synchronic activation of upper and lower motor neurons, MEPs can be recorded on single or multiple muscles. Therefore, TMS allows an accurate mapping of muscle representation in the primary brain cortex and estimating of the speed/magnitude of the MEPs. From these maps, the size and location of muscles and movement cortical representations can be determined. These features can all be used to characterize characteristics (size, spreading,...) of CNS injuries (Milot and Cramer 2008). TMS-derived metrics thus relate to motor abnormalities. For example, there appears to be a relationship between the area of the motor cortex dedicated to a specific movement and the motor ability. Although the interpretation is complex, Liepert et al. associated larger motor maps with functional recovery after stroke rehabilitation (Liepert et al. 2000). In particular, TMS has been used in combination with MRI to perform early diagnosis of hand function in children with CP (Holmström et al. 2010). The time gained by incorporating TMS to standard diagnostic methods allows bringing forward the therapy and thus increases its rate of success.

TMS can also be used to enhance rehabilitation performance. TMS has potential as a therapeutic tool to balance the hemispheric excitability in the damaged brain. Therapeutic strategies can include the inhibition of the healthy hemisphere or enhancing the excitability in the injured hemisphere (Hoyer and Celnik 2011). Depending on the purpose, the TMS protocols differ in the frequency of the TMS pulses delivered. A decrease in the cortical excitability is achieved by applying low frequency trains (<10 Hz) of repetitive transcranial magnetic stimulation (rTMS). When aiming to facilitate the cortical excitability, high frequency (>10 Hz) stimulation of rTMS is required. Specific applications stimulating at low intensity but with very high frequency rTMS (>50 Hz) have also achieved modulation of the motor cortical excitability. The effect of rTMS lasts beyond the end of the stimulation. This novel form of rTMS is known as Theta Burst Stimulation (TBS) (Brunoni et al. 2008). The therapeutic potential of such techniques is very promising and exert long-lasting effects in motor recovery have been suggested. In Stroke patients, TMS has been used to safely improve motor performance (Hoyer and Celnik 2011).

TMS can also be applied in patients that are unable to control certain cortical zones. In many cases it is thought that this is due to neurons that cannot pass the excitatory threshold. TMS could be used to help these patients to recover to some extent the neural control of such zones by lowering the threshold. In other words, TMS-mediated brain priming prior to therapeutic intervention can facilitate the patients' ability to overpass the excitatory threshold and increase the success of the subsequent therapy. In addition, TMS has been used in combination with behavioral and neuroimaging studies, to develop models of functional connectivity between different brain regions and test theories of neural mechanisms that underlie stroke recovery (Hoyer and Celnik 2011).

Despite the promising potential of TMS for the treatment of CP, few studies have been published in the literature most of them being limited to treat spasticity (D'Agati et al. 2010; Benini and Shevell 2012; Valle et al. 2007). In all cases, a moderate to substantial improvement of spasticity has been reported, while non-adverse effects have been observed. However, the effects of TMS may be temporal. Therefore, repeated sessions may be required to ensure long-term effects (Holt and Mikati 2011).

2.3.3.2 Transcranial Direct Current Stimulation

As mentioned earlier, the manipulation of cortical excitability may have therapeutic benefits for patients with neurological impairments, and specifically for patients with CP (Vidailhet et al. 2009; Hayek et al. 2009). In rats, increased cortical excitability has been found to enhance brain plasticity (Holt and Mikati 2011). Transcranial direct current stimulation (tDCS) has been proposed as an alternative form of non-invasive neurostimulation to promote plasticity and modulate brain excitability. tDCS has been reported to lead to functional changes in discrete areas of the cerebral cortex by shifting membrane potential. In tDCS, low intensity currents (1–2 mA) are applied directly to the brain area of interest over a sustained period of time (5–30 min). tDCS is less focal than TMS, mainly due to the relatively large size of the electrodes used to deliver current over the scalp. However, tDCS unlike classical neurostimulation methods, does not produce muscle fasciculation that can be uncomfortable and often painful for the patient (Hayek et al. 2009). Thus, tDCS-based neurostimulation sessions are likely to be more tolerable, although it does not avoid classical side effects such as headache, dizziness, nausea or itching sensation (Nitsche et al. 2008).

Similar to TMS, tDCS can also enhance excitability via anodal polarization or decrease it via cathodal polarization (Song et al. 2011). Tests on healthy adults demonstrated that tDCS can increase cognitive performance on a variety of tasks, depending on the cortical area being stimulated (Chi and Snyder 2011). tDCS has been shown to be an effective treatment for migraines, depression or pain, but also constitutes an interesting tool for the modulation of motor cortex excitability (Nitsche and Paulus 2000). Nitsche et al. demonstrated that the application of tDCS can modulate the cortical excitability and influence spontaneous neural activity influencing synaptic function (Nitsche et al. 2008). To the best of our knowledge, there are no studies done in children with CP using tDCS. It is important to highlight that tDCS is a technique that is just starting to be tested in the clinical field, so, protocols for safety and effectiveness have not been yet to be standardized, even for adults (Nitsche et al. 2008).

2.3.4 Assistive and Rehabilitation Robotics

Medical Robotics is a relatively new field that aims to augment the capabilities of either the clinician or the patient. It has been interpreted as technology for the recovery and functional compensation of missing motor skills and sensing, assuring safer environments and environments that promote regaining of movement. In the field of CP, two main branches of medical robotics are worth to be mentioned: Rehabilitation Robotics and Assistive Robotics. Rehabilitation robotics pursue the recovery or regaining of impaired motor function, while Assistive Robotics are intended to substitute or compensate missing motor and sensing skills. Rehabilitation systems differ from assistive devices. The former are designed to facilitate recovery by supporting therapy and monitoring the patient's progress, while robotic assistive devices and exoskeletons focus on providing dexterity, natural mobility, and sense of touch to missing or paralyzed limbs (Dellon and Matsuoka 2007).

Besides recovering the motor function and improving movement coordination, training with robotic devices may serve to accomplish secondary objectives within rehabilitation such as the so called "trick movements" or "compensation strategies". In this case, the user learns new motion approaches to handle daily activities. Furthermore, the simple fact of promoting the movement of lower and upper limbs can prevent secondary complications such as muscle atrophy, osteoporosis, and spasticity (Riener et al. 2005).

An important aspect in robot-aided rehabilitation devices is the intrinsic interaction between the human and the robot (Pennycott et al. 2012). Currently, the field of rehabilitation robotics is progressively oriented to a human-centered approach in which robot performance is quantified by how the robot physically interacts with the patient. This interaction is mutual. In rehabilitation robotics a clinician or technician controls the robot by setting parameters that define the intervention. Whereas in assistive robotics devices, the robot is programmed to execute or assist in the execution of the preprogrammed tasks according to the motor limitations of the patient.

In comparison to the classical scale of performance, human–centered robot interaction implies a totally different set of requirements than what is used in industrial robotic systems. Unlike traditional robotics, the environment in which human—medical robot interactions take place is characterized by fast dynamics and prone to unexpected changes, adding difficulty to the design. Such requirements are safety, flexibility and mechanical compliance of the device, gentleness

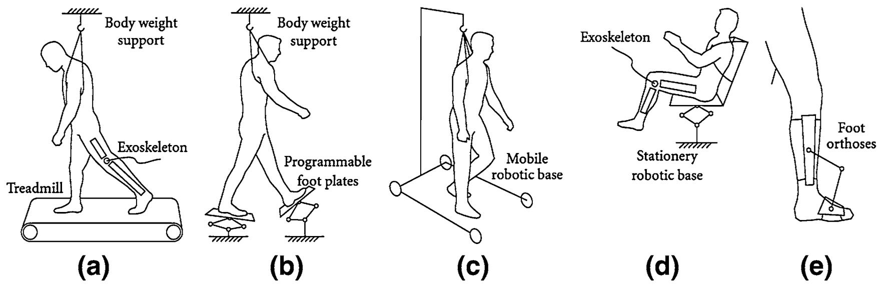

Fig. 2.2 The most common robotic systems used for lower limb rehabilitation; (**a**) treadmill gait trainers, (**b**) foot-plate based gait trainers, (**c**) over-ground gait trainers, (**d**) stationary gait and ankle trainers; (e) active foot orthoses (Díaz et al. 2011)

and adaptability towards the patient, ease of use, friendly user interface, humanoid-like appearance and behavior (Riener et al. 2006).

Robotic systems for lower-limb rehabilitation are generally classified according to the rehabilitation principle (Fig. 2.2) (Díaz et al. 2011). In the following sub-sections we will elaborate upon exoskeletons, orthoses and assistive devices. We will furthermore highlight a promising new type of robotic device "soft" exoskeletons; as well as a tool to augment efficacy of robot therapies, virtual reality and interactive games.

2.3.4.1 Exoskeletons

Partial body-weight supported therapy (PBWST) is an active, repetitive and task-specific approach used to facilitate execution of stepping and locomotion. The main objective of PBWST is to achieve a more normalized gait pattern. During classical PBWST, an overhead harness system supports the patient's body weight, while the therapist manually guides the foot and leg movements. It has been observed that the use of this kind of robotic platforms considerably reduces the level of muscular loading undergone by patients during normal gait rehabilitation and minimizes energy consumption and fatigue (Hornby et al. 2005). Advanced configurations of body-weight supported therapy (BWST) allow the patient to do complete walking exercises while being suspended from a harness. These walking cycles can be carried out directly over-ground or assisted on a treadmill. There are evident benefits of BWS treadmill training, but the manually assisted movement training remains difficult for physical therapists. The labor-intensive task of the therapist consists of manually guiding the patient's limbs into a gait pattern that progresses to a normal gait pattern. Therefore, the duration of the rehabilitation is usually defined by available man-hours and the fatigue of the therapist, and not so much by the needs of the patient. As a result, rehabilitation sessions are usually shorter than required to gain an optimal therapeutic outcome. In addition, the movement repeatability of manually-assisted rehabilitation is poor and objective measures of patient's performance and progress are missed.

Nowadays, powered exoskeletons are integrated with treadmills or other kind of mobile platforms to solve this issue. Exoskeletons are mechatronic systems that wrap around the operator's limbs allowing the replication or enhancement of forces at body segments. In that case, the exoskeletons are externally linked to lower limbs of the patient, so that the patient is assisted to execute normal gait patterns and the therapist is released from the task of manually guiding walking. The use of exoskeletons doubles patient's benefit: longer rehabilitation sessions are achieved and the execution of gait normal patterns is more precise (Herr 2009). Furthermore, by using different types of sensors (cameras, microphones, accelerometers or inertial sensors…) and actuators, the motor performance of the user can be monitored and quantified.

Studies comparing over-ground walking with treadmill based therapies, as BWST, suggest that over-ground walking may be superior for gait training (Willoughby et al. 2010). The fact that treadmill exercise requires a higher control of propulsion and balance compared to over-ground walking may explain the additional benefits (Dodd and Foley 2007). Nevertheless, powered exoskeletons used in BWST therapy entail a number of issues such as energy consumption, duration of batteries, the actuation mechanisms or ensuring the portability of the device without affecting the natural movement of the patient that still need to be solved in order to spread the use of this technology.

Besides powered exoskeletons, passive exoskeletons can be also used in BWST. The main difference is that the energy needed for moving a passive exoskeleton is fully supplied by the user while in active exoskeletons a power source supplies at least part of it. However, the mechanical design of passive exoskeletons is often insufficient and demands considerable physical effort in comparison to active wearable robots.

There are two essential requirements that need to be fulfilled by any exoskeleton to achieve efficient restoration of normal gait: the joint stability and joint control. The behavior of the robot, and thus the prediction on treatment outcome, are influenced by the quality of these requirements. Therefore, a close study of the human neuro-physiology during walking such as muscle dynamics or central pattern generators is needed to further the development of rehabilitation prototypes. Currently, there is insufficient evidence to state that robot-assisted gait training improves walking function more than other motor training methodologies (Swinnen et al. 2010). Based on the available data and compared with other walking rehabilitation therapies, assessing walking overground or on a treadmill with or without BWS, effectiveness is not greater with robot-assisted gait training than with other training modalities (Field-Fote et al. 2005). Although the effectiveness of robot-assisted training in children with CP was proven in a number of experiments (Borggraefe et al. 2010), performed clinical studies still show little evidence for a superior effectiveness of the robotic therapy.

2.3.4.2 "Soft" Exoskeletons

Rehabilitation robotics is in continuous progress and exoskeleton technology represents one of the most challenging areas. Advances in materials, mechanics, electronics, sensors, controls, artificial intelligence, communication, power sources and actuation must be integrated together. On top of that, safety must be a paramount issue since the fundamental criterion for an exoskeleton involves the inherent coupling between the human and the mechanical systems. It is therefore essential to design control systems that combine the positive attributes of conventional exoskeletons with a more compliant and safer interaction capacity.

Based on previous experience, we know that 2 h training is not sufficient to obtain significant improvements of motor control in patients with CP. However, nowadays it is still a challenge to design a rehabilitation exoskeleton that can be worn during the whole day so that it can be used in daily activities without needing the supervision of physiotherapists. Soft exoskeletons are postulated as the new generation of exoskeletons aiming at reaching such goal. Nowadays, only limited information regarding the design of "soft" wearable robots for rehabilitation purposes is available. However, the potential impact and numerous advantages of soft exoskeletons have recently been demonstrated. For example, Rocon et al. developed a soft exoskeleton to detect and suppress upper limb tremor (Gallego et al. 2011). Future advances will try to incorporate wearable "soft" robots into an overall network architecture to provide continuous monitoring of patients and build a complete health management system (Swinnen et al. 2010).

2.3.4.3 Assistive Devices and Orthoses

Orthoses should be considered as an important tool in locomotion rehabilitation for CP patients. Orthoses are used to support, align, prevent, or correct deformities of the limbs and are designed with one of two main goals: either to affect the body structure or to assist locomotion. In case of children with CP, orthoses are frequently designed to achieve both of these aims.

Upper extremity orthoses have proved to be effective in achieving some task specific goals as they can improve grasping and increase the range of motion to perform a given activity (Yonclas et al. 2006). Braces are indicated to stretch muscles that are over-flexed. Back braces are of special interest in children with CP as they might help straightening the back of children having trouble to sit down or even, to correct the spine developing a deformity. Hand splints and soft body jackets are also used to give support and comfort to individual particularities of patients.

Lower limb orthoses may improve gait efficiency by restoring clearance of the foot from the ground during swing phase, appropriate prepositioning of the limb at the end of swing phase and achieving an adequate step length. Orthoses may reduce energy expenditure by decreasing the need for compensatory gait deviations to achieve locomotion. In the case of lower extremity orthoses, the foot-to-ground contact is normalized by correcting foot and/or ankle alignment.

Precisely, Ankle Foot Orthoses (AFOs) are the most frequently prescribed devices for children with CP (Brehm et al. 2008). The general role of the AFOs is to limit unwanted ankle movement, primarily ankle plantar flexion but indirectly knee and hip function are also positively affected. As a result, AFOs manage abnormal plantar flexion, prevent contractures and improve gait. Children with spastic CP often acquire a dynamic equinus deformity, preventing them from putting their heel flat and as such attain a stable base for stance or walking. Assuming the ankle can be placed in a neutral position at rest; such deviation can be corrected by one or several AFO constructions, depending on the capabilities and particularities of the patient. However, it is important to underline that in patients with spasticity the AFOs can prevent or delay the development of a deformity, but not overcome pre-existing abnormalities.

To date, the studies examining the efficacy of orthoses for walking children with CP have included small numbers of children. The evidence to support specific orthotic interventions for children with CP remains to be demonstrated using more robust research methods.

2.3.4.4 Virtual Reality and Interactive Gaming

Current bottom-up motor learning theories state that improved motor performance and postural control is achieved by repetitive motor practice. This type of training requires high levels of attention and motivation that might be difficult to achieve in children (Brütsch et al. 2011; Banz et al. 2008). In addition, active participation is an important prerequisite for motor learning and for improved motor and functional outcomes. However, children with CP tend to be less participative than typically developing children (Mitchell et al. 2012).

In this context, the use of Virtual Reality (VR) and Interactive Gaming is becoming a key component of modern rehabilitation systems to assist traditional therapeutic approaches. VR serves both to provide augmented feedback on the motor performance of the patient, and to enhance motivation and attention through the implementation of attractive and challenging games. That way, the accomplishment of intensive and prolonged practice can be facilitated in children. Some authors report that games could hold the children's attention for sessions of 60 min (Qiu et al. 2009). However, other studies describe that children lost their interest in the game after 15 min (Brütsch et al. 2011). Nevertheless, even in that latter case authors emphasized that all children declared they enjoyed playing the games during the sessions. In addition, it seems that patients undergoing VR-based rehabilitation present a more active participation (Brütsch et al. 2011). However, the scope of these results is limited. Further research might be needed to reveal whether participation rates are correlated to the improvement of functional outcomes.

VR offers a number of desirable characteristics for rehabilitation such as the possibility to design patient-centered strategies by tailoring the game to the age and patient's disability level. The therapist can adapt the practice intensity in each session to the progress made by the children. The competitive nature of most children makes the sense of self-efficacy provided by the augmented online feedback a successful incentive to enhance their involvement with the therapy. It appears that challenging VR environments promote the creativeness of children. Several studies report that the use of VR in children with CP improved their self-image and motivation towards the rehabilitation (Brütsch et al. 2011).

It has been hypothesized that VR might accelerate the recovery process by targeting specific brain networks. In particular, You et al. found measurable changes in cortical reorganization in the lower extremity of stroke patients after rehabilitation via fMRI (You et al. 2005).

VR usually links the patient's motor outcome during rehabilitation with actions in the virtual world. A high percentage of children with CP present severe functional and motor disabilities usually characterized by slow speed and disturbed motor control. This obstructs them from participating in daily activities done by their peers. In that sense, the effectiveness of VR should be emphasized as it allows children to participate in more activities (Brütsch et al. 2011; Parsons et al. 2009).

Despite the promising potential of VR and Interactive Gaming in motor rehabilitation, their contribution to improve motor function and performance is still unclear. Several studies show improvement in walking function and speed after rehabilitation with VR (Mirelman et al. 2010; Patritti et al. 2010) while others report insignificant or no improvement at all (Brütsch et al. 2011). In particular, the review by Mitchell et al. exposes the little research done in this field in patients with CP (Mitchell et al. 2012). In fact, the incorporation of VR to traditional therapies for children with CP may be less encouraging. One of the main limitations found is the relatively large motor function needed for utilizing this kind of systems. The use of adaptive robotic systems together with VR is a possible strategy to overcome that issue. In addition, the load of sensory stimulation should be carefully considered specially when dealing with patients with cognitive impairments. Another approach is to use a filter approach for standard or customized interfaces. One such example is ENLAZA, an inertial sensor based interface that enables children with CP to play games on the computer and independently conduct an electrical powered vehicle. The core of ENLAZA is a Kalman filter that takes out the non-voluntary components of movement and derives the intended direction for the cursor o car (Raya et al. 2012). In general, virtual environments are recommended to be as simple as possible while keeping the ability of capturing the attention of the users. In a more advanced approach, the complexity of the virtual environment is personalized accorded to the processing ability of the patient (Wolbrecht et al. 2008). The relation between the ability of processing sensory cues and the ability to keep attention hasn't been investigated yet in children with CP (Qiu et al. 2009), so further studies might be required to establish methods to determine the proper volume of sensory stimulation needed by each patient.

2.4 Conclusion

A lot of promising techniques and technologies are emerging that have the potential to reveal how motor control is organized in the human brain and body. Additionally they could provide insight into the cortical reorganization that takes place upon and after cerebral injury. This knowledge should be used to personalize therapies, not only to the individual patient's motor outcomes but also to the source of their disparities. We have tried to summarize technologies that are being developed or used in related fields (e.g. Stroke rehabilitation) and that show great potential for application in CP rehabilitation. To take full advantage of this potential, researchers and clinicians should actively engage in transferring knowledge and developments from the technical field to the clinical scenario.

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Chapter 3
Spinal Cord Stimulation for Parkinson's Disease

Juan Pablo Romero-Muñoz, Francisco Miguel Rivas Montero, Ilaria Fojadelli and Romulo Fuentes

Abstract The fast ageing of population has an inevitable impact on the prevalence of neurodegenerative diseases, including Parkinson's disease (PD), which have been associated with alterations in the central and peripheral mechanisms resulting in specific patterns of gait and balance disturbance. These motor changes in PD often restrict functional independence and are a major cause of morbidity and mortality among these patients. The onset of falls and gait impairment is an important marker of reduced survival, irrespective of the nature of the underlying form of parkinsonism. The best treatment available for treating PD is still the dopamine replacement therapy, but it is not exempt of adverse effects almost as impairing as the disease after a period of effectiveness. Other therapy developed, the Deep Brain Stimulation (DBS), is very effective but highly invasive, and is restricted to a very low percentage of patients due to important comorbidity in elder population. Considering this disease as an excessive synchronic impairment allows using some principles proved useful treating other neurological conditions such as epilepsy. Afferent stimulation of the central nervous system has been shown in PD rodent models to be effective to produce a dramatic recovery from akinesia and restore gait. This stimulation can be achieved through epidural stimulation, a much less invasive manner. This is a novel use for a neuromodulation technique widely used for chronic pain treatment.

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3.1 Parkinson's Disease

Parkinson's disease (PD) is one of the most common movement disorders in elder population, usually occurring between 40 and 70 years old. The number of individuals with PD over age 50 in western countries was between 4.1 and 4.6 million in 2005 and will double to 8.7–9.3 million by 2030 (Dorsey et al. 2007).

Although the most widely known characteristic of this disease is resting tremor, its most impairing symptom is the lost of ease for rapid movements, also called bradykinesia. Other main symptoms of the disease are also rigidity of joints and impaired postural reflexes. At the beginning of the disease these symptoms may appear only in times of stress. Up to ten years before the typical motor manifestations of the disease some non motor symptoms can be identified. Such symptoms include, among others, loss of sense of smell, constipation, depression and disturbances during REM sleep (Tolosa and Pont-Sunyer 2011).

Other symptoms such as marked postural instability, freezing of gait or cognitive impairment are only present on advanced phases of PD, resulting in patients progressively loosing independence for daily living activities.

Akinesia/bradykinesia, rigidity, resting tremor and lost of postural reflexes are not only present in Parkinson's disease, but they are part of a syndrome called parkinsonism which includes several diseases that share a common pathophysiology that is the impairment of dopaminergic system in the basal ganglia. Basal ganglia physiology will be commented later in this chapter in extent, but its main function is thought to be the modulation of cortical input to select specific motor action for activation from a behavioral repertoire.

The etiology of Parkinson's disease is yet unknown but is probably multifactorial, resulting from the interaction of genetic factors (so far 16 genes have been identified, including Parkin (PARK2), which is the most investigated, but the most common is the LRRK2) (Sloan et al. 2012) and environmental ones. It is estimated that the risk of PD in a parent or sibling of any individual with PD is around 2 %. The risk of developing the disease if there is no familiar history of PD is around 1 % (Albin et al. 1989).

Diagnosis of the disease is predominantly clinical and most patients do not require the use of additional tests. In all patients, it is a must to exclude if there is not another probable cause of parkinsonism that could justify the symptoms, such as vascular disease affecting basal ganglia, trauma, brain tumors, toxins or drugs that block dopaminergic conduction. Iatrogenic causes are not uncommon because the latter drugs are commonly used for problems such as nausea, dizziness or even flatulence, and in some countries can be some times obtained without a prescription over the counter. The patients with secondary parkinsonism due to use of dopamine blocking drugs benefit from management of the primary cause and they have not progressive or degenerative evolution of symptoms.

Some imaging tests can be used to support diagnosis, among them maybe the most useful is the single photon emission computed tomography (SPECT). In this test several trackers are linked to the dopamine transporter in nigrostriatal synapses, reflecting the number of functional receptors in different brain areas. In Parkinson's disease, the images show a reduced number of transporters in basal ganglia and this functionally correlates with disease progression. This test can support, but can not stand alone the PD diagnosis without a compatible clinical scenario, because its positive results can also be the result of other types of parkinsonism besides PD.

As one of the main characteristics of this disease is the outstanding response to the levodopa treatment, indeed, the response of symptoms to levodopa could be used as a diagnostic criterion.

3.2 Therapies

Currently there are several drug and surgical therapeutic available options for Parkinson's disease. The main goals of these are:

- Symptomatic: to improve symptoms and signs of disease
- Neuroprotective: to interfere with the pathophysiological mechanisms of the disease
- Restorative: to provide new neurons or promote the functionality and growth of the remnants.

Parkinson's disease is a neurodegenerative disease and therefore incurable with our current knowledge. In most cases its progression is inexorable, so the long-term goal is to preserve the patient's motor skills as long as possible, by a multidisciplinary management.

3.2.1 Pharmacotherapy

As the disease symptoms are the result of the deregulation of the levels of neurotransmitters in the brain of affected patients, one of the main goals is to correct such impairment. In PD patients two situations are well established, the main one is a deficit of dopaminergic neuro-transmission, and the second one is a relative excess of cholinergic function (Bermejo-Pareja 1991).

- Anticholinergics (trihexyphenidyl, biperidene, benzatropine, procyclidine): Used mainly in young patients with predominant tremor. Its most common side effects are derived from peripheral cholinergic effects such as dry mouth, acute angle glaucoma, constipation, and urinary retention. As cholinergic neurotransmission is also related to memory and attention levels, other side effects can be impaired memory, confusion and hallucinations.

- Amantadine: Initially developed as an antiviral drug, its mechanism of action is not well known. Rarely used as the sole therapy, it is usually used in patients with poor initial response to anticholinergics or to control dyskinesias in patients with dopaminergic therapy. It can cause hallucinations, lower limb edema and livedo reticularis on the legs.
- Monoamine oxidase (MAO) B inhibitors: Inhibit the action of one of the main enzymes responsible for breaking down the dopamine, among others monoamines. Selegiline has been shown to prolong the half-life of levodopa, decreases the off-periods (periods when symptoms gets worst, even with dopamine treatment, due to the fluctuations of its effect). Rasagiline has been shown to delay the progression of the disease.
- Dopamine agonists: They are the most effective treatment for PD after levodopa. Often used in the initial therapy to delay the use of levodopa. Some of their side effects can be impulse control disorders such as hypersexuality, pathological gambling, eating disorders, and repetitive attitudes.
- Levodopa: This is the best therapy available for PD long or medium term, depending on the profile of each patient. The main limiting adverse effect of this drug is that after a periodof chronic usage, its effect is not uniform throughout the day, causing fluctuations in the motor performance, the so called "on" and "off" periods. For this reason its usage has traditionally been delayed as much as possible, and used as one of the last pharmacologic resourses, but considering that it is also the best available drug, it is used some times to achieve a high performance in relatively young and active patients.
- Duodopa. Newly approved therapy reduces the occurrence of fluctuations by the continuous injection of a gel containing dopamine in the duodenum through a gastrostomy.

3.2.2 Neuromodulation Treatment

Deep brain stimulation is usually considered for patients with severe motor fluctuations without severe cognitive impairment. It is a procedure aimed to deliver electrical pulses at a particular frequency and intensity at subthalamic nucleus or internal globus pallidus, allowing an important reduction in the total dose of dopamine administered to these patients. Besides the surgical risk of electrode implantation that limits this therapy for relatively young patient, there is also concern for potential effects in the cognitive function of the patients treated with DBS (Halpern et al. 2009). The usual parameter ranges for DBS are voltage (1–7 V), pulse width (65–450 μs) and frequency (130–200 Hz).

3.3 Basal Ganglia Overview

The basal ganglia are a group of subcortical gray nuclei whose function is very important for the initiation and control of voluntary movements and the implementation of automatic motor plans (walking, arm swing during walking, swallowing), maintaining muscle tone and posture. They also appear to have a role in some cognitive functions ("strategic thinking", executive functions) and on the acquisition and retention of motor programs (Hoover and Strick 1993). Using the phylogenetic approach, the basal ganglia can be classified into three groups:

1. Arquiestriatum, formed by the amygdala, which has an important role in the limbic system and emotional processing.
2. Paleoestriatum or globus pallidus, consisting of a lateral (GPe) or medial (GPi) segment.
3. Neostriatum or striatum consists of caudate, putamen, nucleus accumbens and olfactory tubercle.

Physiologically, the term basal ganglia (BG) has no precise anatomic limits and includes different systems such as the ensemble of the corpus striatum (caudate nucleus and the lenticular nucleus, which includes the putamen and the globus pallidus) and other subcortical allied nuclei such as the subthalamic nucleus (STN), the substantia nigra [SN, consisting of the pars compacta (SNc) and pars reticulata (SNr)] and, more recently, the pedunculopontine tegmental nucleus (PPTg).

Inputs to the basal ganglia are generated from the cerebral cortex (in particular the primary motor strip and primary somatosensory cortex) and then are received by the basal ganglia and the substantia nigra.

To get to a full understanding of basal ganglia function it is necesary to know that there are two pathways or manners in which the motor output is modulated or modified before its final action through the peripheric nervous system.

1. The *direct pathway* refers to the group of striatal neurons characterized by containing mainly D1 dopamine receptors and co-expressing the peptides substance P and dynorphin (Obeso et al. 2002). These neurons establish a monosynaptic, inhibitory connection from the putamen to GPi/SNr. Activation of the direct pathway will result in an inhibition of the GPi/SNr, which in turn holds a tonic inhibition over brain stem motor centers and thalamocortical pathways. Suppressing the activity of GPi/SNr will result in the activation of these two tonically inhibited targets, which will ultimately cause a motor program to be initiated (via brainstem centers) or a movement facilitated via cortical control. Thus, generically, the activation of the direct pathways is regarded as related to the initiation and maintenance of motor activity.
2. The *indirect pathway* refers to the striatal neurons expressing mainly D2 dopamine receptors, which send their GABAergic axons to the external segment of the globus pallidus (GPe), connecting with the STN, which in turn projects to the GPi/SNr. The STN uses glutamate as a neurotransmitter and

therefore exerts an excitatory effect on the GPi/SNr and to other brain stem nuclei that are connected with the STN (i.e., PPTg and SNc). Thus, activation of this pathway (i.e., increased firing rate of the striatal D2 neurons) has the opposite effect of the direct pathway, it will keep or increase the activity of the GPi/SNr, which is inhibitory over their targets (brain stem motor centers and thalamocortical projections), thus preventing the initiation of a motor action or terminating an ongoing one. The effect of dopamine in this pathway results in the decreased activity of the D2 striatal neurons (D1 and D2 receptors have opposite effects in the expressing neuron) which in turn is permissive for the prokinetic effect resulting from activation of the direct pathway.

The balance between the functional status of the direct and indirect pathways determines the final effect of GPi and SNr on brain stem motor centers and thalamocortical neurons, which is prokinetic if there is a direct pathway predominance and antikinetic if there is an indirect pathway predominance, although a recent study suggest that the simultaneous transient activation of both pathways is functional in the initiation of actions (Cui et al. 2013). It is important to highlight that this two pathways coexist within the striatum, thus are exposed to the same dopamine levels. Via differential action through D1 and D2 receptors, dopamine will activate the direct pathway while decreasing activity of the indirect pathway, having an overall pro-kinetic effect. Lack of dopamine, on the other hand, will turn the direct pathway resistant to activation and the indirect pathway more active, having the effect of hampering the initiation of motor actions, which is ultimately one of the major symptoms of PD (Obeso et al. 2002).

We have said that the BG is a key component of a complex network of neuronal circuits organized in parallel to integrate activity from different cortical regions (Tolosa and Pont-Sunyer 2011) of the brain and produce the proper motor outcome. The loop we just described can be actually conceived as five related cortico-BG-thalamo-cortical loops: motor, oculomotor, associative, limbic, and orbitofrontal. In addition, the BG are intimately interconnected with other parts of brain stem nuclei such as the locus ceruleus (noradrenergic), raphe nuclei (serotonergic), and the reticular formation.

Overall, dopamine acts as a modulator of the balance of the direct and indirect pathways of the BG, allowing for the selection, initiation and finalization of specific motor behaviors (Grillner et al. 2005; Grillner 2003; Grillner and Wallen 2004).

3.4 Oscillatory Neural Activity in Neurological Diseases

Although known for several decades, the function of the oscillatory activity in the brain is still debated. The relevance of oscillatory activity and rhythms in the brain has been widely described and studied since late XIX century, leading to its characterization in relation to different neuropathological and clinical states, being epilepsy one of the best known. More recently, findings of correlation between neurophysiological oscillations and normal behavior suggest that rhythmic neuronal activity is one important feature in the coordination of the different neuronal circuits and normal functioning of the nervous system.

Until late XX century, the electrophysiological information obtained for diagnosis was mainly accessible in a non invasive manner, thus limited to cortical recordings, which meant that the subcortical brain structures were a mystery. With the introduction of chronic implants of multi-electrode arrays in animal models, and deep brain stimulation in humans, a huge amount of information on subcortical structures electrical activity was obtained. Different frequencies of synchronized field potential activity were demonstrated to exist between the basal ganglia and cortex (<10 Hz alfa, 11–30 Hz beta and $>$ 60 Hz Gamma). These frequencies are dynamically affected by the task performed and expressed according to the level of dopaminergic activity (Brown 2003).

Initially, modulating or modifying this neurophysiological rhythms was done mainly locally, to target an adequate electric field in a specific deep brain structure and to modulate its activity to alleviate symptoms of specific disorders: Ventral intermedial thalamus for essential tremor, tremor-predominant PD and cerebellar outflow tremors; subthalamic nucleus (STN) for Parkinson's disease and Globus Pallidus interna (GPi); ventrolateral for dystonia.

One of the most striking alterations of the BG physiology in parkinsonism is the change in the pattern of synchronization of discharges between neurons, which results in characteristic oscillations of the local field potential signals recorded from BG structures. In the human subthalamo-pallidal-thalamo-cortical circuit, two modes of synchronization has been characterized, one at low frequency range (<30 Hz), and the second at high frequencies (>60 Hz) (Brown 2003). The relative power of these oscillation modes is correlated with the motor status (moving or not moving) and with the dopamine levels in the circuit. Generically, it can be said that low frequency oscillations are associated to low levels of dopamine and lack or decreased motor activity, while high frequency oscillations are associated with normal or high levels of dopamine and the execution of actions. Whether the low frequency oscillatory modes are linking the low dopamine levels to the motor impairment is still a matter of debate.

The concept of low-frequency oscillations being associated to hypokinetic states, and high-frequency oscillations to movement, has provided a theoretical frame to explain the rather unknown mechanisms of the DBS. It has been proposed that DBS operates by blocking the low-frequency activity and enhancing high frequency activity (Brown and Eusebio 2008). This claim is supported by the observation that high-frequency DBS causes disruption of pathological low-frequency oscillation and motor improvement (Eusebio et al. 2011). While the DBS approach requires the insertion of electrodes in the brain tissue, there are means to affect the oscillatory patterns of the brain without invading it. Bailey and Bremer in 1938 reported EEG changes with electrical stimulation of the vagal nerve (Bailey and Bremer 1938). In 1951, Dell and Olson identified evoked responses in the ventroposterior complex and intralaminar regions of the thalamus by stimulating the proximal end of the cut cervical vagus nerve (Dell and Olson 1951). Since, investigators have known the effects of vagal nerve stimulation (VNS) in the brain. Many subsequent experiments confirmed the effects of VNS on EEG (i.e., low-frequency stimulation causes synchronization, high-frequency stimulation causes desynchronization).

In 1985, Zabara reported the effects of VNS on seizure control in animal studies. In 1988, Penry, Wilder, Ramsay, and colleagues performed the first implant of a vagal stimulating device into a human (Dell and Olson 1951; Zabara 1985a, b). Stimulation of the trigeminal nerve has also proved effective in epileptic seizure control in animal models (Fanselow et al. 2000) and epilepsy patients (DeGiorgio et al. 2003, 2006).

As already discussed, the predominance of slow frequency oscillatory activity in both animal models and patients of Parkinson's disease (Brown et al. 2001; Hammond et al. 2007; Costa et al. 2006) and epilepsy (Fisher et al. 2005) have been widely documented. Given that efferent electrical stimulation is capable of abolish pathological oscillatory brain activity and the associated symptoms in epilepsy, it is reasonable to propose that the same therapeutic effect could occur if afferent stimulation is performed in Parkinson's disease. This hypothesis lead the research group of Nicolelis (Fuentes et al. 2009) to propose epidural electrical stimulation of the dorsal columns, hence named spinal cord stimulation (SCS) as a symptomatic treatment for Parkinson's.

3.5 Spinal Cord Stimulation for PD

The first evidence suggesting the effectiveness of SCS for PD was obtained from rodent models, where SCS caused a dramatic restoration of locomotion in both acute pharmacologically induced dopamine-depleted mice and bilateral striatal 6-hydroxydopamine-lesioned rats. The stimulation was performed by placement of a high thoracic epidural stimulator, the most effective frequencies demonstrated was about 300 Hz but lower frequencies still had some positive effect in restoring locomotion. Due to the importance of reticular activating substance in brainstem and its possible participation on this effect on gait improvement by the startle reflex, rats received a strong sensitive afferent stimulus such as air puffs or trigeminal nerve stimulation without an equivalent effect to the one observed with epidural stimulation.

The functional recovery in these animal models was paralleled by a disruption of aberrant low-frequency synchronous corticostriatal oscillations (<25 Hz), leading to the emergence of neuronal activity patterns that resemble the state normally preceding spontaneous initiation of locomotion. It is proposed that the neurophysiological changes evoked by afferent stimulation have a permissive role, meaning that they lead to facilitation of the normal brain output to initiate movement rather than imposing it by means of the electrical stimulation itself.

Another interesting theory proposed by these researchers is based in the higher cortical input required by basal ganglia in this state to produce movement. In an abnormal state such as the dopamine depletion, the basal inhibitory output to the brainstem and ventral thalamus is increased so the initiation of movement is inhibited. As the anterolateral thalamus is the theoretical input gate on the peripheral stimulation, the high frequency stimulation would produce a higher cortical stimulation and thus will also increase the intensity of the cortico-basal input being that enough to "go through" and produce initiation of movement.

As explained, motor symptoms of PD have been considered to arise from the imbalance of activity in the direct/indirect pathways (decrease of the direct, or increase of the indirect pathway). According to this model, the result of the activity of the direct/indirect pathways is to increase or to relieve the tonic inhibition that the pallidal nuclei (GPi and SNr) exerts over its targets. In the context of control of initiation of motor actions, textbooks traditionally mention the thalamocortical neurons as the target of the pallidal projections. The brainstem can be emphasized as the receptor of the pallidal projections, and using the same concept of activation of direct/indirect pathways, the key motor role of basal ganglia can be formulated as the selective initiation and termination of stereotyped or rhythmic motor sequences, typically controlled by brainstem and spinal cord circuits, often referred to as motor programs (Mink 1996; Hikosaka et al. 2000; Grillner et al. 2005). Either emphasizing the thalamus or the brainstem as the receptors of the pallidal projectiosn conveying the output of the direct/indirect pathways balance, unlocking the neural circuits from low-frequency oscillation modes, seems to be key to restore the ability to initiate actions.

3.6 First Studies with Humans

SCS is currently the most widely neuromodulation method used for alleviating intractable pain, for example, pain from failed back surgery and other chronic pain conditions that do not respond to pharmacological treatments. This approach owes its origin to the scientific foundation laid down by the Melzack and Wall (1965). For SCS, electrodes are implanted in the epidural space and electrical current is applied to the dorsal surface of the spinal cord, mainly recruiting the afferent fibers of the dorsal columns, creating a tingling sensation in the dermatomes whose fibers traverse the regions being stimulated. Through ill-defined mechanisms, this barrage of non painful sensation attenuates the patient's perception of pain; instead of feeling pain, the patient feels non painful paraesthesia in the affected area. The SCS hardware consists of an electrode lead, an extension cable, a pulse generator, and a programmer. For pain management programming involves selecting the electrode stimulating configuration, adjusting the amplitude, width and frequency of electrical pulses. Amplitude indicates the intensity of stimulation. This is set within a range of 0–10 V according the type of electrode used. Ideally paraesthesia should be felt between 2 and 4 V. Pulse width usually varies from 100 to 400 us. Frequency of pulse wave is usually between 20 and 120 Hz (Jeon 2012). In addition, this technique continues to evolve encroaching into other areas of therapeutics apart from chronic pain and because of its configuration and the possibility of frequency and intensity regulation, could be used as a means for afferent stimulation (Kunnumpurath et al. 2009).

The existence of the SCS technology and expertise for pain treatment enabled the rapid testing of it in Parkinson's patients. Shortly after the publication of SCS results in animal models of PD, a medical group in UK implanted two advanced PD patients with spinal cord stimulators at high cervical level (Thevathasan et al. 2010). No motor improvement was observed upon stimulation, nonetheless, this study failed in reproducing the electrode geometry and location of the animal study (Fuentes et al. 2010). This negative result illustrates the importance of accumulating evidence and expertise from animal research as a previous step to engage in clinical trials.

The first demonstration of alleviation of symptoms in Parkinson's with SCS is a single case report from Gilles Fénelon (Fénelon et al. 2012). The protocol was performed in a patient with a previously implanted SCS electrode for pain management placed at T9-T10 level. To demonstrate the benefits of SCS independent from Levodopa therapy, the stimulation was performed without dopaminergic medication. The results were quite good with a 50 % improvement in motor UPDRS score and a significant reduction of tremor in all four limbs. The patient also reported no pain induced by the stress of SCS and did feel an improvement in stiffness when the stimulator was active. The second report is from Okayama University Hospital (Agari and Date 2012). This study included 15 patients presenting low back or leg chronic pain. In this study, preoperative and postoperative assessments were performed at 3, 6 and 12 months, with similar results to those of the Fenelon study: significant improvements in UPDRS test and in 10-m walk test. The symptomatic improvement persisted during the whole follow up period. In this case the stimulator was also placed at the thoracic level between T7 and T12 levels.

A third report published another single case of a advanced PD patient with chronic pain in the limbs, who received a epidural stimulation electrode at D9-D10 level. Along with a considable reduction in pain, the patient experimented improvement in gait, postural stability, and non-motor symptoms like bladder control and incontinence (Landi et al. 2012). Yet, a fourth report about a patient with PD and chronic neuropathic pain treated with SCS, shows not only alleviation of pain, but significant improvements in PD motor symptoms. Remarkably, the improvement of the symptoms increases over time, from a UPDRS motor score at early postoperative of 28, it goes down to 22 after a year, and further down to 16 at the end of the second year (Hassan et al. 2013).

3.7 Discussion

Spinal cord stimulation, a neuromodulation procedure used normally to treat intractable chronic pain conditions, has been proposed as a therapeutic option for Parkinson's disease, based on the idea that it restores normal oscillatory patterns of supraspinal brain structures via ascendant sensory pathways. The first experiments in rodent models of PD further supported this notion, leading to the testing of SCS in PD patients.

To propose a mechanism that explains the prokinetic effect of SCS, first of all, we have to identify the neural pathways activated by SCS. According to available evidence and theoretical studies, at low and moderate intensities (the ones normally used with therapeutic aims, this is, above sensory threshold and bellow discomfort threshold) the spinal elements activated by SCS are the outer fibers of the dorsal columns and the dorsal roots (Holsheimer 2002). These pathways convey the somatosensory and propioceptive input to cortex through lemniscal pathways and the ventral posterolateral nucleus of the thalamus, thus providing an anatomical substrate to convey the desyncronizing input of the SCS stimulation to the cortical areas, which in turn project to striatum (Fuentes et al. 2010).

Another possible mechanism to explain the prokinetic effect of SCS is the activation of the pedunculopontine nucleus (PPN) via ascending projections from thoracic and cervical spinal cord (Jenkinson et al. 2009). The activation of the PPN via ascending pathways would have two effects: to initiatiate movement by direct descending drive to locomotor circuits; and second, an indirect effect through the ascending thalamocortical pathways, which in turn would activate and desynchronize cortical motor areas and structures within the basal ganglia (Fuentes et al. 2010).

Importantly, so far, the successful use of SCS in Parkinson's patients is paralleled by alleviation of pain. In the case of the patient of the Fenelon report, this pain is not secondary to Parkinson's, and this patient, beside experimenting improvement in gait and posture, presents a dramatic improvement in limb tremor. On the other hand, the patients from the Agari and Landi reports, present pain and sensory symptoms seemenly related to advanced Parkinson's. In these cases no alleviation of tremor is described, but improvement of gait and posture. In the case of the two latter reports, it is not easy to determine if the motor improvments are totally or partially independent from pain managment. Although it might appear as intuitive that the allevation of pain could improve motor performance, the poor understanding of the mechanisms underlying the pain and dysesthesias related to advanced Parkinson's disease does not allow making conclusive assertions yet.

It has to be considered also that maybe chronic pain associated plasticity in some brain pathways such as cortico striatal circuits (Baliki et al. 2012) may be one of the causes of the successful outcome in some of these experiments, this hypothesis has to be tested in future SCS implanted in PD patients with no chronic pain.

So far, both in rodent models and patients of Parkinson's diseased, SCS have proven to have prokinetic effects that are expressed as increased locomotion in the rodent models and improvement of gait, balance and posture in the patients. The future efforts in this promising field should be focused mainly in two directions. First, the confirmation, either in non human primate models of Parkinsons or Parkinson's patients, of the beneficial effects of SCS in the motor symptoms. Second, the study of the neuronal mechanisms underlying these benefits, which would allow optimizing and exploiting the full potential of this approach.

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Part II
Spinal and Brain Plasticity

Chapter 4
Spinal Cord Plasticity and Neuromodulation

Stefano Piazza, Johannes Brand and Carlos Escolano

Abstract Rehabilitation of people with spinal cord injury, traumatic brain injury, and other neurological disorders can be improved by the use of methods that rely on modulating and guiding the plasticity of the central nervous system including the spinal cord itself. This chapter first provides a general overview of the evidence for spinal cord plasticity. It reviews the definitions of quality of life (QOL) and discusses how typical research priorities are not well aligned with the priorities expressed by people with these disabilities. Typically, research as well as therapeutic efforts focus on such functions as locomotion and arm/hand control. In contrast, studies of people with spinal cord injury and other injuries or disorders of the nervous system reveal that their highest priorities are often restoration of such autonomic functions as bladder and bowel control and sexual function. This review therefore focuses on rehabilitation methods such as neuromodulation, including sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS), that target restoration of these functions, with some additional discussion of the pain abatement that is often produced incidentally with use of these methods. In designing new therapies and planning new research programs, it would be highly beneficial to take into serious consideration assessments of their potential to improve QOL and to use QOL measures as an additional metric in evaluating the impact of results.

Keywords Spinal cord injury · Spinal plasticity · Quality of life · Neuromodulation · Neuroprosthetics · Autonomous functions

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4.1 Introduction

Plasticity in the nervous system is a well documented phenomenon that has been recognized since the early studies by Ramón y Cajal (1914) and by many others since that time (Hebb 1949; Cramer et al. 2011). Until relatively recently, it was widely thought that such plasticity was confined exclusively to the brain (Cramer et al. 2011). Many studies have now made it apparent that activity-dependent plasticity is widespread throughout the entire central nervous system (CNS) (e.g., Chamberlain et al. 1963; Wang et al. 2006; Courtine et al. 2009). Recognition of this widespread plasticity introduces the possibility of many new therapeutic interventions for the rehabilitation of people disabled by a variety of neurologic diseases or by brain or spinal cord injury (SCI). Spinal cord plasticity in particular has been largely unrecognized and its potential uses in rehabilitation still receive little attention despite substantial evidence that the spinal cord is highly plastic (Wolpaw 2012). The spinal cord's unique role as a final common pathway gives it a critical position in the execution of all behaviors. Its relative simplicity and accessibility encourage exploration of its plasticity as a potentially beneficial approach in clinical applications.

In this review we give a brief overview of current clinical and experimental evidence for activity-dependent spinal cord plasticity. We evaluate this evidence based on its relevance for treating people disabled by SCI. Since recent studies indicate that people with spinal cord and/or brain injury and disease often place highest priority on restoration of lost autonomic functions such as bladder and bowel control and sexual function (Anderson 2004), we discuss the methods that guide spinal cord plasticity to address impairments in these areas. Thus, in contrast to many reviews, as well as to the most prevalent clinical therapeutic interventions, we do not discuss rehabilitation of locomotor function but instead focus on restoration of autonomic function.

4.2 Background Review

The CNS has traditionally been thought to be hardwired and inflexible. The work of recent decades has shown that the CNS changes continually throughout life (e.g., using mechanisms such as synaptic plasticity, neuronal plasticity, and glial, vascular, and humoral plasticity) and that this plasticity involves regions from the cortex to the spinal cord [see (Wolpaw 2010) for a review]. Recognition and understanding of both the plasticity changes that occur after injury, and the processes that can be accessed, are essential for interventions that will restore spinal cord function to enable or improve such functions as locomotion, bowel and bladder function, and sexual function. The plasticity of the spinal cord, though a potentially fruitful target for therapeutic rehabilitation approaches, has received little attention. It is only recently that it has become apparent that the spinal cord participates in an important way in the CNS plasticity responsible for learning new behaviors. This section reviews past and recent findings documenting and elucidating activity-dependent plasticity in the spinal cord and its therapeutic potential.

4.2.1 Spinal Cord Plasticity

Spinal cord plasticity accounts for the lasting changes in spinal cord-mediated functions produced by peripheral and/or descending inputs. This section summarizes six major bodies of data that give evidence for spinal cord plasticity in health and disease. They are based on results from normal and injured animals and humans. It is important to note here that all six cases cite evidence coming from the effects of injury or training on locomotion and other voluntary limb movements. Although locomotion and other voluntary limb movements are not the focus of this chapter, their prevalence in such studies is indicative of the emphasis that researchers have placed on these functions.

The first body of evidence for spinal cord plasticity comes from the fact that the spinal cord changes after injury or disease that disrupts supraspinal control (Ronthal 1998; Hiersemenzel et al. 2000). This phenomenon was first demonstrated by Anna DiGiorgio in laboratory experiments using anesthetized dogs, rabbits, and guinea pigs (DiGiorgio 1929a, b). In these experiments, descending input to the spinal cord was altered by a lesion to one side of the cerebellum. This lesion caused an immediate asymmetric hindlimb posture (i.e., one leg was flexed and the other was extended). After a variable delay, the thoracic spinal cord was cut, thereby removing the descending input responsible for the asymmetry. When the delay was short, the transection eliminated the asymmetric posture. In contrast, when the delay was longer, the asymmetric posture persisted even though all descending input had been eliminated. This experiment was the first to show clearly that altered descending input that lasts for sufficient time produces spinal cord plasticity that persists after the input ceases. These results were subsequently confirmed in studies with rats (Chamberlain et al. 1963).

The second body of evidence for spinal cord plasticity comes from studies showing that the isolated adult spinal cord is capable of activity-dependent plasticity (Courtine et al. 2009; Rossignol et al. 2011). Treadmill walking is a rehabilitation therapy widely used around the world for people with SCI (Dietz et al. 2008). It was first demonstrated by Shurrager and Dykman that spinalized cats (i.e., cats with transected spinal cords) can improve locomotion with training (Shurrager and Dykman 1951). Several research groups have confirmed this phenomenon and have described its major features (Barbeau and Rossignol 1987; Barbeau et al. 1999). In the typical protocol, cats were spinalized at the thoracic level and then began a training regimen (for 30–60 min per day) of walking with their hindlimbs and with weight support, at the same time that they were electrically stimulated in the perineum. The result was that the cats' locomotion improved over days and weeks, that they walked faster and for longer periods, and that eventually they did not need weight support or electrical stimulation to do so. This work was extended using rats, showing that EMG measures from tibialis anterior and soleus muscles follow patterns of activity during the stance and drag phases after training that are similar to those found prior to injury (e.g., Courtine et al. 2009).

The third body of evidence comes from very recent studies developing methods for inducing spinal cord plasticity by means of pharmacological and molecular interventions to facilitate axon regrowth, to replace lost neurons, and to reestablish synaptic connections [see (Fouad et al. 2011; Marsh et al. 2011) for reviews]. The rationale beyond these interventions is to suppress the effects of inhibitory peptides such as chondroitin sulphate (CSPG), neurite outgrowth inhibitor protein A (NogoA), semaphorins, and other proteoglycans, which are generated after SCI at the injury site and which inhibit axonal regeneration or/and axonal growth. For example, the enzyme chondroitinase ABC (ChABC) has been used to promote long distance regrowth of CNS axons across the lesion site by breaking down CSPGs (Moon et al. 2006). The administration of the enzyme chondroitinase (cABC), which overcomes the inhibitory effects of NogoA, promotes axonal regeneration and functional recovery of motor and bladder function (Barritt et al. 2006). Also, neurotrophic growth factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT-3) promote plasticity in the spinal cord and brain (Zhou and Shine 2003). Other promising interventions include implantation of cells derived from fetal spinal cord, radiation aimed at the lesion site, and transplantation of olfactory ensheathing glia (OEG) into a lesion site after SCI (Marsh et al. 2011). It is possible that these methods that enhance plasticity might be combined with traditional rehabilitation therapies to develop new treatment strategies.

The fourth body of evidence comes from recognition of the fact that perinatal spinal cord plasticity is responsible for the acquisition of basic behaviors such as locomotion and withdrawal from pain, and that normal adult reflex patterns are shaped by descending input during the first years of life. This phenomenon was demonstrated in a 1999 study by Levinsson et al. (1999). In this study, three groups of rats (normal neonatal rats, normal adult rats, and adult rats with spinal cords transected just after birth) were given nociceptive stimulation. In normal adult rats, the painful stimulus excited the appropriate muscles to withdraw the limb from the painful stimulus. In contrast, the painful stimulus often produced inappropriate muscle contractions in normal neonatal rats, resulting in limb movement toward the painful stimulus. The adult rats with spinal cords transected just after birth showed a pattern similar to that of the neonatal rats. This finding demonstrates that the removal of descending input (by spinal cord transection just after birth) prevents the development of the adult withdrawal pattern. Analogous effects on locomotion patterns are observed in humans with cerebral palsy (CP) as a result of the perinatal supraspinal lesions associated with CP (Myklebust et al. 1986). In normal infants, muscle stretch produces stretch reflexes not only in the stretched muscles but also in their antagonist muscles. The latter stretch reflexes normally disappear during childhood development to produce normal adult reflex patterns. However, antagonist reflexes persist in adults with CP presumably because the descending input responsible for development of normal adult reflexes has been removed due to the perinatal supraspinal injury associated with CP. This phenomenon contributes to the motor disability of people with CP, which might be improved by guiding spinal cord plasticity during childhood.

The fifth body of evidence for spinal cord plasticity comes from the observation that acquisition of motor skills in adults is associated with changes in spinal reflexes. The spinal reflexes most studied are the spinal stretch reflex (SSR) and the H-reflex [see (Wolpaw 2010) for a review]. In a 1993 study by Nielsen et al. (1993), examining the soleus muscle H-reflexes of four groups of people (sedentary, moderately active, extremely active, and professional ballet dancers), H-reflexes were larger in the moderately active subjects than in the sedentary subjects, and even larger in extremely active subjects. However, the H-reflex was lowest in the dancers, even though they were the most active group. The authors suggest that the dancers' decreased reflexes probably contribute to their ability to maintain the muscle co-activations needed for acquisition of this athletic skill. It can be further hypothesized that the induced plasticity in spinal reflex pathways may predict the success of rehabilitation treatments in restoring function after stroke or in other neurological disorders.

The sixth source of evidence is that humans, monkeys, rats, and mice can change spinal reflex pathways by means of an operant conditioning protocol (Wolpaw 2010). The reflex-conditioning protocol induces the plasticity in the spinal cord that gradually changes the amplitude of the reflex (larger or smaller) as a result of the operant conditioning; at the same time, synaptic inputs and intrinsic properties (such as firing threshold and axonal conduction velocity) of the motor neuron also change (e.g., Carp et al. 2001). Of great interest for locomotor rehabilitation is the observation that appropriate reflex conditioning can improve locomotion after spinal cord injuries in both rats and humans (Chen et al. 2006; Thompson et al. 2013). In these and other studies by this group, the behavioral effect of training was found to depend on multi-site plasticity. At the same time, the acquisition of the simple new skill (higher or lower H-reflex) also produces compensatory plasticity to preserve old behaviors (Chen et al. 2011).

Taken together, these data provide evidence of activity-dependent spinal cord plasticity. This plasticity might be used as the basis for the development of new and effective therapies for people with SCI or other disorders of the central nervous system. In addition to the potential therapeutic benefits, a better understanding of spinal cord plasticity is also of interest in modeling the more complex processes of the CNS because of the spinal cord's relative simplicity (i.e., its major cell types and pathways are well known) and because of its accessibility to monitoring, to direct excitation, and to short- or long-term interruption of connection with the brain. Thus, a better understanding of spinal cord plasticity could help define mechanisms and principles of plasticity that are likely to apply throughout the CNS.

4.3 The Priorities of People Disabled by SCI or Other Neurological Disorders

The studies described in the previous section indicate that there is a rich history of research focusing on issues pertaining to gait function after SCI. This focus is also reflective of the focus of rehabilitation efforts on behalf of people with SCI, particularly for restoration or improvement of gait. It seems natural to assume that locomotion is a function that people with SCI would want to restore. It is the deficit most obvious to people without disabilities. However, SCI causes loss of other important functions that are not always directly visible to others. These deficits include bladder, bowel, sexual and sensory dysfunctions, as well as neuropathic pain and autonomic dysreflexia (malfunction of the autonomic nervous system due to overstimulation after a SCI). In 2004, Anderson conducted a survey of people with SCI to determine their priorities for functional restoration (Anderson 2004). She asked 681 people (51 % with tetraplegia, 49 % with paraplegia) about their desires for functional restoration. Her study showed that in the group of people with tetraplegia:

48.7 % selected *arm and hand function* restoration as their top priority
13 % selected *sexual function*
11.5 % selected *upper-body/trunk strength and balance*
8.9 % selected *bladder/bowel function and the elimination of autonomic dysreflexia*
7.8 % selected *regaining walking movement*
6.1 % selected *regaining normal sensation*
4 % selected *eliminating chronic pain*

The same study showed that for the group of people with paraplegia:

26.7 % selected *sexual function* restoration as their top priority
18 % selected *bladder/bowel function and the elimination of autonomic dysreflexia*
16.5 % selected *increasing upper body/trunk strength and balance*
15.9 % selected *regaining walking movement*
12 % selected *eliminating chronic pain*
7.5 % selected *regaining normal sensation*
3.4 % selected *arm and hand function*

These results may surprise researchers and therapists without disabilities, who have traditionally focused on therapies to restore locomotion in this population. While the high priority of arm and hand function for patients with tetraplegia is probably not surprising, the high ranking of recovery from sexual dysfunction, bowel/bladder problems, and autonomic dysreflexia were unexpected. It is noteworthy that in both groups these functions are generally given higher priority than regaining walking or removing neuropathic pain. Gender and the time after SCI were not significant factors in the results. Chronic SCI patients (>3 years) ranked the elimination of neuropathic pain slightly higher than did acute patients. The question raised by these results is why patients systematically selected functions like sexual, bladder, and bowel function as more important than restoring walking.

4.3.1 Quality of Life

A meta-study by Tate and colleagues reviewed quality of life (QOL) issues for people with SCI (Tate et al. 2002). For the studies they reviewed, the four most important QOL factors were, in descending order: access to the community; marriage; social support; and community integration. The authors surmised that these priorities were probably determined not only by the physical limitations of SCI, but also by their social and psychological implications. Romantic relationships might be heavily impeded by the social and psychological consequences of sexual dysfunction, and bladder and bowel problems might play a significant role in limiting community access and community integration. In contrast, wheelchair use is understood by and accepted by society at large and may therefore not be of as great a concern.

The results of Anderson's and Tate's studies provide a sharp contrast to the research effort that has been invested in the improvement of walking function. Restoration of walking is often the focus of rehabilitation efforts, but it is generally not the highest priority for the people surveyed in these studies. (Nevertheless, it should be noted that although many people with SCI have problems in sexual function, relatively few seek treatment (Laumann 1999) and thus it might be difficult to recruit people in this category for scientific studies.) Moreover, improvements in autonomic functions might be more difficult to quantify than improvements in locomotion. Nevertheless, future research efforts should carefully consider and take into account these QOL-related preferences, and perhaps even use QOL measures as primary outcome metrics for comparing different rehabilitation strategies.

To consider and evaluate QOL issues, it is useful to take a closer look at how QOL is defined and measured. In 1958 the World Health Organization (WHO) defined health as "a state of complete physical, mental, and social well-being and not merely the absence of diseases and infirmity" (World Health Organization 1958). Other definitions are also found in the literature. For example, Post and colleagues (Post and Noreau 2005) did an extensive review of QOL definitions and divided them into three main categories: (1) health-related quality of life (HRQOL); (2) well-being; and (3) a combination of HRQOL and well-being. In general, HRQOL definitions are usually based on the concept of health as defined above by the WHO; well-being definitions use a more subjective perspective and consist of components related to mood and subjective evaluation of life-satisfaction. For the well-being definition of QOL, health is a predictor of well-being rather than a specific part of it. Like some other authors, Post and his colleagues suggest a subordinate construct, which contains both HRQOL and well-being and which additionally distinguishes between objectively assessable and subjective components.

Numerous questionnaires for assessing HRQOL have been developed. One by Lundquist et al. is specific for SCI (Lundquist et al. 1997). The generic questionnaire SF-36 by Ware and Sherbourne (1992) is commonly used. It consists of 36 items using the 7-point Likert scale for scoring. The questions can be categorized as relating to physical factors or mental health factors.

There are several questionnaires for assessing well-being. The results of these surveys indicate that the sense of well-being is not influenced by the severity of disability (Post and Noreau 2005) and that the mental health-related scores of people with SCI do not differ significantly from the scores of people without disabilities. While this might reflect the true state of these subjects, it might, as is true of all issues assessed, be due to inadequately phrased questions or to the lack of disability-specific questions. The finding may not be as surprising as some might think, since well-being is subjective and it includes mood, outlook, and life satisfaction, which are very personalized and not necessarily determined by disability. Moreover, these subjective qualities vary from day to day in any individual's life and are in any case difficult to accurately quantify.

In our view, the subordinate construct of HRQOL and well-being suggested by Post and Noreau (2005) and by others is probably a good approach to quantification of the QOL of an individual. Nevertheless, in assessing the QOL of a group, the well-being measure may not provide much additional information due to the large variations across individuals. Thus, the HRQOL assessment in and of itself may be the most useful metric to assess QOL. Moreover, it is easier to use in measuring QOL improvements due to SCI rehabilitation therapies because of its greater simplicity and objectivity. Nonetheless, HRQOL questionnaires could be improved to become more accurate predictors of QOL for people with SCI; in their current form they may be too general and the typical questions related to mental health might be expanded to incorporate factors pertaining to the subjects' social environment.

4.4 Neuromodulation for Restoring Autonomic Functions

As noted in the previous section, the restoration of certain autonomic functions is of primary importance for the improvement of the QOL for many people with SCI. Improvement in these autonomic functions can be addressed using electrical stimulation.

Modern efforts in the application of electrical stimulation for the restoration of bladder and bowel functions in humans date back to 1940s [see Fandel and Tanagho (2005)]. Attempts to directly stimulate pelvic nerves were later performed by Dees (1965). One of the main questions addressed in these and other studies was the identification of the best site for the stimulation. Various sites for stimulation were proposed and attempted: transurethral bladder (Katona 1975);

direct detrusor (Boyce et al. 1964); pelvic floor (Caldwell 1963); spinal cord at the level of the sacral root (Nashold et al. 1971; Brindley 1972) and tibial nerve stimulation (McGuire et al. 1983) [for a complete historical overview please see (Fandel and Tanagho 2005)].

With the successful inhibition of voiding reflexes obtained with the application of electrical currents in the sacral root area of a baboon with overactive bladder syndrome (Brindley 1974) came the introduction of the technique of *neuromodulation*, defined by Tanagho (1993). As neuromodulation has been increasingly used in the treatment of bladder and bowel dysfunctions, there has been increased interest in using it also for pain relief (Siegel et al. 2001; Whitmore and Payne 2003) and for restoration of sexual function (Jarrett et al. 2005; Pauls et al. 2007). We will review each of these areas in turn and will discuss the neurophysiological processes underlying each function.

4.4.1 Bladder Neurophysiology

Bladder functions include storage of urine and voiding. To perform these operations, the nervous system must appropriately coordinate signals from the voluntary and the sympathetic systems (Fig. 4.1). The pontine micturition center, a small group of neurons in the brainstem, represents the neural junction between the voluntary signals generated in the cortex, and the afferent signals indicating the degree of fullness of the bladder. Impulses from the pontine micturition center descends through the spinal cord to modulate the reflexes that control urine storage and voiding. When the ascending or descending pathways are damaged, as in the case of SCI, the subject may lose the ability to inhibit or coordinate bladder emptying, and problems like urinary incontinence or incomplete bladder emptying may occur (Mayer and Howard 2008).

4.4.2 Bowel Neurophysiology

The bowel is responsible for absorbing nutrients from food, moving unabsorbed material toward the rectum, and defecation. In the resting state, the internal anal sphincter, which is not subject to voluntary control, is contracted, while the external anal sphincter is relaxed. To allow defecation, the puborectalis muscle reduces its pull on the junction between the rectum and the anal canal, the internal anal sphincter relaxes, and the external anal sphincter voluntarily relaxes (Benevento and Sipski 2002). SCI can disrupt these events. Among people with SCI, the incidence of gastrointestinal problems, including fecal incontinence, pain in evacuation and severe constipation, is estimated to be 27–62.5 % (Han et al. 1998; Stone et al. 1990). Bowel dysfunction is so significant and prevalent that it is considered one of the principal reasons why many people with SCI do not return to

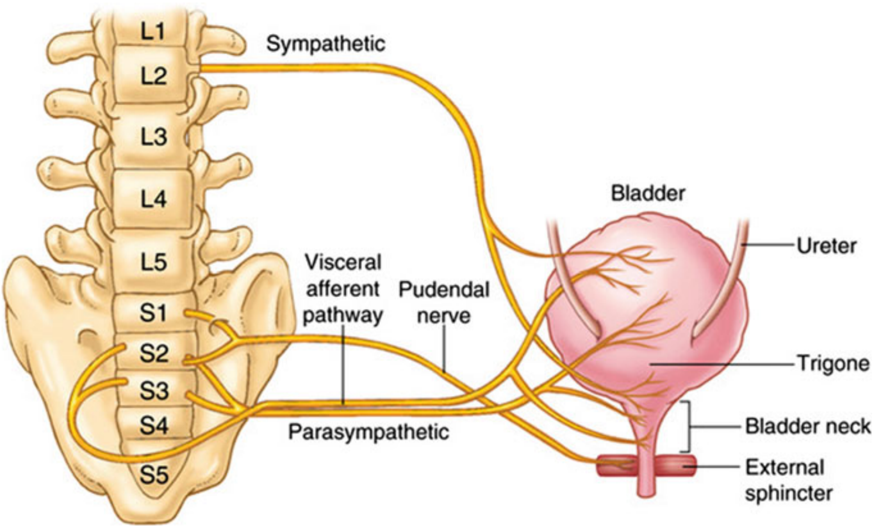

Fig. 4.1 Sacral plexus and bladder innervation. (Courtesy from: percutaneous tibial nerve stimulation for overactive bladder: anatomy and bladder innervations from Atlas of Bladder Disease, Volume 1, Chap. 20. ISBN: 978-1-57340-307-8 Published: 2009-12-09 Authors: MacDiarmid, Scott; Staskin, David)

work after injury (Karlsson 2006), leading to an often profound effect on QOL (Macmillan et al. 2004). Bowel-related dysfunctions, particularly delayed or unplanned evacuation, are also a primary impediment to social interactions for people with SCI (Lackner and Gurtman 2005). In addition, the higher tonus and uninhibited activity in the anal sphincter after cervical and thoracic lesions may also cause severe pain. Painful anal fissures, hemorrhoids, anal incontinence, and constipation, can ultimately lead to the need for colostomy, which often does not reduce the pain even though the rectum and anal region are bypassed (Karlsson 2006).

4.4.3 Neuromodulation Treatment for Bladder and Bowel Dysfunction

Typical treatments for bladder and bowel dysfunction are primarily conservative and may include dietary and lifestyle advice, drug treatment, and biofeedback. However, these treatments do not guarantee symptom resolution, and side effects from drug therapies might not be tolerated. Although surgery is sometimes considered, it involves significant morbidity and its efficacy is variable (Benevento and Sipski 2002).

Neuromodulation is another approach that offers an alternative solution for bladder and bowel dysfunctions when other approaches are not sufficient (Paris et al. 2011). Neuromodulation techniques are minimally invasive. The two main categories of neuromodulation techniques are sacral nerve stimulation (SNS) and percutaneous tibial nerve stimulation (PTNS). Low-level chronic electrical stimulation *(*1–5 V, 1–20 Hz, pulsewidth 200–210 μs*)* is applied to spinal circuits to produce a physiological response in the organ responsible for the impaired function (Banakhar et al. 2012; Brill and Margolin 2005).

4.4.3.1 Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) can simultaneously influence the function of all the structures involved in urinary and fecal continence and evacuation. SNS is used to treat urinary retention and the symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency frequency. It can alter colonic motility, pelvic floor and anal sphincter function, and afferent sensation. SNS to treat bladder disorders in humans was first described by Tanagho and Schmidt (1982), and Tanagho (2012). Simultaneous improvements of bowel functions were soon observed in some patients treated with SNS (Pettit et al. 2002). Further investigation in the following years led to the application of SNS for the cure of fecal incontinence by Brindley (1990).

Current SNS therapy consists of the release of mild electrical pulses, with current amplitude set just above or below the threshold of patient sensation and a potential of 1-5 V. The pulses are released in a train of frequency of 1–20 Hz, with pulse width of 200–210 μs. Device application is a two-stage process. First, a percutaneous electrode is implanted in the sacral root at the S3 level, and stimulation is applied using an external pulse generator. The patient is observed for at least one month, to eliminate the risk of lead migration. If the main symptoms improve by more than 50 % at the end of the month, the second phase of the therapy begins, and a permanent implantable pulse generator is inserted in the patient's buttock (Lombardi and Del Popolo 2009). The electrical stimulation of the sacral nerve causes the contraction of the external sphincter and pelvic floor muscle, and modulates reflex pathways that influence the pelvis area.

Medium- to long-term beneficial effects have resulted from SNS treatment of people with various urinary tract symptoms (Lombardi and Del Popolo 2009), fecal incontinence (Lombardi et al. 2009, 2011), or both (El-Gazzaz et al. 2009, Jarrett et al. 2004). Studies such as that by Lay and Das (2012) suggest that SNS is successful for the treatment of overactive bladder for 70 % of the patients with the SNS implant. A review by Burks and Peters (2009) reports short-term efficacy (i.e., return to complete continence) for urinary urgency for 50 % of patients using SNS, and efficacy for the main symptoms of incontinence which resolved for 90 %. In the same review, between 58 and 68 % of patients treated with SNS experienced long-term clinical success, with complications (e.g., hematoma, wound infections, chronic pain at the generator site and lead migration) ranging from 12 to 53 %

(Gaynor-Krupnick et al. 2006; Sutherland et al. 2007; Aboseif et al. 2007). For fecal incontinence, the overall success rate is estimated to be 79 % for patients with a permanent SNS implant (Melenhorst et al. 2007).

Despite the clinical benefits, the precise mechanism of action of SNS is still uncertain. The electrical stimulus appears to affect afferent and efferent feedback mechanisms at both spinal and supraspinal levels, involving all aspects of the sacral nerve plexus and extending to the cortical level (van der Pal et al. 2006). The influence on bladder functions seems related to effects on the afferent fibers, consisting of myelinated delta fibers and unmyelinated C fibers (Mayer and Howard 2008). In healthy subjects, the efferent signals from the pontine micturition center modulate sacral cord reflexes responsible for keeping the C fibers silent during the filling phase (Mayer and Howard 2008). When descending impulses from the pontine micturition center are blocked, the activity of the bladder may increase, generating urge incontinence (Groat 2006). SNS modulates micturition reflex loops by providing stimulation with a lower amplitude than the activation threshold of somatic muscles, generating an effect similar to the influence generated by the pontine micturition center (Mayer and Howard 2008).

In improving bowel function, SNS appears to affect the somatic pudendal nerves and direct efferent nerves to the pelvic floor muscles to improve external anal sphincter function (Kenefick 2006). In addition to the achievement of adequate sphincter functions, the efficacy of SNS for improving bowel function appears to be due also to alterations in rectal sensation, colonic and rectal motor activity, and stool consistency (Melenhorst et al. 2007).

Side effects of SNS-based therapies (e.g., pain, lead migration and infection) are associated with the implantation procedure and with acceptance of the implant by the body. They are reported to occur in 3–16 % of SNS implants (Siddiqui et al. 2010; Al-Shaiji et al. 2011).

4.4.3.2 Percutaneous Tibial Nerve Stimulation

SNS is considered a minimally invasive technique, but implantation of the device nevertheless requires a general or regional anesthetic (Burks and Peters 2009). It involves a small risk of complications including infection, pain at the implant site, migration of the electrode, and equipment failure. An alternative neuromodulation technique is *percutaneous tibial nerve stimulation* (PTNS), or posterior tibial nerve stimulation, and it is significantly less invasive. It was first developed and described in 1983 by McGuire and colleagues (McGuire et al. 1983), but was approved as a therapy for incontinence only in 2000. Although it is less invasive than SNS, PTNS is based on the same hypothesized mechanism of action. However, instead of directly stimulating the spinal cord at level S3, PTNS takes advantage of a retrograde pathway passing through the posterior tibial nerve that is accessed just above the ankle. The key potential benefit of this approach is that it is less invasive and therefore entails fewer associated clinical risks and lower costs.

Application of the PTNS device consists of the insertion of a fine needle next to the tibial nerve and placement of a surface electrode (grounding pad) on the foot (Vandoninck et al. 2003). The two electrodes are then connected to an external low-voltage generator. The stimulation delivered to the tibial nerve generates a retrograde stimulation of the sacral plexus, thus activating the same circuits as those activated in SNS (Hotouras et al. 2012). The treatment protocol requires once- or twice-per-week treatments for 6–12 weeks, for 30 min per session (Hotouras et al. 2012). People who respond to treatment may require occasional follow-up treatments (i.e., about once every 6 months) to sustain improvements (Hotouras et al. 2012). A recent literature review (Biemans and van Balken 2012) reports successful treatment of 36.7–80 % of patients with bladder-related disorders and successful treatment of 53 % of patients with fecal incontinence. Although the estimates vary due to differences in the evaluation scales used, studies generally agree that the method is highly successful (Moossdorff-Steinhauser and Berghmans 2012).

PTNS is considered a low-risk procedure. The most common side effects are temporary and minor, resulting from the placement of the needle electrode: minor bleeding; mild pain; and skin inflammation. The review by Biemans and van Balken (2012) reports a 14–16 % PTNS-related occurrence of at least one of the following moderate adverse effects: generalized swelling, worsening of incontinence, headache, hematuria, inability to tolerate stimulation, leg cramps, intermittent foot/toe pain, and vasovagal response to needle placement. No serious side effects have been reported. It is thus considered to be a safe, well tolerated, minimally invasive procedure that appears to be effective in treating patients with urgency and mixed fecal incontinence. Nevertheless, despite its effectiveness in the short term, it requires regular application of the stimulus with the percutaneous needle (Al-Shaiji et al. 2011) and is thus likely to be replaced eventually by methods that have longer-lasting effect.

4.4.4 Neuromodulation Treatment for Sexual Dysfunction

The impact of SCI on sexual function depends on many factors, including the degree of injury, the location of the injury in the spinal cord, gender, and other factors. The sexual functions typically affected include physical responses such as penile erection in men or vaginal lubrication in women and subjective responses such as sensation of pleasure. Fertility may also be affected. The majority of men with SCI have poor sperm quality and ejaculatory dysfunction, making sexual reproduction difficult or unlikely (Brackett et al. 1996). In contrast, women affected by SCI are more likely to preserve their ability to conceive (Charlifue et al. 1992).

Penile erection in men is generated physically by a sacral stimulus following a parasympathetic neurologic pathway, and it is generated psychogenically under the control of the hypogastric plexus at the level of T11-L2. Depending on the characteristics of the spinal cord lesion, one of these two mechanisms can be affected, but it is rare that both mechanisms are non-functional (Benevento and Sipsi 2002; Hubscher 2006). Ejaculation is a more complicated neurological process, requiring the coordinated action of the sympathetic, parasympathetic, and somatic nervous systems, and it is more profoundly affected by SCI (Benevento and Sipsi 2002). In women, the arousal phase of the sexual response is typically characterized by lubrication of the vagina, clitoral swelling, and other physical changes. For women with complete upper motor neuron (UMN) injuries affecting the sacral segments, the ability for reflexive but not psychogenic lubrication is generally maintained (Hess and Hough 2012). For women with incomplete UMN injuries affecting the sacral segments, it is thought that the capacity for reflexive lubrication as well as psychogenic lubrication may both be maintained (Bérard 1989). More than 50 % of the people affected by SCI may completely lose the ability to reach orgasm; for the others, the latency to orgasm seems to be greater than in healthy people (Benevento and Sipsi 2002). All these physical and psychological factors may thus contribute to affect sexuality and sexual activity in people with SCI.

Treatments to recover sexual functions include pharmaceutical treatments, mechanical stimulators, and more invasive methods such as penile implants, prostheses, or use of a vacuum constriction device. Kreuter and colleagues maintain that successful SCI rehabilitation of sexual function requires a holistic approach, taking into account the patient's physical, psychological, and interpersonal circumstances as well (Kreuter et al. 2010). SNS appears to improve sexual function in people with SCI (Gill et al. 2011). SNS has achieved significant clinical improvement in men with neurogenic erectile dysfunction associated with urinary incontinence (Lombardi et al. 2008). Women receiving SNS for urinary incontinence reported improvement in sexual function measured by a sexual-function index of arousal and lubrication (Lombardi and Mondaini 2008; Jarrett et al. 2005; Gill et al. 2011). The mechanism by which these therapeutic effects are achieved is still unknown. Lombardi (Lombardi et al. 2008) hypothesizes that the SNS may act directly on sexual function through the stimulation of the pelvic and pudendal nerves, which innervate S3. The effect on the pudendal afferent pathways may enhance a person's consciousness and control of the pelvic floor, which leads to improvement of both urinary functions and sexual function (Lombardi et al. 2008).

4.4.5 Neuromodulation Treatment for Pain

From its earliest applications in treatment of bowel and bladder function, neuromodulation techniques have evolved to increasingly address relief from neuropathic pain, chronic pelvic pain, and chronic pain from trauma to peripheral nerves (Aló and Holsheimer 2002; Mobbs et al. 2007; Feler et al. 2003). The mechanism of action of spinal modulation for the control of pain is still not clear, but it is assumed to be based on the gate-control theory of Melzack and Wall (1967), and Melzack and Katz

(2004). A review by Mayer and Howard (2008) found that SNS produced significant alleviation of pelvic pain, with over 50 % improvement in most studies. A review by van Balken et al. (2003) reports lesser but still significant results with use of PTNS: greater than 50 % pain reduction in 21 % of the study population (33 people) for chronic pelvic pain, and more than 25 % in reduction in 39 % of the population. A study by Mobbs et al. (2007), taking into account multiple types of peripheral nerve stimulation for upper and lower limbs, including PTNS, and using a larger study population (n = 175), presents more encouraging results: 61 % of subjects reported greater than 50 % relief from chronic peripheral pain. Such results hold promise for improving long-term outcomes in pain relief, as well as for increasing the number of pain conditions that can be treated with neuromodulation therapy (Kim et al. 2010).

4.5 Conclusions

Research and clinical therapies for helping people with SCI and other disorders of the nervous system have traditionally focused on developing effective methods to restore or improve voluntary motor behaviors such as locomotion and arm/hand movement. The typical focus on restoration and improvement of these voluntary movements does not align with the results of studies measuring the rehabilitation priorities of people with SCI who indicate that the functions of highest priority are not necessarily locomotion or hand/arm function. Instead, people with SCI often place highest priority on restoring such autonomic functions as bladder control, bowel control, and sexual function. Improvement of function in these areas would more closely align with the preferences of people with SCI and other nervous system disorders or injuries.

In recent years, it has become increasingly evident that not only the brain but also the spinal cord is capable of significant plasticity during normal development. This plasticity occurs in response to training and in response to injury. Recent recognition of spinal cord plasticity and growing elucidation of its mechanisms now make it possible to design new therapies based on the modulation of spinal cord function. Several effective neuromodulation techniques are currently available for the rehabilitation of a variety of functions ranging from the voluntary to the autonomic level. Two neuromodulation methods for improving these functions are currently in clinical use. Sacral nerve stimulation (SNS) involves implantation of a stimulating electrode at the sacral level in the spinal cord. Stimulation at low voltage results in effective improvement in bladder and bowel control, as well as improvement in sexual function. Percutaneous tibial nerve stimulation (PTNS) also uses electrical stimulation, but the electrode is placed not in the spinal cord but just above the ankle instead. While PTNS incurs fewer complications because it is less invasive, the beneficial effects of this method are not long-lasting and the treatment must be repeated periodically. The mechanism responsible for the effects of SNS and PTNS is as yet uncertain, but both methods appear to induce modifications to neural circuits, from the excitability of the peripheral innervations to activity in the brain. Both SNS and PTNS have been shown to provide significant benefits where conservative therapies are not sufficient. Moreover, with these techniques, the improvement of a specific targeted function is often accompanied by additional improvement of similar functions (e.g., bladder and bowel control and penile erection), related functions (e.g., recovery of sensory capabilities), and, unexpectedly, the reduction of pain. These changes are likely to contribute indirectly but substantially to other more general aspects of quality of life (QOL) such as self-confidence, sexuality, willingness to participate socially, and many others.

Since it is now evident that people with SCI and other neurological disorders prioritize the functions that improve QOL somewhat differently from the priorities typically envisioned by rehabilitation researchers, it now appears more important than ever to take the target population's preferences into account when planning individual studies and in developing research programs that address rehabilitation of this population. QOL measures might, in fact, also represent a valuable additional metric for evaluating the efficacy of rehabilitation efforts. A standardized QOL questionnaire might be useful for comparing one therapy to another, and one study to another. To this purpose, it would be advantageous to design new QOL questionnaires sufficiently specific and informative, and incorporating functional-deficit questions, for assessing QOL in people with SCI.

Neuromodulation techniques for rehabilitation are still at the beginning of their development. The underlying mechanisms of their effectiveness are not yet completely understood. A deeper understanding of these mechanisms should help to disclose the full potential of neuromodulation techniques and extend the applicability of these techniques to a broader population with a wider array of disabilities.

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Chapter 5
Neural Interfaces as Tools for Studying Brain Plasticity

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Abstract The restoration and rehabilitation of human movement are of great interest to the field of neural interfaces, i.e. devices that utilize neural activity to control computers, limb prosthesis or powered exoskeletons. Since motor deficits are commonly associated with spinal cord injury, brain injury, limb loss, and neurodegenerative diseases, there is a need to investigate new potential therapies to restore or rehabilitate movement in such clinical populations. While the

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feasibility of neural interfaces for upper and lower limbs has been demonstrated in studies in human and nonhuman primates, their use in investigating brain plasticity and neural mechanisms as result of clinical intervention has not been investigated. In this chapter, we address this gap and present examples of how neural interfaces can be deployed to study changes in cortical dynamics during motor learning that can inform about neural mechanisms.

Keywords Brain–machine interfaces · Neural decoding · Cortical dynamics · Brain plasticity

5.1 Introduction

The goal of neurorehabilitation is to reduce impairments resulting from neurologic disease or injury to enable an individual to perform at his maximum capacity, thereby allowing greater participation in society. While this can be achieved through provision of mechanical assistance or actual physical help, neurorehabilitation seeks to promote functional restitution through sensorimotor adaptation and central nervous system plasticity (Macdonald et al. 2012). This process, which involves learning new skills after neurologic injury or disease, requires the presence of preserved, possibly re-organized, neural networks for movement, sensation, planning, cognition, language, and motivation that can be recruited for training.

A neurorehabilitation program typically consists of therapeutic exercises, such as strengthening and functional re-training, taught and facilitated by a therapist. Although many of these treatment interventions, including pharmacotherapy, have poorly defined physiologic bases, others, such as constraint-induced movement therapy, have well documented effects on cortical re-organization and plasticity (Taub et al. 2002). A recent trend in neurorehabilitation is the incorporation of technological advances as an adjunct to re-training, a substitute for function, or a means of shaping neural plasticity. Robotic-aided therapy, neuromodulation through central nervous stimulation, and neuroprostheses (Harvey 2009; Reinkensmeyer and Boninger 2012; Mehrholz and Pohl 2012; Hömberg 2013), are widely regarded as important aids in the rehabilitative process. Technology can also be used as a method to measure functional recovery and neuronal plastic changes (Rossini et al. 2007; Lo 2007; Sawaki et al. 2008; Zollo et al. 2011; Roy et al. 2011; Yozbatiran et al. 2012).

The restoration and rehabilitation of human movement are of great interest to the field of brain machine interfaces (BMIs), i.e. devices that utilize neural activity to control limb prosthesis or powered exoskeletons (Lebedev and Nicolelis 2006). Since movement deficits are commonly associated with spinal cord injury, brain injury, limb loss, and neurodegenerative diseases, there is a need to investigate new potential therapies to restore and rehabilitate motor control in such patients.

In this regard, the feasibility of brain-machine interfaces for upper and lower limbs has been demonstrated in studies in nonhuman primates (Fitzsimmons et al. 2009; Velliste et al. 2008) and humans (Hochberg et al. 2006; Bradberry et al. 2010, 2011; Presacco et al. 2011, 2012).

Remarkably, neural interfaces are also significant to the field of cortical neurophysiology and brain plasticity. Cortical control of neuroprosthetic systems and learning to use new tools are known to require adaptation in neural networks involved in motor planning and motor execution (Ganguly and Carmena 2009; Velliste et al. 2008). The long-term use of a BMI device has been shown to result in the formation of a stable, addressable and robust cortical map for 2D prosthetic control (Ganguly and Carmena 2009), and by examining the neural interface during learning of the neuroprosthetic, it is possible to gain understanding of the cortical representation for prosthetic control of movements at multiple scales depending on the source signal used for decoding (Ganguly and Carmena 2009; Bradberry et al. 2010, 2011; Presacco et al. 2011, 2012). Thus, neural interfaces allow for a time-resolved examination of changes in the cortical neurophysiology of movements during long-term training of the patient. Moreover, the neural interfaces may be able to demonstrate and quantify changes in the brain as it adapts to disease and responds to therapies.

The growing literature describes the potential role of BMI systems in demonstrating neuronal activity and, perhaps subsequently assisting re-learning (Birbaumer 2003; Hinterberger et al. 2005; Ifft et al. 2012; Yang et al. 2012). Training with BMI systems can result in plastic changes that recruit a relevant group of neurons spared by injury or disease (so-called “neuronal ensemble”) or elicit changes in neural activity that would have otherwise been impossible to perform in the absence of motor function or difficult to accomplish through traditional therapeutic exercises alone. Future BMI systems must consider the importance of incorporating response inhibition signals that reflect suppression of a planned movement and reprogramming the signals when a planned movement changes (Mirabella 2012). This, in turn, should result in a more specific motor output with enhanced volitional control of a limb or a prosthesis.

Since neural interfaces partly rely on the detection of brain signals, they offer a new window through which can be viewed cortical adaptation and the brain’s regulation of output in response to disease or treatment. As a person restores previous or learns new skills (desired outcome), modifies or develops compensatory movement patterns, neural interfaces have the potential to elucidate neuronal ensemble activation pattern changes that reflect a typical motor output. Through multiple observations of modifications in cortical signals and linking them to particular behaviours, the specificity and sensitivity of neural interfaces as a predictor of therapeutic effectiveness can be sharpened. At the very least, neural interfaces can describe physiological characteristics that are amenable to neurorehabilitation efforts. It is this promising application as an additional option to detect cortical activity and that goes beyond its probable therapeutic effects that makes neural interfaces an even more attractive neurorehabilitation tool, therefore, providing a ‘reverse translational’ benefit.

Too often, clinicians and researchers alike immediately seek to demonstrate the efficacy of an intervention even before achieving a clearer understanding of the underlying pathology of a targeted characteristic or behaviour. Perhaps this practice may explain why some investigations have failed to demonstrate robust treatment efficacy, or why there is a limited clinical applicability of interventions proven to be efficacious by therapeutic trials. Through a better appreciation of the fundamental pathology and a clearer understanding of neuronal responses to disease or therapy, the confidence of assigning a person to the appropriate neurorehabilitation intervention will be improved significantly. Having this predictive information a priori will allow clinicians to more accurately match a patient to particular treatment without delay. Thus not only will this paradigm help enhance the effectiveness of neurorehabilitation strategies, but also improve utilization of resources by avoiding unnecessary and ineffective therapies. In this respect, neural interfaces can have predictive power for therapeutic outcomes by accurately describing changes in neuronal ensemble activity shaped by injury or disease, and their treatment.

5.2 The Neural Interface Framework

A brain–machine interface (BMI), also known as brain–computer interface (BCI), or more generally, a neural interface, is device that translates neural activity into output control signals, that can be used to control an external device such as a computer; a prosthetic limb; or a powered exoskeleton. Generally, BMIs systems can be decomposed into five different stages: *Acquisition, Decoding, Stimulation, Application* and *Feedback (*Fig. 5.1*)*. The *acquisition* of neural activity is typically accomplished with electrode arrays inserted into the brain, that record localized single or multi-unit activity as well as local field potentials; subdural grids positioned on the surface of the cortical mantle that record the electrocorticograph (ECoG), which represents the activity of larger neuronal populations; or noninvasively via electroencephalography (EEG), which records brain waves from slow cortical potentials in the delta (0.1–4 Hz) to gamma (typically <100 Hz) range from the whole scalp.

The *decoding* stage can in turn, consist of signal conditioning, feature extraction and/or a decoding model. For example, in the case of scalp EEG, the signal conditioning may include channel deletion of bad or contaminated ‘artifactual’ channels, re-referencing, band-pass filtering, and/or spatial filtering (Bradberry et al. 2010). Feature extraction refers to the identification of the signals that encode the output, and thus maximize the decoding. For scalp EEG, these features are usually the amplitudes (or the spectral estimates) of particular evoked potentials (e.g., P300), particular rhythms (mu: 8–12 Hz), or time-shifted fluctuations of slow cortical potentials in the delta band (0.5–4 Hz) (Presacco et al. 2011). It is important that the selected features encode the relevant output accurately, and that

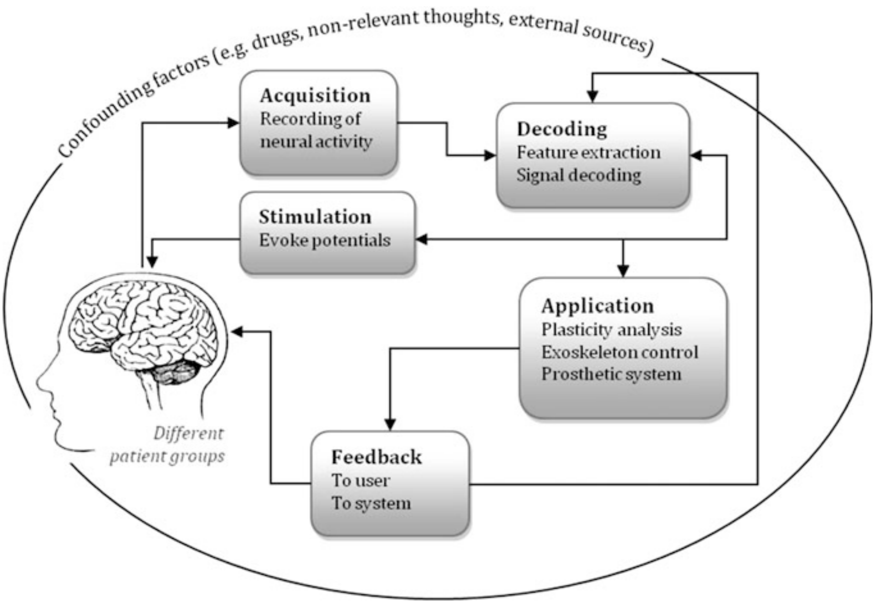

Fig. 5.1 Neural interface control scheme

the chosen feature representation space is 'intuitive' so that training time with the neural interface can be minimized (Bradberry et al. 2011). The *decoding model* refers to the mapping of these signal features into device commands using special translation algorithms. An effective translation algorithm ensures that the user's range of control of the chosen feature(s) will enable the selection of the full range of device commands and demonstrate long-term robustness or stability (Wolpaw et al. 2002). Decoding models are usually discrete or continuous time. Neural classifiers are normally used in discrete decoding model (e.g., to infer intended movement class 'left hand' vs. 'right hand'), whereas Wiener or Kalman filters are normally used for the decoding of continuous variables such as movement kinematics or surface electromyography (sEMG) patterns (Bradberry et al. 2010, 2011; Flint et al. 2012).

For example Fitzsimmons et al. (2009) recorded a total of 200–300 well-sorted single units from implants in two monkeys by a multichannel acquisition processor. Movements of the right legs of the monkeys were tracked using wireless, video-based tracking system. The limb tracking information was used to extract experimentally relevant parameters as X, Y and Z coordinates of the joint markers, joint angles, foot contact, walking speed, step frequency and step length. Then the extracted leg kinematic parameters were reconstructed from neural neuronal ensemble activity, using a linear decoding algorithm called Wiener filter. Prediction of leg kinematics was performed using multiple Wiener filters applied to the activity of the entire population of the recorded neurons or subpopulations.

Linear decoding produced accurate predictions of leg movements. The best-extracted parameters were X and Y coordinates of the ankle and knee angle. Prediction was worse with parameters, which scale was small as there was a little amount of hip movement. Presacco et al. (2011, 2012) decoded EEG signals and achieved comparable accuracies to these intracortical recordings. Naturally, there are also differences between the multiple-unit recording and the scalp EEG methods since the latter collects information about the 'neural symphony' from all over the cortex and for example the worst decoding accuracy was observed in the ankle (Presacco et al. 2012).

For a successful decoding, the use of essential strategies to extract the information that is needed. Of course, in the case of able-bodied subjects, neural activity is trained to map actual movement; however, in the case of users with limited, or lack of motor movement, the most common approach due to the nature of most patients (usually quadriplegics) has to do with movement imagery (kinesthetic) of different parts of the body or the desired movement. This strategy harness the organization of the primary sensorimotor cortices, which are organized in such a way that imagined movements cause specific spatial activation (patterns) distinguishable by classification algorithms (i.e., pattern recognition; principle component analysis) or continuous decoders, therefore can be used to control an external system. Another common approach is self-regulation of brain activity, where the user is trained by neurofeedback of, for example, mu rhythm amplitude or brain responses resulting from external stimuli (SSVEP, P300).

5.3 Reading and Writing the Brain

The inputs and outputs of the neural interfaces can be used to inform the scientist or clinical researcher about the specific brain areas that contain valuable and decodable information, or that are critical for decoding. To achieve this, it is imperative to estimate the relationship between decoding accuracy and the number and location brain sources (in sensor and/or source spaces) that maximize decoding accuracy. This can be accomplished using channel ranking or other criteria (Bradberry et al. 2009, 2010, 2011). Once the channel sensitivity (e.g., which sensors carry the highest amount of information about movement or motor intent) is known, this information can be used for 'writing' into the brain (block labelled *Stimulation* in Fig. 5.1) or reading signals from the brain to extract movement intent to control external devices (block labelled *Applications* in Fig. 5.1). For example, the channel sensitivity analysis could be used to guide stimulation of cortical brain areas using, for example, transcranial direct current stimulation (tDCS). Although this specific use of neural interfaces is relatively new, there are a few studies that have used tDCS to modulate event-related desynchronization during motor imagery in patient populations (Kasashima et al. 2012) to promote cortical plasticity (Wang et al. 2010).

5.4 Case Study: Studying Neuroplasticity Using the Neural Interface Approach

To illustrate the use of the neural interface approach to study neuroplasticity, we review the behavioural changes and cortical networks associated with learning to use a new tool. This example uses non-invasive magnetoencephalography (MEG) to record and extract slow neuromagnetic cortical potentials associated with center-out hand movements under normal and perturbed conditions in healthy subjects (Bradberry et al. 2009). In this study subjects lied supine inside the MEG (Fig. 5.2).

Subjects were exposed to normal and perturbed screen cursor-hand relationships (a 60° cursor rotation) to induce visuomotor adaptation, which was analysed in four stages (pre, early, late and post-exposure). As expected, users were able to learn the visuomotor adaptation with enough practice (Fig. 5.3). Behavioural indexes of adaptation such as the initial directional error (IDE, in degrees) between the desired and the actual hand trajectories showed that subjects were able to learn the internal model of the screen cursor rotation during the adaptation period. Interestingly, after-effects were observed during the post-exposure phase as the subjects performed movements in the undistorted environment using the newly acquired internal model.

Then, Bradberry et al. used slow neuromagnetic signals ($N = 61$) in the delta, theta and alpha range (up to 15 Hz) to decode hand movement speeds using a Wiener filter with memory (See Bradberry et al. 2009 for details of the protocol and decoding analyses). The main finding was that MEG signals contained decodable information about hand movement velocities at each stage of adaptation. Importantly, the decoding framework allowed the analysis of the common and unique neural sensorimotor networks (in sensor and source spaces) that were deployed for task planning, execution and adaptation learning (Figs. 5.4, 5.5 and 5.6).

Fig. 5.2 Center-out hand movement adaptation set-up. In the *left* and *middle panels*, a subject is shown lying with his head inside the MEG recording dewar holding an optic pen on a sheet of glass. Note that vision of the hand and upper limbs is occluded with a *black cloth*. The *right panel* depicts the subject's view of the computer screen where visual feedback of the pen position (*cursor*), center location (*home*), and peripheral target (*target*) was displayed in real time. From Bradberry et al. (2009), with permission

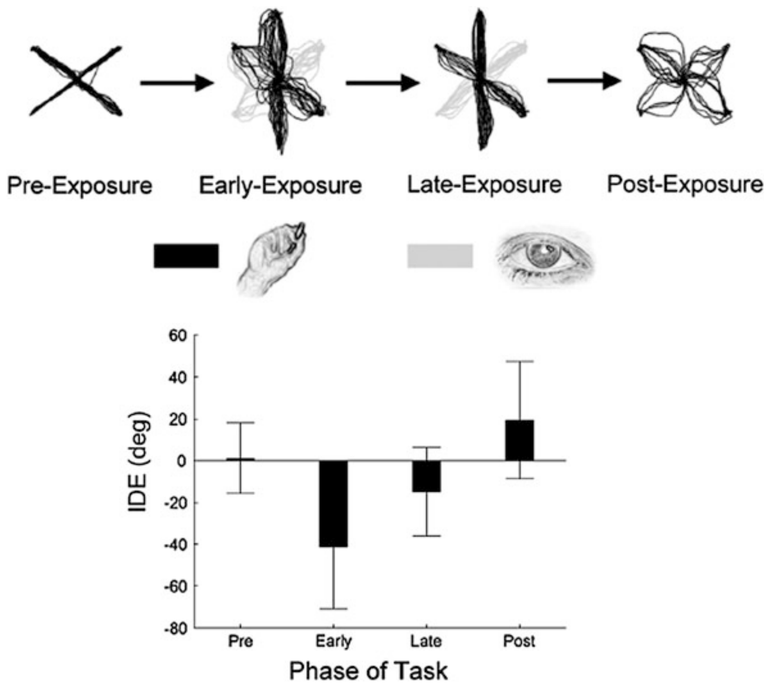

Fig. 5.3 Subjects adapted to the screen cursor-hand rotation (60°) from early to late exposure. The *top panel* depicts the changes in kinematics as subjects learned the novel visuomotor transformation. The *bottom panel* shows the initial directional error (IDE, in degrees), which during early visuomotor adaptation resulted in a large IDE error, which was reduced significantly by late adaptation. Removal of the screen cursor rotation during post-exposure resulted in the so-called after-effects (distorted kinematic trajectories) due to visuomotor incongruence. From Bradberry et al. (2009), with permission

Analysis of the sensorimotor network engaged for hand movement showed a bilateral network with a strong contralateral component that peaked about 100 ms prior to a change in movement kinematics. The brain signal information extracted at time lag (t = −100 ms) accounted for about 12.8 % of the decodable information from MEG signals. Other lags showed a Gaussian distribution along the lag times (only lags from −30 to −130 ms are shown in Fig. 5.5). This analysis showed that kinematic information is represented in cortical network distributed along central and posterior brain areas and along the recent past.

Figure 5.6 depicts the cortical sources engaged at different stages of adaptation in Talairach space. The estimated cortical sources included contralateral motor cortex due to the right hand dominance of the subjects. Overall, precentral and postcentral gyrus, the precuneous, the inferior and superior parietal areas, the medial frontal gyrus, supplementary motor area, and the superior frontal gyrus were recruited during the task.

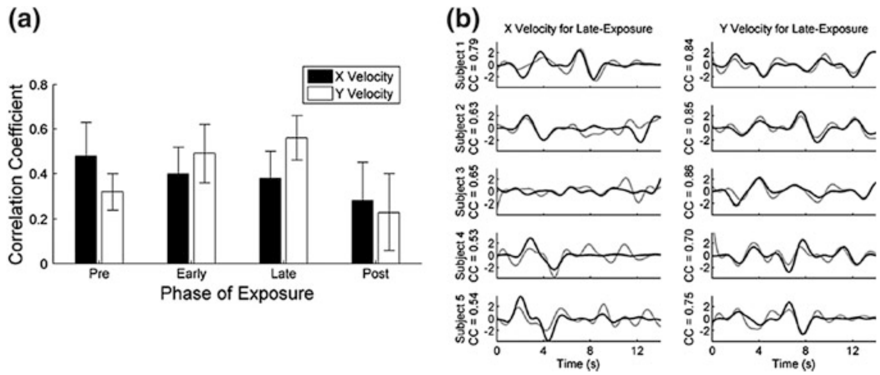

Fig. 5.4 Hand kinematics can be decoded from a multitude of MEG signals using a Wiener Filter. **a** Pearson's correlation coefficient between MEG-inferred X and Y hand velocities and the actual measured velocities as a function of stage of visuomotor adaptation. **b** Examples of reconstructed hand velocity kinematics. From Bradberry et al. (2009), with permission

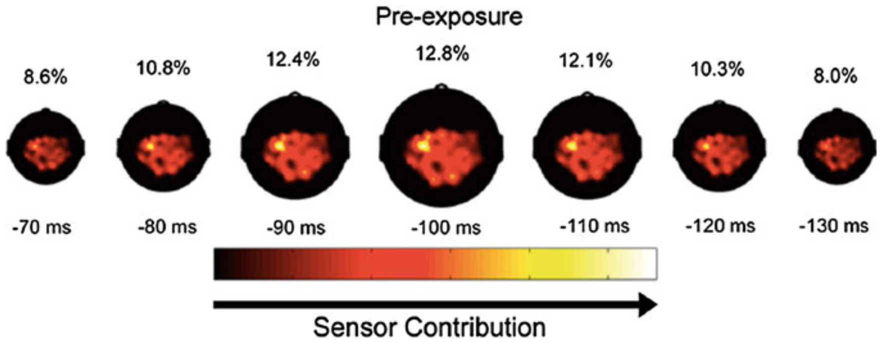

Fig. 5.5 Sensorimotor networks associated with hand velocity during pre-exposure. From Bradberry et al. (2009)

The cortical networks are of course estimated from the brain of healthy subjects, but they provide normative data for subjects with neurological insult (e.g., stroke) or disease (e.g., Parkinson's disease) that can be harnessed to learn about normal and abnormal patterns, and changes in cortical networks as a function of disease progression or intervention. For example, the importance of various brain areas could be assessed through the decoder's inputs and its accuracy to characterize the impact of a neurological insult (stroke or Parkinson's disease) on movement learning, planning or execution. Unfortunately, this type of information is rarely acquired in clinical interventions that address the lower-limbs such as gait rehabilitation. Thus, it is proposed that neural interfaces can provide a window to study neuroplasticity of affected networks due to disease progression and/or intervention.

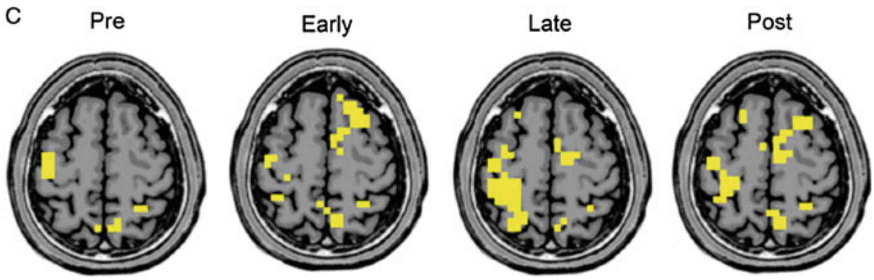

Fig. 5.6 Estimated cortical sources involved in hand velocity encoding during visuomotor adaptation learning as a function of adaptation stage. Sources are represented on an axial slice from an MRI template (z = 55). The sources and their Talairach coordinates (x, y, z) were the PrG (−41, −11, 55), PoG (−45, −17, 55), SPL (30, −46, 55), PCu (3, −61, 55), IPL (−41, −41, 55), SMA (5, −2, 55), MFG (19, 18, 55 and −24, 20, 55), and SFG (19, 12, 55). From Bradberry et al. (2009), with permission

5.5 Conclusions and Future Challenges

The goal of neurorehabilitation is to reduce impairments and enable an individual to perform at his maximum capacity, allowing greater participation in society. Learning new skills after neurologic injury, disease or physical disability involves recruitment of preserved neural networks for movement, sensation, planning, cognition, language, and motivation, and is carried out through various interventions including medications and therapies. Fortunately, new basic and clinical research in neurorehabilitation is successfully marrying traditional therapy techniques with neurotechnology such as neural interfaces.

Importantly, technology in rehabilitation is used not only for re-training, facilitation of recovery, or substitution of function, but also used to measure and quantify functional recovery and central nervous system plasticity, which is critical to document the outcome or treatment efficacy; better understand pathomechanisms of disease and mechanisms of action of clinical interventions; predict outcomes (what type of pathology will respond to neural interface); and even justify reimbursement when applied to healthcare (e.g., in the USA, payment for services eventually will be linked to demonstration of good outcome).

In addition, the deployment of neural interfaces to restore motor function is likely to result in changes of the neuronal electrical activity, leading to induction of plastic changes that in turn will enhance recovery or allow for functional restitution, which are the goals of neurorehabilitation. Furthermore, the use of BMI systems can potentially result in training-induced plastic changes, which in turn may lead to enhanced volitional control of a machine or prosthesis. Advantages of BMI systems include their interactive mode, which engages the patient consistently during acquisition of skill, through therapies, to manipulate spare neuronal electrical activity.

BMI technology may also help recruiting of neural ensembles spared by injury or disease that would have otherwise been difficult through traditional therapeutic exercises alone, while providing information about cortical adaptation, both desired and unwanted, as a person restores previous or learns new skills, or develop compensatory movement patterns, which are not always wanted. Overall, neural interfaces can uncover information about how effective a particular therapy or intervention is in terms of inducing plastic changes.

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Chapter 6
Neuromodulation on Cerebral Activities

Sylvain Cremoux, Jaime Ibanez Pereda, Serdar Ates and Alessia Dessì

Abstract During a motor task, a causal relation occurs between the motor command generated in the cortex and the proprioceptive feedbacks that go from the activated muscles through the corticospinal pathway. This causal relation is of interest in neurorehabilitation to improve motor function for people with motor difficulties. Previous neurorehabilitation methods used external stimulation to modify the corticospinal pathway controlling the motor function of the affected body parts. An alternative to these approaches is to reinforce the corticospinal pathway by identifying the cortical motor command naturally generated when a person imagines or attempts a movement, and combine it with peripheral nerve stimulation. The research group of Professor D. Farina has developed a method exploiting Brain–computer Interface technology to detect the cortical motor command and use it to trigger peripheral nerve stimulation in order to reinforce the efficiency of the corticospinal pathway. A detailed description of the method and an interview with Prof. D. Farina is presented in this chapter.

Keywords Corticospinal pathway · Peripheral nerve stimulation · Movement imagination · Motor related cortical potentials

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6.1 Introduction

Neural plasticity is an active topic of research in the field of neurosciences referring to the changes in the neural structures due to modifications in the environment, behavior or body injuries. Gaining knowledge about the mechanisms underlying neural plasticity is of great relevance for neurorehabilitation purposes, i.e. rehabilitation of certain functional abilities that have been lost due to neural damages.

One of the phenomena underlying neural plasticity is the associative long-term potentiation (LTP), which is based on the Hebbian learning theory (Hebb 1949). Associative LTP suggests that the concomitant activation of two connected neurons leads to the reinforcement of the synaptic efficiency of the neural pathway linking them. As part of a rehabilitation procedure, associative LTP can be of interest to restore the functional control of body limbs affected by neural injuries by controlling the activation of two selected neural sources. Based on this concept, several neuromodulation protocols have been proposed using external stimulation in patients with motor disabilities (for a review, see Boroojerdi et al. 2001). On one hand, studies have shown that it is possible to induce brain plasticity by using transcranial magnetic stimulation (TMS). On the other hand, functional and structural changes were also elicited after stimulation of the peripheral nerve of a targeted muscle. Finally, a method called Paired-Associative Stimulation (PAS) combined central and peripheral stimulation to induce LTP. All of these studies have revealed that it is possible to selectively modify the neural structure, and that a temporal association between the brain and muscle activity has to be respected in order to strengthen the corticospinal pathways.

Recently, the research group of Professor D. Farina has proposed an alternative to these neuromodulation protocols using Brain–Computer Interfaces (BCI). The technique relies on the detection of a specific cortical pattern to trigger an external stimulation of the peripheral nerve of a targeted muscle. Their studies revealed that muscle-specific neural adaptations can be achieved and that it is possible to induce cortical plasticity using an asynchronous BCI system. This technique is extensively described in the main body of the present chapter. Additionally, an interview with Prof D. Farina is included at the final part of the chapter, where further information regarding the studies described and future challenges are commented.

6.2 Background

The technique proposed by the research group of Professor D. Farina relies on two distinct fields of research: Neuromodulation protocols and BCI systems. Both fields are presented in order to give the reader a clear perspective of the background underlying the experiments proposed.

6.2.1 Neuromodulation Protocols

Previous studies have shown the possibility of inducing neuroplasticity in the nervous system using different kind of stimulation on the peripheral targeted nerve and/or over the targeted sensorimotor cortical regions. Protocols applying TMS alone have proven to be useful to modify deliberately the neuronal excitability, synaptic plasticity or behavioral function outlasting the stimulation period. In this case, several configurations of the stimulation pulses lead to different motor cortex plasticity protocols, such as repetitive TMS, transcranial Direct Current Stimulation, or Theta Burst Stimulation (for a review, see Ziemann et al. 2008). On the other hand, protocols applying only peripheral nerve stimulation (Ridding et al. 2000, 2001) have revealed changes in the excitability of the primary motor cortex in normal human subjects. In this case, a period of at least 1.5 hours of peripheral nerve stimulation is necessary to produce significant changes of the cortical excitability. Stefan et al. (2000) proposed to use together cortical and peripheral nerve stimulation. In their study low-frequency peripheral nerve stimulation is paired with TMS over the contralateral motor cortex inducing plasticity in the motor cortex. Their results highlighted the importance of the time interval left between the peripheral and the cortical stimulations (Kumpulainen et al. 2012). More recently, Thabit et al. (2010) developed a movement-related cortical stimulation protocol in which the motor cortex is stimulated with TMS at specific times with respect to the mean expected reaction time of voluntary movement performed by the subjects measured. Their results revealed that the timing of the stimulation with respect to the reaction time expected of the voluntary movement plays a critical role on the consequences over the motor cortex. This was one of the first studies in which artificial stimulation, applied by TMS, is paired with endogenous cortical activity, i.e. cortical activity when a subject performs a movement, supporting the possibility of its use for rehabilitation of neurological disabilities.

6.2.2 BCI Systems

During the last decade, BCI systems have been proposed to help patients with neurological disabilities communicate with the environment and to move with the help of assistive technologies like wheelchairs or neuroprosthetic devices. Recently, a greater attention has been given to the development of BCI systems on electroencephalographic signals (EEG) for neurorehabilitation purposes (Daly and Wolpaw 2008). On one hand, protocols proposed neurofeedback training, that is, the visualization of the cortical activity along the expected cortical activity during specific task in order to recover a "normal" cortical activity leading to functional recovery (Buch et al. 2008). On the other hand, protocols aim at using the BCI-based control of an external assistive device to generate a proprioceptive feedback. The afferent information generated by these feedbacks is expected to induce corticospinal plasticity leading to functional recovery. In this case, the use of the EEG signal is of interest due to its intrinsic capacity to characterize subject's intentions to move.

6.3 Using EEG/BCI to Induce Brain Plasticity

The previous section showed that, on one hand, the combination of endogenous cortical activity and external stimulation can induce cortical plasticity and, on the other hand, the intention to move can be detected by EEG-based BCI systems. By combining these two approaches, the research group of Professor D. Farina proposed an alternative technique to induce neuromodulation. This technique combines a novel EEG-based BCI approach for the detection of the intention to move with peripheral electrical stimulation in order to induce corticospinal plasticity. For this purpose, three goals are addressed: (1) detect and identify the cortical potentials related to the motor task; (2) accurately define the timing to send the peripheral stimulation; (3) development of a self-paced BCI system detecting online the optimal instant at which peripheral stimulation has to be generated to increase the excitability of the corticospinal pathway.

The level of activity of the motor cortex prior to and during the execution or the imagination of a voluntary motor task can be characterized by the movement-related cortical potentials (MRCP), which refers to the changes of the direct current amplitude of the EEG signal before and during a motor task. The MRCP for voluntary motor tasks consists of an initial negative potential, that is, a slow decrease of the EEG amplitude occurring before the onset of the movement, and followed by a positive potential (Fig. 6.1). This negative potential can be separated into a readiness potential (RP), that is, a first slow decrease occurring 2 s before the movement onset and a steeper decay 0.4 ms before the movement onset. In addition, the RP presents a stable time pattern synchronized with the onset of voluntary movements, which makes the RP perfectly suited to detect a movement intention before it starts (for details see Sect. 6.4 Q2).

In order to maximize the plasticity-induced of the corticospinal pathway, the time at which the stimulation is delivered is crucial (Kumpulainen et al. 2012). The research group of Professor D. Farina proposed to use the MRCP to decide the best timing to send the peripheral stimulation (Mrachacz-Kersting et al. 2012). In this experiment, three groups had to perform imaginary movements as described in Fig. 6.2. During the imaginary movement, single peripheral nerve stimulation was applied at three different latencies according to the movement detection: (1) before the movement execution phase (RP), (2) at the peak negativity of the RP and (3) during the holding phase. Changes in the excitability of the corticospinal pathways were assessed by TMS before and after the experimental procedure. Results revealed that the corticospinal excitability significantly increased when the peripheral stimulation was applied during the peak negativity of the RP only. These results demonstrated that the peripheral stimulation combined with

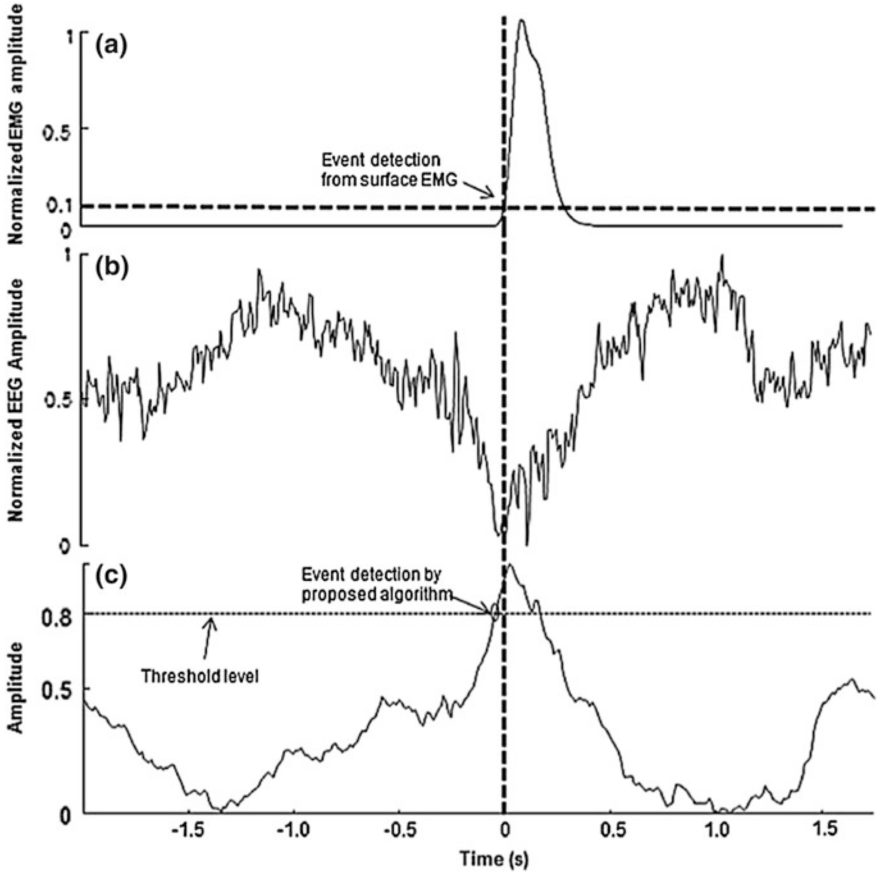

Fig. 6.1 General scheme of detection during movement execution task. Representative sample from one subject: detection of an initial negative phase of MRCPs in an EEG channel obtained through the set threshold. **a** Rectified and averaged EMG trace for event detection, the *horizontal dashed line* is the EMG detection threshold and the *vertical line* is the reference point for detection latency. **b** Single trace of MRCP in the EEG channel, obtained by the optimized spatial filter during self-paced motor execution task. **c** Output of the matched filter. The *horizontal dashed line* is the detection threshold of the proposed algorithm. All *vertical axes* are in arbitrary units. Original figure is presented in Niazi et al. (2011)

movement imagination could strengthen the corticospinal pathway only when the peripheral stimulation is applied during the negative peak of the movement potential (for details see Sect. 6.4 Q1).

In order to get a self-sufficient system to induce neuroplasticity, the research group of Professor D. Farina (Niazi et al. 2012) proposed to combine peripheral stimulation (Mrachacz-Kersting et al. 2012) with a BCI system that detects online the movement onset in an asynchronous way (Niazi et al. 2011), i.e., when the subjects perform movement executions/imageries at their own pace. Several

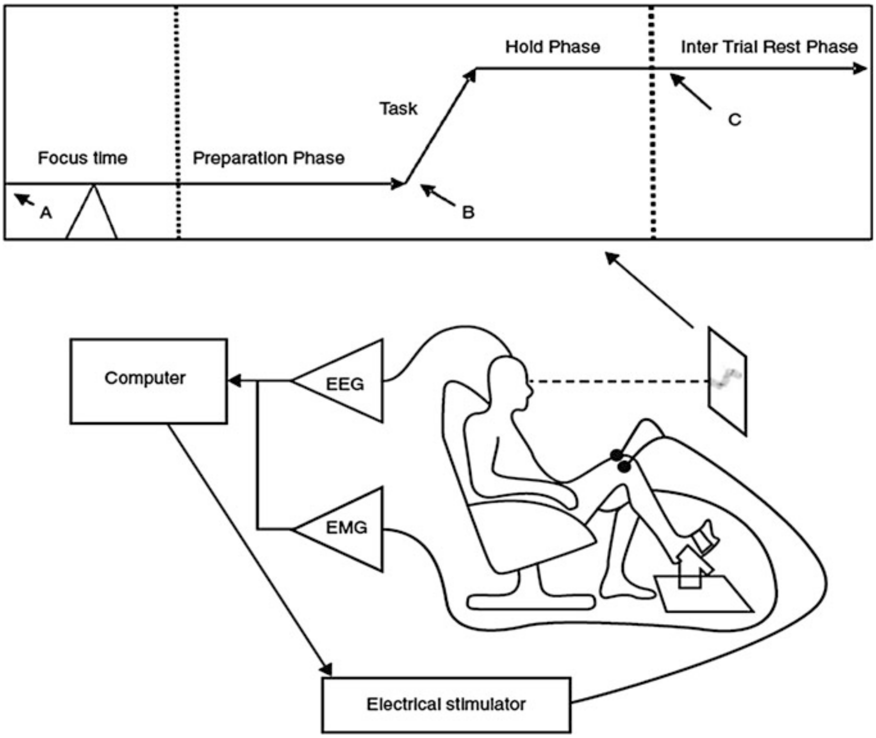

Fig. 6.2 The visual cue—the interface instructing the subjects to perform the imaginary movements: A *moving cursor* starts from point A at the beginning of each trial. In the focus time subjects concentrate on the screen, in the preparation phase subjects mentally prepare for performing the imaginary dorsiflexion, while the movement should be executed at the time instant when the cursor hits point B. The imaginary contraction is held throughout the hold phase and released after point C. Original figure is presented in Mrachacz-Kersting et al. (2012)

techniques were compared to correctly detect the RP during self-paced movement executions and imaginations in healthy and stroke patients (Niazi et al. 2011). Results demonstrated that an optimized spatial filtering technique and matched filters allow the detection of the movement intention based on the RP detection with a good performance.

An experimental procedure to test the reliability of this neuromodulation paradigm based on a BCI system was realized over 16 healthy participants. The accuracy of the BCI system was evaluated by comparing the true positives versus false positives rate, i.e., the actual detection of movement intention versus false detection. Changes of the excitability of the corticospinal pathway were assessed using TMS before and after the experimental procedure (Mrachacz-Kersting et al. 2012). Results revealed that the BCI algorithm was sufficiently accurate in the detection of the movement intention to increase the corticospinal excitability

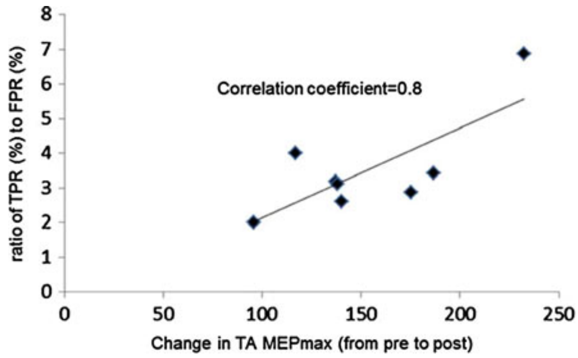

Fig. 6.3 Correlation graph. Correlation between change in the maximal motor evoked potentials (MEP) of the tibialis anterior (TA) from pre- to postmeasure of TMS and ratio (%) of True Positive Rate (TPR) to False Positive Rate (FPR). The change in MEP (*horizontal axis*) refers to the change in the corticospinal excitability while the ratio of TPR to FPR (*vertical axis*) refers to the ability of the BCI system to detect movement intention. Original figure is presented in Niazi et al. (2012)

(Fig. 6.3). This type of technique may be used in rehabilitation procedures in order to increase motor skills.

However, even though this technique showed its efficiency to increase the excitability of the corticospinal pathway, no study has yet revealed that this increase is correlated with an increase of the functional abilities (for details see Sect. 6.4 Q3 and Q4). Future studies should assess the links between the corticospinal excitability and functional abilities in order to confirm the usefulness of this, or any other, technique as neurorehabilitation protocols.

6.4 Interview Part 1: Methodological Aspects and Procedure

Q1: *The timing for triggering the stimulation is important. Could it be better optimized?*
Dario Farina (D.F.): We put a lot of emphasis on the latency of the external stimulus with respect to the cortical activity measured with EEG because we have shown that if the stimulation is later or earlier than 500 ms nothing seems to happen in the cortical structures. However when we stimulated at the peak negativity, we had a variance of possible detection of that peak negativity which was in the order of 100 ms. So I would not say that further improving the latency is a critical aspect in this technological development.
Q2: *Why did you choose the MRCP rather than other EEG-measurable cortical patterns like for example the Event Related Desynchronization?*
D.F.: If we are looking at the whole cortical potential, MRCPs are the only neurophysiological processes that allow prediction of the movement.

Sensory-motor rhythms allow a good detection of the movement with much later latency. In the previous question we said that the latency may not be important but in this case we are talking about latencies bigger than hundreds of milliseconds. We would lose too much time by using the sensory-motor rhythm. On the other hand, the MRCPs have a bandwidth from Direct Current to 1 Hz, so it is an extremely small amount of information that we are extracting from the EEG signal. There is no doubt that if we used an entire bandwidth, which means information from the sensorimotor rhythms, we would detect the desired events with much better accuracy. This could be useful for an asynchronous BCI but it would not be useful for our application because you would lose too much time, making this technique completely useless in order to induce neural plasticity.

Q3: *Movement normally includes more than one muscle. How is this taken into account in your experiments if stimulations are only delivered to one muscle?*

D.F.: It would be interesting to investigate if the intervention is more effective the more you approach functional tasks. Our single electrical stimulus is very far from the functional task, the foot doesn't even move. We literally just have an afferent volley, artificially produced by the electrical stimulation. If we can reproduce the entire movement, that would be much closer to what our brain areas would normally receive when they execute the functional gait movement.

Q4: *How do you think the changes regarding cortical excitability will improve functional ability to perform daily living activities?*

D.F.: That's the one-million-dollar question. In healthy subjects, it is not even clear how the corticospinal excitability changes are related to functional performance of the task. The corticospinal excitability should be related to the excitability of the corticospinal pathway, which is certainly responsible for the neural coding of the movement. The expectation is, if that changes, maybe a movement will be executed with a better strategy in terms of lower motor neurons recruitment. Of course, all of this has to be proved. On a very global level, a new study with stroke patients has shown that there are some functional improvements in some clinical scales that come in parallel with the increase of the enhancement of the cortical excitability. For example, the group of stroke patients that tried the intervention was able to walk the 10 m path faster, on average, than the control group. Now, how these improvements are correlated between each other and what are the neurophysiological mechanisms that make such improvements are completely open questions.

6.5 Interview Part 2: Applications and Future Challenges

Q5: *What is the main contribution of these studies?*

D.F.: These studies belong to the large category of neurofeedback and neuromodulation, in which you record a neural signal and you provide a feedback associated to this signal. The feedback is an afferent electrical stimulation but the specificity of this feedback is not too relevant, it could also be the movement of a robotic hand, a vibration, etc. The idea is to relate a motor imagination with an afferent stimulation precisely delayed with respect to the mental task. By doing that the corticospinal pathway will be strengthened. The main novelty of these studies is putting together a completely self-paced system for which a computer algorithm interprets the cortical activity and send a peripheral stimulation with a very precise delay. This has been demonstrated to increase the corticospinal excitability in healthy subjects and in stroke patients. It is a new approach for neuromodulation based on EEG recordings and also one of the few applications of BCI for neuromodulation.

Q6: *Which impairments would benefit from these techniques?*

D.F.: Naturally we thought that the obvious targets would be brain-damaged patients because the technique is devoted to increase the excitability of the brain areas. I could think of several other possible applications, for example, neurological tremor is another pathology in which you may want to provide enough afferent stimulation to desynchronise pathological cortical oscillations with respect to afferent input. I could see similar techniques applied for tremor suppression, which has also a cortical origin. Therefore pathologies that are related to cortical impairment or brain damage should benefit from this technique.

Q7: *What results do you expect to obtain when applying this technique on stroke patients?*

D.F.: There are always more difficulties in applying this, or any other, technique in patients. The signals that you are recording may be different and may not even be present. These differences are interesting because they could be used as biomarkers of the excitability without using TMS. One could follow the cortical recovery by only looking at the characteristics of the MRCP in comparison to healthy individuals but it has not yet been tested. However, I don't exclude that there would be a number of patients with whom we could not use this technique. On the other hand, the technique could be also extended in various ways. We were trying to enhance the normal physiological pathway but, in the same way, you can enhance alternative pathways. For example, you can make a connection by recording the cortical activity and stimulating the ipsilateral side, trying to strengthen a pathway as an adaptation strategy. Of course, this is just a speculative kind of statement. What I am saying is that, there is so much to do, especially from the clinical side, and it is impossible to predict how much these techniques can impact the rehabilitation in the long term. Certainly there will be a long time period before these kinds of technology will be used as clinical applications. I think that it is reasonable to expect that this strategy should be helpful in the rehabilitation process. The important thing is what these results may trigger. Here (Summer School on Neurorehabiliation, ed.), we were discussing about translating these results to robotics, exoskeletons or orthosis which seems to me much more reasonable from the functional point of view. One thing is to give an electric tap to the nerve, which is very unnatural; another thing is to move the foot passively or partly passively exactly as it would be executed with that motor command. My expectation is certainly not that the techniques should be taken as they are, immediately employed by a number of hospitals, which decide that these results are extremely interesting, and they want to try them [smile]. This is only a proof-of-concept. There are still many steps to do but I am convinced that the way, at least, is correct.

Q8: *Are there any drawbacks to use this technique in a clinical setting?*

D.F.: I cannot see big drawbacks, not even in the practical implementation. Many drawbacks in neuro-rehabilitation techniques are the practical implementation on a daily basis because it had to be robust and so on while this kind of approaches wants only to retrain. This is not something that one has to aim to give at the hospital or at home to the patient. It can be just a rehabilitation strategy on top of many others—maybe not implemented with the strategy described here but implemented with the same kind of concept. So, something hospital-based is a good perspective.

Q9: *Would the experimental protocols used be suitable in a clinical environment?*

D.F.: Everything we are including in our experiments is already available in most hospitals. EEG and peripheral stimulation are done continuously. The rest is a computer analysis and the requirements are minimal because the processing is not very complex. For this kind of intervention, there are no elements that are completely stranger to the clinics. Mounting the EEG always takes a bit of time because you have to check signals quality, etc. If you want something faster, the EEG part could be improved, for example, with the inclusion of active electrodes, with systems that imply a minimal time in the mounting and in checking the signal quality. My main message is that everything used in our experiments is not different from what is done in a clinical environment. On the other hand, there is an open question on the clinical applicability in terms of how much our proposed system will be accepted by the patients, how easy will it be to explain to them what to do, how much time the clinicians will need to mount the electrodes etc. This is a whole thing that one can discuss with the clinician.

Q10: *At which stage of the rehabilitation would this intervention be applied?*

D.F.: Naturally it would be more effective the closer the interventions are performed with respect to the stroke event. After a certain limit though, because you have to recover from the brain damage and the subject, in the very first period, is usually not available for rehabilitation or for training. I would say that the intervention we are proposing should be applied to stroke patients as soon as the standard physiotherapy starts. When the medical staff says that the patient can go under a rehabilitation treatment, this kind of intervention could be easily added. The patients that we have analyzed started the interventions for our clinical study after they had already started a number of interventions but that was a clinical study and we needed to recruit stroke patients in collaboration with a hospital, taking into account their conditions.

Q11: *How is this intervention going to be applied to a certain kind of stroke patient that presents a lesion over a certain hemisphere and region? How can it be asserted that the reinforced corticospinal pathways are the optimal ones?*

D.F.: It's reasonable to think that if you try to reinforce the physiological pathway that was working in that way before the damage you cannot induce any additional damage. I mean that the subject can also employ additional strategies but still he has a pathway reinforced which is responsible for a movement that is physiologically optimal, because it corresponds to the healthy conditions. The adaptation strategies in stroke are so heterogeneous that it is difficult to say what is best in a general sense. Probably the best would be to analyze the patients individually in collaboration with the medical staff. Sometimes the best intervention may even be to learn a completely different neural strategy, which is functionally not very different from the healthy condition. However, it's not excluded that you can use this kind of technique to do that.

6.6 Conclusions and Future Challenges

During the last decade a number of therapies based on stimulation of the central and peripheral nervous system have been proposed to induce changes in the corticospinal pathways by increasing the cortical excitability in specific regions. A novel intervention developed by the research group of Prof. D. Farina, exploited EEG-based BCI technology to detect the cortical motor command generated when a person imagines or attempts a movement and combined it with electrical stimulation of the targeted muscle. This intervention obtained positive results with both control and stroke patients and demonstrated its efficiency to increase the excitability of the corticospinal pathway. In the case of stroke patients, unpublished results from the research group of Prof. D. Farina suggested that this intervention improved functional abilities in clinical tests, for example the time spent in a 10 m walk.

As Prof. Farina pointed out in the interview, this intervention is a "proof-of-concept". Future developments in this framework will be oriented in proving the system's performance under clinical conditions, taking into account different muscles, limbs and/or more functional tasks, and testing alternative ways to deliver proprioceptive feedback. In conclusion, "there are still many steps to do but the way, at least, is correct".

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Chapter 7
Challenges in Measurement of Spasticity in Neurological Disorders

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Abstract Current challenges in the upper motor neuron syndrome (UMNS) management include identifying and establishing correct strategies to evaluate spasticity in clinical and research settings. There are a number of measures frequently used in a clinical environment. They are mainly qualitative tools that range from questionnaires to scales that are practical but imprecise. Alternative, quantitative measures that provide an accurate evaluation of spasticity are currently available for use, however they require specialist training and equipment. The advantage of quantitative assessments is that they can also differentiate between different components of spasticity and their contribution in the symptomatology. However, the use of these precise tools requires a longer time than is usually available in clinical practice. This chapter presents an overview of the different methods that exist to evaluate spasticity and proposes different management strategies. There is still a need to converge the efforts of researchers in different

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fields to develop accurate practical tools and algorithms that allow for precise evaluations in clinical practice.

Keywords Spasticity · Upper motor neuron syndrome · Evaluation · Quantitative measurement

7.1 Introduction

Spasticity is one component of the upper motor neuron syndrome (UMNS), a central nervous system disorder usually caused by damage to nerve pathways within the brain or spinal cord. Clinically, spasticity is defined as "a velocity-dependent increase in the tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from the hyperexcitability of the stretch reflex". This definition was provided by Lance three decades ago (Lance 1980), and is still the most widely used. Spasticity may occur in association with conditions where the brain and/or spinal cord are damaged, such as in spinal cord injury, multiple sclerosis, stroke, traumatic brain injury, amyotrophic lateral sclerosis, or they fail to develop normally such as in cerebral palsy, hereditary spastic paraplegias, and metabolic diseases such as adrenoleukodystrophy, phenylketonuria, and Krabbe disease. Spasticity affects around 85 % of subjects with multiple sclerosis (Sommerfeld et al. 2004), 35 % of chronic hemiplegic stroke subjects (Sommerfeld et al. 2004) and between 65 and 78 % of subjects with spinal cord injury (Maynard et al. 1990).

Spasticity is a major problem that adversely impacts the quality of life of affected subjects, producing stiffness and ultimately may lead to muscle shortening (contractures) and musculoskeletal deformities. These changes interfere with voluntary movements and daily functions like ambulation, hand dexterity, balance, speech and swallowing amongst others. This increase in muscle tone or stiffness might also cause discomfort and pain, interfering with rehabilitation in patients with certain disorders. Symptoms may include hypertonicity (increased muscle tone), clonus (a series of oscillating muscle contractions), exaggerated deep tendon reflexes, muscle spasms, and scissoring (involuntary crossing of the legs).

There are several therapies to treat spasticity, including physical therapy, occupational therapy, pharmacological treatments and surgery. Despite the great variety of treatments, their effectiveness is still limited. Clinical methods to assess efficacy are very practical, but imprecise, in the measurement of spasticity or evaluation of therapy outcomes. Experimental methods are, on the other hand, very accurate but highly complex, often requiring very long preparation sessions with many complex and expensive experimental devices. In order to enhance the rehabilitation of patients suffering from spasticity, treatments should give measurable improvements. Therapy outcomes need to be accurately evaluated without requiring complex experimental procedures or equipment.

This chapter aims to introduce the reader to the challenges that are present in measurements of spasticity. In an attempt to illustrate the concepts in an easy to follow manner, the chapter has been organized as follows: first, we introduce the reader to the clinical aspects of spasticity, covering basic concepts of the neurophysiology of the disease and giving a more extended description of the problems of spasticity measurements. Next, we present a review of current methods for measurement of spasticity and therapy outcomes, as well as the characteristics of spasticity. Finally, we present the conclusions of this work.

7.2 Background

Spasticity is a common feature of muscle impairment in the UMNS. Although Lance's definition of spasticity (given in the introduction) is the most widely accepted, it still makes it difficult for clinicians to understand the pathophysiology of this disease, and to quantify its severity. Confusion in the use of terminology complicates assessment and treatment planning by health professionals, and it results because clinicians often confuse the other signs of the UMNS and describe them indistinctly as spasticity (Ivanhoe and Reistetter 2004). The resistance of spastic muscle to stretch is dynamic and increases with the amount of stretch, and especially, with the velocity of the stretch.

7.2.1 Neurophysiology

The neurophysiological bases of spasticity have been widely discussed. Several theories ascribe the problem to an "abnormal process" of the signals arriving from the Central Nervous System (CNS) (Biering-Sorensen et al. 2006; Fleuren et al. 2010; Gómez-Soriano and Taylor 2010). Although the basic underlying mechanism of these abnormal processes is not clear, is likely that the major contribution is disruption in balance between the inhibitor and excitatory control signals coming from the CNS to modulate motoneuron excitability.

The basic neural circuit underlying spasticity is the stretch reflex arc, composed of the muscle spindle receptors, their afferent projections to spinal motoneurons, the spinal motoneurons themselves, the motor axons, and the muscle fibers they innervate. This reflex is important in coordinating normal movements in which muscles are contracted and relaxed. Stretch receptors in the muscles (muscle spindles) sense the amount of stretch in the muscle and send a signal to the spinal cord, via the sensory afferent pathways. The brain responds by sending a message back to contract or shorten the muscle. A loss of inhibitory control releases the hyperexcitability of the stretch reflex, and is generally thought to be the primary cause of spasticity.

The main components of spasticity are muscle stiffness (intrinsic biomechanical properties of the muscle) and hyperexcitability of the stretch reflex (Gottlieb et al. 1978; Rack et al. 1984). This augmented excitability of the stretch reflex could be explained by increased reflex gain after its activation or by decreased reflex threshold. A possible factor is an intrinsic decrement in α motoneuron excitability threshold, with a great increment in monosynaptic reflex excitability. There is also extensive evidence supporting the view that the reflex is triggered after smaller stretch stimuli (lower threshold), rather than by increases in reflex gain. There is still a need for practical measures that can differentiate between the contributions of the two components (intrinsic muscle stiffness and hyperexcitability) of spasticity to the symptomatology.

7.2.2 *Measurements*

Currently, there is no practical method providing an objective overall evaluation of spasticity. There are several available methods to assess the degree of spasticity of the patient, which can be classified as qualitative (clinical) methods or quantitative (experimental) methods.

7.2.2.1 Qualitative Methods

The principal advantage of the current qualitative methods is that they are relatively easy to use, quick to perform, and the clinician does not need novel instrumentation to make a measurement. They can be used in standard clinical environments without additional cost. However, these methods lack accuracy, precision and objectivity, instead providing a subjective way to track progress after therapy.

7.2.2.2 Quantitative Methods

The advantage of many quantitative methods is that they can assess different neurophysiological and biomechanical parameters, like EMG, joint torques and angles, allowing a deeper insight into physiological mechanisms of the disease. Quantitative methods also provide objective methods of assessment. The principal weakness of these methods is that they require complex instrumentation, such as mechanical devices, biosignal amplifiers, sensors and electrodes. These requirements increase costs, require personnel to perform measurements, and require additional preparation time, which makes sessions troublesome for patients and clinicians, and increases costs, hampering implementation in clinical environments.

The challenge in assessment of spasticity and the response to different therapies is to find the balance between practical clinical, and advanced experimental methods, in order to overcome the limitations imposed by both types of methods. Priorities for routine diagnosis are that methods should be fast and easy to perform rather than highly precise, as clinicians should examine patients in a functional context. The efficacy of uncomplicated clinical methods, such as the Ashworth and Tardieu scales to evaluate spasticity, has been proven over many years (see below). To evaluate and track the progression of spasticity with accuracy requires technical equipment and knowledge. If the measurement is too complicated, clinical professionals will not use it regularly. As an alternative, an appropriate and accurate way to assess spasticity and response to treatment might be to determine the threshold for stretch reflex, as it is sensitive to changes in response to treatment and other factors. However, simple and precise ways to assess stretch reflex are still lacking.

The following sections will review current clinical and experimental methods for the diagnosis and assessment of spasticity, highlighting their strengths and limitations.

7.3 Qualitative Measures

Qualitative methods to measure spasticity share some features that make them the most frequently used in clinical practice. They are fast to complete, easy to learn, relatively simple, and appropriate for most of the muscle groups. Most have been created so that a single evaluator can perform them manually, without requiring expensive and specialized equipment. On the other hand, they are subjective and validity and reproducibility of the technique depend on the experience of the assessor and on the control of potential influencing factors.

The contribution of both neural (stretch reflex) and mechanical components (elastic and viscous) should also be carefully considered when assessing spasticity. However, most of the methods available in clinical practice are qualitative methods with insufficient sensitivity to differentiate among different components of spasticity. These methods are mainly based on scales that evaluate different aspects of the pathophysiology of spasticity, such as the resistance produced by muscles against passive movements (Ashworth Scale) or the frequency of spasms (Penn Spasm Frequency Scale).

Other methods are based on questionnaires that assess the impact of the disease on the patient's activities of daily life. Although these scales have been widely studied and tested, they may have limited reproducibility when comparing between different patients or when different clinicians perform the exams. In addition, many of them only focus on one single symptom or specific sign of spasticity, which hardly correlates with presence of other associated symptoms, hampering the assessment of the overall state of the patient.

7.3.1 Ashworth Scale and Modified Ashworth Scale

The Ashworth Scale (AS) and the Modified Ashworth Scale (MAS) are currently the most widely used methods to evaluate spasticity in both clinical practice and in advanced research settings (Pandyan et al. 2002). The original AS is an ordinal qualitative scale that was developed in 1964 to evaluate the response to a given antispastic medicine (Carisoprodol) on spasticity in Multiple Sclerosis (Ashworth 1964). This scale is a subjective graduation of the perception of the tone or resistance to manual externally imposed passive movements through the joint range of motion (ROM). This resistance is commonly used as a measure of spasticity, even though spasticity is only one of the factors that contribute to this tone. Changes in intrinsic properties of the muscle (contractures, composition modification with loss of sarcomeres and viscoelastic components) and joint, presence of pain, the activity of the agonists and antagonists and other factor are frequently involved in mediating this resistance (Kheder and Nair 2012). AS graduates tone in five categories ranging from 0 (normal state in absence of resistance) to 4 (the most severe rigidity with contractures).

Bohannon et al. described the modified Ashworth (MAS) in 1987 to raise the sensitivity of the AS in the evaluation of the lower levels of spasticity. The MAS adds an extra category between the grades 1 and 2, referred to as 1 + (Bohannon and Smith 1987). Some authors maintain that this new category brings ambiguity to the scale, and that the MAS should be considered a nominal assessment rather than an ordinal scale. The AS and MAS are non-instrumented and relatively simple and quick to execute. However, the reliability of these scales has been shown to be variable according to the examiner experience and to the limb, joint, and underlying pathologies being evaluated. AS have been reported to be more reliable than the MAS (Pandyan et al. 1999).

When assessing the lower extremities, the AS seems to have better inter-rater reliability in the distal than in the proximal muscle groups. Studies evaluating the intra-rater reliability of the MAS in CP have found conflicting results that range from low through moderate agreement, to good and very good (Numanoglu and Günel 2012). The inter-rater reliability of the MAS is better for upper limbs than for lower limbs (Pandyan et al. 1999), especially for wrist and elbow flexors. Both scales can detect changes after treatments in both upper and lower limbs and in different pathologies, although they have shown low sensitivity to change (Platz et al. 2005).

Despite the wide use of these scales, there is still a need to determine accurately, guidelines describing recommendations about the way to conduct the evaluation. While most authors agree the movement should be performed in less than a second, there is still variability in the speed, the starting limb positioning for the evaluations, the influence of pain and limited passive ROM, and the definition of catch and release. Detailed guidelines to use AS and MAS would be desirable to improve the reproducibility and reliability of these scales Table 7.1.

Table 7.1 The Ashworth scale (Ashworth 1964) and the modified ashworth scale (Bohannon and Smith 1987)

Ashworth scale		Modified Ashworth scale	
0	No increase in tone	0	No increase in muscle tone
1	Slight increase in tone giving a catch when the limb was moved in flexion or extension	1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) in 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 movement (ROM)
2	More marked increase in tone but limb easily flexed	2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in tone, passive movement difficult	3	Considerable increase in muscle ton, passive movement difficult
4	Limb rigid in flexion or extension	4	Affected part(s) rigid in flexion or extension

7.3.2 Tardieu Scale and Modified Tardieu Scale

The Tardieu Scale (TS) was developed on 1954 to assess spasticity considering the velocity dependent variability component that is included in the definition (Tardieu et al. 1954). Boyd et al. presented a modified version that is called the Modified Tardieu Scale (MTS) in 1999 (Boyd and Graham 1999). Although the scale can be used for adults and children with neurological conditions, these scales are more frequently used in practice in pediatric populations with Cerebral Palsy. The TS and the MTS assess the response of the muscle to stretch applied at three different speeds (V1, V2 and V3) Table 7.2.

When the examiner moves the joint at V1 we obtain the passive range of motion (R2). If the examiner moves the muscle quickly, (V2 or V3) we obtain R1. These scales emphasize the importance of the dynamic component of spasticity, represented by means of the difference between the angles (R2−R1) for a given joint. The difference R2−R1 is a useful tool to measure the severity of the disorder, and help the clinician to plan treatments for spasticity. The greater the difference, the higher the dynamic component, which means better response to antispastic treatments. The lower the difference R2−R1, the more likely it is that the stiffness comes from muscle contracture, which means that the expectation of response to antispastic treatments is poor.

The MTS has shown adequate to excellent intra-rater reliability for the majority of the muscle groups usually evaluated in patients with spasticity after brain injury (Mehrholz et al. 2005; Singh et al. 2011). The inter-rater reliability of the MTS ranges from low to adequate for the same muscles (Ansari et al. 2008). The inter-rater reliability of the TS is adequate to excellent and the test-retest reliability is

Table 7.2 Modified Tardieu Scale (Numanoglu and Günel 2012)

Modified Tardieu scale			
Quality of muscle reaction (X)		Velocity of stretch	
1	Slight resistance throughout the course of passive movement, no clear catch at a precise angle		
2	Clear catch at a precise angle, interrupting the passive movement, followed by release	V2	Speed of the limb segment falling under gravity
3	Fatigable clonus (<10 s when maintaining the pressure) appearing at a precise angle		
4	Infatigable clonus (>10 s when maintaining the pressure) at a precise angle	V3	As fast as possible (faster than the rate of the natural drop of the limb segment under gravity)
5	Joint immovable		

excellent when using goniometry and inertial sensors (Paulis et al. 2011). The TS was able to detect changes over time in patients after a specific treatment for spasticity in one study, although there is still a lack of studies evaluating the actual responsiveness of the scale (Gracies et al. 2000).

7.3.3 Tendon Tap (Clinical Hammer)

Tendon hammers are commonly employed in clinical practice to elicit spinal reflexes. A muscle tendon percussion efficiently activates a reflex arc that leads to a momentary contraction of the specific muscle. This reflex response is correlated to stretch reflex threshold and provides information about the presence and the severity of the spasticity of the subject (Wood et al. 2005). It is routinely used in neurological examinations because it is a very simple and fast technique that provides valuable information at virtually no cost. The symmetry, or asymmetry, of the reflex between the two sides is suggestive of integrity, or abnormality, of the corticospinal tract, respectively.

There are a high number of classifications in the literature that try to grade the deep tendon reflex according to the intensity of the response, although there is not yet consensus about the use of any specific scale (Meythaler et al. 1996; Meythaler et al. 2001; Walker et al. 1990). The most common scales, the National Institute of Neurological Disorders and Stroke scale (NINDS) and Mayo Clinic scale, have both failed to provide better than fair inter-observer reliability (Manschot et al. 1998).

Tendon jerks are more easily elicited in people with spasticity and therefore it has been suggested that these could provide a means to quantify the phenomenon. However, there are some limitations in the magnitude of this response that varies with the force exerted by the tap, the position on which the tendon is hit, and with the subjectivity of the scoring Table 7.3.

Table 7.3 Tendon reflex scales (Manschot et al. 1998; Meythaler et al. 1996; Meythaler et al. 2001)

NINDS scale for tendon reflex assessment		Deep tendon reflex score		Mayo clinic scale for tendon reflex assessment	
0	Reflex absent	0	Reflexes absent	−4	Absent
1+	Reflex slight, less than normal: includes a trace response or a response brought out only by reinforcement			−3	Just elicitable
		1	Hyporeflexia	−2	Low
2+	Reflex in lower half of normal range	2	Normal	−1	Moderately low
3+	Reflex in upper half on normal range	3	Milder hyperreflexia	0	Normal
4+	Reflex enhanced, more than normal: includes a clonus if present which optionally can be noted in an added verbal description of the reflex	4	3 or 4 beats clonus only	+1	Brisk
				+2	Very brisk
		5	Clonus	+3	Exhaustible clonus
				+4	Conclusions clonus

7.3.4 Spasm Scores

A spasm is defined as the sudden extensor or flexion contraction of a muscle group. Spasms are highly correlated with the intensity of spasticity. The measurement of spasms and its changes provide a more comprehensive understanding of the spasticity. Penn et al. described the Penn Spasm Frequency Scale (PSFS) that aims to score the presence of spasms and their frequency and severity over a one-hour time span. This simple and fast, self-report measure assesses a patient's self-perception of the frequency and severity of the spasticity (Penn et al. 1989). Subsequently, Priebe et al. introduced the modified PSFS that added a second part to score independently the spasm severity in spasticity secondary to spinal cord injury (Priebe et al. 1996) Table 7.4.

In general, qualitative clinical methods to assess spasticity or other symptoms of the UMN are poorly correlated. There is still a lack of consensus about the use of quantitative objective methods. Due to the complexity and the time-consuming nature of quantitative methods, most of the assessors still choose to evaluate spasticity by means of a combination of qualitative measures including assessment of different aspects of the UMNS that are tightly linked to spasticity.

Table 7.4 Penn spasm frequency scale and its modified version (Penn et al. 1989; Priebe et al. 1996)

PSFS score	Modified PSFS	
	Spasm frequency scale (modified form Penn)	Spasm severity
0 No spasms	0 No spasms	1 Mild
1 Mild spasms induced by stimulation	1 Spasms induced only by stimulation	2 Moderate
2 Infrequent full spasms occurring less than once per hour	2 Infrequent spontaneous spasm occurring less than once per hour	
3 Spasms occurring more than once per hour	3 Spontaneous spasms occurring more than once per hour	3 Severe
4 Spasms occurring more than 10 times per hour	4 Spontaneous spasms occurring more than ten times per hour	

7.4 Electrophysiological Measures

One of the most common methods to evaluate spasticity is to register the electrical activity of muscles, especially in a research environment. The rationale for this approach is that the mechanical properties and responses of muscles are closely related to their electrical activity.

Most electrophysiological-based methods register electrical activity of muscles by means of electromyography (EMG). There are different techniques to obtain and record this activity, most of which measure the neuromuscular reflex response to evoked stimuli. The main difference among these techniques lies in the way in which the stimulation is delivered: electrical stimulation to the peripheral nerve; biomechanical stimulation (pressure or changes in elongation by tendon tapping); or the response to external muscle stretch (Voerman et al. 2005).

The principal advantage of these methods is that they offer an understanding of what happens to the neuromuscular circuit when spastic reflexes occur: they are very important for the understanding of physiopathological mechanisms (Burridge et al. 2005).

The main limitation of these methods is that they do not have direct clinical relevance, when assessing spasticity, due to test response variability between subjects, and to the lack of correlation with the clinical scales. In addition, they require additional instrumentation and data analysis. Nevertheless, combined with biomechanical based methods, they can provide neuromuscular insight, in correlation with biomechanical properties, which allows features of spasticity such as the threshold angle at which spastic reaction is triggered, to be studied.

7.4.1 EMG Response to Electrical Stimulation

7.4.1.1 Hoffman Reflex and H/M Ratio

The Hoffman reflex (H-reflex) is a spinal reflex caused by a stimulation of the peripheral nerve and the subsequent activation of Ia afferent fiber bypassing the muscle spindle. This electrical pulse is conducted to the posterior horn of the spinal cord and is transmitted to the α-motoneuron, through a predominantly monosynaptic pathway. Next, the stimuli travels orthodromically to the muscle, generating a reflex response that constitutes the H-reflex and that can be registered. Amplitude and latency of the H-reflex are the most useful parameters in practice, offering information about the excitability of the α-motoneuron and its changes (Yates et al. 2011). The H-reflex is a low threshold reflex that is provoked at low stimulus intensities. If we gradually increase the intensity of the stimulation, the motor axon is also activated and we will progressively register another response that is called M-wave, which appears at a higher threshold. In the beginning of this increase of the intensity of the stimulation, initially the H-reflex will also increase and gradually the M-wave will appear. After that, if the stimulus is increased further, the H-reflex will decrease and the M-wave will rise, until a threshold is reached where the H-reflex will not be detected and the M-wave will be prominent (Hiersemenzel et al. 2000).

Several factors need careful consideration when assessing the H-reflex, in order to ensure correct accuracy, and reproducibility, of the technique. Among these factors, positioning (subject, head, join, limb), correct placement of the electrodes, differences in skin properties, subcutaneous fat, sensory input, duration and frequency of the stimulation, number of measurements, muscle activity, and subject age and height, need to be determined to ensure technique precision (Phadke et al. 2010). Due to these factors, the amplitude of the EMG signal has shown variability between subjects and between sessions. This amplitude is more comparable if expressed relative to the size of the EMG response evoked by a supramaximal stimulation of the motor axons in the nerve innervating a given muscle from which reflex response in measured (H_{max} and M_{max}). To decrease variability, some authors prefer the ratio H_{max}/M_{max} to evaluate α-motoneuron excitability with increased reliability (Gómez-Soriano et al. 2012).

7.4.1.2 F-Wave

The F-wave assesses spinal excitability by means of peripheral nervous system conduction. It is obtained by applying supramaximal electrical stimulation to the motor nerve that leads to the generation of an action potential in the muscle. In this method, the stimulation travels in two directions, orthodromically to the muscle provoke a contraction (generating the M-Wave) and antidromically to the spinal cord to activate the α-motoneuron cell body. Then, the impulse goes back orthodromically via the α-motoneuron to activate the muscle and generate a signal that is called F-wave (Blicher and Nielsen 2009). The F-wave is the second signal to register after stimulation (after the M-wave). The main properties of the F-wave evaluated are amplitude, latency and duration. Stroke patients have shown increased F-wave frequency, and this has been correlated with motoneuron hyperexcitability (Argyriou et al. 2010).

7.4.2 EMG Response to Mechanical Stimulation

7.4.2.1 Tendon Reflex (T-Reflex)

T-reflex or phasic stretch reflex implies the assessment of the electrical response to mechanical stimuli (tapping a tendon) with a hammer. The pressure made to the intrafusal fibers activates the Ia afferent fibers that generate signals transmitted directly to the ∝-motoneuron. This response is essentially equivalent to the H-reflex, with the difference being that the stimulation is elicited in the muscle spindle, rather than directly on the nerve. The T-reflex generates a contraction of the extrafusal fibers of the muscle (Liu et al. 2011) that can be recorded with surface electromyography. The most important parameters evaluated are latency and amplitude, although other parameters such as reflex duration, torque, and loop delay, are often used and correlate with clinical assessments. As described above for the H-reflex, positioning of the limbs and the electrodes, intensity and frequency of the stimulus, and other factors may influence the outcome, and affect accuracy and reproducibility of the technique (Heckman and Rymer 2008).

7.4.3 EMG Response to Movement

7.4.3.1 Stretch Reflex

The stretch reflex of the muscle has demonstrated spring-like behavior, which means that the muscle displays proportional changes in force as the muscle length varies (Powers et al. 1988). Hyperactive tonic stretch reflex has been widely recognized as one of the key features of spasticity. This hyperactivity is attributed mainly to a considerable reduction in stretch threshold that has been demonstrated in spastic muscles (Zhang et al. 2000). The stretch reflex is triggered at lower stimuli than non-spastic muscles, and this threshold decrease is correlated with increasing reflex joint torque (Chardon et al. 2010).

Some factors may increase the variability of the results and should be taken into account when evaluating the reflex response. Some of these factors are: the amount of force required to exert contraction, the velocity, the strength and the duration of the contraction/relaxation, the extension of the area to elicit the reflex response of the tested muscle and the concomitant contraction of non-tested muscles. There are some approaches to address the limitations brought by these factors including systems, such as an automated hammer, which will be described later in this chapter.

The majority of studies found augmented reflexes in people with UMNS, with or without spasticity, in comparison with healthy controls. Most of the studies failed to demonstrate the existence of a correlation between the amount of the increase in stretch responses and the severity of spasticity, especially when spasticity was assessed with clinical measures such as AS and MAS, although recent studies have reported more promising results (Biering-Sorensen et al. 2006). Therefore, electrophysiological techniques are not routinely useful tools for evaluation of spasticity in clinical practice. However, they are promising instruments to help reach a better understanding of the pathophysiology of spasticity and seek to characterize if changes in electrical stimulation in spasticity correlate with variations in the severity of spasticity (Min et al. 2012). These techniques are also unique to determine threshold and amplitude of stretch reflex, that in combination with the evaluation of torque responses through biomechanical techniques, represent a reliable and reproducible way to evaluate spasticity.

7.5 Biomechanical Measures

Biomechanical measures provide valuable information when quantitative data are necessary. However, they often require complex devices and considerably long setup time, which hinders their application in a clinical environment. They offer high repeatability, and objective, contrastable information, to the field of research and evaluation of treatments. Biomechanically based methods provide a more accurate assessment during passive movements than traditional clinical scales, allowing measures of velocity, angles, resistance to passive movements, and stiffness. A great advantage of these methods is that they can be correlated with clinical scales. The big pitfalls are the instrumentation needed for these methods, which must be coupled to the body, as well as the time required for data analysis, that makes their use in daily clinical practice unfeasible. In addition, their measures are highly dependent on the joint and the plane of movement, skipping other symptoms of spasticity such as spasms, clonus or hyperreflexia.

The methods proposed so far may be classified in a number of ways, depending on the joints involved, patient involvement, physical parameters being measured etc. The classification of those methods used in this chapter is presented in Fig. 7.1. The first distinction has been made based on various conditions in which increased muscle tone is observed: i.e. while stretching the muscle, tapping the tendon or voluntarily performing a functionally relevant movement.

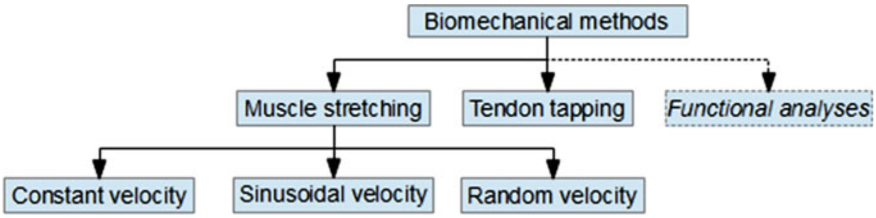

Fig. 7.1 Classification of the biomechanical methods of spasticity measurement

7.5.1 Muscle Stretching

These methods may be considered, in most cases, as an instrumented way of performing typical clinical tests where the physician passively flexes or extends the limb in order to evaluate resistance. However, there are significant differences between the various methods proposed.

The first difference is in the joint and muscles investigated. Most of the quantitative methods are applied to a limited number of joints. Usually spasticity is evaluated in the elbow, knee or ankle joint unilaterally. However, there have been systems proposed, that allow evaluation of spasticity in other joints, such as in the wrist (Walsh 1992) or metacarpophalangeal joints (Kamper and Rymer 2000). In general, subjects should remain passive and relaxed during the measurement. In a few cases, the subjects should voluntarily preactivate their muscles prior to stretch (e.g. (Powers et al. 1988; Powers et al. 1989)). This approach attempts to eliminate the influence of the difference in the stretch reflex threshold between various subjects.

Various parameters of the motion and of the reflex response may be measured. In most cases, the parameter of interest is the torque evoked at the joint versus the actual joint angle. Because spasticity is velocity-dependent, it is important to know the measurement velocity. Typically, motion is performed at a constant velocity ("isokinetic"). Usually, a constant angular velocity and not a constant muscle stretching velocity is applied, since the second depends on the relative location of muscle tendons. It is often assumed however, that the muscle is stretched at close to a constant velocity, and this is true for a good portion of the ROM in most cases.

The manual measures, in which tonic stretch reflexes are elicited by the examiner, (typically by manipulating the subject's limb to cause rotation of the evaluated joint), may be considered a kind of isokinetic measure, provided that the examiner moves the limb smoothly. Such methods are considered quantitative, if the characteristic of movement is measured in an objective way. An example of such a system was developed by the Newcastle CREST group and is presented in Fig. 7.2. The clinician acts in the same manner as when performing the standard Ashworth test, except that instead of holding the patient's arm directly, a small handle is used. The joint angle and force achieved during the pull are measured, and the spasticity is quantified by calculating the slope of the graph of applied

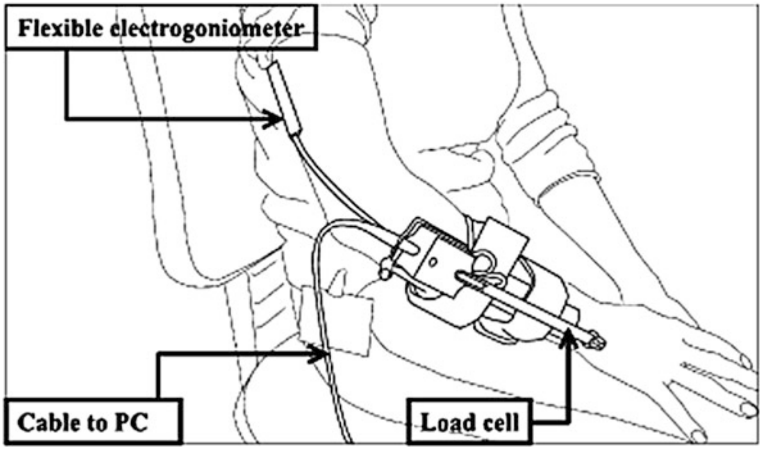

Fig. 7.2 Schema of the manual device for spasticity measurement developed by the Newcastle CREST group (from (Pandyan et al. 2001))

force versus passive range of movement. The greater the resistance to the applied force the steeper the slope (Pandyan et al. 2001).

Increased muscle stiffness, manifested as increased torque during passive movement, may be of muscular (i.e. due to changes of intrinsic muscle structure) or neural (i.e. due to altered reflex properties) origin. In order to be able to apply correct treatment, it is important to determine the source of the increased muscle tone correctly. For this reason biomechanical measures are often complemented by EMG measurement. If an increase in stiffness is accompanied by an increase in EMG activity, it suggests a reflex response. Other methods, which allow the distinction between various origins of the resistance, are discussed below.

Two distinct parameters of the reflex response may be altered by spasticity: the “set point”, (the angular threshold of resistance); and the “gain”, (the slope of the resistance versus joint angle curve) (Katz and Rymer 1989). Some systems, such as that proposed by the Newcastle CREST group, determine the level of spasticity based on the slope of the torque (or sometime force) versus joint angle curve. Katz and Rymer (1989) found that it is mostly the “set point” which is affected by the spastic hypertonia, and not the gain. Thus, it seems reasonable to determine the set point of the increased resistance, i.e. the angle where torque or EMG starts to increase significantly. Kim et al. (2011) have proposed a portable measurement system, equipped with flexible electrogoniometer and EMG sensors, which allows determination of the onset of the tonic stretch reflex while an examiner passively moves the limb. The use of an electrogoniometer allows the moment of the increased EMG activity to be correlated with a particular joint angle, and by the differentiation of the angular signals, determination of the angular velocity at which the test was performed.

The advantage of using instruments to record measurements during manually applied tests, is that they are simple to administer, whereas their accuracy is higher than qualitative tests. The main disadvantage is that if the movement is applied by the examiner, the characteristics of the movement (i.e. velocity versus angle profile) cannot be pre-defined or accurately repeated. This is the reason why, in the cases when higher repeatability of measurement conditions is required, powered devices are used. These are typically equipped with motors, which may drive and resist (active systems) or only resist (passive systems) the movement, ensuring that it follows the pre-defined profile.

Probably the most commonly used devices are **isokinetic dynamometers**, which are commercially available and used for multiple purposes (i.e. determining muscle strength, performing muscle strengthening exercises, rehabilitation). They are also often used for spasticity measurement. Typical tests incorporating isokinetic dynamometers are performed at two or three angular velocities. Testing at a lower velocity than the one at which reflex response is observed allows identification of the intrinsic resistance component and at a higher velocity allows identification of the reflex component. The great advantage of isokinetic dynamometry is that the velocity and amplitude of the applied movement, is standardized, however, some authors argue that the use of isokinetic dynamometers, increases repeatability only slightly compared to handheld dynamometers, whereas their use significantly increases complexity and costs of the measurement (Boiteau et al. 1995; Lamontagne et al. 1998; Lebiedowska et al. 2003).

Because the threshold velocity for eliciting the stretch reflex is not known, evaluators need to be careful when selecting the velocities used to perform the test (Boiteau et al. 1995), and the results obtained by various subjects cannot be easily compared (Biering-Sorensen et al. 2006). Rabita et al. (Rabita et al. 2005) have shown that normalization of the resistance observed at various velocities, by expressing it as a percentage of the values measured at the lowest velocity, gives results that correlate well with the AS score.

The angular range over which a constant velocity can be maintained is limited due to unavoidable acceleration at the beginning and deceleration at the end of the motion. It becomes especially significant when high velocities are applied over a short range of movement. Also it is not clear at which velocities isokinetic measurements should be performed. These are some of the arguments supporting performing measurements while motion is provided in a sinusoidal (e.g. (Lehmann et al. 1989; Rack et al. 1984; Stefanovska et al. 1989)) or random (e.g. (Hunter and Kearney 1982; Kearney et al. 1997; Powers et al. 1988)) waveform.

The simplest method of providing joint motion in a sinusoidal waveform is the **pendulum test**, however, it is not possible to perform this test at multiple frequencies. Wartenberg proposed this test in 1951 (Wartenberg 1951). The subject sits on a couch with lower leg hanging and is instructed to stay relaxed. The examiner extends the leg to the horizontal position and releases it, which allows the leg to swing freely due to gravity, and stopping after a few swings because of quadriceps femoris muscle resistance. The motion of the leg are measured by the electrogoniometers and the relaxation index, often calculated as the ratio between the initial flexion and the final position of the knee joint, is determined. The relaxation index is used to estimate the severity of spasticity, and it has been shown that, when computed in the way described above it has a good correlation with the AS score (Leslie et al. 1992).

Some alternative ways to determine the relaxation index have also been proposed (Johnson 2002). The pendulum test is easy to apply, and provides reliable results, but it is used only for evaluation of spasticity in the knee joint, and with adaption for the elbow joint as well (Lin et al. 2003; Liu et al. 2011). It is hard to use the pendulum test in cases of severe spasticity.

Performing measurements at various speeds and various frequencies allows better discrimination between intrinsic and reflex components of the stiffness. For this purpose mathematical models including mechanical properties of neuromuscular system have been developed. Parameters are identified when performing movements at various velocities. The models and identification techniques being used differ in their complexity, and one of the most sophisticated techniques applied so far for spasticity quantification includes a parallel-cascade system identification method (Mirbagheri et al. 2007). In this work, the two components of the stiffness are split into parallel branches, an intrinsic and elastic one. A second-order model having inertia, viscous, and elastic parameters described the intrinsic stiffness. Reflex delay and a third-order model having gain, damping, and frequency parameters, described the reflex stiffness. In order to identify the parameters of this model the elbow joint is perturbated by applying pseudorandom binary sequence position inputs with low amplitude and a high switching-rate (150 ms).

The system identification techniques, such as the one described above, are very powerful in discriminating various components of resistance and in the quantification of spasticity, however, they require a complex set-up and fast movements at various velocities in random order. Although they allow precise identification of the system parameters, they may be very unpleasant for the subject. Furthermore, since strong motors are used, special attention must be paid to ensuring the safety of the subject.

7.5.2 Tendon Tapping

The stretch reflex may be elicited in a number of ways, e.g. by muscle stretching (similar to the Ashworth test, and the above described biomechanical methods), through electrical stimulation (as it is the case for some electrophysiological methods) or by short percussion of the muscle tendon. The clinical tendon tap method is an elegant way of eliciting a stretch reflex. However, in order to obtain repeatable results, the applied force and the position on which tendon is struck should be standardized.

A simple approach to standardizing the force is to allow the reflex hammer to swing through a measured arc before striking the tendon. However, if more precise control of the applied force is needed, a device equipped with electronic control of the applied force may be used. A few such systems have been proposed so far (Chardon et al. 2009; Fryer et al. 1972). In particular the device proposed by the Chardon et al. (Chardon et al. 2009) is an attractive option. It not only allows for standardization of the applied force, but it also allows measurement of the tension in the tendon at rest, and during a reflex response, thanks to the force sensor integrated into the tapper. When performing measurement using this system (see Fig. 7.3) a small linear actuator is fixed to the mechanical frame at an angle 90° to the tendon and aligned in such a way that the end of the tapper touches the skin. Then, a series of constant small amplitude stimuli is applied and the tendon tension and EMG activity of the muscle is measured. Afterward, the tapper is methodically lowered in increments of 1 mm, using a micrometer attached to the actuator, what allows for preactivation of the muscle. The same series of stimuli is generated at each tendon indentation. This approach allows an accurate estimation of the stretch reflex threshold as well as passive muscle properties, and thus quantifies spasticity in a rather simple and cost-effective way. However, the joint has to be immobilized in order to ensure reliable measurements. Thus, if the device is to measure reflex for various joints, a complex mechanical construction may be needed.

7.5.3 Functional Analyses

One of the main goals of spasticity treatment is to increase ability to perform voluntary movement. Therefore, it can be argued that it is necessary to investigate the behavior of spastic muscles during voluntary, and not passive movements. The most obvious way to perform such measurement is with movement analysis and energy expenditure measurement during gait (for lower extremities) or reaching

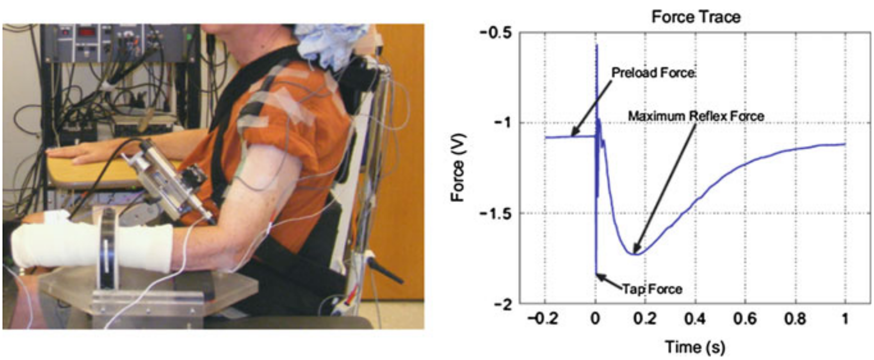

Fig. 7.3 A device for automatized tendon tapping measure. *Left* experimental set up: a position-controlled linear actuator (Linmot, Inc.) is placed perpendicular to the tendon of the biceps brachii, while the tension in the stimulated muscle tendon and the EMG activity of that muscle are measured; *Right* exemplary force trace recorded by the force sensor during tapping (Chardon et al. 2009)

and grasping activities (for upper extremities). Motion analysis systems, such as those described in Chap. 16 of this book, may be used. Such analyses provide comprehensive data, but also require employment of complex devices and time-demanding data processing. Performing such analyses would also be difficult in cases of severe spasticity. Furthermore, spasticity is only one of the components of the motor impairment caused by pathologies of the CNS. Other components are weakness and impaired motor coordination. Dysfunctional walking or reaching is an effect of all three impairments, and such functional analyses usually do not distinguish between the contributions of these factors. Thus, while functional analyses may provide useful information about the walking and reaching problems of people affected by spasticity, they should not be considered as a way of measuring spasticity *per se* (Johnson 2002; Wood et al. 2005).

7.6 Measuring the Effectiveness of Spasticity Treatment

To understand fully the importance of properly measuring the efficacy of treatments to overcome effects of spasticity, it is necessary to better understand what is required to adequately measure the changes that occur due to the treatment. One common treatment for spastic muscle behavior is the injection of Botulinum toxin type A (BtA). This treatment has been used for a number of years for cosmetic reasons as well as to treat other ailments. BtA injection is expensive, however it is generally considered safe (Kolaski et al. 2008) even when used for an extended period (Mejia et al. 2005). The effects and required dosages are well documented for those treatments where it is used extensively. More recently is has become widely accepted as a treatment for spastic muscles.

Botulinum toxins are a group the most lethal toxins known, however when injected into muscle in minute amounts, they can have beneficial therapeutic effects. Seven distinct serotypes are produced by Clostridium botulinum, with type A the one most commonly used therapeutically. BtA acts at the neuromuscular junction to inhibit the release of acetylcholine from the presynaptic nerve terminal without affecting the synthesis or storage of acetylcholine. The complete action of BtA is described in the literature (Davis and Barnes 2000; Dressler and Adib Saberi 2005) however, the effect is to cause muscle weakening (Blasi et al. 1993). When injected into a hyperactive muscle the weakening effect can reduce muscle size (Dressler and Adib Saberi 2005). Dosage is varied, depending on the size of the targeted muscle (Davis and Barnes 2000), while effectiveness may vary across patients (Pullman et al. 1996). Adverse systemic effects are rare, though they may occasionally be serious (Howell et al. 2007) and may include flu-like signs, transient fatigue, and nausea (Brin 1997). The muscle is progressively reinnervated by nerve sprouting making the action of the toxin temporary.

Many studies have assessed the effect of BtA injections on persons suffering from spasticity. It is not the purpose here to review them all, however those mentioned give an indication of the outcomes and methods of assessment commonly used. BtA has increasingly been considered a valuable treatment option for the management of muscle tone in children suffering from CP (Graham et al. 2000). These children are often at high risk of developing bone deformities during the growth phase which may require surgery to correct. BtA injections to the affected muscles can to delay or avoid surgery, as well as prevent secondary complications such as pain and other musculoskeletal problems while the child is growing.

In a report of three case studies Gooch and Sandell (1996) found that injection of BtA reduced pain, and improved ease of care in two children with CP, and reduced spasticity, and improved function temporarily in a third. Corry et al. (1997) performed a randomized, double blind study, on 14 patients with CP and found that BtA injection into the upper limb provided a modest functional change at 2 and 12 weeks, but the ability to pick up coins did not improve, and in some cases was worse. Vles et al. (2008) used a parent reported Visual Analogue Scale to evaluate the effect of BtA treatment of 55 children with CP, and found improvements in nursing, standing, and walking, but no significant improvement in pain. The treatment had no effect for 7 of the children, and 5 children had side effects. Moore et al. (2007) reported no long term cumulative or persisting benefit using BtA in leg spasticity over 2 years when 64 children with CP were assessed using PEDI and Gross Motor Function Measure (GMFM). They suggested that the measures may not have been sensitive in the situation, and that benefits perceived in other studies using impairment measures may be spurious. Py et al. (2009) used GMFM and clinical examination to assess the effectiveness of injecting BtA into the lower limbs of 54 children with CP, and found it clinically effective for 51 % with improved function for 24 % after one month. Lukban et al. (2009) reviewed trials between 1990 and 2008 that assessed the effectiveness of BtA for the treatment of CP. Outcomes were reported in terms of a variety of outcome scales which limit the comparison of results across trials. They also detail five systematic reviews of these trails. Four of these reviews concluded that the data was inadequate to support treatment.

BtA is also commonly used in the treatment of spasticity associated with other pathologies. Das and Park (1997) treated six post stroke hemiplegia patients with BtA injections and concluded that the treatment reduced spasticity in the upper limb with a subjective improvement in functional ability. Opara and colleagues (2007) reported that 20 patients following spinal cord injury (SCI), or suffering from MS, with moderate to severe spasticity in the lower extremities, showed improvements in pain measures, with side effects on only one patient. Marciniak et al. (2008) investigated the use of BtA with 28 patients following SCI and reported improvements in self-identified goals of function, hygiene, and pain.

Gait analysis (GA) has become a useful method for planning and assessment of treatments for spasticity especially in persons with CP (Boyd and Graham 1999; Boyd et al. 2000; Galli et al. 2007). This method allows a quantitative assessment of changes due to treatment, however the measurements are linked to assessments of the effect of the treatment on a joint or limb, and it is difficult to determine the specific effect of the injection on the treated muscle. Galli et al. (2007) reported a significant improvement in foot and ankle range of motion for 15 children with CP 1.5 months after injection of BtA into the calf muscles. Boyd et al. (Boyd and Graham 1999) devised new GA measures for ankle moments and reported improvements in ankle kinetics at 12 and 24 weeks after injection of BtA into the gastrocnemius-soleus muscles for 25 children.

The mechanisms by which injection with BtA changes muscle behavior over longer periods are not yet adequately explained and precise measurements are necessary to fully understand the effect this treatment has on muscle mechanical behavior. It has been found that BtA reduces muscle spindle afferent discharge providing relief through partial motor paralysis and a decrease in reflex muscular tone without affecting muscle strength (Filippi et al. 1993). Pandyan et al. (2002) assessed elbow flexor spasticity following stroke 4 weeks after BtA injection to the elbow flexor muscles in 14 subjects using MAS, EMG, and elbow and grip strength measures. They observed that while MAS was unable to detect changes, EMG activity reduced while elbow and grip strength increased. They concluded that the MAS is an inappropriate measure of spasticity, and that BtA treatment reduces spasticity measured by EMG activity, but does not necessarily cause a reduction in force generating capabilities of the joint. There is however some suggestion that when BtA injections occur over a prolonged period, muscle atrophy (Dressler and Adib Saberi 2005; Fortuna et al. 2011) and a loss of contractile tissue occurs (Fortuna et al. 2011), while other authors (Naumann et al. 2006) suggest that there are no persistent histological changes in the nerve terminal or the target muscle.

Though there is some doubt regarding the reversibility of BtA (Gough et al. 2005) there are no current published studies looking at the long term effect of BtA on human muscle, but several animal studies have raised concerns that BtA may have long-term effects. Chen et al. (2002) looked at the effect of BtA on juvenile rat gastrocnemius muscle, and found that its use lead to decreased muscle fibre cross-sectional area and muscle mass. This was not reversed by exercise, and they suggested that BtA injections could compromise muscle growth. More recently a study using rabbits (Galli et al. 2007) suggested that repeated BtA injections could cause muscle atrophy and a loss of contractile tissue. Clearly more research is needed to assess the long-term effect of BtA injection in human muscle tissue.

In a review of the use of botulinum neurotoxins Koussoulakos (2009) states “The experimental clinical studies carried out so far to test the efficacy of botulinum neurotoxins in various pathological circumstances are not considered fully reliable on universal standards.” The author goes on to note that even for well-designed and well-performed experimental studies outcomes may be affected by placebo effects to the control group (Willis et al. 2007) or to a lack of objectivity in subjective evaluation that may be affected by the patients mood. Despite this the author suggests the reality of the nontoxicity of BtA and reported health improvements support its use. The description of the benefits of BtA injection to the large numbers of patients across many studies varies a great deal.

It is difficult to compare results due to the wide variety of assessments used such as pain, muscle tone, joint angles or walking speed, and the range of muscles and muscle groups (both upper and lower body) treated. While some level of flexibility is necessary for clinical studies especially in the face of limited numbers of patients suffering from highly variable pathologies a complete understanding of the efficacy of BtA injection is impossible without some consistence and highly repeatable form of measurement which is flexible enough to be used across multiple joints in both the upper and lower body. Koussoulakos (2009) suggests that the following questions need to be answered, "(a) which muscles are better targets for maximalization of functional profit for each patient, (b) what are the optimal doses, (c) does an increase in the injected dose restrict the number of treated muscles, and (d) what is the most effective combination of various treatments for each case?"

Discussions of the effect of BtA treatments are usually based on outcome measures such as walking speed or joint angle changes, which are accurate when measured in a gait laboratory, however such measurements do not have the specificity to adequately answer the questions posed above. The effect on muscle mechanics following treatment by BtA injection is also not well understood. For the treatment of CP the stated goal may be to weaken muscles (Gough et al. 2005), which may not be a desirable longterm outcome. The actual requirement may be to delay the onset of the heightened stretch reflex so that it occurs at greater joint angles or higher angular velocities when greater muscle strength may be beneficial.

When treating spasticity, it is important not only to focus on the spasticity, but to remember the other deficits which may be more functionally limiting than the spasticity itself. While many clinical studies have shown improvements from BtA treatments for spasticity one of the few quantitative studies (Chen et al. 2005) showed that changes in muscle behavior might be present following treatment that was not apparent to qualitative assessment. There is a potential benefit to those who treat spasticity through the use of BtA injection from a greater understanding of the short and longer term effects of such treatments on the angle and speed at which the stretch reflex becomes apparent as well as the long term effects on muscle structure and strength.

While BtA injection is by no means the only treatment of spasticity it is one that is common and gaining popularity. This review of how its effect has been measured and reported in the literature serves to highlight the importance of accurate and repeatable quantifiable measures not only for the most beneficial and cost effective treatment of spastic muscles but also for the assessment of any clinical treatment.

7.7 General Recommendations

The measures that may be most applicable in a given situation will depend on the purpose for which the measurement is to be used. Most of the reasons to perform spasticity measurement may be qualified to one of the following categories:

1. Clinical
   - Diagnosis.
   - Assessment of severity.
   - Evaluation of response to therapy
2. Research
   - Understanding biomechanical and electrophysiological features of spasticity in different pathologies.
   - Understanding the effect of different therapies on every component of spasticity.
   - Generation of models to standardize and optimize management of spasticity with different therapies and to make predictions of response to treatment.

Each measurement technique has different requirements for complexity and accuracy (and impact on the subject) ranging from a yes/no in the case of diagnosis, to an accurate assessment of the velocity or muscle length required for the onset of the stretch reflex in a particular muscle.

The goal of diagnosis is to identify the existence of spasticity in different parts of the body, as a result of the UMNS, or to assess the extent of symptoms following SCI. In this case it is important to determine if a particular muscle is affected by the spasticity, rather than to quantify with accuracy the severity of spasticity. Thus, the popular qualitative measures, such as Ashworth or Tardieu Scales, which give a basic indication of level of involvement, are suitable. The tendon tap method may also be applicable for assessments that are limited to the knee joint.

In order to apply the correct treatment, and to track the evolution of the disease, it is often necessary to assess the severity of spasticity. The measure used in this case must quantify the severity of spasticity accurately, provide repeatable results, be applicable for various muscles and should not be too complex to apply. In these cases the instrumented muscle stretching measures in which force is administered either manually, or by the device (e.g. isokinetic dynamometry), may be applicable. However, these measures should ideally be accompanied by EMG measurements in order to distinguish between the 22 neural and muscular origins of increased muscle stiffness, and to track changes in muscle tissue properties. An automated tendon tapping device could also be used for the above application, however, its reliability is not yet proven and its construction needs adaption to allow reflex measurement for various joints.

The same measures as used for assessment of spasticity severity, can often be used for the assessment of therapy outcomes, however, the therapy outcomes measurement may not need to focus on the spasticity itself, but instead on how the severity of spasticity, and the muscles involved, effect the quality of daily living. Thus, movement analysis and energy expenditure measurements during functionally relevant movements may also be applicable.

The goal of research is to obtain a better understanding of spasticity, its influence on movement, the origin of the increased muscle stiffness, and the influence of the body adaptation mechanisms to the new conditions. Here it is necessary to distinguish between various components of the stiffness. In such a case the reliability of the method is more important than its ease of application. In these cases system identification techniques, such as those where force is applied at various velocities in order to distinguish between various components of spasticity or electrophysiological methods, will be most appropriate. These techniques would also allow a better understanding of the way in which different agents act on the different components of spasticity.

7.8 Conclusions and Future Challenges

Quantifying spasticity is important for evaluating of the effects of the treatment, but although it is an easy to recognize the phenomenon, it is much more difficult to quantify it (Biering-Sorensen et al. 2006). It is not surprising, given the variations in understanding of what spasticity is, that there is no agreement on the way in which it should be measured (Wood et al. 2005).

Quantitative measurements are widely used for research purposes and are more accurate than qualitative clinical techniques. However, these procedures are less practical for use in a clinical environment, where test application requires rapid testing methods that do not cause significant delays in medical practice. When selecting the spasticity measurement method a trade-off has to be made between reliability and reproducibility of the obtained results on one side, and the complexity of the set-up used and time necessary to perform the measurement on the other side.

As new measuring devices and techniques are developed, they will gradually generate a better understanding of the causes and symptoms of spasticity, and this will in turn allow more targeted diagnostic tools to improve treatment and further our understanding of the condition.

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Chapter 8
Motor Control and Emerging Therapies for Improving Mobility in Patients with Spasticity

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Abstract Treatment of spasticity has traditionally been targeted at reducing stretch reflex activity and muscle tone. However, these spasticity indicators and the actual movement disorder following a spinal or supraspinal lesion have been found to be unrelated. Increased muscle tone could be considered secondary and adaptive to a primary disorder and necessary for the continuing support of the body during locomotion. It is evident that antispastic medication is necessary for patients who experience severe pain and discomfort associated with increased muscle tone during rest. However, most therapies currently prescribed are directed at reducing excitation or increasing inhibition and may potentially interfere with voluntary movement. Impairment of walking may be due to a lack of descending input and a reduction in the afferent input to the spinal neuronal circuits. The result is reduced muscle strength, decreased physiological modulation of reflexes and muscle activity as well as cocontraction of agonist and antagonist muscles. Future therapeutic approaches aiming to assist ambulation in mobile spastic patients should focus on the treatment of these aspects in order to improve a patient's movement ability. Emerging therapies include robot-assisted treadmill training, repetitive

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electrical stimulation, paired associative stimulation (PAS) and H-reflex conditioning which may provide a new approach for restoring motor function in the spastic patient population.

Keywords Spasticity · Motor control · Locomotion · Muscle tone · Reflex excitability

8.1 Introduction

Performing even the simplest movement is often a frustrating task for patients affected by spastic syndrome. Spasticity is a movement disorder caused by a loss of descending control or as an adaptation to the lack of supraspinal control slowing down voluntary limb movements (Burke 1988). This disorder is a common consequence following the incurrence of Central Nervous System (CNS) lesions such as those resulting from spinal cord injuries (SCI), stroke, multiple sclerosis or traumatic brain injuries.

There is still no absolute agreement on the relationship between spasticity and movement ability which is mainly due to the diverse definitions of spasticity. According to Lance's (1980) definition, spasticity is described as a motor disorder that manifests itself clinically as a velocity dependent tendon jerk hypereflexia and increased muscle tone. Bobath's (1980) definition includes the presence of hypertonus caused by tonic reflexes, muscle co-contraction, and abnormal movement patterns (Bobath 1980; Sinkjær and Magnussen 1994), therefore strongly relating spasticity to movement function. Although it is recommended to perform combined neurophysiological-biomechanical assessment of spasticity during active functional movement, the clinical diagnosis of spasticity is currently based on Lance's definition and consists of a bedside assessment examination of the tendon jerk reflex and of the joint's resistance to passive movement in relaxed patients.

According to the clinical assessment, current therapeutic approaches are designed to reduce muscle tone and attenuate or abolish reflex activity at both the presynaptic and motoneuronal level. However, although reflexes in spastic patients are exaggerated during a relaxed state which is partially due to a lack of inhibitory drive, no signs of exaggerated stretch reflexes are evident in contracted muscles. An explanation is that in healthy subjects reflex activity is increased during voluntary contraction in part due to a depression of inhibitory mechanisms but in spastic patients these mechanisms cannot be further reduced as they are already inhibited at rest (Nielsen et al. 2005). Also, reflexes are not the only mechanism involved in the control of functional movement (Dietz and Sinkjær 2007). During locomotion although the short latency component of the stretch reflex (SLR) is increased in spastic patients, the afferent feedback to normal muscle activation is reduced and so is the ability to modulate the ongoing muscle activity to deviations in the walking surface (Mazzaro et al. 2007). While it is proposed that antispastic treatments could reduce the occurrence of cocontraction of agonist and antagonist muscles and increase a patient's walking speed, the effect of the treatment on afferent inputs could interfere undesirably with voluntary activity. In addition, without the development of spastic muscle tone some patients would not be able to maintain an upright stance and walk so drugs prescribed to decrease muscle tone could be detrimental. However, it is excepted that antispastic medications could increase the quality of life for those who do not retain any walking ability and are suffering from contractures or painful spasms. In conclusion, although extensively used in the treatment of patients with spastic movement disorder, antispastic drug therapy could be inadequate for the treatment of those who have preserved some motor function and in particular, locomotor ability.

In this chapter, the effect of the most commonly prescribed antispastic therapies on the ambulation ability of patients will be described. An analysis of the altered physiologic mechanisms that could lead to the motor impairment will be provided in order to identify potential new therapeutic approaches which aim to increase the quality of life of patients who preserve some motor ability. A particular focus will be given to the motor impairments related to locomotor tasks and rehabilitation techniques which aim to improve walking. Although spasticity is also associated with conditions such as multiple sclerosis and other hereditary brain and spinal disorders, since the affected physiological mechanisms or impaired functions may be different depending on the etiology or the site of the lesion of the symptoms, this chapter will focus only on spasticity originating from CNS lesions due to SCI and stroke (for reviews of spastic movement disorders in other conditions see Dietz and Sinkjær (2007) and Nielsen et al. (2005)).

8.2 Clinical Assessment of Spasticity and Current Treatment Approaches

The primary aim of any prescribed treatment is to improve the quality of life for people with spasticity and their caregivers. Therapy directed at reducing or eliminating spasticity almost universally involves a multimodal approach. It is thus extremely relevant in order to select the appropriate therapeutic approach to quantify the severity of the spastic phenomenon and its impact on a patient's daily life.

8.2.1 Clinical Assessment

The clinical assessment of spasticity and the effect of treatment are usually evaluated in a bedside examination by judging a joint's resistance to passive movement and an evaluation of tendon reflexes. A standard analysis of the nervous system forms the first step of the clinical examination and includes an assessment of both strength and reflexes. Next, with the patient fully relaxed, each joint is moved through its full range of motion at various speeds. When stretching a limb affected with spasticity, the examiner will find a "catch" which is felt as a sudden increase in resistance to the stretch. A note of this is recorded including the speed at which it occurred. Performing the range of motion may also provoke the "clasped-knife" phenomenon. Clasped knife occurs when the spastic muscle is stretched: the resistance to stretch is initially large but then suddenly diminishes. The clinical evaluation often results in the level of spasticity being associated with a score on the Ashworth or modified Ashworth scale. For a comprehensive description on qualitative and quantitative measures of spasticity please refer to Chap. 7.

Current clinical treatment of spasticity involves a wide variety of therapies ranging from non-invasive to invasive procedures. For mobile as well as immobilized spastic patients physical therapy aims to minimize biomechanical side effects of the condition, such as the changed intrinsic properties of soft tissue and muscle fibers which can restrict the range of motion and diminish the functional use of any residual voluntary movement. For example, daily passive muscle stretching assists in reducing muscle tone and in maintaining joint mobility, improving the range of motion and motor function.

8.2.2 Current Therapies

When the goal is to reduce hyperexcitability of motoneuronal and/or interneuronal spinal mechanisms, antispastic drugs are usually recommended. Baclofen is the most widely used antispastic drug which works by attenuating hyperreflexia, decreasing the excitability of the motoneurons by activation of GABA B receptors. However, this also has an effect on voluntary contraction and so can diminish any residual motor function (Elbasiouny et al. 2010). Another category of commonly prescribed drugs are the benzodiazepines. One drug in this group, Diazepam, works by increasing the GABA presynaptic inhibition in the spinal cord and carries the risk of producing sedation and addiction (Elovic 2001). These side effects can be reduced with the addition of Clonazepam, another benzodiazepine more commonly prescribed to reduce spasms during the night (Adams and Hicks 2005; Adams et al. 2007).

Dantrolene Sodium has been shown to reduce muscle tone and hyperreflexia by acting peripherally on intrafusal and extrafusal muscle fibers by decreasing the release of Ca^{2+} from the sarcoplasmic reticulum (Pinder et al. 1977). This however may also cause a reduction in the amount of muscle force during voluntary contractions (Ellis and Carpenter 1974).

Clonidine and Tizanidine typically cause less muscle weakness compared to the previously mentioned medications and may be better suited when it is important for the patient to retain muscle strength. The drug effect on spasticity is due to their action on the CNS. Clonidine for example, is an alpha-2 adrenergic agonist commonly used to treat hypertension (Adams et al. 2007). It enhances alpha-2-mediated presynaptic inhibition of sensory afferents abolishing the spinal polysynaptic reflex (Elovic 2001). Tizanidine works by inhibiting the release of excitatory amino acids in spinal interneurons (Kita and Goodkin 2000).

If spasticity is restricted to a few muscles or a delimited muscle group, injection of Botulinum Toxin may be another treatment option. Botulinum Toxin acts on the neuromuscular junction to inhibit the release of acetylcholine. Intramuscular injection is effective in reducing pain and muscle spasm but produces a negative side effect of excessive weakness in the treated muscle (Burgen et al. 1949).

Orthopedic interventions can be used in combination with physiotherapy and Botulinum Toxin injections in cases of local spasticity (Rekand et al. 2012). Tendon extension, tendon plasty or osteotomy can be considered in patients with intractable local spasticity with joint deformation. In the most severe cases when the previously described treatments are judged insufficient, surgical techniques involving the ablation of motor nerves and/or rhizotomy which involves the cutting of posterior roots to interrupt the peripheral reflex arc, could be an option.

As previously mentioned, since drug treatments commonly produce weakness as a side effect, physical activity is essential for patients who have preserved some motion ability. It has been demonstrated that leg cycling has a positive anti-spastic effect since, as a rhythmic movement, it may change the properties of spastic muscle and soft tissue and also the neuronal excitation of the affected leg (Motl et al. 2003).

Body weight supported treadmill training (BWSTT) is suitable for patients with incomplete SCI as some motor function is preserved below the neurological level and with training there is a potential for recovery of some locomotor function. BWSTT is a gait training strategy which involves unloading the lower extremities of a patient by supporting a percentage of their body weight. The therapy uses an overhead suspension system consisting of a harness and counterweight over a motorized treadmill. By supporting a percentage of the body weight, stepping is made easier for the patients and BWSTT also provides postural stabilization allowing them to remain upright while the spine and trunk remain supported (Dobkin et al. 2003).

Physiotherapists provide manual guidance to facilitate stepping and support the trunk and hips to ensure accuracy in the movement. During stepping the therapists assist in knee extension during swing phase and in extension during stance by specific hand placement on each leg. They can also assist in the foot placement on the treadmill and in toe clearance.

The evidence for this type of rehabilitation training is based on animal experiments on adult spinal cats. Studies have shown that interactive locomotor training using a treadmill and body-weight support can improve locomotor performance (Barbeau et al. 1987). Patients with incomplete injuries have demonstrated an improvement in their over ground walking ability from the training program (Dietz et al. 1994; Wernig et al. 1992). BWSTT also proved to be effective in the treatment of SCI with various degrees of spastic paresis (Wernig et al. 1992).

As a task-specific training, BWSTT allows patients to 're-learn' by practicing walking with many repetitions of complete gait cycles at an early stage of gait rehabilitation instead of only single elements or preparatory maneuvers. BWSTT is beneficial for incomplete SCI rehabilitation as it is a whole body therapeutic exercise and by the patient using their legs, muscle atrophy is prevented and also treated to avoid further damage and loss of muscle mass. The training can also improve fitness level, restore muscle strength and improve mobility and coordination if routinely carried out.

It should be considered however that reports on the effect of BWSTT in walking rehabilitation of post-stroke patients have been inconclusive. Some studies favor BWSTT to other forms of walking rehabilitation such as conventional physiotherapy and over ground walking exercise whereas others have found there to be little difference (Aaslund et al. 2013). At present, evidence suggests that BWSTT is equally effective but not a superior method of rehabilitation when compared to other means of walking therapy and should not be used routinely as a substitute for over ground walking (Dobkin and Duncan 2012). It should still be recognized that BWSTT may be a good supplement to over ground walking rehabilitation for enabling a higher intensity of task orientated training and a suitable means of ensuring safety during ambulation for those with walking difficulties (Aaslund et al. 2013).

8.3 Spasticity and Motor Control

A number of concerns arise when considering the implications the currently available treatment options could have on patients preserving locomotor ability. Drug prescription is not necessarily the most adequate treatment for this patient population and the heavy prescription of medication for spasticity associated pain has been observed to be inversely related to a patient's ability to achieve ambulatory distances (Khout et al. 2011). Surgical approaches such as selective dorsal rhizotomy combined with physiotherapy have been found to improve mobility in children with spasticity related to cerebral palsy, however it is not frequently used as a treatment for SCI patients (Dietz and Sinkjær 2007; Adams and Hicks 2005). Other surgical techniques such as tendon lengthening or transfer are theorized to reduce spasticity by altering tension in the intrafusal muscle spindle, reducing the stimulus for further contraction in the effected muscles but have been found to give varied and unpredictable results (Adams and Hicks 2005). Finally, as previously mentioned the effects of BWSTT in walking rehabilitation have been suggested as not being more effective than conventional physiotherapy.

The ability of currently available treatments to improve patient's mobility is based on the traditionally assumed contribution of increased reflex excitability to the increase in muscle tone and to the role of hyperreflexia and increased muscle tone in the motor impairment of the patient. However, as has already been

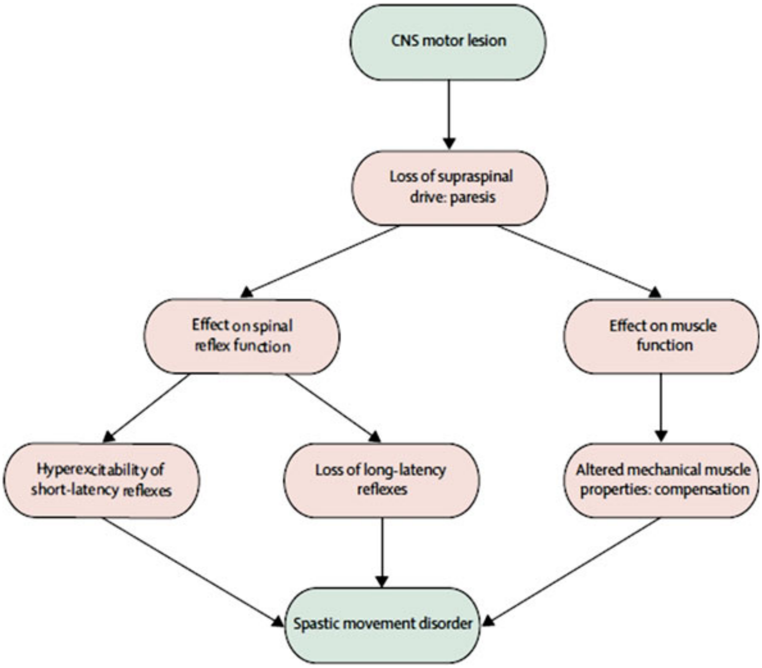

Fig. 8.1 A lesion in the central motor system leads to the excitability of spinal reflexes changing and supraspinal drive is lost. Because of these changes, there is an adaption of the muscle function leading to the muscle properties altering. The overall result is a spastic movement disorder (from Dietz (2002) and Dietz and Sinkjær (2007))

suggested, these aspects may not actually be the cause of the impairment and require further discussion focused on the recovery of the task which significantly affects the daily life of patients: locomotion.

How does spasticity affect locomotion? Studies on functional movements show that typical clinical measures do not relate to the actual problems faced by the patients with locomotion. Following a lesion in the CNS, the central pattern of the leg muscle activation is to a large extent preserved and the tendon jerk hyperreflexia (the monosynaptic reflex hyperexcitability) which is a significant finding of the clinical assessment is of minor involvement in the actual spastic movement disorder (Fig. 8.1).

8.3.1 Contribution of Reflex Hyperactivity to Increased Stiffness

Based on Lance's (1980) definition of spasticity, current therapies focus on the reduction of reflex excitability and muscle tone. Increased tone is often thought to be related to a hyperactive stretch reflex (Sinkjær and Magnussen 1994; Broberg and Grimby 1983). However, this direct association is inaccurate since the total mechanical stiffness in the contracting muscle is the sum of the actual reflex-mediated stiffness (stretch reflex-mediated contraction of the muscle fibers), the passive stiffness (the response due to the passive tissues) and the intrinsic stiffness (response due the properties of the fibers contracting prior to the stretch) (Sinkjær and Magnussen 1994). Research also suggests that the non-reflex part of stiffness which arises from the sum of the passive and intrinsic responses, may be responsible for the increased stiffness in spastic patients (Dietz et al. 1991). But how can we divide the non-reflex response and reflex-mediated response? By imposing an angular rotation around the ankle joint and measuring the torque increments, Sinkjær and Magnussen (1994) compared the non-reflex and reflex mediated stiffness between spastic and contralateral leg of spastic hemiparetic patients and healthy subjects.

As shown in Fig. 8.2, the reflex-mediated torque exceeded the non-reflex torque with a factor of two in both the spastic and the contralateral leg of a representative hemiparetic patient. The reflex and non-reflex torque are both increased in the spastic leg but the amplitude of reflex-mediated torque in spastic leg is still in the range observed for healthy subjects. This may be explained by an altered regulation of the inhibitory spinal mechanisms in the active/contracted muscle (as compared to the relaxed muscle) which produces a comparable reflex response between patients and healthy people when the muscle is active as compared to hyperreflexive reflexes in the relaxed spastic muscle (Nielsen et al. 2005). Presynaptic inhibition, post activation depression, and reciprocal inhibition are depressed in healthy subjects when the muscle is contracted. The different inhibitory mechanisms are decreased at rest in patients due to a deficient descending central control of the different reflex pathway and cannot be further

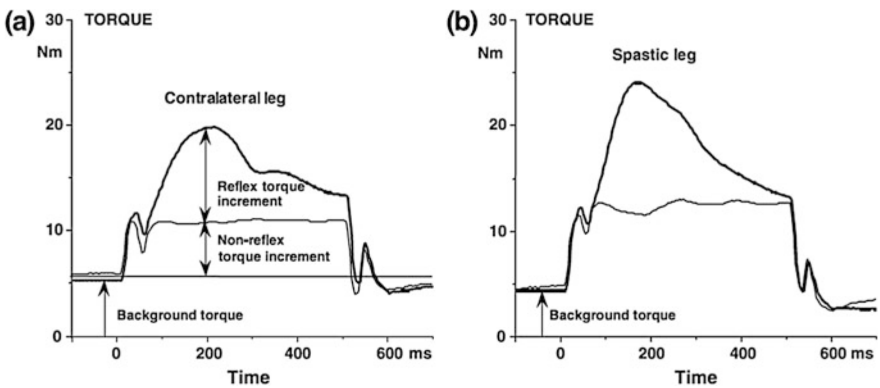

Fig. 8.2 Total and non-reflex torque responses to a stretch of the plantar flexors in a hemiplegic patient. The increase in angle joint torque in the contralateral (**a**) and spastic (**b**) plantar flexors of a hemiplegic patient was measured after imposing a well-defined passive dorsiflexion. The non-reflex torque is measured during the electrical stimulation of the tibial nerve. Taken from Sinkjær and Magnussen (1994)

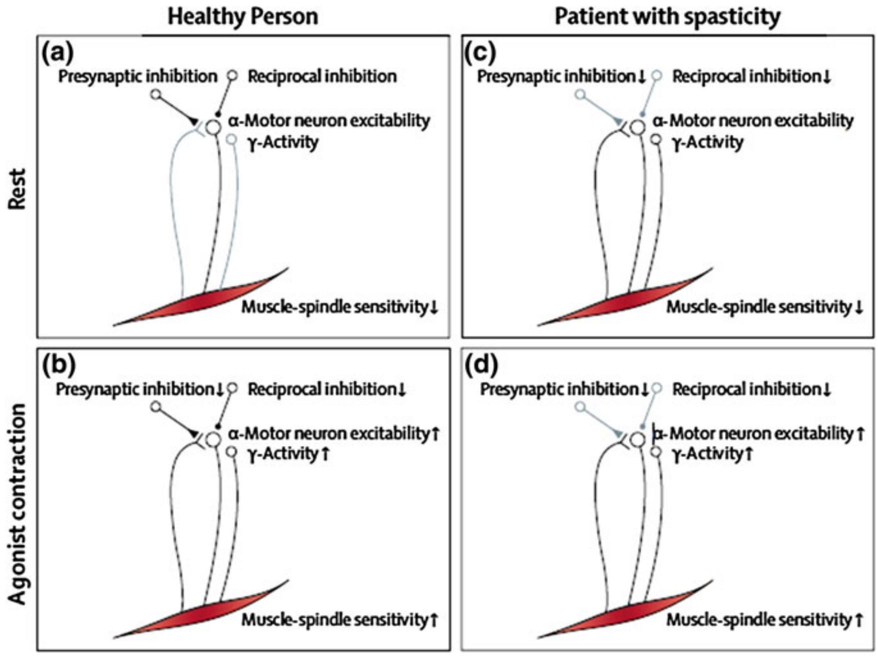

Fig. 8.3 Short-latency reflex behavior in passive and active muscle. In healthy people the stretch reflex activity is low at rest (**a**), which is explained by low excitability of spinal motor neurons, low muscle-spindle sensitivity, low discharge rate of Ia afferents, and pronounced presynaptic inhibition (Ib and Ia reciprocal inhibition). During voluntary contraction of the muscle (**b**) motor neuron excitability, spindle sensitivity, and Ia afferent discharge increase, whereas presynaptic inhibition (Ib inhibition and Ia inhibition) decreases. Stretch reflex activity is consequently high. In spastic patients, presynaptic Ib and Ia inhibition is already decreased at rest (**c**) and stretch reflex activity is high already. During voluntary contraction (**d**) there is little change in these parameters and the stretch reflex activity is not very different from that at rest. The *arrows* designate whether the mechanism is decreased or increased during contraction compared with rest. Taken from Nielsen et al. (2005)

decreased during muscle contraction, leading to a reflex-mediated response comparable in spastic patients and healthy subjects (Nielsen et al. 2005). In spastic patients, this deficient control causes a similar muscle activity during contraction and in rest. See Fig. 8.3.

The increased stiffness of the spastic leg, compared to the unaffected limb in patients and compared to healthy subjects, is mainly caused by a large passive stiffness. This is probably due to other issues related indirectly to the spasticity. These include changes in the muscle tone, ligament and tendon properties which also occur following a CNS lesion. Since these changes develop over time following an acute lesion (Nielsen et al. 2005), they may be secondary to the disorder and could be viewed as a compensatory and adaptive method of the system to regulate the muscle tone on a simpler level to maintain support of the body during movements. Several studies have shown that the passive stiffness of a joint may be increased by up to 400 % in patients with a CNS lesion (Nielsen et al. 2005). These changes are particularly evident for antigravity muscles such as the leg extensors (Toft et al. 1991) and can be viewed as the system working to maximize on the remaining function and allow patients with CNS lesions to walk (Latash and Anson 1996). Targeted treatment of these changes could actually have a detrimental effect for the patient, reducing any walking ability which had remained.

The following conclusions can be therefore reached. Firstly, the muscle's resistance to passive stretch is not only determined by the stretch reflex-mediated stiffness (Lowenthal and Tobis 1957) but also by the passive stiffness of tendons, joints, and muscles (Dietz et al. 1981) and therefore the non-reflex stiffness of the contracting muscle fibers (Dietz et al. 1991) should be taken into account. In addition, the increased passive stiffness may be a secondary adaptive mechanism that facilitates the mobility of spastic patients and will be discussed further in the subsequent section. Currently spasticity is assessed using the clinician's own reaction to handling a patient's limb. It can be inferred that clinicians need to evaluate a patient carefully and verify the presence of certain signs of increased stretch reflex excitability that contribute to the increased resistance to passive stretch as only patients with increased stretch reflex excitability may benefit from antispastic therapy.

8.3.2 Hyperreflexia and Afferent Feedback During Locomotion

Patients with spasticity have a gait pattern which typically features a low level of leg muscle activity (EMG) when compared to that measured in the unaffected side (in hemiparetic patients) or healthy individuals (Berger et al. 1984; Dietz 2003b; Dietz and Berger 1983). The severity of the paresis determines the amount of reduction in EMG activity in the spastic muscle, however the temporal pattern of reciprocal antagonistic muscle activation remains largely unchanged (Dietz 2003b; Kautz et al. 2006; Maegele et al. 2002). Leg extensor EMG amplitude modulation occurs in healthy people typically during the stance phase of gait but in spastic patients it can be reduced or lacking.

Sinkjær and Magnussen (1994) observed a maximal voluntary contraction (MVC) in the plantar flexors muscle of the spastic leg that was only 23 % of the value observed in healthy subjects. This reduction is probably due to the decreased excitatory input to the motorneuron pool arising from the CNS lesion affecting the pyramidal tract. The contralateral leg also showed a lower MVC (65 %) than found in healthy subjects. This could be due to the small percentage of pyramidal tract fibers (around 10 %) remaining on the ipsilateral side but the immobility of the patients could also have an influence on the strength reduction in the non-affected leg (Sinkjær and Magnussen 1994). Plantar flexor spasticity has also been shown to be positively related to temporal asymmetry during gait and negatively related to gait velocity (Lin et al. 2006; Hsu et al. 2003). The spasticity of the affected ankle plantar flexors is reported as the most important factor influencing temporal and spatial gait asymmetry (Lin et al. 2006; Hsu et al. 2003). Recent studies have evidenced the importance of ankle dorsiflexor strength as an independent determinant of walking endurance in stroke survivors with spastic plantar flexors (Shamay and Hui-Chan 2012). These findings suggest that stroke rehabilitation programs which aim to improve walking endurance should include strengthening exercises for the ankle dorsiflexors (Shamay and Hui-Chan 2012).

Studies examining perturbations of gait during treadmill walking by using brief acceleration impulses during the stance phase in healthy individuals have identified that short-latency reflexes (SLR) are followed by larger extensor (Dietz 1992, 2002, 2003a) and dorsiflexor (Christensen et al. 2001) long-latency reflexes (LLR) to compensate. When this same experiment is repeated in patients with spasticity, the compensatory muscle activity associated with the LLR is not significant (Berger et al. 1984; Sinkjær et al. 1999). If perturbations are applied after stance with a stretch of the leg flexor muscles, there is a smaller compensatory EMG response on the spastic side than on the unaffected side with no preceding SLR potential (Nardone et al. 2001; Dietz and Berger 1984). There is a similar reflex behavior during displacements applied to activated limb muscles in both non-functional and functional movement situations. The overall result is a reduction in the adaptability of the muscle activity to the ground conditions (Mazzaro et al. 2007). When there is a reduced ability to modulate the reflex activity over the same range as that found in a healthy individuals, this might contribute to the spastic movement disorder (Burne et al. 2005; Dietz 2002).

Mazzaro et al. (2007) investigated the contribution of afferent feedback to the soleus muscle activity during locomotion in stroke spastic patients. The perturbation unloaded the plantar flexor muscles removing the afferent input to the motor neurons. Although the soleus SLR response was facilitated in the tested patients, the afferent-mediated contribution to the ongoing soleus EMG was depressed to an extent related to the level of spasticity, see Fig. 8.4. However, the ongoing soleus EMG was not significantly different between patients and healthy subjects, suggesting that the reduced proprioceptive contribution in spastic patients is to some extent compensated by a change in the descending drive and/or other sensory input. These compensatory mechanisms however may not be enough to reproduce a natural walking pattern with appropriate corrective responses.

The results from Mazzaro et al. (2007) suggest that a contribution of afferent feedback to the on-going locomotor soleus activity is reduced in people with spasticity and could explain the reduction in muscle activity modulation.

Group Ib and II afferent pathways were suggested to contribute to the locomotor soleus activity during the stance phase of walking. Although in spastic patients the afferent input from groups Ib and/or II afferents may be unaffected, the neural circuits integrating these afferents may be less facilitated, for example due to a decreased facilitatory descending input (Mazzaro et al. 2007).

Accordingly, despite Ia mediated stretch reflex being facilitated in spastic patients, afferent feedback to muscle activity during locomotion is depressed. Thus

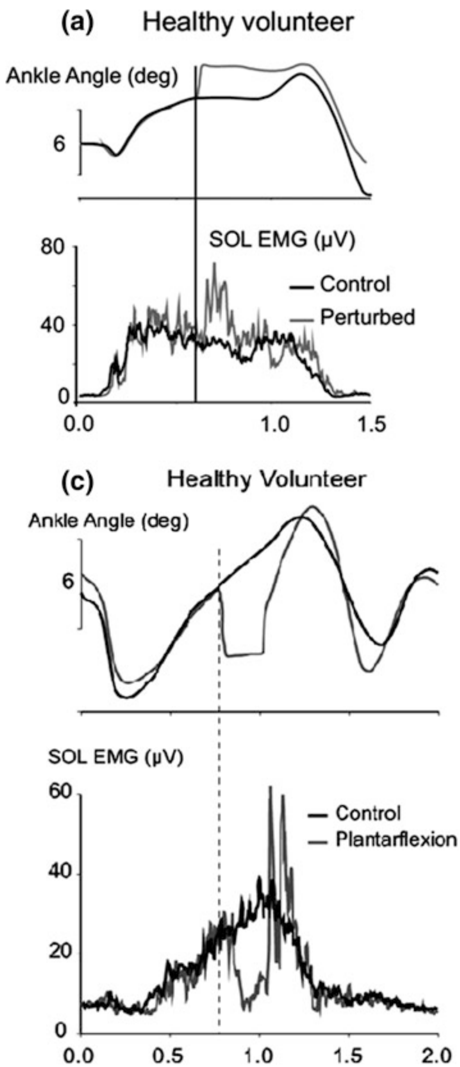

Fig. 8.4 Soleus stretch reflex responses and fast plantarfexion perturbation during walking. Averaged data recorded from 25 trials for a healthy volunteer (*left*) and a patient (*right*). *Top graphs* display the ankle joint displacement while on the *bottom* the EMG muscle activity is shown during control step and perturbations. **a**, **b** The soleus stretch reflex response, **c**, **d** the unloading response due to the removal of afferent feedback by a fast plantarfexion perturbation. Taken from Mazzaro et al. (2007)

antispastic medications depressing reflex excitability, in particularly Tizanidine which specifically depresses the group II pathway (Jankowska et al. 1998), may further impair the locomotor ability of these patients.

Spastic patients demonstrate a lack of physiological reflex modulation during locomotion. As previously mentioned, stretch reflexes in spastic patients during voluntary contractions are not significantly larger than those measured in healthy subjects since as the reflex response is already increased at rest, during the stance phase of locomotion it cannot be much further increased (see Fig. 8.3) (Kita and Goodkin 2000; Burgen et al. 1949; Sinkjær and Magnussen 1994). However the physiological modulation of SLR and H-reflex, both mediated by Ia fibers, become impaired in people with spastic paresis (Sinkjær et al. 1999). Bakheit et al. (2003) reported a relation between the Ashworth scale and the soleus H-reflex. Other studies have suggested a disturbed phase-related modulation of the reflex that was higher during the end of the hip extension phase and the initial hip flexion phase in stroke patients compared to healthy persons (Kamiya et al. 2006). Another observation is that the modulation of cutaneous reflexes is reduced during gait (Jones and Yang 1994). Furthermore the quadriceps-tendon jerk reflex depression is absent in patients with spinal lesions and is associated with a loss of modulation during the gait cycle, however this change is less evident in patients with cerebral lesions (Dietz and Sinkjær 2007).

During normal movements, disynaptic reciprocal inhibition and presynaptic inhibition of Ia afferents to antagonist motoneurons increase in healthy subjects in relation to agonist contraction, conveying the antagonist muscles in a state of maximal relaxation. Due to an inadequate control of the process of switching off the muscle activity, this does not always happen in spastic patients (Nielsen et al. 2005), resulting in a cocontraction of agonist and antagonist muscles that can be identified in some patients during the stance phase of walking (Dietz et al. 1981; Knutsson and Richards 1979; Levin et al. 2000). Extensor muscle activation has been found to be dependent on the foot position before heel strike (i.e. the plantar-flexed position of the spastic-paretic foot) which can cause premature leg extensor activation during the stance phase of gait (Dietz et al. 1981; Knutsson and Richards 1979; Levin et al. 2000). While during slow movements the altered reciprocal activation may not be so functionally relevant, during the fast stretch of the antagonist muscle that occurs most significantly at the transition from flexor to extensor activity, associated with the impact force of the forefoot during locomotion (Dietz et al. 1981; Knutsson and Richards 1979; Levin et al. 2000), a stretch reflex response can be elicited in the antagonist muscle and may contribute to the slow speed adopted by spastic patients (Nielsen et al. 2005). However, while Ia reciprocal inhibition of the ankle plantar flexor muscles is decreased in the majority of patients, this is not seen in the reciprocal inhibition of ankle dorsiflexors (Crone et al. 1994). This may be due to supraspinal control of flexor and extensor muscles in the lower limbs that produces more significant control of flexor muscles than of the extensors and can explain the characteristic pattern of increased extensor muscle tone and flexor muscle paresis which is typically identified in spastic patients (Nielsen et al. 2005).

From these studies into motor control and spasticity, it has emerged that a contribution of afferent feedback to the on-going locomotor activity is reduced in people with spasticity and could, along with a reduced descending drive, explain the reduction in muscle activity modulation. This needs to be considered when determining a suitable therapy for the patient.

8.4 Emerging Therapies

For most patients who have suffered a spinal cord injury (SCI) or stroke, recovery of locomotor function has the highest priority. As identified previously, therapies aiming to increase the motor ability of spastic patients should focus on increasing walking speed and symmetry by improving muscle strength (in particular dorsiflexors), enhancing the muscle activity and reflex modulation as well as reducing agonist and antagonist cocontraction. There has been a significant amount of research focused at developing new therapies for improving locomotion in patients with spasticity however not many of these therapies have been applied in clinical practice. Below are outlined potential emerging therapies which could have a positive outcome for the patient population.

8.4.1 Gait Machines

Although body-weight supported treadmill training (BWSTT) (see Sect. 8.2.2) has been shown to greatly enhance ambulation following incomplete SCI some disadvantages can still be observed. One of the major disadvantages is the time and effort required by the two or three therapists to assist the gait of severely affected subjects, when controlling the limbs and trunk movements. Other negatives include observations that the gait patterns resulting from the training may not be accurate compared to normal walking and patients often have problems controlling their trunk movements and have poor ankle plantar extension and dorsiflexion. This results in patients developing hip movement compensatory strategies which can require high energy expenditure.

Therefore to improve in BWSTT, robotic rehabilitation devices for re-training impaired function have been developed. One example of a robotic rehabilitation driven gait orthosis is Hocoma's Lokomat (Colombo et al. 2000, 2001). The use of Lokomat is similar to BWSTT but the former provides swing and stance assistance by using a motorized exoskeleton and incorporates sensors (e.g. position and force) and actuators to control the generated movements. Programmed actuators at the bilateral hip and knee joints and a controller allow the Lokomat to produce a physiological gait pattern to provide the necessary afferent input to improve locomotion (Mirbagheri et al. 2011). As well as being used for pure training, the device can use the sensors and actuators to measure physiological and other properties of the patient in order to cater the rehabilitation to individual ability and level of injury (Lünenburger et al. 2005). This robotic rehabilitation approach can deliver constant secure guidance of the legs in a physiological gait pattern, high repetition accuracy, improvement in over-ground speed, gait endurance, temporal/spatial characteristics of gait, and improved temporal patterns in EMG activity and provides prolonged training duration compared to manual treadmill training (Wirz et al. 2005). Using a driven gait orthosis relieves the therapists from the tedious job of manually moving the legs of the patient during the BWSTT.

A recent study by Mirbagheri et al. (2011) found that reflex stiffness which abnormally increases in SCI was significantly reduced (up to 65 %) following 4 weeks of Lokomat training. Intrinsic (muscular) stiffness also decreased significantly (up to 60 %). Maximal voluntary contractions (MVCs) were increased substantially (up to 93 % in extensors and 180 % in flexors) following the 4-week training protocol. The findings of the study demonstrate that training with the Lokomat following incomplete SCI is effective in reducing spasticity and improving volitional control.

However, as mentioned in the section on BWSTT as a current therapy (Sect. 8.2.2), robotic gait training like BWSTT may be less successful in patients suffering with spasticity following a stroke. There are also factors to consider such as difficulty in judging how engaged each subject remains during practice sessions. Robotic assistive devices and BWSTT have a downside as the walking movement is generated for the patients and it is easy for them not to maximize their effort during the therapy. Progress in rehabilitation requires procedural and declarative learning and both require focus and attention. It has been argued that inattention may be easier to recognize during more conventional over ground walking training and physiotherapy (Dobkin and Duncan 2012).

8.4.2 Functional Electrical Stimulation (FES)

While functional electrical stimulation has been indicated as a treatment option for spasticity for some time, its actual use in a clinical setting is not widespread.

Electrically eliciting contractions of paretic muscles is a method of treatment based on the enhancement of recurrent inhibition, the negative feedback loop provided by Renshaw cells to the motoneurons, which is decreased in some spastic patients (Salm et al. 2006; Raynor and Shefner 1994). It is proposed that stimulation of spastic muscles can lead to reciprocal inhibition of spastic antagonists through the stimulation of spinal interneurons (Robinson 1995).

When directly applied to spastic muscles and/or their antagonists, the reduction of spasticity is attributed to the stimulation of cutaneous afferents, which could suppress motoneuronal excitability by depressing the propriospinal interneurons or induce long-term synaptic changes in primary afferents in the dorsal horn. Stimulation of peripheral nerves, instead, induces a complete and reversible conduction block of sensory and motor muscle activity but may prevent the transmission of residual voluntary activation of muscles that might have remained after incomplete SCI. In addition, it has been observed that repetitive electrical stimulation increases cortical excitability that outlasts the stimulation. Researchers have reported a reduction of spasticity that can last for 30 min to a day after the stimulation was applied (Dewald et al. 1996) suggesting that treatments based on electrical stimulation may have carry over effects. This technique seems to be effective in the treatment of limb muscle weakness and spasticity (Khaslavskaia et al. 2002).

Electrical stimulation can also be used to elicit purely sensory stimulation (submotoric stimulation) with the primary purpose of reducing muscle tone and improving motor control through increased afferent inputs (Wu et al. 2006). Submotoric stimulation is thought to influence the excitability of the alpha motoneurones (Robinson 1995) and trigger sensorimotor reorganization (Peurala et al. 2000).

FES can also be used to compliment other movement therapies to augment their rehabilitation potential. FES combined with BWSTT has been found to accelerate gait training and increase walking speed and lower extremity muscle strength in patients (Postans et al. 2004). Peripheral stimulation can be used to facilitate muscle activation during the stance and swing phase. Although this technology appears beneficial it does require trained experts to use and is limited by its current availability to patients.

With the attempt of exploring the effects of combining physical and electrical therapy, very few studies have investigated the clinical performances of stroke patients performing leg cycling with muscle contractions aided by electrical stimulation (Janssen et al. 2008). It has been observed that a short bout of leg cycling can improve patients' functional performance but electrical stimulation had no additional effects. Lo et al. (2009) have been the first to propose combining FES and wheelchair leg cycling as a therapeutic approach to reduce spasticity. The FES-LW (lower limb-wheel chair) system can provide a stroke patient with increased mobility and also the ability to propel a wheelchair themselves. It was observed that there was a positive effect on reducing spasticity immediately after testing in both FES-LW and the LW training, but no significant difference was found between leg cycling with or without FES (Lo et al. 2009). However, the application of FES to the affected leg during cycling had an additional effect on reducing spasticity in a group consisting of subjects with higher levels of muscle tone.

Contrarily, the simultaneous combination of electrical stimulation and passive locomotion-like movement had significantly greater immediate effects on gait velocity than those of either electrical stimulation or passive locomotion-like movement alone in patients with hemiparetic stroke (Yamaguchi et al. 2012).

Yamaguchi et al. (2012) adopted a therapeutic strategy consisting of phase-related electrical stimulation for inducing modulation of the excitability changes of the soleus H-reflex during passive hip flexion–extension movements. The tibialis anterior muscle was electrically stimulated at the end of hip extension and at the initiation of hip flexion during the gait cycle whereas the soleus was stimulated during the initial hip extension and the knee was fixed in full extension by a rigid knee brace. Yamaguchi et al. (2012) reported an increase in walking speed and a decrease in spasticity as assessed by the Ashworth scale after treatment. These findings suggest that electrical stimulation combined simultaneously with passive locomotion-like movement may be a valid therapeutic approach.

8.4.3 Increasing Cortical Excitability

Khaslavskaia et al. (2002) demonstrated that there is an increase in motor cortex excitability of the targeted muscle after repetitive electrical stimulation. Motor evoked potentials (MEP) elicited by transcranial magnetic stimulation (TMS) on the tibialis anterior were measured before and after repetitive electrical stimulation of the common peroneal nerve. An increase in MEP amplitude was evoked which lasted up to 110 min after the end of nerve stimulation. MEPs elicited by transcranial electrical stimulation (TES) were also increased but to a lesser degree (around 50 %) compared to MEPs elicited by TMS stimulation. Since TES is believed to mainly activate the axon of the cortical cells, the increase in MEP cannot be exclusively due to an excitability increase at the cortical level (Khaslavskaia et al. 2002). However, these results suggest that an increased sensory input can drive long term cross system changes in motor areas of the cerebral cortex that may, in part, compensate the loss of descending input after CNS lesions (Khaslavskaia et al. 2002).

The development of non-invasive techniques of cortical stimulation like TMS shows potential in the treatment of neural dysfunction. It is hypothesized that an increase in activity in the motor cortex by cortical stimulation would increase the inhibitory influence on spinal excitability through the corticospinal tract, thereby reducing the hyperactivity of reflex pathways and reducing spasticity.

There are several recent studies which have combined peripheral nerve stimulation with direct stimulation of the motor cortex using TMS in a protocol termed paired associative stimulation (PAS) (Mrachacz-Kersting et al. 2007; Poon et al. 2008). A promising study by Mrachacz-Kersting et al. (2012) substituted TMS with a physiologically generated signal within the human brain. A single electrical pulse was delivered to the common peroneal nerve to generate an afferent volley timed to arrive during specific phases of the cortical potential generated when a movement was imagined. MEPs recorded before and after the intervention demonstrated that a significant increase in cortical excitability could be obtained with a far less number of repetitions than in conventional PAS protocols (Mrachacz-Kersting et al. 2012).

8.4.4 Conditioning of the H-Reflex

The final therapeutic approach to be discussed is based on research by Pomerantz et al. (2010). The proposal is for H-reflex operant conditioning by a training protocol aiming to voluntary increase or decrease reflex response to promote functional recovery in incomplete SCI patients. It has been shown that H-reflex conditioning induces and guides CNS multi-site plasticity (Thompson et al. 2009). Up-conditioning the right soleus H-reflex in rats with right-sided contralateral column transaction did strengthen the soleus burst and improved the symmetry of the step cycle (Chen et al. 2006). Up or down conditioning protocols also resulted in an increased or decreased H-reflex respectively during locomotion (Chen et al. 2005). However some portions of the CNS, such as the cortical spinal tract, contralateral sensorimotor cortex and cerebellar connection to the cortex, are required to remain intact for a successful conditioning (Chen et al. 2012). Operant down conditioning of the soleus H-reflex appears to be possible in healthy and in incomplete SCI patients although the effect of the conditioning may appear more slowly in the latter. An improvement in 10 m walking time was observed in successfully conditioned patients, together with an improvement in muscle activity and kinematics. In addition, a study by Chen et al. (2006) has demonstrated that reciprocal inhibition can also be conditioned. This evidence suggests that reflex conditioning protocols could become an important new approach to restoring motor function in patients with incomplete SCI and other chronic neuromuscular disorders.

8.5 Conclusions

Spasticity is associated with an inappropriate resistance to movement, exaggerated reflex activity, painful spasms and general interference to functional movements that can be detrimental to a patient's quality of life. For most patients with spasticity arising after a CNS lesion, recovery of locomotor function is the highest priority. In order to develop and select the optimal treatment approach there is a need for a widely accepted definition of spasticity and a clinical assessment technique more related to movement ability. The current evaluation methods used to diagnose spasticity can lead to treatments being prescribed which only patients without walking ability can benefit from. For this patient population antispastic treatment to decrease muscle tone can improve their quality of life and relieve them from severe pain provoked by contractures or spasms. However conventional drug therapies may diminish residual motor function and reduce muscle strength and so are not suitable for patients retaining some locomotor capability. In functional movements, the changes of muscle fiber and passive tissue properties that lead to spastic muscle tone compensate for the loss of neuronal drive. Accordingly, an assessment of spasticity that evaluates how spasticity affects movement and specifically locomotion must be introduced as a common clinical practice. The common motor impairment associated with spasticity arises from reduced muscle strength, decreased physiological modulation of reflexes and muscle activity, and cocontraction of agonist and antagonist muscles rather than from increased muscle tone and hyperreflexia. Any treatment selection must focus on each individual patient in order to identify and overcome the symptoms that are causing the impairment. Drug therapies may be appropriate for some patients but their effects on walking ability need to be better understood and considered before prescription. It is vital for a clinician to evaluate their patients carefully and determine whether there is evidence of increased stretch reflex excitability as well as an increased resistance to stretch. Antispastic therapy may only be beneficial for patients with increased stretch reflex excitability (Nielsen et al. 2005).

Complementary therapeutic interventions in patients with spastic paresis of either spinal or cerebral origin should be focused on exercise, gait training and relearning through methods employing artificial sensory feedback to restore physiological mechanisms impaired by the loss of descending drive, such as reciprocal and recurrent inhibition. Emerging techniques such as driven gait orthoses, repetitive electrical stimulation, paired associative stimulation (PAS) and H-reflex conditioning focus on these aspects and show promising results but large scale clinical studies are still required to further explore their benefits. Future research should further investigate these techniques with the perspective of developing new rehabilitative approaches aiming to restore motor function in spastic patients.

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Part III
Emerging Technologies

Chapter 9
Reverse-Engineer the Brain: Perspectives and Challenges

Eloy Urendes Jiménez, Antonio Flores Caballero, Francisco Molina Rueda, Javier Iglesias Giménez and Roberto Oboe

Abstract The human brain is the control center of the human body, receiving, decoding, and sending sensorial information throughout the body. It is associated with motor skills and cognitive and sensing abilities. Nowadays, certain areas have been identified with specific human functions, such as vision, motor control, and language, etc. However, the human brain is still an unknown mystery. The capability of the brain to reorganize in response to behavior and/or injury, the neuronal pathway defined by the brain to interact with the environment, the process of learning of new information, and the acquisition of new skills are an intensive research field that requires a professional multidisciplinary team. After CNS damage or physical limitations, a human function is completely or partially lost. Neuronal engineering tries to restore this lost connection through technology. To achieve it, modern neurotechnology is focused on the development of new accurate systems to access the neural information, acquire neural signals at high spatial and temporal resolution at the single-cell level, and decode and use it to restore or compensate a lost function. Advances in electronics have allowed us to design new devices, such as neural sensor probes, in the form of microelectrode arrays, which are inserted directly into brain tissue. In this way, the information is

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extracted directly from the neural source. Depending on the information, it can be used to extract commands and restore the lost pathway or to model the behavior of a brain area. Nowadays, complex mathematical models are implemented to mimic the behavior of a neuron group. The potential is large in this area, since a neural model that is implemented could replace a damaged neuron group in the future. Currently, research lines are intensive in the treatment of patients with disabilities through neural interfaces, such as prostheses for the upper limb, visual prostheses, and brain computer interfaces. However, there is a long way to go, such as the biocompatibility between user and device and selectivity and stimulation of neurons, muscles, and nerves. There is a large open field in this research and technical challenges for the future in the neurorehabilitation field.

Keywords Neural pathway · Microelectrode · Neural interface · Neurostimulation · Biocompatibility

9.1 Introduction

In recent decades, there has been a significant increase of life expectancy in industrialized countries. The main reasons are the improvement in quality of life due to improved nutrition and hygiene conditions and the prevention and control of infectious diseases. In fact, the main causes of mortality in the world are now related of chronic diseases, representing 63 % of all deaths (WHO 2012). This change and evolution of the structure of modern society from infectious diseases toward the prevalence of chronic diseases is increasing health spending. In this context, techniques and technology are focused to help people affected by chronic diseases to improve their lifestyles and quality of life. In this way, health care costs for both the patient and health system can be reduced.

Bioengineering is an interdisciplinary field that combines advanced technology knowledge with medicine and biological sciences to define and solve complex health-related problems, improving human health. There are multiples areas in the field of bioengineering—e.g., biomechanics, clinical rehabilitation, bioinstrumentation, and biomaterials. The bioengineering field includes the definition and development of systems for both rehabilitation and functional compensation, the creation of new living tissues, and even the design of tools, such as biocompatible devices.

The bioengineering market is big and growing fast. In fact, the annual revenue in the US bioengineering market is about $1 trillion USD for medical devices and biopharmaceuticals (Henton et al. 2012). The National Academy of Engineering (NAE) identified three grand challenges for engineering in the 21st century in relation to the health field: advance health information, engineer better medicines, and reverse-engineer the brain (Glenn et al. 2011). One of the main research lines is focused on this last grand challenge: understanding the brain and applying technological knowledge in engineering to define solutions for health problems. This research area is a multidisciplinary field that requires close collaboration between engineering, biology, and clinical staff.

The human brain is a distributed, parallel, and hierarchical biological computer, composed of about 10^{11} neural cells (Nurmikko et al. 2010). This neural multi-circuit maintains the activity associated with motor skills and cognitive and sensing abilities. Plasticity in neurons and synapses of the central nervous system (CNS) supports the learning of new information and the acquisition of new skills. Physical damage or chronic diseases in the CNS break the “neural pathways,” reducing or removing human capabilities. The main goal of neurorehabilitation is to restore this broken pathway to recover a lost human function or compensate for or minimize it. There are an important number of techniques and technologies focused on this field presently. The right fusion between them can be used to restore this pathway (broken, damaged, or injured due to different circumstances, like illnesses with side effects affecting the CNS/PNS, locomotive system, and/or the senses) between the CNS/PNS and the external world or to use their limited or invalidated extremities without, or at least fewer, limitations.

In the repertoire of these practices to “re-enable CNS pathways,” there are techniques based on advanced electronic devices, such as brain implantable systems and intracranial probes, like the one described in (Nurmikko et al. 2010). These techniques are technically considered invasive brain-to-computer interfaces. Also, there are techniques based on noninvasive neuroimaging methods; brain signals recorded in this way have been used to power muscle implants and restore partial movement with success, more or less. Although they are easy to wear, noninvasive implants typically produce poor signal resolution due to the low nature levels of the recorded signals; dispersing and blurring of the electromagnetic waves are the most common problems of noninvasive technologies. Although the waves can still be detected, it is more difficult to determine the area of the brain that created them or the actions of individual neurons.

A mixture of both previous technologies exists to solve the intrinsic problems of devices inserted/attached directly to brain tissue; there are partially invasive interfaces that reside inside the skull cap but do not touch the brain tissue.

Chemical or pharmacological methods are another intensive research field that can be represented by Akkurt et al. (2010). The mathematical approaches are really interesting and useful to model the behavior of a CNS pathway using complex mathematical rules; an example is Lu et al. (2011). In this chapter, different research areas will be presented, focused on this challenge to “reverse-engineer the brain.”

This chapter is organized as follows. Sect. 9.2 provides an introduction to the advanced methods in the present day for recording brain activity. The acquisition of neural information can be achieved from within the brain or outside according to the method of invasiveness. Accessing and decoding this information are the first steps towards recovering a lost function. In Sect. 9.3, it is shown how the acquired neural information can be used to restore the broken CNS path. The knowledge gained from previous neural decoding and new neuroengineering techniques and technologies is the source to develop new devices and interfaces to recover a specific lost function, such as vision or motor skills. In Sect. 9.4, new challenges in the neuroengineering field are presented to get long-term reliable and effective devices. Finally, conclusions are summarized in Sect. 9.5.

9.2 Accessing and Decoding the Brain

For successful restoration of human capabilities, the neuroscience field aims at decoding neural information to understand brain functioning. The techniques used to acquire brain signals, which are decoded to extract neural information to understand the brain, can be classified according to their invasiveness: invasive and noninvasive methods.

On the one hand, an invasive method requires open surgery to penetrate the skin, break the skull, and cut the membranes that cover the brain. In this way, electronic devices can be implanted into the brain tissues. Advances in the field of neural electronics have allowed the creation of tools, such as biocompatible microelectrodes arrays, which are implantable into brain tissue at a given location, to capture neural information with spatial and temporal resolution at the single-cell level (Nurmikko et al. 2010). The relationship between these brain locations and their function is an intensive research focus to define the neural information pathways.

On the other hand, a noninvasive method relies on electrical measures of brain activity without the need for surgery. This method is based on an electrode cap with electrodes placed directly on the user's head. In this way, the brain signals are acquired. To achieve good signal quality, a special abrasive gel and conductive cleaning pastes are used on skin areas where electrodes are located.

Invasive methods have the advantage of achieving a good signal quality and a high spatial resolution level. However, it requires surgery. Below, invasive methods are presented in detail, and noninvasive methods are introduced in this section. For full details, the reader can see the next chapters focused on noninvasive methods.

9.2.1 Invasive Technology

Techniques based on brain implantable intracranial probes, *invasive methods,* depend upon electronic device development—more precisely, on ultraminiaturized embedded systems. These probes read cerebral activity (that can be used for detecting movement intention or any other purpose depending on the reading zone) in the form of electric potential changes, using an electrode array consisting of multiple needles in a square formation. Each needle is the sense part of an electronic circuit, which sends measured data using only 1-2 wires and recently wirelessly.

Earlier experiments using this technology take us as far back from 1969–1970 to the University of Washington School of Medicine in Seattle (Fetz 1969). Actually, invasive intracranial probes and implants are related to solving vision and have targeted repairing damaged sight; now, there is a blind patient capable of performing simple tasks unassisted (Kotler 2002). Restoring movement is the other main task for these invasive devices. Invasive devices produce the highest-quality signals of BCI devices but are prone to scar tissue build-up, causing the signal to become weaker or lost as the body reacts to a foreign object in the brain.

An invasive device, which can be understood like an output-only system, presented in Nurmikko et al. (2010), is full of innovations compared to past devices of the same family—intracranial probes. One of the most notable improvements that can be seen in the previous paper is the inclusion of all required electronics within the implanted probe; thanks to this improvement, the signal-to-noise relationship (SNR) can be minimized to the minimum possible level.

At this point, the reader needs to know more about SNR and A/D (analog-to-digital conversions). Each probe's needle takes data from the brain in the form of electric potential level (voltage); this is an analog measurement, and due to the low voltage level nature of brain signals, the data measured with the needle can be too similar in terms of voltage levels with the read noise. The relation between noise and measured data is technically known as SNR, but with the inclusion of all needed electronics (preamplifiers + A/D converters + serializer) in the intracranial probe, the SR problem is minimized.

About the powering of this device, it presents an innovation in the field of implantable probes (this is not a new invention in other technical fields). The electric power is delivered in a wireless way, using the electric-to-magnetic/magnetic-to-electric power conversion principle of classical transformers, but due to the low power requirements of the device, these needed parts can be placed under the skin, one connected to the probe device and one over the skin, outside of the skull, obviously.

Thanks to previously described improvements, these new types of intracranial probes are safer and better protected than the relatively old example shown over a monkey's skull in Nurmikko et al. (2010), which needs to mount all the necessary components (A/D converters, electronic PCB for data exchange, battery, etc.) over the subject's skull; the reader can easily imagine the huge problem of carrying a device like this, both for the subject's health and for the probe's integrity. The improvement in embedding the electronics within the internal probe in conjunction with wireless data transmission, is also a forward step from the health point of view; these techniques avoid the problem of connecting wires from the intracranial probe to the skull's outside, which is very useful to avoid potential infections due to this open connection between the brain and outside world.

Also, this new probe still uses needles (very small and short needles) inserted directly into brain tissue; this can cause injures, and with enough time, the subject's immunological system can reject the "strange" corpses inserted into the brain tissue—the needles.

There is another important aspect on the usage of these devices that use needles into the brain; for instance, the European Society's general reaction for these types of devices is a commonly approved rejection, and they are a nonauthorized practice in Europe.

9.2.2 Noninvasive Technology

Noninvasive methods have their start point with the discovery of the electrical activity of the human brain in 1924 by electroencephalography (EEG). In 1924, Hans Berger was the first scientist to record human brain activity. EEG is the most studied potential noninvasive interface, due to its fine temporal resolution, ease of use, portability, and low cost, but it is a technology very susceptible to noise. One of the most successful researches about noninvasive devices is a study based on P300 signals. Patterns of P300 waves are generated involuntarily (stimulus-feedback) when people see something they recognize and may allow these devices to decode mean of thoughts without training. Brain-computer interface (BCI) is a noninvasive device based on the electrical activity in the brain and the development of the EEG. The intensive research based on noninvasive BCI starts in the 1990s. Below, this device is presented in the next section and in detail in the next chapters.

9.2.3 Towards a Brain Model

About the mathematical approach, it has full interest, because mathematically based methods try to mimic a system behavior, and the most important thing of this is that the system can belong to any research field; it can be a mechanical system, an electric system, a hydraulic one, or a mixture between different system types, and it can be a neural system, too. This process of extracting a system behavior and describing it using formal mathematical language is called "modeling."

The research shows the process involved around the modeling of a neuron group, based on strong and deep mathematical methods and extensive evaluation and quantification of the modeled system's output performance, to check the viability of the mathematically modeled neuron group.

This study shows the great potential behind these modeling techniques, also in the very first basic steps. If the behavior of a neuron group can be replicated artificially, it could be implemented to replace damaged or injured neuron groups; this idea was transmitted to the reader by Lu et al. (2011). Obviously, this model of a neuron group needs to be implemented in hardware that allows for a fast execution time, at least equal to or less than the required time for the natural neuron group.

9.3 Restoring Functions: Neural Interface as New Possibility for the Treatment of Patients with Disability

Neural engineering is a field that requires a professional interdisciplinary team, such as engineers and neuroscientists, to understand the functioning of the nervous system and to develop interfaces from the latter to machines in order to treat neurological and musculoskeletal diseases (Lovell et al. 2009).

The current design and development of neural prostheses are largely targeted to compensate for the loss of function in a sensory or motor system. Progresses have been made in the last decade in the development of specific prostheses to (i) replace lost receptors for hearing (cochlea implant) and vision (retinal and cortical implants), (ii) control upper limb prostheses by the user's intention, and (iii) replace loss of motor control through functional electrical stimulation to produce muscle activity/movement (Lovell et al. 2009). Therefore, neural interfaces (NIs) have the potential to restore a connection with the world for people with severe movement and sensory disorders. In addition to their clinical impact, NIs could revolutionize the way of studying the central nervous system (CNS) by connecting neuronal circuits with external devices (Vato et al. 2012).

In this section of the chapter, we shall describe the area of biological-machine systems integration (BMSI), focusing on NIs.

9.3.1 Motor Prostheses

Amputation has several etiologies, usually following traumatic injury or the result of vascular diseases, diabetes, osteomyelitis, or tumors. Upper limb amputation usually causes severe disability, altering the quality of life of patients; however, the use of a prosthetic device improves the independence of the patients. In this sense, prosthetic users are usually not satisfied with their prostheses (Cusack et al. 2012).

During the last decade, there has been a renewed interest in the development of advanced, active hand prosthetic devices for amputees and methods for their control (Micera et al. 2008; Yoshida et al. 2010). Opposite to passive prostheses, active devices can be controlled by the user‘s intention (Lovell et al. 2009; Yoshida et al. 2010). Currently available active prostheses achieve movements that are more functional and complex. In this sense, the *"Cyberhand"* is a prosthesis that can provide individual movement of each finger (Dario et al. 2002; Navarro et al. 2005). Despite these improvements, the clinical application of active prostheses is currently limited by the difficulty of decoding the user‘s intention and translating it into commands. Myoelectric prostheses are nowadays the only active prostheses applied clinically (Lovell et al. 2009). On the one hand, high costs have limited the acceptance of these devices. On the other hand, another obstacle in the acceptance of myoelectric upper limb prostheses is the degrees of freedom that must be controlled; the human hand and wrist have more than 20 mechanical degrees of freedom, but currently, upper limb prostheses usually rely on fewer than 6 myoelectric control sources (Cusack et al. 2012).

The nervous system above the level of amputation usually remains intact, so that the brain transmits commands to move the limb, but the movement is not performed. In this situation, the neural signal transmitted to nerves and muscles could be decoded and used to control an artificial limb. In this sense, there are "semi-invasive" active prostheses that utilize neural interfaces, recording signals from peripheral nerves and muscles. According to Yoshida et al. (2010), these interfaces offer a unique solution to the limitations of current clinical prosthetic devices. The neural signal recording is performed with intraneural electrodes. These electrodes, which are located in the extracellular space, can detect the action potentials. Briefly, the approaches for designing electrodes to record nerve activity with the constraint of not damaging the nerve fibers are divided in two groups: (1) extrafascicular electrodes that do not penetrate the nerve fascicle and (2) intrafascicular electrodes that penetrate the nerve fascicle (Lovell et al. 2009). A second approach is the detection of electric signals from muscles. These electric signals are directly associated with the action potentials of the innervated muscle fibers. Compared with the direct nerve recordings, muscle recordings can be performed with relatively simple and risk-free implants.

With regard to muscle and nerve interfaces, there is equivalence between the efferent motor information recorded from the motor unit and efferent information from nerve fibers. Moreover, opposite to nerve recordings, muscle recordings do not allow the identification of afferent activity (Lovell et al. 2009). Therefore, muscle interfaces can only be used to perform control without control by an open feedback loop. This restriction makes the development of interfaces to control prosthetic limbs, based only on muscle recordings, improbable in the next years. The inclusion of neural interfaces that allow users with upper limb prostheses to actively control their movement represents a revolution in the field of rehabilitation. The clinical potential of these systems is relevant; however, the functional and clinical benefits must be weighed versus potential constraints, such as cost, difficulty of decoding the signal, or the lack of knowledge about the long-term biocompatibility.

9.3.2 Visual Prosthesis

Vision impairment causes a severe disability that affects the quality of life of persons. There are many treatment options, but there are diseases that have no effective therapy, such as glaucoma, age-related macular degeneration (AMD), and retinitis pigmentosa (RP) (Lovell et al. 2009). Therefore, these pathologies represent a motivation to develop a visual prosthesis (VP). Currently, there are several research groups that investigate VPs, and there is the expectation that VPs can be commercially available in the next decade. In this moment, there are prototypes with a small number of electrodes implanted either retinally or cortically (Lovell et al. 2009). These systems have been tested in several trials with animals (Wong et al. 2005; Guven et al. 2005) and less so in humans (Yunai et al. 2007).

Where to stimulate the visual pathway is a matter that confronts professionals. According to Lovel et al. (2009), the answer depends on several factors, such as surgical invasiveness, the resolution or selectivity with which the device stimulates, and the range of disease sufferers that are candidates for treatment. Possible neural interface sites for a VP are epiretinal (on the anterior surface of the retina nearest the retinal ganglion cells), subretinal (between the retina and the pigment epithelium, just posterior to the photoreceptors), suprachoroidal (between the choroid and the sclera), transretinal (outside the eye; for example, the sclera), on the optic nerve, and on the visual cortex.

First, several research groups have investigated electrodes in contact with the occipital pole (visual cortex) in individuals with profound blindness. These groups have shown limited success. Dobelle (2000) reported that patients are able to "see" items, such as Snellen letters and count fingers on a hand. Penfield and Rasmussen (1950) indicated that electrical stimulation of the visual cortex with surface electrodes evoked perceptions of points of light, termed phosphenes. The cortical approaches require an invasive process to access to the visual cortex. This procedure has a relatively high risk.

With respect to the neural interface on the optic nerve, several authors have demonstrated relevant findings in patients with retinitis pigmentosa, such as the perception of reproducible phosphenes located in the visual field (Veraart et al. 2003, 2004). Additionally, controlled electrical stimulation of the optic nerve was able to convey visual information useful for the localization and discrimination of objects (Veraart et al. 2003).

Inherited retinal degenerative diseases, like RP and AMD, are diseases wherein the retinal photoreceptor cells are dysfunctional and die progressively. An electronic visual device can be used, such that retinal secondary neurons receive a signal that stimulates an external visual image (Fig. 9.1) (Chader et al. 2009).

There are several versions of retinal implants with epiretinal and subretinal placement (Yunai et al. 2007). Yunai et al. (2007) assessed visual task performance in three blind subjects with RPs implanted with epiretinal prostheses. In this study, the subjects significantly improved the scores on the visual tasks (Yunai et al. 2007). Definitely, these devices could allow restoration of functional sight in patients with improvement in object recognition, mobility, independent living, and quality of life.

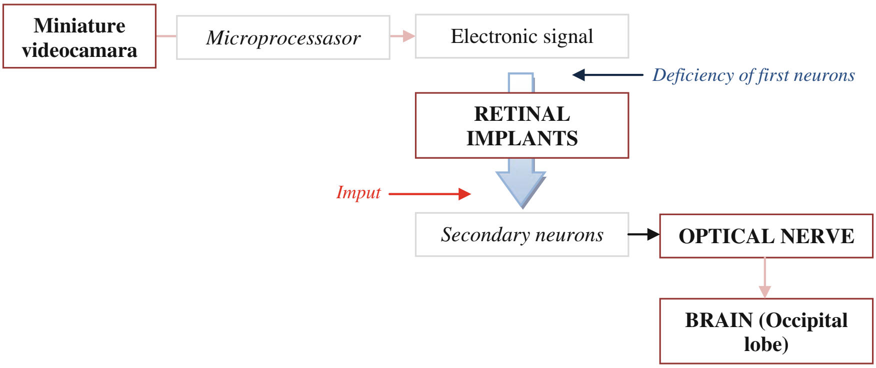

Fig. 1 Components of retinal electronic prostheses

9.3.3 Brain Computer Interfaces

There has been much interest in developing brain-computer interface technology to help improve the quality of life and to restore function for people with severe motor disabilities (Daly and Wolpaw 2008).

Leuthard et al. (2009) defined the Brain Computer Interfaces (BCI) as a device that can decode human intent from brain activity alone to create an alternate communication channel for people with severe motor impairments.

BCI systems could facilitate rehabilitation in subjects with motor disabilities. Firstly, BCI systems can substitute the neuromuscular outputs that are affected due to brain injury by detecting brain signals that control a cursor on a computer or a neuroprosthetic arm (Daly and Wolpaw 2008). Secondly, BCI systems might induce activity-dependent brain plasticity and restore motor function, for example, by demanding close attention to a motor task or by controlling specific brain signals (activation or deactivation) (Daly and Wolpaw 2008).

The BCI platform has 4 essential components. First, brain signals are acquired through invasive or noninvasive electrodes. There are several types of signals, such as electroencephalographic (EEG), electrical brain activity recorded from the scalp; ECoG, electrical brain activity registered under the skill; field potentials, with electrodes monitoring cerebral activity within the parenchyma; and individual units, microelectrodes monitoring individual neural action potential. Second, a signal is processed. This component provides two essential functions—on the one hand, to extract significant identifiable information from the gross signal, and on the other hand, to convert that information into device commands. Subsequently, control functions administered by the BCI system are performed through the device output. Finally, an operating protocol is necessary—that is, the way the system is turned on and off.

9.3.3.1 *Potential Applications of BCIs*

BCIs can be used for restoring normal CNS function. There have been investigations into the therapeutic use of EEG signals. Evidence-based medical investigations suggest an effective motor re-learning intervention after brain injury for activity-dependent CNS plasticity (Daly and Wolpaw 2008; Nudo 2006). Activity-dependent CNS plasticity is not restricted to the healthy CNS and can occur with trauma or disease (Daly and Wolpaw 2008). This plasticity can occur on several levels: synaptic, neuronal, and nerve pathways (Daly and Wolpaw 2008; Teasell et al. 2005).

In stroke patients, the plasticity mechanisms are normal after CNS damage. These changes can positively or negatively affect the nervous system (Daly and Wolpaw 2008). In this sense, if repetitive abnormal movements are performed, the abnormal motor function can exacerbate consistently to activity-dependent plasticity. Therefore, the therapies must be appropriately programmed and designed to achieve successful restoration of the brain function. BCI-based approaches use EEG signals (or other direct measures) to promote and guide CNS plasticity to improve motor function (Daly and Wolpaw 2008).

9.4 Technical Challenges in Neurorehabilitation

As described in the previous sections, there are a few relevant results in neural engineering, showing how it is possible to make use of different technologies to "read" the neurological activity either in the CNS or PNS, in order to gain a better understanding of the functioning of the nervous system or to extract some type of information to be used in restoring some lost capabilities.

The reported applications, even if promising, are far from an arrival point, as many challenges are still to be faced in order to get a set of technologies that make the interfacing to the nervous system reliable and effective long term.

9.4.1 Biocompatibility

If we consider the problem of reading the neural activity, of course the closer the sensing element is to the neuron, the higher the quality and spatial definition of the acquisition will be. This, of course, has led to the use of implantable electrodes, which have better chances to be able to read the activity of a single neuron, compared to surface electrodes. On the other hand, the implantation of electrodes causes inflammatory reactions, requires the use of bio-compatible materials, and faces the problem of possible lesions induced by the initial placement (the electrodes are "shot" with little control on the impact force) or by the relative motion of the electrodes with respect to the neurons (e.g., when an impact causes a cut in the neural tissue or, even worse, a crack in a brittle electrode). All of the above is causing a major concern on the overall long-term bio-compatibility of the implanted electrodes, and it is promoting many research projects in the quest for the "ideal" electrode, which will be placed once and forever in the patient's CNS or PNS, without altering his normal neural activity.

In this sense, many researchers are experimenting alternative solutions, including bundles of microwires (Tseng et al. 2011), which are inherently more resilient to mechanical shocks, compared to the common beds of needles.

9.4.2 Selectivity

Of course, proving the feasibility of a specific solution with a single electrode has little meaning, as a deep understanding of the neural activity requires the analysis of many (possibly hundreds) neighboring neurons.

This aspect affects the design of not only the electrodes but also the interfacing electronics, as the complexity and required data throughput increase with the number of "channels" to be read or stimulated.

Of course, multiplexing techniques (i.e., the use of a single acquiring device, connected to multiple sources through a selector) can be used in order to read or deliver different signals on different electrodes (and, in turn, neurons), but this may not work properly, especially when the stimuli are not sequential but arrive all at the same time, as happens in the image acquisition performed by the retina. Visual prostheses are being developed by many teams around the world, and they usually rely on the use of electrodes acting on the retinal ganglia cells (RGCs). The recognition of an image requires a large number of "pixels," so a visual prosthesis should act selectively on a large number of RGCs, through a large number of electrodes.

9.4.3 Parallel Computing

Once the electrode is reliably attached to a neuron, it is possible either to read the signal related to its activity or to stimulate it. Especially when stimulating a neural circuit, great care has to be paid on the type of signal used, as wrong ones may cause permanent damage (e.g., ion transfer may occur when using unipolar pulses). So, many research groups are proposing specific solutions that best fit different requirements, at the price of some additional complexity and programmability of the driving electronics. Additionally, it must be considered that when the number of electrodes increases, the power consumption and the complexity (and size) of the electronic circuitry are also growing. Recent developments on VLSI are expected to bring benefits on this aspect, together with the development of reliable solutions for the wireless powering of embedded electronic devices.

As mentioned above, parallel neurostimulation may be required in those areas where the stimuli are inherently synchronous on many receptors, as in the vision system. On the other hand, many neural activities evolve in parallel on different neurons, thus needing simultaneous acquisition of several analog signals. So, if we consider the possibility of using neural interfaces to restore lost functions in the neural system (e.g., when a specific neural pathway is malfunctioning), we need to be able to read, process, and generate many signals at the same time.

A relevant application of this concept was brought by the cognitive implants proposed in Lu et al. (2011). As mentioned in the introduction, in this research, it was shown that it is possible to read the activity of a single neuron within the hippocampus, and by using advanced procedures for the identification of nonlinear dynamic models, a reliable simulation model of it has been built. Once the model is available, it has been proposed to be used as a substitute of the actual neural subsystem when the actual one fails in accomplishing its task. In practice, the model should receive readings from the electrodes placed on the input of the impaired neural subsystems, process them in real time according to the pre-identified model, and produce an output to be applied through properly placed electrodes. Given that the overall activity of the hippocampus can not be summarized by a single neuron, it is clear that the scenario above must be multiplied many times, as the restoration of a single neural connection can not have a significant rehabilitative effect. This, in turn, leads to enormous computational power, required by both identification and online neural simulation. As for the first, however, there is experimental evidence that in some cases, the activity to be reproduced is rather general (i.e., it does not depend on the specific individual), so it is conjectured that neural models for specific cells could be obtained by offline processing of the data coming from different individuals. On the other hand, synchronous simulation of several complex nonlinear models requires huge computational power (in terms of digital signal processing) and is still beyond the capabilities of present technologies in order to be embedded in a patient's body.

9.5 Conclusions

The fast development of modern neurotechnology offers new perspectives for human health care. A new horizon of possibilities and hopes opens for people affected by CNS damage, chronic diseases, or physical limitations. On one hand, new techniques and technology are key tools to understand how the brain works. On the other hand, advances in electronic have allowed the rising of new applications and neural interfaces that improve the lifestyle and quality of life of the patient. The goal is that a patient can recover a lost physical function or compensate for it.

In this new paradigm, a close collaboration and coordinated research are required between engineering and medical science. Converging clinical and engineering research is the key to the future in the neurorehabilitation field.

To understand the brain mechanisms, several research lines are concerned with studying the neural pathways, the associated physical function, the process of learning new information, and the acquisition of new skills. New technologies, such as data acquisition systems, brain signal processing software, and complex microelectrodes are powerful tools that contribute to the progress in these areas. Also, advanced mathematical approaches are used to decode the neural information and to mimic the behavior of a neuron group.

Currently, modern microelectrode arrays, inserted into brain tissue, are able to extract information of a neuron group at the single-cell level. These arrays transmit the neural information to the external electronic device by short-range wireless, so a bundle of wires is not used. A surgical operation is needed to insert the microelectrodes into the brain; so, there is risk of infection, and a postoperative period is necessary. Another issue is the biocompatibility between electrode and tissue, which is an intensive research focus to minimize the damage or rejection. Nowadays, these microelectrodes are being tested with monkeys.

Yet, several major challenges must be met and await resolutions related to wireless capability, high performance, material, structural design, geometrical form, security, reliability, and reduction of tissue damage. In the near future, the insertion of microelectrodes will be through a simple surgical operation with a short post-operative period. Patients will wear microelectrodes with long-term performance.

Understanding the brain and the acquisition of brain signals are critical issues for the development of new neural interfaces and the evaluation of the effectiveness in technical and medical terms. Currently, the main interfaces based on brain signals are visual prostheses, prostheses for upper limb amputees, and BCIs to interact with the environment. As discussed above, it is essential knowledge in the medical field to understand, for example, how to stimulate optical or motor nerves.

Although, many research groups are focused on those interfaces, there is still much research work ahead. There are still great technical challenges, such as adaptability, usability, learning, and compatibility. New biomaterials are used to improve human biocompatibility and reduce the rejection situations. A better selective stimulation is being researched to perform a neural task or function, improving the effectiveness of the interfaces for example.

That said, converging clinical and engineering research is the key for neurorehabilitation in the future. Listening to the brain, understanding it, and applying technological knowledge in engineering to represent it and define solutions for health problems are the goals to be achieved in the coming decades.

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Chapter 10
Robotic Rehabilitation: Ten Critical Questions about Current Status and Future Prospects Answered by Emerging Researchers

Antonio J. del-Ama, Alicia Cuesta, Vijaykumar Rajasekaran, Fernando Trincado, HyunKi In and David Reinkensmeyer

Abstract Robotic rehabilitation research and development accelerated dramatically in the last 20 years, yet the success of the field is still debatable. A critical evaluation of the the current status and future prospects of the field is provided by discussing 10 key questions for the field. Five emerging researchers in the field offer responses to the questions, intending to provide a means to step back and see the field through new eyes. A senior researcher in the field briefly comments on this emerging perspective. Enhanced adaptability and intelligence in addition to better integration within the patient's environmental context were identified in this chapter as the areas for future breakthroughs.

Keywords Rehabilitation robotics · Wearable sensors · Neurorehabilitation

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10.1 Introduction

Like the field of robotics in general, rehabilitation robotics is a field in which exciting advances are produced almost daily. Robotic rehabilitation research and development accelerated dramatically in the last twenty years: rehabilitation mediated through robotics has the potential of providing more intensive and repetitive interventions, with less strain and workload for therapists; new objective assessment methods; and even new interventions given the ability of the robot for providing repetitive, precisely controllable, and secure movements. Robots also have the potential to intelligently assist in accomplishing a much broader range of activities of daily living than is currently possible, including walking and manipulation tasks, improving independence and quality of life for many individuals with a severe disability.

Due to the accelerated research and development over the last 20 years, hundreds of robotic rehabilitation device prototypes have been built, substantial clinical data has been obtained from many of these devices, and tens of devices are commercially available. Yet the success of the field is still debatable. In a large survey in the US as recent at 2009, less than 2 % of rehabilitation clinics had used a robotic therapy device (Chen and Bode 2011). Some rehabilitation researchers contend robotic therapy devices are effective, while others view the outcomes achieved by these devices as incremental and clinically insignificant. Some researchers see a brighter future for wearable sensors than robotic devices for rehabilitation therapy. Others contend that exoskeletons are the future of rehabilitation robotics.

A search in the literature reveals several recent reviews about the state of the field of rehabilitation robotics for upper limb (Riener et al. 2005; Pennycott et al. 2012; Kwakkel et al. 2008; Loureiro et al. 2011; Masiero et al. 2009; Norouzi-Gheidari et al. 2012) as well as lower limb (Swinnen et al. 2010; Wessels et al. 2010; Díaz et al. 2011; del-Ama et al. 2012; Moreno et al. 2011; Mohammed and Amirat 2009; Dollar and Herr 2007; Dollar and Herr 2008; Rocon and Pons 2011; Pons 2008) applications. Instead of reviewing this literature again, we critically evaluate the current status and future prospects of the field by discussing ten key questions for the field. These questions are especially relevant for the large number of young researchers starting careers in robotic rehabilitation. To effectively begin research in this field, emerging researchers must critically analyze the substantial body of existing work and form opinions about the field. This chapter is intended to promote this process.

Each section starts with a critical question about robotic rehabilitation, with the first five questions focused on robotic therapy, the next three on assistive robotics, and the final two on long term vision for rehabilitation robotics in general. Then, five emerging researchers in the field offer responses to the questions. The intent is to provide a means to step back and see the field through new eyes. A senior researcher in the field briefly comments on this emerging perspective in the Conclusion section.

10.2 Ten Critical Questions in Robotic Rehabilitation

10.2.1 Are Upper Extremity Therapy Robots as Effective as Rehabilitation Therapists?

ADA[1]: Clinical studies now show that robot-assisted rehabilitation therapy is sometimes comparable and sometimes less effective than conventional rehabilitation (Pennycott et al. 2012; Staubli et al. 2009). There are likely many factors that determine the effectiveness of robot-assisted rehabilitation. Some of these have already been identified, such as task-specific neural plasticity induced by intensive training or the importance of patient engagement, but many have not. Until we understand these factors the outcomes from robot-assisted therapy will be variable. One important direction for future research is that rehabilitation therapists have the ability to be aware of many facts that current robots do not perceive. For example, a rehabilitation therapist can tailor therapy to a patient's specific needs and can detect subtle changes in patient functional status and engagement due to patient mood and/or personality. Capturing therapist-like intelligence in robotic therapy should continue to improve its effectiveness.

AC: Rehabilitation therapists are using robotic therapies more frequently and such therapies are starting to become popular in clinics. On one hand, there isn't enough evidence to say that robot-assisted therapy is more effective than conventional rehabilitation therapies (Kwakkel et al. 2008) but on the other hand several reviews suggest that there is evidence supporting the use of this technology to reduce impairment. One significant aspect of robot therapy when compared with conventional therapy is the possibility of performing many exercise repetitions during arm and hand training. In addition, practicing without active assistance from a therapist has in some cases been shown to be even more motivating because of the computer gaming, feedback, and physical assistance provided by the robot (Loureiro et al. 2011; Norouzi-Gheidari et al. 2012). Robots can also promote increased training at the patient's convenience. In light of these different features, one should not compare robotic and conventional therapies against each other, but rather consider how they can be complementary. Patients will need both to optimize their motor recovery.

VR: A key systematic review of the effects of robot assisted therapy on motor and functional recovery in patients with stroke found that the rate of recovery in robotic therapies is comparable to traditional therapeutic methods (Kwakkel et al. 2008). However, the effectiveness of rehabilitation therapy using robots depends on the device being used, the purpose the device is being used for, and the ability of the device to adapt to the user. One clear advantage of robotic therapy is that

[1] Acronyms refer to authors' names. For details go to 'About the authors' section, at the end of this chapter.

many common exercises can be performed without the need of continuous evaluation by the therapist (Brewer et al. 2012; Lo et al. 2010).

FT: At the moment some therapy robots are better than traditional therapies in two aspects. First, they are able to exercise different limbs independently, such as the fingers (Amadeo, PneuGlove, Reha Digit) (Balasubramanian et al. 2010). Second, they are able to implement protocols to train the coordination between the different joints, since one can accurately define the desired coordination pattern for each patient (Lewis and Perreault 2009).

HI: There are many reports about the effect of robotic therapy compared with that of conventional therapy delivered by therapists. Most of these reports suggest that robots are as effective or even more effective than therapists (Kwakkel et al. 2008; Lum et al. 2002). Some previous studies also reported that rehabilitation with passive (i.e. non-motorized) robots can improve recovery compared with the rehabilitation done by therapist, and almost the same amount of therapist attention is required in both cases (Reinkensmeyer and Boninger 2012; Housman et al. 2009). In terms of financial considerations, some studies reported that robotic therapy is more economical in the long term (Wagner et al. 2011). Moreover, a robot can quantitatively measure the condition and properties of the body, and move the body accurately and repeatedly. These features mean that robotic therapy will likely continue to become a more effective approach compared with conventional therapy in the future.

10.2.2 Are Gait Training Robots a Failure?

ADA: Gait training robots are still in the beginning of their development. Walking is a functional movement that arises from a complex interaction between musculoskeletal structures, whereas many initial lower extremity robots were designed from the viewpoint that walking is a rather fixed mechanical movement (Lei et al. 2006). In addition, loss of walking ability due to neurological disease affects the control systems for walking in ways still not well understood (i.e. spasticity, muscle synergies), and this lack of knowledge precludes development of robots that can provide optimal therapy for walking (Knikou 2010; Van de Crommert et al. 1998; Dobkin and Duncan 2012).

Physical and cognitive information exchange between the user and gait training robots is not transparent enough yet. Physical interaction is still a major issue not solved yet due to the high complexity of musculoskeletal structures and the way power is delivered to the joints: robots drive human joints through application of torque between adjacent limbs, whereas the musculoskeletal system drives joints through application of force through a viscous-elastic actuator: the muscles (Cajigas et al. 2010; Aoyagi et al. 2007; Wolbrecht et al. 2008). Interchange of cognitive information is also far from being transparent, user friendly and multimodal, in the sense of intelligently utilizing multiple channels such as speech recognition, EEG, and EMG (R. Porcar A 2010). Finally, current lower extremity robots address only partial aspects of walking, focusing on the stance and swing phases of stereotypical gait while ignoring functional aspects such as turning, sitting, and climbing stairs. Aspects like balance during standing or walking have not been adequately addressed yet due to the high complexity of the mechanics involved as well as the complexity of the mechanisms needed to assist in training those mechanics.

AC: It is still too early to decide that gait training robots are a failure as the conditions under which such devices can be effective are just beginning to be understood. For example, one promising finding is that a combination of different rehabilitation methods, including robotic training, seems to be more effective than training gait with only one technique (Belda-Lois et al. 2011). Pragmatically, with robotic devices, patients can achieve the goal of standing much earlier than with conventional therapies. In addition, robot-aided training reduces therapist effort, especially when the patient is severely affected. But it is still necessary to continue research to develop better robots that are more functional and useful; there are already examples where such an approach appears to be improving results (Schück et al. 2012).

VR: Gait training robots have never been a failure; they are continuously developing as they receive intense interest. The main reason behind what may be perceived as slow progress are the complexity of balance, postural stability, and locomotor adaptation to the environment (Akdogan and Adli 2011).

FT: Gait training robots are not a failure; rather, we still haven't found the right combination between all the available tools. There are many different approaches at the moment to the problem of rehabilitation, including pharmacological treatments, electrical stimulation, and training with robots, so a key direction for future research is to determine the key principles that connect different approaches together in an optimal way. A good example of this approach is the recent finding that paraplegic rats that received a combination of the three above approaches regained substantial ability to walk (van den Brand et al. 2012).

HI: The commercial success of the Lokomat proves the feasibility of using robotics for clinical gait training robots and is facilitating further development in this area. To draw an analogy, the success of the Apple iPhone dramatically influenced the mobile phone industry by accelerating development of new applications and new kinds of smart phones. Similarly, the success of the Lokomat is accelerating development of new computerized training algorithms and new gait training robots. However, the functional outcomes of robotic gait training are still too small (Hidler et al. 2009), and it is critical to increase these outcomes for gait robots to continue to succeed.

10.2.3 Why Are Robot Therapy Devices Still Used in Less than 2 % of Clinics and Rarely at Home?

ADA: The primary reasons are the lack of scientific evidence of effectiveness, high economic cost and low user friendliness (Wolfe et al. 2010; Domingo et al. 2006).

AC: The main reason is economic, because these robots are very expensive and neither clinics nor patients can afford them. A second, related reason is that there is not enough scientific evidence to affirm that robots are better than conventional rehabilitation therapies in terms of cost-effectiveness (Wagner et al. 2011).

VR: The primary reason is that patients and clinicians are apprehensive or uncomfortable using robotic therapy devices, and this can be resolved by making the devices more user-friendly and interactive. A secondary reason is that patients and clinicians are unaware of how to alter or have difficulty altering robot parameters to best fit each application. This can be solved by making the robotic therapy systems more adaptive to the patient's evolution during therapy.

FT: One important reason is that robotic therapy devices are usually too expensive. However, as these devices spread among hospitals, clinics, and homes, the prices will decrease. In addition, therapists reject the technology in part because of a fear of being replaced by robots. On one hand, this fear seems senseless, as there are many responsibilities of a therapist that it is difficult to imagine a robot assuming. On the other hand, there are studies that show that use of assistive technologies can reduce costs by diminishing the required hours of medical assistance (Hoenig et al. 2003). The idea that the work of rehabilitation engineers could take away somebody's work is disturbing, as many people do not want to live in a world in which robots replace humans in every task. We are still far from this situation, but engineers must aim to facilitate individuals' lives, not replace people, lest we create in world where there are only jobs for robot developers.

HI: First, the therapeutic effect of robotic devices is not much better than conventional therapy (Lum et al. 2002; Reinkensmeyer and Boninger 2012; Housman et al. 2009; Kwakkel et al. 2002). Second, current devices are large and complex. Third, protocols to use robotic therapy devices based on quantitative data are not well established, but instead still rely on qualitative tests (Lum et al. 2002; Reinkensmeyer and Boninger 2012; Housman et al. 2009; Kwakkel et al. 2002). In medicine, the ideal is to provide treatment quantitatively according to the quantitative diagnosis of the body's condition. For example, a doctor will inject a certain amount of a specific drug when the blood pressure of patient drops below a certain level. In the field of robotic rehabilitation, quantitative protocols need to be defined to guide the use of the robots. The measurement and actuation systems of robots will aid in the development of such quantitative protocols.

10.2.4 What is the Key Missing Knowledge Needed to Effectively Build New Robotic Therapy Systems?

ADA: The knowledge needed for designing robotic therapy systems includes: what is the exact physiological structure lost or damaged, what is its function and interrelation with other body structures, and what intervention should be performed on this, and/or, surrounding structures to best recover function. A recent good example of this approach for gait rehabilitation in SCI can be found in (van den Brand et al. 2012).

AC: An important aspect to building new robotic therapy systems will be to take into account new research in neuroscience and neurorehabilitation (Dobkin 2004). In addition, knowing what patients want, what their feelings are, how they feel when using therapy robots, if they feel comfortable or they want to use it, or what they would like to have would also aid in the development of robotic therapy systems (Gelhaus 2011).

VR: Artificial intelligence is needed to make the robotic therapy system more adaptable and controlled in specific ways based on the patient's evolution. Such intelligence will facilitate making robotic therapy systems more user friendly and effective.

FT: The key knowledge needed is how to adapt the robots to the different features of each person. People who have suffered stroke or spinal cord injury are so different from each other that it is very difficult to design a robot for everybody. But this is the only way to bring a device to the market: design for all. There are many different aspects between patients that one must consider in building a new device: physical, psychological, even ethical. Some strategies are being implemented to adapt the robot to the different users (Salter et al. 2006), but there is still much research needed in this area.

HI: The knowledge needed is what sensor information or amount of force is required at what level of precision to assess the patients and to control the device, as it would help decide what sensors and actuators are essential.

10.2.5 Are Wearable Sensors Sufficient for Therapy, and thus Robots Not Needed?

ADA: Therapies involving physical contact with the patient's limbs, such as providing physical guidance for teaching the task or to make the task easier and safer, can benefit from robots (Reinkensmeyer and Patton 2009). However, there are some interventions that can be performed by the patient without physical assistance, where the therapist only gives verbal instructions. In those cases, interventions can be performed by only using wearable sensors to asses and provide feedback (Holden 2007; Merians et al. 2006).

AC: Both wearable sensors and robotic devices are needed to improve patients' recovery, and combining them will produce the best therapies. There are many possible approaches to rehabilitation, and combining different techniques, such as robotic devices, FES, virtual reality, BCIs, along with help from therapists, will likely produce the most effective results (Bergmann et al. 2011; Krebs and Hogan 2012).

VR: Wearable sensors or motion sensing devices like the Kinect can help the therapist in correcting the patient′s posture or motivating the patient to achieve a desired movement or in following a pattern. But robots are helpful for assisting the patient in training to achieve the goal of normal movement. They can also provide greater control over joint trajectories by applying restrictive or resistive forces that motivate the patient in moving joints in such a way as to achieve specific goals.

FT: Wearable sensors cannot physical prevent patients from making compensatory movements that impede the rehabilitation progress. Robots are useful for teaching patients how to perform movements correctly and for preventing compensation (Ball et al. 2007)

HI: Wearable sensors are sufficient for simple assessment and motivation using virtual reality (Morrow et al. 2006). Without robots, physical interaction can be provided by therapists. However robots are still needed because they can provide precise and accurate control of limb movements, and more impressive virtual reality through physical interaction. There are already various wearable sensors that work well, but rehabilitation robots are still developing, which in itself suggests there is a need for therapeutic robots.

10.2.6 What is the Most Important Technological Problem that Needs to be Solved for Robots that Help People Accomplish Activities of Daily Living?

ADA: Creating effective assistive robots will require developing effective and efficient artificial intelligence. Current control strategies are too complex and time consuming (Freeman et al. 2009; Jonić et al. 1999). Assistive robots are aimed to help people in daily life activities, which are carried out in unstructured environments. Unstructured environments mean that the robot cannot have an exact model of every task stored in the memory, but rather has to adapt and learn how to perform the task needed by the user (Cooper et al. 2008). For example, a robotic arm designed to pick up objects needs to learn how to perform the task for different objects and different object locations.

AC: A key problem especially for wearable robots, such as exoskeletons, that can assist in activities of daily living is reproducing human movement in the three planes of space, so that movements are as natural and functional as possible (Waldner et al. 2009). A key question for such robots is whether they should focus on compensation or rehabilitation. In other words, should they force patients to do the "right" movements or instead help patients to recover function by using their own movements? Depending on the answer assistive robots will need to be developed in different ways.

VR: The key problem is controlling a robot in a patient-specific way, making it adaptable with respect to the evolution of the patient (Hesse et al. 2003), and capable of providing various forms of assistance as needed to help perform activities of daily living.

FT: There is still much research needed into machine adaptation to the user. It is important to improve machine learning techniques to detect the user's intention in order to get a natural interaction between the robot and the user. This facilitate development of assistive robots that help users perform desired movements quickly but safely (Ikemoto and Amor 2012). The tradeoff between speed and safety limits the success of current assistive robots.

HI: Developers of assistive robots must consider the social and psychological factors that affect user acceptance (Scherer et al. 2007; Scherer et al. 2005; Batavia et al. 1990). One of the most successful types of assistive devices for people with a physical impairment are spoon holders. Such devices are accepted by users because they are very simple, have a low cost, and function well. Another example is the wheelchair, which users are unfamiliar with at first, but because they substantially improve the individual's life are widely accepted (Sørensen et al. 2003). To increase personal acceptance, robots should be compact and have a familiar design. This requires mechanical and electronic parts to have small size with good performance, which is a substantial design challenge.

10.2.7 Will Legged Exoskeletons Solve the Mobility Problems of People Who Are Elderly?

ADA: It may seem unlikely that elderly people will use exoskeletons, but this is in part because most people who are elderly are not used to using such complicated devices, simply because they do not need to use them, or because they are not motivated to learn new abilities. In addition, legged exoskeletons still have many technological aspects that must be improved in order to result in much more transparent, small, light, easy-to-wear devices that can be incorporated easily into the actual lives of people who are elderly (Kong and Jeon 2006).

AC: Exoskeletons have the potential to help people who are elderly with their mobility, but it's difficult to believe they will because current exoskeletons are complicated to use. If they can be made simpler, they could help people who are isolated (Kong and Jeon 2006).

VR: Legged exoskeletons can solve the mobility problems for elderly people but their use will depend on the motivation of the patient to use them as tools. Legged exoskeletons that rely on substantial effort from the user will have the drawback of causing fatigue, a problem which will be more severe for elderly people. On the other hand, if the legged exoskeleton acts autonomously then it will lead to slacking and undesired disuse atrophy. Using a wheelchair for mobility is currently easier than using an exoskeleton, but the psychological effect of using a wheelchair can be negative, and wheelchairs can require help from others to transport, a problem which wearable exoskeletons have the potential to solve.

FT: Exoskeletons, or exoskeletons combined with functional electrical stimulation (del-Ama et al. 2012), have the potential to assist people who are elderly in being more independent. But it is especially difficult to design rehabilitation devices for people who are elderly for several reasons. First, they are more skeptical about the benefits that such devices can bring to their lives. Second, they often refuse to learn to use something new. So we have to be especially careful to implement devices that are designed with the preferences of people who are elderly in mind (Meng and Lee 2006). For example, regarding exoskeletons, they have to be easy to wear, as simple as putting on trousers.

HI: It is unreasonable at the present time. First, elderly people are less inclined to use new things, so adoption of this new technology will take a long time. Second, easy-to-control, easy-to-wear and simple structures are very important (Pons 2010) and current legged exoskeletons do not posses these features. Therefore the benefits of using an exoskeleton to walk are small compared to the inconvenience of putting one on. Another problem is that legged exoskeletons are not familiar to people yet, and many people hesitate to use new types of devices which are unfamiliar (Scherer et al. 2007; Scherer et al. 2005; Batavia et al. 1990). However, if the function of a device is good enough, it will be adopted by many users. An example is the wheelchair which was at one time unfamiliar to most people but is widely used today. Similarly, legged exoskeleton will eventually be accepted if they substantially improve function.

10.2.8 Will Humanoid Robots Assist Us in Our Daily Activity in the Future?

ADA: It is difficult to envision humanoid robots helping us in the near future. Hand dexterity, artificial vision, navigation in unstructured environments and cognitive interaction with humans are complex problems that are far from being solved. Furthermore, there is no need to build humanoids to perform tasks that can be optimally performed by specific (non-humanoid) robot designs, such as the Roomba robot for cleaning the floor, or computerized systems for control of the home environment.

AC: Someday humanoid robots could possibly help us in mechanical work and with activities of daily living. For example, some studies have already shown that humanoid robots can provide help for some tasks at home (Bäck and Kallio 2012), especially with elder people.

VR: Humanoid robots will help us in the future, and there are already specific applications showing the feasibility of this concept. For example, the small humanoid robot NAO from the Aldebaran robotics group in France was recently used in a hospital environment for monitoring purposes (Bäck and Kallio 2012). However, a key motivation for making humanoids is because of their potential flexibility in providing assistance for a broad range of activities of daily living (Inamura et al. 2009). For such use, there is still much work needed to make humanoid robots friendly, including having appropriate expressions, and making them strong, gentle, and adaptive enough to physically interact with people of different sizes, ages, genders and cultures (Zecca et al. 2008).

FT: In the future, humanoid robots will help people with a movement impairment to perform daily activities independently. It will also be important to design machines that can serve as partners, since in the future there will be more and more elderly people living alone. For these applications a key focus will be to develop the social aspects of the interaction between the robot and the person, an aspect that is currently being improved by many robot developers (Shin and Choo 2011).

HI: In the far future it is certainly possible that humanoid robots will assist people in activities of daily living. But in the near future humanoids for assisting general daily activities are impossible. Many technologies need to be improved to develop effective humanoid robots, including better energy storage, small but powerful actuators, and better artificial intelligence. It is impossible to make humanoid robots small and efficient with current energy storage devices (Madden 2007; Controzzi et al. 2010). Assistive robots also need to have very reliable control because even occasional mistakes will make the user angry or possibly be unsafe. For example, if a robot washes dishes with a 99 % success rate, it will break dishes every few days. Maintenance of the robot will also have to be cost effective; otherwise people will prefer hiring human help rather than using a humanoid. However, demand for humanoid robots will be driven in part by issues such as the desire for privacy, curiosity about robots, and reduced cost compared to hiring humans once humanoid robots are mass produced.

10.2.9 What Will My Rehabilitation Process Look Like if I have a Stroke when I am 70 years old?

ADA: Nothing more to add to the paper (Reinkensmeyer 2011).

AC: Both therapists and robots will be involved in the rehabilitation process, to create a complete treatment approach that helps me recover best from the stroke, similar to (Reinkensmeyer 2011).

VR: The rehabilitation process will be more adaptive, easily accessible, and comfortable enough to undergo from home.

FT: I will be able to move immediately after the stroke using a brain-computer interface that will automatically adjust to my brain features in order to translate my thoughts to commands. This will help me to communicate easily with my caregivers (Hintermüller et al. 2011), in case my ability to talk is impaired, making the rehabilitation process more effective. I will have robots activating my limbs from the very beginning of the rehabilitation process.

HI: In some countries, people want to stay in the hospital for a long time because they want to restore their motor level to as high a level as possible. But there is a problem when people who cannot gain any more motor function remain at the hospital, because for some kinds of injuries and diseases it is impossible to be restored perfectly (Kwakkel et al. 2002; Reinkensmeyer et al. 2004). This wastes money and time on the side of both the patients and the hospital. In the future, the ability to predict how much residual capacity of motor function a person can theoretically re-gain will be improved. The type and duration of therapy will then be based on this prediction, as will the proper type of assistive device, which will range from simple aids to sophisticated robotic devices. The assistive device may also contain modes for a therapeutic purpose. The rehabilitation process will then be focused on training to restore the predicted amount of motor function and on learning how to use the recommended assistive device.

10.2.10 What Key Development Will Allow Researchers to Make a Major Impact on Restoring Human Mobility?

ADA: Making a major impact on human mobility will require continuing to eliminate architectural barriers (Boninger and Cowan 2012), as persons using assistive devices will still likely have limited ambulatory capabilities. For example, curbs, turning, and balancing on uneven surfaces limit walking performance in exoskeletons (Dollar and Herr 2008; Mohammed and Amirat 2008).

AC: Making a major impact on human mobility requires understanding that robots have to be consistent with human movement, giving freedom to patients and promoting function. Robots also have to make patients work during therapy, and compensate for those movements that patients cannot perform. Patients need to feel safe with the robots.

VR: In order to make a major impact in restoring human mobility we need to develop tools which can captivate the patient by providing therapy based on his or her needs, activities, and interests.

FT: Until we involve patients in the design of robots for rehabilitation, we will not make a major impact. There is a lack of inclusion of the users in the process of designing assistive technology. This often leads to applications that don't meet the user's needs. It is very important to take into consideration patients' opinions, suggestions, and ideas in order to develop technologies that impact people's daily life.

HI: Restoring human mobility only with rehabilitation therapy seems to have limitations, and transforming mobility will ultimately also require drug or cell-based treatments.

10.3 Conclusion

DR: Rehabilitation robotics research is alive, well, and in good hands as evidenced by the above analysis. While these emerging researchers recognize the limitations of current robotic rehabilitation devices, they are encouraged by initial positive results. Equally importantly, they are able to clearly elaborate the precise nature of the shortcomings of current devices that still need to be addressed and strategies for addressing these issues. So, while one naturally concludes from their analysis that there are significant and important problems still to be solved in this field, one also concludes that there is a new wave of researchers already engaged in solving those problems.

What advances will this new wave produce? If the above discussion is an indicator, we can expect breakthroughs in two main areas. First and foremost the next generation of researchers will produce robotic rehabilitation devices with greatly enhanced adaptability and intelligence. These smart devices will more accurately tailor therapy and assistance to the needs of individual patients based on quantitative measurement and an improved understanding of neurophysiological recovery mechanisms. They will also incorporate improved user interfaces, making them intuitive and easy to use. Thus, one can expect to see a proliferation of smart algorithms and improved interfaces for rehabilitation robots in the next ten years based on the interests of these emerging researchers.

Second, one can expect to see rehabilitation robots designed to better fit into key niches in the "ecosystem" of rehabilitation care. The next generation of researchers will achieve this by working with users to identify the specific problems they want solved, and developing more cost-effective technologies to meet those needs. As stated by AC, the devices will be "consistent with human movement, giving freedom to patients and promoting function". This means they will allow naturalistic movement in multiple planes, and intelligently assist in complex mobility tasks such as moving through and manipulating natural environments. These devices will also be designed to complement human therapists, and to be used in a rational way within the context of an array of treatment techniques, including electrical stimulation, wearable sensors, and biologic treatments. One can expect, in other words, that this new wave of researchers will move robotic rehabilitation a large step forward toward the goal of fully restoring human mobility.

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Chapter 11
Upper Limb Neuroprostheses: Recent Advances and Future Directions

Aikaterini D. Koutsou, Susanna Summa, Bilal Nasser, Josefina Gutierrez Martinez and Muthukumaran Thangaramanujam

Abstract This review covers the main issues related to the various therapeutic modalities that aim to immediately recover the lost/diminished motor function or resulting carryover effects in patients after a central nervous system lesion caused by injury or disease. The presentation concentrates on upper extremities; yet, most therapeutic modalities are appropriate and applicable for the lower extremities. We critically present the state-of-the-art of methods used for indirect and direct stimulation of the central nervous system, stimulation of peripheral sensory-motor systems, the use of exoskeleton and other robotic platforms for rehabilitation, and the combination of robotic and stimulation systems. The review summarizes who could benefit from the new technologies and what the limitations of the neuroprostheses available today are. We illustrate the methodology by 2 examples: a patient after spinal cord injury and a patient suffering from tremors. These examples were selected to show that the current development of technologies and improved knowledge from the life sciences open new horizons. The message to take home is that an improved therapy that applies the appropriate therapy at the right time after the injury has the chance to improve the quality of life of many

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humans that become victims due to accidents, lifestyle, and many other reasons. The other message that must be the motto of clinicians and researchers is: Get a **smile** and a **happy face** back to the **patient**.

Keywords FES · Neural damage · Neuroprosthesis · Upper limb · Nerve injury · FES combination · Surface stimulation

11.1 Introduction

The convergence of engineering and rehabilitation has led to a new era in the development of technological therapeutic tools to expedite the patient's recovery process. Neuroprostheses (NPs) and hybrid systems could become the key ammunition in the arsenal against motor disability. The main contribution of this chapter is to minimize the concerns of the clinician when it comes to using an NP for motor function rehabilitation. Furthermore, the aim of this chapter is to underline the benefits of the use of NPs in rehabilitation, assess the use of them in different levels of impairment, and suggest ways to overcome the hurdles, which could pave the way for improved acceptance of neuroprosthetic devices by patients and clinicians.

Patients with motor disorders, such as spinal cord injury and stroke, need neurorehabilitation to preserve, retrain, and recover their motor functions. In Spain, 24 % of every 1000 habitants present impairments when it comes to moving an object with their upper limbs. The percentage increases to 25 % of every 1000 habitants that are not able to change their body posture (INE 2008). The need for an effective and accurate neurorehabilitation solution is crucial for these people.

This chapter is structured as follows: in the introduction, a short survey on different neurorehabilitation therapies of motor disorders is presented. In Sect. 11.2, the electrical augmented therapies in motor neurorehabilitation are introduced to the reader. A special subsection is dedicated to peripheral stimulation. The reader can explore and study the use and benefits of motor neuroprostheses (NPs). In next section, 2 examples of imaginary patients illustrate why NPs should be used in motor neurorehabilitation and what the patients and clinicians should expect from their use. The importance of a clinical assessment of NPs is quoted in Sect. 11.4. In Sect. 11.5, the reader will meet the authors' suggestions for future developments and improvements in NPs. Finally, the chapter's conclusions are included in Sect. 11.5.

11.1.1 Conventional Rehabilitation Therapies

Rehabilitation practice guidelines are focused mainly on traditional manual therapies (Lin et al. 2003). In spite of their need for long periods of rehabilitation sessions, these methods present very good results. Traditional rehabilitation therapies for motor injuries are based on functional movements for task-specific training of the central pattern generators (CPGs) and muscle strength training. The outcome of these methods depends simultaneously on the patient's state and the therapist's state. Therefore, the session duration could be shorter, not only because of the patient's fatigue but also because of the therapist's (Del Ama et al. 2012; Moreno et al 2011). In addition, in many cases, there is no objective measure for the rehabilitation achievements and motor function improvements (Dietz 2009).

Various approaches were implemented to rehabilitate patients with motor control disorders. This section discusses the benefits of 2 more recent approaches that have been used to recover movement in humans with upper limb paralysis; it explores the available results of the use of these therapies provided in the literature, their benefits to patients, and the major drawbacks that these technologies confront scientifically, technically, and ethically.

Recently, constraint-induced movement therapy (CIMT) was introduced in the treatment of stroke patients with paresis of the affected upper limb, as long as the motor and sensory deficits of the affected limb were not too severe. CIMT is a rehabilitation treatment that is used to improve upper limb function of patients with central nervous system damage, based on the concept of learned non-use. The main idea of this therapy is based on considerably intensified exercise of the affected limb while the movement of the healthy limb is simultaneously restrained with a splint, light cast, or sling (Taub 2001). The use of CIMT presents several physiological and motor-related drawbacks (Teasell 2012). It may be severely hampered by muscle weakness in the subject or residual functional capacity that is too poor. Based on the studies of (Tarkka and Kononen 2009) in chronic stroke subjects, the time since stroke, the affected hemisphere, or the gender of the subject did not have any significant effect on the degree of functional gain achieved after CIMT.

Pharmacological interventions, such as amphetamine treatment, have been applied in animal models. Preclinical findings have shown that restoration of perceptual, cognitive, and motor function appears to be dose-dependent on drug treatment and transiently facilitated recovery on a cognitive task but not when paired with training. Some studies have found that the beneficial effect of combining amphetamine and rehabilitative training after brain injury is task-specific (Barbay and Nudo 2009). Amphetamines may enhance neural signals to maximize sensorimotor integration and may resolve issues of diaschisis. Although the majority of animal studies with therapeutic amphetamine demonstrated positive outcomes, the findings of clinical trials involving stroke patients are somewhat equivocal. Some results are associated with better relative changes in motor and language function from baseline to last follow-up; however, the activities of daily living have low scores (depression grade at follow-up), and there is increased systolic and diastolic blood pressure, as well as heart rate. Amphetamines can adversely affect behavior in a dose-dependent manner, resulting in hyperlocomotion, which transitions into repetitive stereotypical behaviors as dosages increase.

Other means of enhancing movement are based on training on a one-to-one basis, providing constant and systematic augmented feedback, insisting on prolonged and intensive training that is directed to tasks that require integration of potentially functional structures, progressive increase in difficulty of the training task, and ensuring successful endeavors. This treatment provides an environment that is well suited for relearning movement, because it eliminates the needs for nonexistent strong contraction of postural muscles, thus increasing the safety attitude, thereby allowing other networks to reconnect if any of this is to happen (Popović et al. 2003).

Following these studies, technologies of enhancing movement have been developed for providing prolonged and intensive training, as well as constant and systematic augmented feedback, such as robot-assisted therapy.

11.1.2 Robotic-Assisted Rehabilitation Therapies

An interesting comparison between manual and robotic-assisted rehabilitation therapies shows that the latter overcomes the lack of increased repeatability of the manual techniques and increases the independence and motivation of the patients to train (Prange et al. 2006). Robotic rehabilitation devices have programmable force-stable exercise, and therefore, they guarantee exercise repeatability. In addition, robotic devices can perform exercise, varying the force, velocity, resistance, and movement, while the therapist can not guarantee the repeatability of all these parameters during task repetitions.

Robotic devices are often used for assisting the movement rehabilitation of persons with disabilities (Brewer et al. 2007; Riener et al. 2005). Most works focus on rehabilitation after stroke because it is a large population. Anyway, there are also a lot of studies about robotic rehabilitation after spinal cord injury, cerebral palsy, and multiple sclerosis. The main advantages of robotic rehabilitation are: repeatability and automation and quantification of physical therapy with greater precision of outcomes. Usually, the training session is side by side with a computer game presented on the screen, and the robot assists patient movement to perform the task. Many assistive control strategies have been developed (see review: (Marchal-Crespo and Reinkensmeyer 2009)). Some examples are assist-as-needed control proposed by Reinkensemyer for the neu-WREX (Wolbrecht et al. 2008), a pneumatic exoskeleton for arm rehabilitation, and performance-based progressive assistance proposed by Krebs for the pioneering arm-training robot MIT-MANUS (Krebs et al. 2003). The main goal is to encourage patient effort during the exercise execution.

11.2 Electrically Augmented Therapy

The use of only traditional rehabilitation techniques and robotic devices is insufficient in many cases where the motor function is completely lost and can not be recovered or where the outcome is not permanent. This kind of patient can benefit by the application of electrically augmented therapies. The next presentation includes the main characteristics, benefits for the patients, and drawbacks in the use of brain and peripheral stimulation as presented in the literature.

11.2.1 Brain Stimulation

Changes in the sensory and motor maps usually characterize several disorders that involve motor and sensory disturbances. There are a lot of studies in the literature that have investigated the possibility of rehabilitation inducing plastic reorganization of brain lesion systems. This particular type of recovery is based on 2 mechanisms: compensation and substitution (Robertson and Murre 1999). Luria (1963) referred the compensatory process as a functional reorganization or functional adaptation. In this view, the reorganization of surviving neural circuits could aim to recover neuro-motor functions. The use of brain stimulation in rehabilitation is characterized by the ability of the reorganization of surviving neural circuits after cortex damage. Recovery is achieved by combining motor function training with stimulation training. Training would lead to a redistribution of representations to undamaged areas of the sensory cortex via reorganization (Flor and Diers 2009). Therefore, motor learning, or relearning, is fundamental to neurological rehabilitation. To improve motor performance during learning, we use an iterative process, repeating voluntary movements and identifying and correcting errors. Moreover, Krakauer, even distinguishing recovery from the adaptation process, says that "recovery means that undamaged brain regions are recruited, which generate commands to the same muscles as were used before the injury" (Krakauer 2006). This knowledge is used to develop new rehabilitation treatments. For instance, in sensorimotor rehabilitation, the primary intention would be to stimulate the sensorimotor cortex, in order to induce a plastic reorganization. There are 2 different ways to induce a plastic reorganization:

- Indirect ("passive brain stimulation") stimulation through sensorial feedback for the aim of inducing motor relearning.
- Direct ("active brain stimulation") stimulation intended to influence and eventually to change electrical neural activity

11.2.1.1 Indirect Stimulation

Sensory and motor functions are intimately correlated in motor skills but not in reflex motor or automatic movements. Somatosensory information and feedback can modify the on-going motor behavior, triggering preprogrammed corrective action. Additionally, it was shown that animals with damage to the primary motor cortex would increase their dependency on visual monitoring of reaching, reinforcing the interrelationship of sensory processing and motor control (Nudo et al. 2000).

This reinforcement occurs because the motor cortex and the sensory cortex are found side by side in the parietal lobes of the brain. For this reason, a damaged brain area could be trained, during session therapy, by visual, auditory, or tactile sensory stimulation (indirect stimulation); see (Flor and Diers 2009). For instance, patients with phantom limb pain provided evidence that providing the impression of viewing one intact hand in a mirror instead of the amputated hand leads to better movement and less pain in the phantom limb (Ramachandran et al. 1995).

11.2.1.2 Direct Stimulation

Some stimulation therapies that aim for brain regions directly are transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and deep-brain stimulation (DBS). They are used principally to treat brain diseases or improve functional deficits, as in depression, Parkinson disease, epilepsy, and dystonia (for a review, see: (Wassermann and Lisanby 2001)). rTMS and tDCS are noninvasive procedures. tDCS uses constant, low current delivered directly to the brain area of interest via small electrodes. tDCS was originally developed to help patients with stroke. Their main advantage is the hope for noninvasive, drug-free treatment. Instead, DBS is a treatment that needs a surgical procedure. It consists of an implanted device, which sends electrical signals to brain areas regulating brain activity.

TMS is a subset of electrotypes and used to stimulate the primary motor brain cortex for assessing excitability that is associated with motor relearning and improvement of motor function (Barbay and Nudo 2009). Navigated TMS utilizes individual magnetic resonance images for accurate localization of stimuli; this feature is specifically useful when repeated measurements are performed. Thus, repeatable stimuli can be applied to a certain location; plus, coil orientation and tilting can be controlled. A descendant of TMS, repetitive TMS (rTMS), has been investigated in a variety of neurological conditions and psychiatric disorders, including addictions, depression, and auditory hallucinations. Writer's cramp, or focal hand dystonia, is characterized by involuntary coactivation of an antagonist. (Murase et al. 2005) used subthreshold low-frequency (0.2 Hz) rTMS, which exerted an inhibitory action on the cortex. They found that stimulation of the premotor cortex, but not the motor cortex, significantly improved the rating of handwriting. Tests demonstrated that tDCS could increase cognitive processes on a variety of tasks. An example is shown in (Reis et al. 2009); they used tDCS over the primary motor cortex during learning of a novel motor skill task. Their aim was to find strategies that enhanced skill acquisition or retention. They analyzed the stimulation effect on both within-day and between-day effects and on the rate of forgetting during a 3-month follow-up. Amazingly, they found that tDCS, across the 3-month follow-up period, had favored a consolidation mechanism. This may hold promise for the rehabilitation of brain injuries.

Nowadays, at the point at which research has arrived, we can think of rTMS and tDCS as helpful tools in rehabilitation therapy; instead, DBS seems to promise, in the future, permanent or longer-term usage.

11.2.2 Peripheral Stimulation

The survey on motor rehabilitation therapies concludes with therapies of peripheral stimulation. It is explicitly elucidated that electrical stimulation (ES), a form of physical therapy that elicits muscle contraction using electric pulses over the peripheral sensory-motor system, has contributed to maximizing the efficiency of preserved neuromuscular structures, thereby developing new movement strategies to recovery function, as well as strengthening the atrophied muscles. ES exerts an influence on the afferent nervous system by means of improving the body's circulation and increasing range of motion. The benefits of the use of ES in rehabilitation are very well documented (Prochazka et al. 1997; Houdayer et al. 2002; Hobby et al. 2001; Popović et al. 2001). Patients with motor injuries have shown faster recovery when ES rehabilitation methods are used.

Such ES treatment methods that have been used currently to recover motor functions are: transcutaneous electrical nerve stimulation, cyclic electrical stimulation, interferential current, and galvanic stimulation. Despite of the widespread use of ES on peripheral sensory-motor systems, there is only one electrical stimulation method that directly complies with the functional task, functional electrical stimulation (FES). This is a treatment method that interfaces the preserved body functions and controls the activation of neural pathways by inducing currents in the tissues to interact with motor and sensory systems; so, it provides the necessary drive to the paralyzed structures (Popović et al. 2001).

11.2.2.1 Functional Electrical Stimulation

FES aims to recruit the peripheral nervous system (PNS) and obtain muscle activation, trying to mimic the central nervous system (CNS). Therefore, FES could be defined as a bridge between the CNS and PNS, ensuring signal continuity from motor command to the movement itself. It delivers trains of electrical charge pulses, mimicking, to an extent, the natural flow of excitation signals generated by the CNS in unimpaired structures (Popović et al. 2002).

Motor NPs are series of devices that use FES treatment to substitute or recover a motor modality, which might have been damaged as a result of an injury or a disease (Popović and Sinkjær 2000). Mimicking the CNS motor command is not so simple. In most of the cases, the generation of a movement needs coordinated activation of multiple muscles that act on multiple joints of the limb. In addition, muscle activation is characterized by a nonlinear dynamic. The muscles' coordinated activation requires a computational effort. But, as the synergistic control hypothesis suggests, the nervous system manages and reduces this required computation by activating just a limited number of movement building blocks. Therefore, the main challenge of NPs is to achieve the muscle synergies that would result in the desired movement. The burst sequence to apply seems to be the key to achieving them. NPs consist of a relatively simple electric circuit: the generator (called the stimulator), the electrodes (anode and cathode), and the human tissue. Figure 11.1 illustrates the function of a motor NP via process steps; i.e., the stimulator receives a command signal and proceeds to the generation of trains of pulses of electrical charge and delivers them to the excitable tissues via electrodes (Popović et al. 2003).

The use of NPs in rehabilitation is often called functional electrical therapy (FET) (Popović et al. 2003). The stimulation pattern integrated in FET is timed to mimic the sequence of muscle activation for able-bodied subjects. FET may

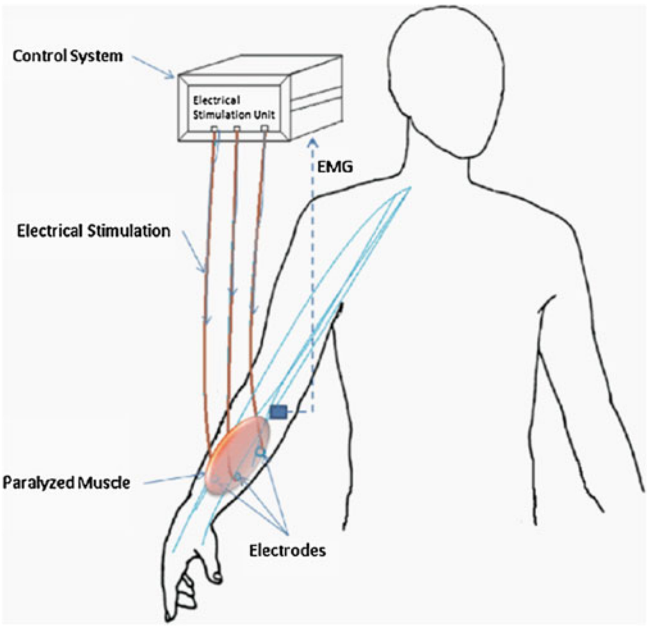

Fig. 11.1 Upper limb neuroprosthesis. An example of how an NP works. The stimulator receives command signals, generates trains of pulses of electrical charge, and delivers them to the excitable tissues via electrodes

increase the effectiveness of the synaptic input and has a specific excitatory effect on the neural circuitry controlling the affected limb and slows down the progress of muscular atrophy and contracture of joints, preserving muscle power, as several researchers in animals (Misawa et al. 2001) and SCI patients have found (Baldi et al. 1998). FET also can activate the afferent pathways of the arm (Popović et al. 2002). Some subjects have exhibited new motor-evoked potential after FET in the muscles of the paretic upper limb, which they did not have before the therapeutic intervention. This finding suggests that the improvement should be attributed to a combination of spontaneous recovery, FET, and activities that the subjects perform voluntarily (Popović et al. 2003; Popović et al. 2004). FET is not only for therapeutic purposes but also for assistive activation that enhances neuroplasticity. Functional exercise, augmented with individualized multichannel electrotherapy, may result in positive changes in cortical spinal excitability in the affected hemisphere, along with enduring improvements in motor behavior in stroke subjects with severe hemiparesis (Tarkka et al. 2011). Therefore, electrical stimulation can be used in therapy (i.e., for the suppression of pathological tremor (Prochazka et al. 1992; Rocon et al. 2010). Electrical stimulation is diffuse in the medical field (Guiraud 2011) among doctors and physiotherapists who use it for patient rehabilitation and functional restoration. From a rehabilitation point of view, it is used after surgery and after stroke. In such conditions, there is a reduction or absence of mobility, so the electrical stimulation allows muscle activation, which is difficult to obtain with traditional exercises. In fact, FET has demonstrated major improvements in the recovery of function, such as decreasing spasm, improved active range of motion, increased muscle tonus, and high score on functional tests (Popović et al. 2004).

NPs in clinical settings and scientific research can be categorized as open-loop or closed-loop FES activation strategies. An open-loop strategy has a simple control design but requires continuous control and intervention from the patient or the therapist. The FES starts with a trigger input that comes from the medical staff or the patient himself. Closed-loop FES control strategies overcome the need of a therapist or patient to control the NP. However, a closed-loop strategy can require complex real-time control that should be able to compensate disturbances and some negative effects linked to leaks in the modeling of muscle activity during a defined movement.

FES devices, and NPs as a consequence, are classified based on the mode of current application (type of stimulation electrodes) as transcutaneous (surface), percutaneous (through the skin), or implanted (Popović et al. 2011). Moreover, in many cases, NPs are also classified by the disease and the cause of motor dysfunction. From a patient's point of view, NPs can also be classified by the impairment level of the patient. In fact, impairment levels allow us to define 2 main categories: temporal and permanent NPs. In particular, with temporal NPs, it is meant that the system is used especially during rehabilitation therapy; therefore, the period of usage is relatively short, while permanent NPs are intended to be used during a lifetime and also as devices that can be "dressed" to perform daily activities (e.g. sitting pivot transfer strategy for paraplegics). Therefore, permanent NPs should be projected as systems that are easily acceptable for individual home use.

The next paragraphs detail the main benefits and drawbacks of each kind of stimulation electrode that have led to the suggestion that the use of implantable NPs is preferable in lifetime users, while surface and percutaneous stimulation NPs could be better in rehabilitation use but could be also helpful for specific daily tasks.

- **Surface electrodes** are placed on the skin over the targeted motor points of muscles. Usually, surface stimulation is performed with electrodes (adhesive or not) that are placed on the skin in the vicinity of the motor nerve of the muscle that is going to be stimulated. Surface FES systems are noninvasive, inexpensive, and simple to apply. All of these features make surface NPs well suited for short therapeutic applications in neurorehabilitation. However, they are unable to isolate deep muscles, may cause skin irritation and pain, and are often non-aesthetic (Popović and Sinkjær 2000). The first problem leads to a very deficient selectivity for small and deep muscles, which poses complexity in positioning stimulation electrodes. The second problem leads to low stimulation force and discomfort caused by electrical stimulation applied over the skin. The pain is definitely a limiting factor in applying surface electrodes in subjects with preserved sensory and diminished motor functions. Pain and tissue damage is related to the electrode's size (Lyons et al. 2004); very small electrodes might lead to pain or tissue damage. One of the suggested techniques for avoiding the last problem is accurately defining the stimulation surface area—if this is too large, the current would diffuse and may not cause the excitation required; if it is too small, it may result in high charge and current density. Other techniques are amplitude modulation (AM) or pulse width modulation (PWM) for the recruitment order of the electrical stimulation. For detailed techniques that are specific for avoiding tissue damage, the reader can refer to D. Popović, T. Sinkjær, "Control of movement for the Physically Disabled," Chap. 4.
- **Percutaneous electrodes** are placed close to the motor point of muscles (Popović et al. 2002). Percutaneous systems use electrodes that are passed through the skin into target muscles and are considered temporal FES systems. The advantages of percutaneous (intramuscular) electrodes over surface electrodes are that they provide higher muscle selectivity and a repeatable response over time with a nonsurgical intervention. Reports of an implantation of over 2000 electrodes, some of them implanted for more than 5 years (Peckham et al. 1988), showed that the risk of infections is low. Possible granulomas at the skin interface are infrequent, but they are treated with local cauterization.
- **Implantable electrodes** are placed around (cuff) muscle nerves or over (epimysial) muscles. Implantable electrodes overcome the main drawbacks of the rest of the electrodes regarding muscle selectivity and infections. However, they present different problems with their use. The mechanisms of failure of FES subcutaneous electrodes may be separated into 3 categories: physiological, biological, or physical (Popović and Sinkjær 2000). The physiological criteria

include insufficient strength, poor recruitment properties (such as nonlinearities), stimulus thresholds that are excessively high or low, poor repeatability, and adverse sensations. The biological failures include those mechanically induced at the surgical installation, excess encapsulation, infection or rejection, and those induced with stimulation. The physical failures are those of the conductor, such as electrochemical degradation or mechanical failures (breakage), and of the insulator. Categorization of electrode failure requires, if possible, the identification of the failure mechanisms to at least this level. Implanted FES systems are intended for chronic use; the stimulator and all electrodes and leads are fully implanted. The implant is powered through batteries (permanent or rechargeable) or via a transcutaneous radiofrequency power and information link (Bhadra and Chae 2009). Recent advances and on-going research in FES and the introduction of implantable systems are enhancing the mobility and activities of daily living among individuals with upper motor neuron deficits (Bhadra and Chae 2009). Implantable neuroprosthetic technology has demonstrated successful control of hand grasp in individuals with spinal cord injury (Peckham and Knutson 2005).

11.2.2.2 Functional Electrical Stimulation in Combination with Other Rehabilitation Tools

Rehabilitation outcomes are improved if a subject takes an active part in the therapy with ES combinations and different rehabilitation therapies, such as hydrotherapy (Popović et al. 2011). Nowadays, NPs more often combine FES with other technologies; they can provide the trigger input for starting FES or provide sensor feedback to the FES loop control or even enforce FES by working in parallel.

EMG and BCI signal analysis for detection of voluntary movements are the two most popular methods of triggering FES in NPs.

- **EMG-triggered stimulation:** Electromyography (EMG) is the procedure of recording the electrical activity produced by skeletal muscles (Kamen 2004). The decomposition of EMG signals can result in movement decision commands to a trigger for electrical stimulation on the affected muscle (called EMG trigger). If the EMG signal exceeds a predefined level, the electrical stimulation takes place to provoke muscle contractions. FES presents a biomechanical delay of movement generation, while Nordez et al. have defined that the electromechanical delay of the movement respecting the EMG signal depends on several factors (muscle, quantification method), but it is supposed to be between 10–50 ms (Nordez et al. 2009). However, this could be sometimes very tricky and needs accurate measurement once applied (Hug et al. 2011). Furthermore, tests have been run by the authors on the upper limb of a group of healthy subjects aged between 25–35 years, and the delay was $\sim$20 ms for the wrist flexors and extensors (rising up to 300 ms for lower limb electromechanical delay). Hence, the EMG trigger can be effectively combined with FES muscle activation to detect a movement before it occurs. Likewise, various studies have demonstrated that using the EMG output signal to control the electrical stimulation of the upper limb proves that it does encourage the recovery of motor function and has effective influence on neuronal plasticity of the brain due to proprioceptive and somatosensory feedback (Overeem 1979; Bello et al. 2009).

- **BCI-triggered stimulation:** Brain-computer interface (BCI) is a direct communication pathway between the brain and an external device (Birbaumer 2006). BCIs are often directed at assisting, augmenting, or repairing human cognitive or sensory-motor functions. BCI is currently used in various applications: to allow paralyzed patients to move cursors, to select letters on a computer (Birbaumer 2006), and to control a robot arm or orthosis. The concept of BCI in combination with neuroprosthetics could be described as receiving brain signal outputs and translating them into motor movement commands and then transmitting them to an external device for the movement execution. The most common noninvasive method used in BCI to record brain waves is the electroencephalogram (EEG) signal. Due to complex human motor activities, particularly in hand movement, the use of EEG is restricted only as a trigger or command (Craelius 2002). Despite this, Pfurtscheller et al. (2005) did show promising results in their studies by using EEG in combination with FES to restore hand grasp functions. The study results showed improvements in a patient by rehabilitating simple hand functionality; e.g., drinking independently from a glass. The combination between BCI and neuroprosthetics has shown a lot of promise for the future development of motor control rehabilitation, in addition to the potential of reading brain activity before any movement occurs while the patient is in the planning state before initiating motor commands. Much development is still required for enhancing BCI techniques in extracting brain activity as well as decomposing the complexity levels of the algorithms used.

In many cases, NPs are combined with other rehabilitation tools in order to overcome FES drawbacks, augment the movement generated by FES, or increase user motivation, (Fig. 11.2). For instance, robotic devices take charge when muscle fatigue is reached by continuous FES. Furthermore, virtual reality and games make the exercises more attractive and encourage the patient to continue.

- **Robotics Systems:** Robot-aided systems generally aim to employ leading-edge robotic technology in neurorehabilitation (Masiero et al. 2009). Many studies have shown good results and improvements in the motor ability of patients (Colombo et al. 2005). Besides, robotic assistance is a very useful tool in reducing the repetitive errors of therapists during progressive rehabilitation sessions of the patient, and incorporating real-time auditory feedback of performance errors might improve clinical outcomes of robotic therapy systems (Secoli et al. 2011). Hughes et al. presented a novel rehabilitation method using ILC mediated by FES. Their study has shown that the FES level does adjust in

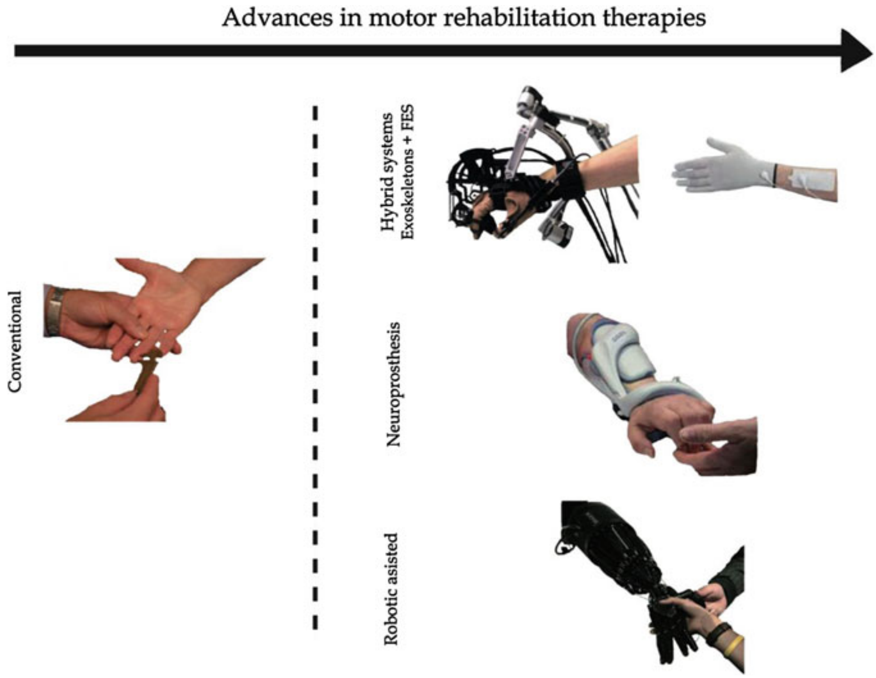

Fig. 11.2 Technological progress of upper limb neurorehabilitation therapies

response to a user's performance, and this has proven effectiveness in combining robotic therapy and functional electrical stimulation (FES) to reduce upper limb impairments (Hughes et al. 2009). Another remarkable approach in robotics was given by Freeman et al. (Freeman et al. 2009); their method improves sensory-motor function of the upper limb by introducing a robotic workstation of the upper extremity using FES. Such approaches provide a controlled environment to apply electrical stimulation coincidentally with the remaining voluntary intention. Nonetheless, robotic assistance has poor efficacy in terms of functional outcome and still needs a lot of development in materials, feasibility, robustness in task performance, and adaptability through patient performance in order to be more effective in helping regain lost abilities (Masiero et al. 2009)—not to mention the increased demands associated with controlling an affected arm make the motor system more prone to slack when distracted (Secoli et al. 2011). Robot-aided devices should be designed to avoid this effect and readjust relatively with patient performance. Check Reinkensmeyer et al. for further exploration of the key problems of current robot-assisted devices (Reinkensmeyer et al. 2007).

- **Gaming and Virtual Reality-Based Rehabilitation:** Games and virtual reality (VR) have recently been employed in rehabilitation for obtaining various gains: patient motivation, cost, and agility. The main aim is to motivate the patient and increase the engagement with volunteering efforts in the session. Adamovich et al. (Adamovich et al. 2009) have designed a virtual piano trainer simulation to train finger motion. The overall designed system has shown very promising results in hand rehabilitation, which demonstrates the effectiveness of adapting entertaining tasks with haptic feedback and the level of motivation and engagement for the user during the rehabilitation session by interacting with the virtual environment (VE) (Lange et al. 2010). It is useful to note that VR or gaming systems must be task-oriented with the case study to increase the effectiveness of the VE interactions with patient performance and avoid any unexpected side effects or distractions that may cause maltreatment of the patient's disability. Hence, new research has started combining FES with video games. The method engages patients with interactive game scenarios and simultaneously applies electrical stimulation to the malfunctioning muscle. Dunne et al. have developed an upper extremity rehabilitation session that supports games for doing specific tasks, such as stretching, doing coordination exercises by using their hands, and using physical or "tangible" input mechanisms (Dunne et al. 2010). Rare research has elaborated good outcomes of this method practically, but theoretically, it does have very efficient applications that might increase the demand of neuroprosthetics in coordination with supplementary systems to entertain and motivate the patient to proceed through the rehabilitation sitting.

11.3 Why Use a Neuroprosthesis and What to Expect in Return

Box 11.1 Spinal Cord Injury Patient Scenario

Phillip is a young man of 23 years; he had an accident while diving from a rocky coast line that provoked in him an incomplete C6 SCI. Phillip uses an electric wheelchair and needs assistance every time he wants to transfer himself from his wheelchair to his bed or his car, because his injury affected his lower and upper limbs. After his surgery, he followed a very intensive rehabilitation program in order to adapt physically and mentally to his new condition. During his acute rehabilitation program, he was retrained for activities of daily living and executed exercises for a range of motions, strengthening, and stretching. He is able to drive a car adapted with hand controls, but he is not able to grasp, because he has no control of his thumb.

Most tetraplegic patients believe that regaining arm and hand function is most important to improve their daily life quality (Anderson 2004). Phillip can use hand straps and zippers in order to wash his teeth or eat his food. SCI patients often present with spasticity or muscle atrophy. Phillip does not present with spasticity; therefore, his neurologist included him in a rehabilitation program in order to preserve and strengthen his muscles. Phillip's therapists execute manual and robotic-assisted exercises, but complete motor recovery is not possible. Phillip can use upper limb exoskeletons, such as (Lucas et al. 2004; Rotella et al. 2009), in order to recover grasp function. But these systems often are bulky and do not augment voluntary muscle activation. Instead, Phillip can use residual motor activities in order to control a device or an NP that activates his muscle to generate the lost motor functions (Rupp and Gerner 2007). Examples of grasping NPs are the Freehand system (Smith et al. 1987) and Bionic Glove (Prochazka et al. 1997). But, we suggest (Popović et al. 2002) a complete review about grasping NPs. At this point, Phillip can only use surface NPs because of the acute period after his accident (Malesević et al. 2012). The use of an implanted FES system can only be applied once the patient reaches stable neurological status, which usually occurs 2 or more years post-SCI (Connolly et al. 2010). Cornwall and Hausman defined the inclusion criteria for a C5-C6 SCI patient to implant an NP (Cornwall et al. 2004). When Phillip fulfills the inclusion criteria of an implantable NP, like (Wheeler and Peckham 2009), he could enjoy the benefits of a permanent implantable stimulation system that offers him independence in his daily tasks. Until then, intensive surface or percutaneous stimulation is necessary in order to preserve his muscles and avoid muscle denervation.

NPs can be used to replace lost motor and sensory function in persons with neurological disorders. However, when should a patient use an NP and what kind of NP should he use? Next, 2 typical scenarios of 2 different patients using NPs try to clarify and simplify the answers to these two questions.

11.3.1 Spinal Cord Injury Patients

Spinal cord injury (SCI) is an injury to the spinal cord that causes a loss of sensation and motor control. SCI can have significantly different physiological consequences that can affect the arms, trunk, legs, and pelvic organs, depending on the level of spinal cord injury. In the past, a spinal cord injury meant lifetime confinement to a wheelchair and even death. Today, it is possible to restore limited motor abilities by treatment and rehabilitation. It is also possible to minimize the disability by greatly improved emergency care.

Nowadays, scientific research is focused on functional connection recovery via advanced computer modeling systems in NPs and in integrated devices that could mobilize paralyzed limbs. The main idea is to electrically stimulate to produce muscle contractions, replacing the electrical signals coming from the brain through the injured spinal cord (Hincapie et al. 2008). The use of FES can improve, augment the residual muscle or nerve activity, or restore it completely in some cases, which can lead to restoration of a disabled movement. Concerning paraplegia (Lynch and Popovic 2012; Guiraud 2011), FES applications are about standing, walking and transferring, rowing and cycling, and controlling the bladder. For instance, FES can enable one to transfer from the wheelchair to the bed, seat car, or toilet (Lengagne et al. 2012). It can also enable patients with high SCIs (tetraplegia) to reconstruct grasp movements (Shimada et al. 2003). In order to understand the use and the benefits of an NP in SCI patients, we ask the reader to imagine the scenario described in Box 1.

11.3.2 Tremor Patients

Tremor is defined as an involuntary, approximately rhythmic and roughly sinusoidal movement (Deuschl et al. 1998). Although it is usually considered a pathological symptom, it often decreases the person's quality of life (Louis 2001; Lorenz et al. 2011). Patients with tremor present with reduced ability to perform simple daily tasks, such as feeding (Hariz and Forsgren 2011). The hands are most often affected, but potentially other parts of the body may also be involved (Deuschl et al. 1998). The pathological motion of the upper extremities commonly consists of both pronation-supination of the forearm and flexion–extension movements of the wrist, but tremor in the fingers is also common (Deuschl et al. 1998, 2012).

Box 11.2 Essential Tremor Patient Scenario

Rebecca is a 63-year-old woman who was been diagnosed with ET. She is not able to drink a glass of water or sign with a pen. Her neurologist prescribed her some medication in order to reduce the tremor. For instance, Propranolol and Primidone are both first-line agents in treating ET. Propranolol has fewer acute adverse reactions than Primidone, such as bradycardia with syncope (Schadt et al. 2005). Unfortunately, with both, not all patients respond to the therapies (Gorman et al. 1986; Koller and Biary 1984). Therefore, her doctor was thinking of a surgical intervention, such as deep-brain stimulation (DBS). DBS is used today for ET if the disabling tremor persists after evaluating the use of medication (Grimaldi et al. 2008). The patient then uses a magnet to turn on the stimulator that is surgically implanted under the skin, temporarily disabling the tremor. However, due to the cost and risks involved, these surgeries are usually performed only when the tremor is severe. Mainly, the risks could be motor and cognitive deficits, and the side effects could be dysarthria and disequilibrium. Unfortunately, Rebecca had some excellent results with DBS for a couple of months, but after that, the tremor was not able to be suppressed, and Rebecca had wrist tremor again.

Then, Rebecca tried an upper limb exoskeleton (Rocon et al. 2007), and she noticed an 80 % reduction of her tremor. But, she said she did not want to wear a heavy and bulky structure every day, because it is not comfortable and everybody will notice her. Her neurologist then made her try another experimental product, a textile garment neuroprosthesis that suppresses tremor by applying FES (Gallego et al. 2011; Popović-Maneski et al. 2011). Rebecca reported that this neuroprosthesis made her able to eat, drink, write, sew, etc. She was excited, but then she noticed that after continued use of the NP, the muscles were fatigued and the tremor appeared again because FES had no effect. Rebecca is a tremor patient with a permanent need of NP for her daily tasks. For this purpose, surface NPs are not the most adequate in her case. An implantable NP with the possibility of changing the therapy parameters at each moment would overcome the muscle fatigue problems and the daily don/doff procedure. At the moment, implantable NPs for tremor suppression are not possible. A new research program is now underway (NeuroTremor 2012); in this new approach, the tremor suppression is achieved by percutaneous neurostimulation of the afferent pathways. In this case, the researchhas to overcome the challenge of using multichannel thin-film electrodes for percutaneous stimulation.

Tremor is associated with several pathologies: essential tremor (ET), the most common type of pathological tremor; Parkinson disease (PD); cerebellar dysfunctions (causing cerebellar tremors [CTs]); and others (Deuschl et al. 1998). ET is the most common type of pathological tremor (Benito-Leon et al. 2003; Louis and Vonsattel 2008). Patients with ET usually present with a postural tremor that is accentuated by voluntary movement. Tremor associated with PD is the second most common type of tremor and is mainly characterized by a resting tremor (Hammond et al. 2007). CT is caused by lesions to the cerebellum resulting from stroke, tumors, or diseases, such as multiple sclerosis (Seeberger 2005). In CT, tremor occurs mainly at the end of a purposeful movement. Nowadays, absolutely effective treatments for tremor are not yet available (Rocon et al. 2012).

In order to reduce the effects of tremor in everyday life, tremor patients often adopt compensatory strategies to perform activities of daily living, such as holding the affected hand with the unaffected hand. The benefit, however, may become more effective with the help of physical therapy. Strength training may improve coordination and reduce the effects of tremor (Bilodeau et al. 2000). In order to understand the use and benefits of an NP in tremor patients, we ask the reader to imagine the scenario in Box 2.

11.4 Clinical Assessment and User-Centered Design Perspectives

I have a bag full of tools but I don't know when and how to use them. (Dr. M. Molinari at SSNR2012).

During the last decades, diverse types of NP solutions have been presented to clinicians. However, the development phase of an NP is done with no optimal interaction between engineers and clinicians, and several problems may emerge: lack of clinical assessment, fractional fulfilment of patients' needs, lack of validated therapeutic algorithms, and untrained clinicians that can use NPs. The next paragraphs present a number of perspectives and considerations that may be jointly taken by NP designers and clinicians in the process, going from an analysis of the user's needs based on clinical assessment to clinical integration and training.

- **Clinical Assessment and Need:** A clinical assessment to quantify the need for NPs is vital in conditions that have an upper limb motor component; they are high-level SCI, amyotrophic lateral sclerosis (ALS), Friedreich ataxia (FRDA), multiple sclerosis (MS), stroke (CVA), and peripheral nerve injuries (below the brachial plexus). There are studies carried out by Harkema (Harkema et al. 2011) that suggest that task-specific training with epidural stimulation might promote neural plasticity. Clinical reasoning-based decision-making by clinicians on potential functional outcomes is important when prescribing a neuroprosthesis. Setting goals based on existing motor function will pave the way for integrating external peripheral inputs with central processing of function.
- **User-Centered Design for Neuroprostheses:** The anticipatory planning of the application phase of a device could be enabled with a user-centric design process. There are several examples of this in the literature for similar rehabilitation devices (van der Linden et al. 2012; Markopoulos et al. 2011; Elsaesser and Bauer 2012; Money et al. 2011; Taylor et al. 2011; Kashfi 2010; Fidiopiastis et al. 2010; Sivak et al. 2009; Wu et al. 2009; Zayas-Cabán et al. 2009; Ma et al. 2007, Lacey and MacNamara 2000). When NPs are designed, in addition to defining the inclusion/exclusion criteria and treatment parameters, there is a clear need to offer NPs with patient-specific treatment pathways. Surveys and interviews should be carried out with both patients and physiotherapists to distill user perspectives of these devices. Sometimes, a patient's perception of how a neuroprosthesis looks can alter compliance. User-friendly interactive design of control mechanisms of such devices could not only increase compliance but dissolve the technophobic barrier, if it existed.
- **Therapeutic Algorithms:** When therapeutic algorithms are formulated for NPs, they have to be validated at the clinical trial phase, if possible in more than one patient with different neurological sequelae. As motor recovery could be specific to every patient, recovery pattern trends with the NPs need to be constantly analyzed and the device updated, if possible in real time. Patient experiences

and perspectives, in addition to physical outcome measures, need to be collated for continued development of the device.

- **Clinical Integration and Training:** NPs need to be prescribed by physiotherapists and clinicians who are specifically trained and certified in the use of the device. Every NP should be available with access to continued training and competence certifications in place during the lifetime of the device

11.5 Conclusions and Future Directions

This chapter presented a survey on upper limb electrically augmented therapies, focusing especially on motor NPs. Motor function injuries have led us to define 2 main categories of NPs: temporal and permanent. Temporal NPs can be used during the rehabilitation period in the clinic or home, whereas patients outside of the daily clinic use permanent NPs during their life, which makes patients prefer noninvasive NPs for temporal use and implanted NPs for lifelong use. Electrically augmented therapies can accomplish great results in neurorehabilitation. The main benefits of this therapy in rehabilitation are listed here:

- Brain Stimulation
  - Reorganization of the surviving neural circuits
- Neuroprosthesis
  - Conserve neuromuscular structures
  - Augment and recover lost motor functions
  - Strengthen the atrophied muscles
  - Decrease spasms
  - Increase active range of motion

Nevertheless, NPs in rehabilitation are not extended as much as robotic devices. Amongst the main reasons for this prevalence are the lack of training for clinicians using NPs and the limited specification of the target user group generated by engineers. Hence, the main points that need attention in order to augment the use of NPs from both health care givers and individual home users and make a difference that the device is bringing in a patient's quality of life are:

- Each NP should be accompanied by a very well-defined patient's inclusion/exclusion criteria and well-defined instruction manual.
- The clinicians should be informed of the features of the NP besides when and how it should be used.
- NPs should be developed based on the level of impairment and not merely on the motor function injury itself.
- Reduce the pain and skin issues of surface stimulation.

- Address the lack of biocompatibility of permanent implantable devices as well as the efficiency of the energy transfer between the implant and external unit and batteries employed for implantable stimulation in the market.
- Improve the user interface.
- Improve hardware and the sensors for the status feedback (kinematics sensors, electrodes, and appropriate amplifiers for recordings of the muscle activity)
- Artificial control of the NPs should match the biological control of the preserved biological systems; control schemes should be designed to limit the duration of stimulation to reduce muscle fatigue, joint torque, spasticity, joint contractures, osteoporosis, and stress fractures, among others.
- NPs should be aesthetic, easy to don/doff, safe, and reliable

Meanwhile, NP research is continuously developing and expanding, and the authors believe that there are some matters that also require the attention in development and do have high expectations of NP improvement, such as neuro-regeneration with NP, multiple controls of freedom with NP, and the lost synchronization of velocity electrical stimulation with neural control in NP.

- **Neuroregeneration** is the optimum solution of neurological injuries. It includes neurogenesis, neuroplasticity, and neurorestoration as a therapeutic approach (Enciu et al. 2011). During the first weeks after an SCI injury, the molecular and cellular environment of the spinal cord changes constantly (Mayo Foundation). Therefore, acute SCI patients present with major probabilities to achieve successful neurorestoration.
- **Brain Stimulation** was largely explained in this chapter. Two of the most innovative electrically augmented therapies are rTMS and intracortical microstimulation. The benefits of the former were well presented in this chapter, and regarding intracortical microstimulation, a miniaturized system capable of stimulating and recording neural activity in anesthetized laboratory rats has recently been presented (Azin et al. 2011). This study shows that this spike-triggered intracortical microstimulation device can modulate the neuronal firing rate. With this, the authors open a new challenge of repairing interrupted cortical pathways. Therefore, the possibility of reshaping connectivity patterns after brain injury is becoming real.
- **Neuroprostheses of multiple degrees of freedom** The upper limb possesses a large number of degrees of freedom, which makes the NP's development very complex, and the rehabilitation process needs to cover many aspects and specifications. Connelly et al. (2010) and Oblak et al. (2010) have presented multiple-degree VR and haptic systems, respectively. Others have implemented exoskeleton robotic devices (Kawasaki et al. 2007; Mouri et al. 2009). Nonetheless, neither of them was able to cover all the degrees of freedom of the upper limb. Development of the available systems is still in progress to overpass the limitations, plus FES combined with robotics would acquire advanced achievement on very precise movements that involve multiple degrees of freedom.
- **Synchronization of electrical stimulation and neural control** M. Goffredo et al. have introduced a unique FES-assisted rehabilitation system that uses a

markerless motion estimation algorithm and neural controller. The controller drives a biomechanical arm model and provides the stimulation, such that it could be used in the future to drive a smart functional electrical stimulation system in synchronization with neural control (Goffredo et al. 2008). Furthermore, T. Cowan et al. (Cowan and Taylor 2005) proposed a controller of an electrical stimulation system that could use an intended movement plan to generate a set of stimulation patterns. Such approaches and others can vastly improve existing electrical stimulation systems to initiate stimulation synchronously with neural control and specific movement measures in association with brain activity and neurorehabilitation.

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Chapter 12
BMIs for Motor Rehabilitation: Key Concepts and Challenges

Magdo Bortole, Marco Controzzi, Iolanda Pisotta and Andrés Úbeda

Abstract Controlling devices using the mind has always fascinated humans. The number of opportunities that have now been opened is unimaginable—for example, the possibility of just thinking while a robot does the task for you or commanding an exoskeleton attached to your body that augments your strength and agility. But not just that: try to imagine the possibility of feeling it as a part of your body or to receive sensory feedback from artificial sensors placed away from your own body. Possibilities like these, very common in science fiction movies in the last decades, are now becoming a reality. Our brain is very powerful, and scientists have devoted much effort to understand and use this power. In recent years, new technologies helped scientists to create brain-machine interfaces (BMIs), bringing the possibility to record and analyze brain signals. By means of thousands of tiny electrodes implanted inside the brain, it is now possible to record this electrical activity, and from these signals, the intentions of the user can be decoded and exploited to command robotic devices. Based on this new technology, a user would be able to control a robotic device while feeling real sensations of what the device is touching, grasping or holding. The most important field where

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this emerging technology is being applied is motor rehabilitation. Stroke, Parkinson and spinal cord injury patients may have their quality of life really improved by this technology in the very near future.

Keywords Brain-machine interface (BMI) · Somatosensory feedback · Brain plasticity · Neuroprosthesis

12.1 Introduction

Our brain is made of billions of neurons that are connected with each other by means of dendrites and axons. While people are thinking, moving, or even blinking their eyes, these neurons are communicating with each other through small electrical signals that move very fast, carried by ions on the membrane of each neuron. As the brain activity is based on these electrical impulses that flow between neurons, it is theoretically possible to measure this electrical activity using appropriate sensors and electronics circuits. This brings out the possibility of linking the brain to external devices by means of brain-machine interfaces (BMIs).

BMIs are a direct communication pathway between the brain and an external device, with the aim of restoring communication and functions that are lost after a brain injury or spinal cord injury (Lebedev and Nicolelis 2006). BMIs are used in two different ways: (i) stimulation: neurons or nerves are stimulated by applying current (Fuentes et al. 2009), or (ii) recording: the activity of neurons is recorded with the goal of decoding the user's intention (Mak and Wolpaw 2009).

Regarding the stimulation approach, electrical deep-brain stimulation has been used in patients affected by Parkinson's disease as a valuable complement to pharmacological therapies but involving invasive surgical procedures. In the case of spinal cord injury patients, neuroprostheses, combined with functional electrical stimulation (FES), are the only possibility to partially restore lost motor functions by stimulating muscles with implantable intramuscular or surface electrodes (Millan et al. 2010).

Considering the recording approach, the brain activity (that is, the extracellular potential generated by neurons during their activity) can be collected with different levels of invasiveness. Most of the current BMI systems in use rely on brain signals that are recorded noninvasively by electroencephalographic (EEG) techniques, placing electrodes on the scalp, with safe and relatively inexpensive equipment but with limited accuracy due to the presence of the scalp and the distance from the signal's source. On the other hand, there are a lot of very promising research studies (Donoghue et al. 2007; Kim et al. 2008) using invasive technologies. Usually, the more invasive the system is, the more accurate the signals that are collected, making single units the most suitable method to record signals from the brain. However, other issues and precautions must be taken into account during the choice of the recording method, especially if humans are involved during the experiments.

The aim of this chapter is to report and discuss the state of the art of BMI technology and related research, focusing on the field of rehabilitation to promote recovery after brain damage.

12.2 Background

A BMI system can be defined as "*a system that measures and analyzes brain signals and converts them in real time into outputs that do not depend on the normal output pathways of peripheral nerves and muscles*" (Wolpaw et al. 2000). BMIs provide new hope of restoring motor functions of severely disabled people by controlling external devices with volitional commands extracted from brain signals. The hardware and software could replace injured human nerves by reading brain signals and convert them into commands for external electromechanically actuators (Wolpaw et al. 2002).

Nowadays, there are several methods of recording brain signals. They can be divided into two basic groups: **invasive** and **noninvasive** (Lebedev and Nicolelis 2006). All of these BMIs require some effort for calibration and operation, and this effort is variable depending on the technology used.

The most extended **Noninvasive** technology is electroencephalography (EEG), thanks to the simple setup required and its high safety during the recording phase. In this method, EEG signals are recorded with simple electrodes placed on the scalp. The main disadvantage of EEG recording is that the registered signals have a limited frequency and resolution and are more susceptible to noise and interference (Mak and Wolpaw 2009). Generally, EEG-based BMIs are developed to decipher the subject's voluntary intention, which differs depending on the cortical areas activated during the recording. Through measurement of electrical activity of neural populations and by providing the subject with online feedback about the cortical activity associated with mental practice, motor intention, and other neural recruitment strategies, it is possible to perform progressive task-oriented activities (Lebedev and Nicolelis 2006). Because of their portability and their relatively simple setup, EEG-based BMIs have been used widely in all sorts of applications, such as communication and control, motor substitution, entertainment, and motor recovery (Millán et al. 2010).

Invasive techniques, such as electrocorticographic (ECoG) or intracortical methods, provide a wider frequency range and better signal-to-noise ratio, but the placement of the electrodes and part of the electronics require surgical procedures, with high risk of tissue damage and infection, compromising the long-term stability of this kind of BMI (Hochberg et al. 2006). To date, several experiments have been conducted successfully using these techniques implanted in primate subjects (Carmena et al. 2003; Serruya et al. 2002), while more recently, thanks to the advances of the last decades, researchers are conducting experiments using human subjects (Donoghue et al. 2007; Kim et al. 2008). Since the source of the signals is generally close to the electrodes, the measurements are more precise, and, for example, in the case of the primary motor cortex, they can be exploited to obtain better control of external devices (e.g., robotic arms). The extensive and validated physiological background of signal recording enables researchers to develop highly accurate BMI systems.

In the last years, both invasive and noninvasive BMIs have aimed at enabling motor function in individuals with neurological injury or disease. Current research has focused largely on so-called motor restoration—i.e., the problem of restoring the original motor function and, therefore, achieving performance similar to healthy individuals. Being an excellent therapeutic tool for improving impaired neuromuscular systems, BMIs have gained relevance as the ultimate strategy for functional compensation. A noninvasive BMI that is based on the recording of neural activity by EEG is the most widely used technique, due to the convenience of the experimental setup (Ushiba J. 2010). It is used in the rehabilitation of patients suffering from stroke-induced hemiplegia and for improving communication and control in severely disabled individuals (such as ALS or locked-in patients) through the modulation of brain rhythms (Millán et al. 2010).

Whereas noninvasive BMIs have potential advantages for functional motor compensation (Belda-Lois et al. 2011; Prasad et al. 2009), a large population of stroke patients show persistent deficits that can not be solved with current rehabilitation methods (such as daily physiotherapy), because they do not restore normal motor behaviors. For these cases, traditional methods have to be considered ineffective. Within the noninvasive BMI features, volitional control of cortical signals can be employed for the rehabilitation of motor and cognitive impairments in, for example, hemiplegic or paraplegic patients (Daly et al. 2009; Dobkin 2007).

BMIs with intracranial electrodes make it possible to control motor functions, like reaching and grasping and also assisting bipedal locomotion. The work of Nicolelis has demonstrated the feasibility of making a robot walk based on brain signals registered from a monkey, while the monkey receives visual feedback from the robot (Lebedev and Nicolelis 2011). Recently, this group of researchers has demonstrated that through intracortical microstimulation, it is possible to deliver a sort of artificial tactile feedback to the subject (O'Doherty et al. 2011). They have developed, for the first time, brain-machine-brain interfaces (BMBIs) that send somatosensory feedback directly inside the brain. Thus, a subject using this kind of BMBI will not only actively control a prosthetic limb through his brain activity but also theoretically feel it as a part of his/her own body. These results suggest that bidirectional BMIs could be useful for providing feedback for future users of neuroprostheses—a key aspect in the functional substitution of missing limbs. Also, the belief that BMIs could induce neuroplasticity has received important support from the scientific community (Wang et al. 2010; Dobkin 2007). The main finding is that learning to control BMIs triggers plastic changes in different brain areas of the users. In other words, as a consequence of constant training, the brain changes its activity in order to enhance performance of the specific tasks.

Further potential advantages of the BMI approach are to retrain motor functions by means of functional electrical stimulation (FES) or to use a whole-body exoskeleton controlled by brain signals. Exoskeletons are wearable robots attached to a subject's limbs, with the aim of replacing or enhancing their movements (Pons 2008). Most of the current lower limb exoskeletons are not developed for over-ground gait training. Usually, these systems are based on a gait orthosis and a body weight support system in combination with a treadmill (Díaz et al. 2011). Sometimes, these platforms exploit virtual reality environments that can motivate and involve the patient to actively perform the target movements. Nevertheless, performing gait in a real environment can be the most challenging scenario for patients. Ambulatory exoskeletons with control strategies that use brain signals of the user to perform movements in real environments can bring the possibility of enhancing the retraining of motor functions (Hidler et al. 2005). Also, BMIs can be used to control neuroprostheses aimed at replacing or restoring lost motor functions in paralyzed people. By movement-related signals extracted from the brain, external effectors (such as FES [functional electrical stimulation]) can compensate for the loss of voluntary functions in spinal cord injury (SCI) patients. In the framework of neuroprostheses for hand movement restoration, most of the tools use surface electrodes to externally stimulate muscles, such as the NESS-H200 system (Bioness Inc., Valencia, USA) (Millan et al. 2010) and other prototypes (Thorsen et al. 2001; Mangold et al. 2005). Such techniques provide the possibility of restoring movements, such as grasping, in quadriplegic patients by artificially eliciting muscle contractions (Hochberg et al. 2006).

Although BMI systems are very promising in the restoration of motor functions, several open issues, such as portability, biocompatibility and cost, need to be solved before these techniques can be exploited in clinical and real environments (Lebedev and Nicolelis 2006).

12.3 Selected Issues in BCI Research

12.3.1 Biocompatibility and Transmission of Invasive BMIs

In invasive BMIs, the sensors that are used to read brain signals are small electrodes placed inside the brain. Shaped as an array of small flexible needles, these electrodes are nowadays very tiny, which allows capture of the signal related to the activity of a single neuron (Carmena et al. 2003). In recent developments, recording electrodes have been designed as cube electrodes that possible to record information of make 1000 neurons (Nicolelis 2012).

The main issue of the electrodes implanted inside the brain is related to the biocompatibility between the electrodes and tissues. Due to the usual inflammatory reaction when a foreign body is put into contact with human tissue, a deposit of protein material on the surface of the electrodes can occur, and therefore, some electrodes can experience a reduction in sensitivity. Under a technological point of view, electrodes are very durable and can capture electrical activity for many years.

With electrodes that are implanted directly in the gray matter of the brain, it is possible to get high-resolution signals compared to noninvasive approaches and, thus, much clearer information related to brain activity. After that, these electrodes collect a small part of this brain electrical activity, and the raw signal is sent to an electronic circuit that amplifies and filters it, extracting the information related to the brain activity. Since the signal quality degrades quickly and proportionally to the distance between the electrodes and the electronic board, the board is implanted as close as possible to the electrodes, but outside the brain. After the process of filtering and amplifying has been performed, the electronic circuit is in charge of classifying the features from the signal collection and converting and sending the features to the external device.

Normally, a wireless transmitter is implanted in the patient's head outside the brain. This approach is safer for the patient, since the transmission of the data is only allowed after closure of the surgical holes, without damaging the brain. To power all of this circuitry, a small rechargeable battery is also implanted subcutaneously with its own electronic circuit. The battery pack can be recharged by an electromagnetic field, without any physical connections between the charger and the battery. A processing unit near the patient receives the preprocessed signals sent wirelessly out of the brain. This unit extracts some features of these signals related to the user's intention, most of the time related to the motion intention.

Usually, the best performance with extracting the features is obtained by exploiting classifiers based on artificial neural networks. These algorithms are able to manage a large amount of data with a high level of accuracy after the proper training. During the training phase, the user is asked to perform precise repetitive movements or just think about them, while the algorithm is recording the related features.

12.3.2 Brain Plasticity

Humans and some others primates, thanks to the plasticity of the brain, are able to learn how to use new tools, assimilating them with, for example, an extension of the visual receptive fields along the length of a tool used to reach objects (Head and Holmes 1911).

Plasticity occurs on a variety of levels, ranging from cellular changes due to learning to large-scale changes involved in cortical remapping in response to injury. One of the common consequences of the plasticity of the brain is the acquisition of novel motor skills, measured by a reduction in reaction time and in the number of errors and/or by a change in movement synergy and kinematics. It has been demonstrated that the process of learning produces an evolving reorganization within the motor cortex that might lead to substantial cortical and subcortical remapping with long-term usage. In addition, recent magnetic resonance imaging research on humans indicates that cortical cells can regain and maintain the level of activity needed to perform prosthetic control tasks, even after a long period of complete immobility (Shoham et al. 2001; Kennedy et al. 2000).

A more promising exploitation of the plasticity of the brain is the possibility of incorporating prosthetic devices into the body representation. Most of the studies concerning the development of neural upper limb prostheses have focused on decoding intended trajectories from motor cortical neurons and using these signals to control external devices (Taylor et al. 2002). Plasticity of the cortical circuits that are involved could allow control of these movements directly from cellular activity, even outside the primary or secondary homunculus representations of the motor cortex.

In order to underline the importance of these findings, there are several examples that can be developed. The control of a hand exoskeleton in a post-stroke patient can be considered. In this case, it is very common that the activity of the neurons related to hand movements is partially or totally compromised. Thanks to brain plasticity, the patient can efficiently control his hand exoskeleton using different parts of the brain.

Another important aspect of plasticity is related to the dynamic changes of the tuning curve of brain cells. During the learning process, the cells' tuning properties change. By using control algorithms that track these changes, subjects could perform complex tasks using far fewer cortical units than expected and reduce the invasiveness of the surgical implant (Taylor et al. 2002). Thanks to these results, there is now a widespread perception that brain plasticity will be one of the main keys of the success of BMIs in the near future.

12.3.3 Distribute Coding Principle

One of the main discoveries of the past two decades is that the information that is present in a small portion of the motor cortex contains part of the information of the whole cortex. Previous theories hypothesized that parts of the human body were mapped in specific cortical areas, indicating that their activity could be controlled by only these regions. Surprisingly, the last advances in this field show how, for many sensory, motor, and cognitive functions, the information can be found over the whole cortex, suggesting that it flows within the cortex using more than one neural pathway. In other words, these cortical areas are not compromised with regard to a unique function, although they have a different probability of controlling a particular movement/stimulus (Wessberg et al. 2000).

This discovery reveals how the localization of the implant is not so crucial for the efficiency of the recording and how the information can be collected almost everywhere with different levels of accuracy. The information is distributed along large territories of the brain, and it could be compared to a hologram, where the information is stored by pixels, each of them containing a little bit of information, but only the union of a great number of them can form the whole image. The number of single units captured (or recorded, in the case of the brain cortex) gives the resolution (Carmena et al. 2005). This finding is really promising for the control of an assistive device after brain injury. In addition, in contrast to most of the past electrophysiology studies in which the activity of each neuron was analyzed separately, nowadays, we know that by looking at a single neuron's activity, we are not able to extract useful and reliable information from the brain (Schmidt 1980). Using a single microelectrode, it is possible to monitor neural activity only during a small amount of time (from minutes to a maximum of 2 h).

In conclusion, the action of the brain can be described only through a distribution strategy—in other words, by looking at the ensemble activity of the neurons. Today, thanks to existing microelectrode arrays, it is possible to monitor and record neuronal activity for several months (Nicolelis 2011).

12.3.4 Tactile Proprioceptive Feedback

Recent research was able to not only record and decode information of the brain but also send information back to the brain (O'Doherty et al. 2011). This information, called somatosensory feedback, consists of a small array of electrical pulses sent to the brain by an electronic unit. It can represent some tactile information or other kinds of sensations felt by the patient. In the experiments, 2 monkeys performed an active exploration task in a virtual environment with 3 targets, obtaining tactile proprioceptive feedback from the correct target and a reward if they selected that target. The first experiments were performed with a joystick. After disconnecting the joystick, the monkeys were still able to select the correct target by controlling the actuator with brain activity and sensing the tactile feedback. The results obtained are of great importance, as they can be used to restore feedback for paralyzed patients.

The electrical feedback stimulation can cause some interference to the brain signals that are recorded by the electrodes. To avoid this interference and make it possible to collect signals and send feedback at the same time, the information is shifted in time. This means that while the brain is receiving feedback, the recording process is stopped for a little time. This little block in the recording process is called the black window, so that artifacts can be avoided when delivering the feedback current into the brain without compromising the recording process.

12.4 BMIs for Rehabilitation: Present and Future Challenges

12.4.1 Need for More Electronic Power

The number of different user movements that can be decoded by a BMI system is directly related to the number of neural signals recorded. Nowadays, several experiments that used signals of 100 neurons showed that it is possible to decode the movement of the contralateral arm. It is expected that signals from about 50,000 to 100,000 neurons are necessary to control the movements of a whole body.

The scientific progress made in the last years has made it possible to theoretically control a whole body. To improve BMIs and implement such control, there is a need for more electronic and computational power. The electronics inside the brain have to be able to collect, filter, amplify, and transmit more channels of information in real time when recording 50,000 neurons. All of the electronic circuits implanted into the patient's head have to be compact and have low power consumption in order to be powered by a long-life battery. The wireless transmission of the information in real time is another key issue related to the engineering challenge. The processing unit outside the brain that runs the decoders is another bottleneck. It has to be a compact portable computer, like a smartphone or a small laptop, and must be able to receive and decode a lot of information in real time.

12.4.2 Parkinson Prosthetic Device

In the last years, several methods to treat motor symptoms derived from Parkinson disease have been employed as therapeutic strategies. Dopamine replacement has been useful in treating symptoms in the early phases but fails to maintain its effects in long-term treatments. The use of deep-brain stimulation shows an important effect in reduction of motor symptoms, such as tremors and difficulty moving. However, only 10 % of patients are suitable for this surgery, and it is risky and highly invasive (5 % of the patients may die in the intervention).

The method proposed by Fuentes et al. 2009, is a much safer and cheaper alternative. In their work, they demonstrate that is possible to stimulate the surface of the spinal cord to obtain the same effects of deep-brain stimulation. The experiments have been carried out successfully in mice, rats and monkeys, showing that a prosthetic device can act as a sort of pacemaker for Parkinson disease (see Chap. 3 of this book). In future experiments, this new procedure should be investigated in extensive experiments using primates to evaluate the potential viability of the Parkinson prosthetic device in the treatment of human patients with Parkinson.

12.4.3 The "Walk Again" Project

The use of BMIs for rehabilitation depends highly on the type of disease. In the case of a stroke victim, the rehabilitation procedure depends on the type of the brain lesion, which strongly influences the way the signals from one part of the brain can be rerouted to another. In the case of spinal cord injury, the brain is not harmed, so that patients are able to generate commands through normal brain activity. The Walk Again Project pursues the idea that BMIs can be used clinically in motor rehabilitation. As a first challenge, this project aims to restore the mobility of a paraplegic teenager who, using an exoskeleton controlled by a BMI, will be responsible for the opening kick of the 2014 FIFA World Cup in Brazil (Nicolelis 2012).

Moreover, the use of neuroprosthetic devices based on BMIs can also allow scientists to do more than help disabled people. They can make it possible to explore the world in revolutionary ways, for instance, by providing healthy human beings with the ability to augment their sensory and motor skills. Recently, several alternative applications of BMI technology have been explored, such as the enhancement of human performance (Haufe et al. 2011) and the assessment of subconscious perception (Porbadnigk et al. 2010, 2011). Data from this work may set interesting and challenging research for the future of BMIs.

12.5 Conclusion

The scope of this chapter has been to give a general overview on the main issues concerning the present and future of invasive brain-machine interfaces applied to motor rehabilitation.

Invasive BMIs provide new hope for restoring motor functions of severely disabled people, and current studies have overcome the initial difficulties related to technical aspects. Noteworthy advances in the implantation of BMIs have been analyzed to such an extent that research on invasive BMIs shows an amazing improvement that only 10 years ago seemed to be impossible to achieve. Current invasive BMI electrodes, in addition to signal processing techniques, are able to record information from single neurons, and when arranged in arrays, they are capable of recording signals from more than 1000 neurons simultaneously.

The problems related to the biocompatibility of such devices in tissues have been solved in the past decade. In addition, thanks to the new generation of deformable electrodes, the damage occurring during the placement of the sensors has been partially overcome. The cortical information can even be transmitted wirelessly, reducing the possibility of infection after the surgical procedure.

One of the main discoveries of the last years is that for many sensory, motor, and cognitive functions, the information in the same area is being distributed all over the area; so, a small portion of such an area contains the information of the whole area. Moreover, the brain is able to generate control patterns in different areas that are not necessarily related to the main motor cortex. This plasticity of the brain allows one to control external tools as if they were a real part of the body and opens a new door to future motor substitution applications for people with severe motor limitations.

From these findings, present and future challenges have emerged, showing a very important development of BMI procedures in current research trends. For instance, recent research was able to not only record and decode information of the brain but also send tactile information back inside to the brain. These studies provide new hope for future motor substitution. Recently, it was also demonstrated that it is possible to stimulate the surface of the spinal cord to treat Parkinson disease, instead of using more risky methods, such as deep-brain stimulation. All of these findings show a number of important implications for present and future research trends in motor rehabilitation, making invasive BMIs an encouraging technology of the near future.

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Chapter 13
Virtual Reality

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Abstract This chapter provides an overview on the use of Virtual Reality (VR) in rehabilitation with respect to recent neuroscience and physical therapy reviews of individuals with motor impairments. A wide range of technologies have been employed to provide rehabilitation supported by VR. Several studies have found evidence of the benefits of VR rehabilitation technologies. However, support for their efficacy is still limited due the lack of generalizable results and the uncoordinated effort of many individual, heterogeneous studies that have been conducted. Although VR has clear potential as a rehabilitation tool to improve treatment outcomes, future trials need to take into account the individual perspective of each patient group and consolidate research methodologies across trials to allow for stronger conclusions across the heterogeneous field of neurorehabilitation.

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Interventions must be designed with a strong focus on the patient's needs and clinical outcomes, rather than on the technology available to the clinician.

Keywords Virtual reality · Video games · Game-based rehabilitation · Neurorehabilitation

13.1 Introduction

Effective neuromuscular rehabilitation is crucial for the recovery after traumatic events, such as traumatic brain injury (TBI), spinal cord injury (SCI) and stroke. The world's shifting demographics towards older populations as well as higher prevalence of obesity and health risk factors is expected to lead to an increasing number of cardiovascular diseases and stroke episodes (Population Reference Bureau 2010). Due to advances in medical care, technology, and the ability of stroke units to rapidly provide primary care, there is an increasing rate of stroke and cardiac arrest survivors. Unfortunately, these incidents are rarely without a long-lasting impact on the patient's health. These factors taken together with the rising cost of the world's healthcare systems (Kaiser Family Foundation 2011) support the need for more effective rehabilitation interventions and supportive technologies, such as the use of virtual reality (VR) systems. However, in order to offer patients the best possible therapy it is necessary to analyze and validate the benefits of VR technology as an adjunct or alternative to traditional treatment in the field of neurorehabilitation.

An optimal rehabilitation strategy requires the clinician to select appropriate exercises individually aligned to the needs of the patient, as well as to provide adequate feedback (Dobkin 2004). High numbers of repetitive exercises are commonly part of standard treatments. This requires the patient to perform additional exercises at home without the supervision of the therapist, which further complicates the sustained quality and adherence to the treatment program. Repetitive exercises without therapist supervision, and therefore no feedback, can lead to lack of motivation causing the patient to poorly perform the rehabilitation routine in quality and quantity. Additionally, the therapist can only rely on the patient's verbal report on frequency and quality of the exercises performed, which hinders the ability of the therapist to adequately adjust the rehabilitation routine. These factors arguably lead to poorer rehabilitation outcomes and could even cause further injuries. Hence, the monitoring of quality and quantity of home-based rehabilitation interventions can potentially have a large positive impact on the quality and adherence to long-term treatments and rehabilitation outcomes.

Recent advances of video game technology and VR systems have led to an increasing use of these systems for rehabilitation purposes. Henderson et al. (2007) define VR as a "computer based, interactive, multi-sensory environment that occurs in real time". Bohil et al. (2011) state that "VR system components work in concert to create sensory illusions that produce a more or less believable simulation of reality". An additional VR definition by Weiss et al. (2004) states:

> Virtual reality typically refers to the use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments that appear to be and feel similar to real-world objects and events (Weiss et al. 2004).

VR technology has been a widely applied rehabilitation tool, addressing many different disorders and therapeutic needs. In this chapter, we will limit our discussion to the use of VR as a therapeutic tool to regain or improve physical function after neurological injury.

This chapter provides an overview of the use of VR technology in rehabilitation with respect to recent reviews on neuroscience and stroke research (Bohil et al. 2011; Henderson et al. 2007; Laver et al. 2011) and motor impairments (Holden 2005; Sveistrup 2004), with a specific focus on physical rehabilitation. This work differs from previous reviews by focusing on how technology and rehabilitation needs alignment, especially in neuromuscular rehabilitation.

13.2 Virtual Reality Technologies in Rehabilitation

This section provides a general basis for understanding VR as a technology and its potential application in rehabilitation.

Depending on input and display devices, VR systems can be divided into fully immersive and non-immersive setups. The advantage of fully immersive systems is the user's strong "sense of presence" which has been attributed to the convergence of the system's multisensory input (Henderson et al. 2007). In non-immersive systems, the VR system often consists of a computer monitor, mouse, keyboard and possibly joysticks, haptic devices and force sensors. The multi-sensory illusion of actually being in the virtual environment can motivate patients to continue training over multiple therapy sessions.

VR systems are often comprised of a multitude of technologies, software and hardware devices. Most of these devices are unfamiliar to patients and therapists. Hence, the fields of human–machine-interaction/human–computer-interaction are of critical importance to the use of VR technology in rehabilitation settings. The most prevalent sensory stimulations in VR systems are found in visual, auditory and haptic (tactile) modalities (Bohil et al. 2011). Visual feedback is traditionally provided by computer screens, large screen projection, wall projectors ("CAVEs"—Cave Automatic Virtual Environments, where the virtual environment is projected on a concave surface), and head-mounted displays (HMDs). HMDs are head-worn display units consisting of one small display for each eye, earphones and often a head-tracking unit. Acoustic feedback in mono or stereo sound can be provided by speakers, headphones or other more sophisticated surround sound systems. Haptic feedback is less common but extremely important for specific applications. It can be provided by robotic actuators or haptic gloves that vibrate against the skin or within the device.

Fig. 13.1 Virtual hand controlled by an amputee via pattern recognition of myoelectric signals

Input devices are important for each VR system to provide the user with intuitive ways to control events within virtual environments. Examples of commercial devices include standard PC peripherals such as: keyboard, mouse and joystick; posture platforms; marker-based motion capturing and tracking systems (e.g. OptiTrack), infrared light (e.g. Microsoft Kinect, ARTTRACK3), instrumented gloves (e.g. AcceleGlove and CyberGlove) and inertia trackers in handheld devices (e.g. accelerometer/gyroscopes in smart phones or the Nintendo Wii); and more recently, brain-computer interfaces (BCIs) that detect electroencephalography patterns of the user (e.g. Emotiv Epoc). On the research side, the prediction of motion intent based on patterns of myoelectric activity is also used as input for VR systems (Ortiz-Catalan et al. 2013). Figure 13.1 shows a transhumeral amputee controlling a virtual hand through pattern recognition of the myoelectric activity recorded on the surface of the subject's stump (Fig. 13.1).

VR software solutions require a complex integration of virtual environments (VEs) and the previously discussed VR hardware. Several development frameworks are available in order to create complete VR solutions. These frameworks include game engines such as Unity, Gamebryo, CryEngine, UNiGiNE, Ogre3D and Unreal Engine as well as simulation and VR engines such as Quest3D and WorldViz Vizard. Only the latter already provide the capability to interface with a wide range of trackers and input devices. Regardless of the development platform developers need to be aware of the specific requirements of the target population and provide clinicians and patients with appropriate performance feedback and options to tailor the application towards the individual needs of each patient. Traditional off-the-shelf games often do not provide such options and lack the customizability that is needed to address individual rehabilitation needs (Lange et al. 2010).

Middleware such as the Flexible Action and Articulated Skeleton Toolkit (FAAST) (Lange et al. 2011b) and MiddleVR can be utilized to seamlessly integrate VR hardware into existing and newly developed games. FAAST is a depth-sensing framework that enables clinicians to use full-body tracking with the Microsoft Kinect to play off-the-shelf computer games. Gestures can be customized to fit the needs of each individual user. MiddleVR is a sophisticated VR

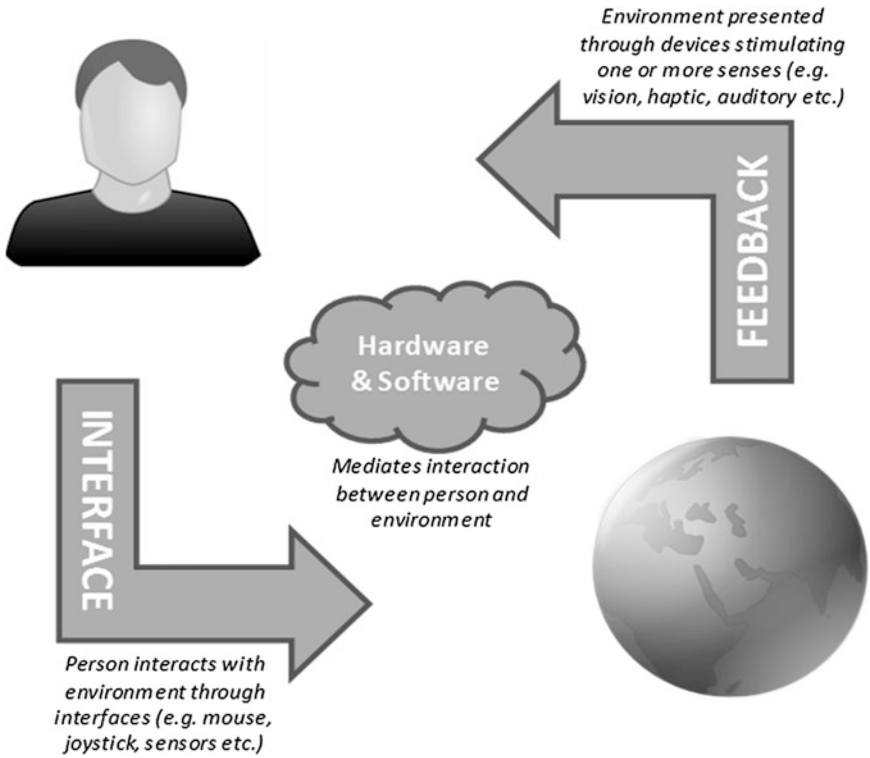

Fig. 13.2 Illustration of the role of VR as a therapeutic tool in neurorehabilitation

toolkit that enables developers to immerse users by implementing VR input and output devices as part of the user experience.

Despite the wide range of available VR software and hardware the user still has to take a central role in the virtual rehabilitation ecosystem. Specifically, the needs of clinicians and patients have to be addressed in order to create rehabilitation tools that provide additional benefits beyond traditional therapy. Instead of interacting with the real world, users interact with VEs in order to train skills as part of their rehabilitation routine. Interfaces and feedback are essential for a VR system to connect the user with the VE (Fig. 13.2).

Each patient has individual strengths, weaknesses and therapy goals and each clinical setting has different requirements for documentation, safety and therapy protocols. Only when user interfaces and feedback mediated through VR software and hardware accommodate these individual user goals, VR technology can have a positive impact on neurorehabilitation (Fig. 13.2).

By example of a VR driving application, the role of each of Fig. 13.2's elements becomes apparent. Exemplarily, the user can interact with the VE by using a joystick, steering wheel, pedals, gears or even gestural input (user interface) to control a car on a computer screen (visual feedback). Additional feedback can be provided by adding various car-related sounds, tactile information (e.g. force feedback for the steering wheel) and visual information (e.g. additional screens for side windows and mirrors). Further hardware elements such as motion platforms can be added to increase realism of the VR simulation system. The software is needed to translate the user input into events and actions within the VE (e.g. steering changes the path of the car). Further, the software is responsible for providing task content of appropriate difficulty level (e.g. different locations and traffic conditions) and giving feedback based on the user's performance (e.g. providing scores and reports).

Recent advances in game development technology and the availability of low-cost tracking devices have greatly enhanced the capabilities of interfaces, VR hardware and software to connect the user with a meaningful VE for therapy. However, clinicians and developers need to work together to assure that feedback and task content within the VE are tailored towards the user's individual needs. Mainstream VR systems for neurorehabilitation will only become a reality when all elements of a therapeutic system are adaptable to the user's specific goals while still being affordable for widespread use in clinics and patient homes.

The remainder of this chapter will discuss how previous studies have utilized and evaluated clinical VR systems and what we can learn from these existing results in order to better address the needs of patients in neurorehabilitation.

13.2.1 Literature Summary

Despite recent technological advances that make VR systems more appealing to clinical practice, there is still a considerable lack of scientific evidence of how VR systems can be meaningfully implemented in existing rehabilitation routines. There is some evidence that VR training for surgical skills has shown transfer to real work activity (Gurusamy et al. 2008, 2009; Torkington et al. 2001). However, there is limited evidence of the same kind of transfer for VR-based functional motor tasks (Holden 2005). Furthermore, there is little consensus in the literature about how VR technologies can be utilized in the clinical setting and how efficacy can be demonstrated across patient populations.

A number of recent reviews have been published on the use of VR and video games for physical rehabilitation after a stroke. VR systems in rehabilitation of both upper and lower limbs were evaluated in the Veterans Affairs/Department Of Defense (VA/DoD) clinical practice guidelines for the management of stroke rehabilitation (2010). The VA/DoD working group came to the conclusion that VR systems are recommended for upper and lower limb rehabilitation after stroke. This conclusion was based on studies by Kim et al. (2009), Yang et al. (2007), Mirelman et al. (2009) and Jaffe et al. (2004). According to these studies, chronic hemiparetic patients with stroke showed significantly greater improvement in the Berg Balance Scale, gait velocity, cadence, step time, step length, and stride length when they receive an additional 30 min of VR therapy each session compared to the control group (Kim et al. 2009). Post stroke patients who received VR-based treadmill training maintained a significantly faster community walking speed (Yang et al. 2007). Patients using a robot with a VE showed improvements in gait velocity, distance, and community ambulation compared to the control group using a robot without VE (Mirelman et al. 2009). Significant improvements in gait velocity of patients with virtual versus real stepping paradigms were reported by Jaffe et al. (2004).

No recommendation for or against the use of VR systems was given in a systematic review of upper limb rehabilitation by Henderson et al. (2007). The authors evaluated existing scientific evidence for the effectiveness of VR in upper extremity stroke rehabilitation. They included six studies in their review and examined the effects of immersive and non-immersive VR compared to conventional therapy or no therapy in hemiplegic stroke survivors. They concluded that current evidence on the effectiveness of VR rehabilitation for upper extremities in patients with stroke is limited, but sufficiently encouraging to justify additional clinical trials in this population.

Miller et al. (2010) conducted a literature review to determine the effectiveness of VR interventions for motor rehabilitation in stroke victims and found that there is evidence that using VR systems for motor rehabilitation is beneficial. However, all six reviewed studies reported small sample sizes in mostly uncontrolled trials, using high-cost VR interventions that mostly targeted upper extremities. Therefore, additional controlled investigations are needed to determine whether VR interventions are more beneficial than standard therapy protocols and whether costly VR systems are needed.

In a review by Holden (2005) VR interventions for motor deficits in stroke, acquired brain injury and Parkinson's disease were assessed. The author summarized the utility of VR applications in four major findings: (1) people with disabilities appear capable of motor learning within VEs; (2) movements learned in VR by people with disabilities transfer to equivalent real world tasks in most cases, in some cases even generalizing to other untrained tasks; (3) all of the few studies that have compared motor learning in real and virtual environments found some advantage for VR training; and (4) no occurrences of cyber sickness in impaired populations have been reported to date in experiments where VR has been used to train motor abilities.

Sveistrup (2004) published a review on VR technologies specifically applied to motor rehabilitation. The reviewed studies conclude that VR technology allows therapy to be provided within a functional, purposeful and motivating context. Adaptation of task difficulty level to the subject's skills was identified as an important factor to engage the patient in a repetitive exercise program and to prevent boredom and fatigue during therapy. The author cites studies from a wide range of different clinical domains, each showing the potential of VR technology. However, high costs of VR systems and lack of compelling evidence for the efficacy of VR interventions across different domains of motor rehabilitation require a strong focus on further validation and development of low-cost hardware and software.

More recently, Bohil et al. (2011) reviewed the use of VR applications in several clinical domains including psychiatry, neurorehabilitation and pain treatment. The authors specifically discuss the concepts of presence and immersion as "the physiological product of technological immersion" and "the sense of being there". Even though the reviewed studies did not specifically address neuromuscular rehabilitation, parallels regarding the users' needs and the applied solutions can be drawn between rehabilitation disciplines. For instance, VR has been shown to be effective in engaging the sensorimotor system and providing means to monitor small changes in user performance.

Bohil et al. (2011) further discuss VR applications in two areas of neurorehabilitation: balance disorders and functional recovery after stroke. In this context the authors review two articles of August et al. (2006) and Adamovich et al. (2009) in which evidence is shown that VR interventions help to engage primary and secondary motor areas related to recovery of muscle control after stroke. Bohil et al. (2011) also review the findings of Baram and Lenger (2009) and Baram and Miller (2006) who concluded that VR systems can provide feedback through multimodal stimulation that helps engaging in reflexive responses and bypassing damaged brain areas. Similar promise was shown with using VR technology for hand rehabilitation. The authors cite Henderson et al. (2007) and Merians et al. (2002) whose patients showed significant improvements in the movement, use and control of their hands relative to baseline and to other rehabilitation approaches after performing VR exercises with visual, auditory or haptic feedback. The studies of Merians et al. (2006) and Adamovich et al. (2009) were reviewed for their use of force-feedback data gloves to interact with VEs. The authors report improvements of the patients' individual finger control, thumb and finger range of motion, and thumb and finger speed. The promise of VR technology has been shown across a wide range of domains of neurorehabilitation and Bohil et al. (2011) conclude that with increasing quality, higher immersion and presence of VR systems, barriers for adoption in research and clinical practice are likely to be overcome.

Laver et al. (2011) conducted a Cochrane Review to evaluate the effects of VR and interactive video gaming on upper limb, lower limb, and global motor function after stroke. Nineteen trials were included in this review, allowing the authors to collate results and identify medium effect sizes on recovery of arm function and activities of daily living. However, individual studies are very heterogeneous and too small to gain deeper insights into the exact mechanisms that make VR systems successful for the recovery of motor function. The authors further conclude that recent advances in VR technology and increasing research activity in the field of virtual rehabilitation are promising. Reports of adverse side effects such as motion sickness and nausea have been rare, so that larger randomized controlled clinical trials that compare VR therapy to standard interventions are justified and needed to advance the field of VR neurorehabilitation further.

13.2.2 Advantages of VR Rehabilitation

Based on the previous review of the VR rehabilitation literature, several important strengths of VR rehabilitation have been identified. These strengths have to be considered carefully to evaluate whether using a VR application provides any benefit over traditional therapy. The key question then becomes: why not just practice the real-world functional task instead of using expensive hardware and software? In order to answer this question, the following discussion on the advantages of VR rehabilitation applications is focused on a few important aspects relevant to motor learning. Motor rehabilitation should be focused on functional movements in a relevant environment with high intensity, a large number of repetitions and appropriate feedback (Timmermans et al. 2009). Repetition is important to promote motor learning and cortical plasticity. The learning process must be reinforced by feedback which links the patient's performance to a successful task outcome. Lastly, motivation is needed to repetitively carry these tasks out over an extended period of time. VR technology is believed to provide all of these critical components to provide an engaging and relevant task environment that can be tailored to the needs of the patient (Henderson et al. 2007).

13.2.2.1 Individualized, Task-Specific Training

It is well known that task-specific practice is needed for motor learning to occur. Butefisch et al. (1995) demonstrated that short, repetitive, task-specific training (15 min/day, 2 times/day) is sufficient to improve strength and function of the affected hand in stroke patients. By designing VEs that look like the real world and also incorporate challenges that require real world functional behaviors, motor functions for everyday tasks can be selectively trained. However, task specificity on its own is not sufficient to provide adequate therapy content. The concept of client-centered rehabilitation and individualized therapy goals have become a central aspect of modern neurorehabilitation. Clinicians are encouraged and expected to focus on the strengths, weaknesses and individual circumstances of each patient in order to restore a person's participation in daily life (World Health Organization 2001; Ylvisaker 2003). These circumstances also include the patient's social environment like family members and friends who should be integrated in the long-term planning of a rehabilitation strategy. VR applications can provide the means to safely expose the patient to realistic and functional training environments which can be tailored to the individual's level of ability (Koenig et al. 2011; Koenig 2012). Supervising therapists can precisely manipulate and control task complexity and intensity while the patient is still following a therapy plan at an inpatient or outpatient setting. Once a patient is discharged from the clinical setting friends, family and the patients themselves are often on their own to continue an exercise regime. In these situations online tools, telerehabilitation tools and affordable VR systems can greatly enhance long-term outcomes by motivating the patient to adhere to a therapy plan without constant supervision by clinicians. However, these home-based and client-centered scenarios have to be considered and explored by researchers and VR developers alike in order to provide VR systems that are affordable, user-friendly and motivating. Consequently, all involved stakeholders (i.e. patients, clinicians, researchers, patients' families) should be actively involved in the VR development and research processes (Koenig et al. 2012).

User interfaces can play an important role in making VR applications more user-friendly and motivating. Until recently, game interfaces were limited to a computer mouse, arrow keys on a keyboard, or a joystick. Recent advances in video game technology have revealed more low-cost devices that can sense the user's motion. Exemplarily, the Microsoft Kinect can sense the full-body pose for multiple users without the use of markers or handheld devices. The Kinect sensor and several similar devices which were originally designed for recreation are now being adapted by clinicians for therapeutic purposes (Lange et al. 2011a). Several tools are available to design custom body postures and gestures for playing off-the-shelf games. The Flexible Action and Articulated Skeleton Toolkit (FAAST) (Lange et al. 2011a, b) allows clinicians to specify gestures that are customized for each patient. This allows individuals with different levels of abilities to play the same game as part of their rehabilitation or simply for recreation. In addition to such off-the-shelf use of video game technology, interactive (serious) games can also be specifically designed for rehabilitation (Lange et al. 2011a).

13.2.2.2 Motivation

VR offers a realistic, safe and motivational setting in which complex activities can be practiced. However, the user can also be provided with a sense of achievement, even if he/she cannot perform that task in the 'real world'. In an overview of VR technology by Rizzo and Kim (2005) motivating game factors are described as one of the major advantages of VR systems, especially as part of clinical assessments. When patients are engaged in gaming tasks, attention is drawn away from the fact that an assessment is taking place, thus providing a more accurate estimate of naturalistic capability. Further evidence suggests that when a user concentrates on the game rather than their impairment, exercises becomes more enjoyable, motivating and more likely to be maintained over the many trials needed to induce plastic changes in the nervous system. For example, Harris and Reid (2005) observed children with cerebral palsy playing VR games. Motivational factors for each game were analyzed and discussed. Variability of content, being challenged with an appropriate level of difficulty and competing against others appeared to be the most relevant motivational factors of the tested VR games. Motivation was also important in a study of King et al. (2010), who investigated augmented reality computer games which provided rewarding, goal-directed tasks for upper limb rehabilitation via a gravity supported reaching task. Motivational factors for exercising with the system included intellectual stimulation, feedback (e.g. game scores), physical benefits from exercising, social play with peers, appropriate levels of difficulty and the ability to relate to the game.

13.2.2.3 Feedback

Feedback can be very important for the user's motivation. The user always needs to know when and why a task was completed (un-)successfully in order to promote (errorless) learning and prevent frustration. Feedback can be given as absolute (correct/incorrect) or graded information (error scores, deviation from optimum) and in different modalities. Most computer applications and VR systems present the user with visual and auditory information. For VR systems, this can encompass stereo speakers and PC monitors on the lower end of the cost spectrum as well as projection screens, head-mounted displays and surround sound systems as more costly alternatives. An example of a traditional VR system is the Vivid Group's Gesture Xtreme VR system by Kizony et al. (2003), which has been used for neurological rehabilitation. The user stands or is seated in front of a large video screen and a speaker system to provide multimodal input for functional motor rehabilitation tasks.

More recently, tactile user feedback has been introduced to VR systems. Haptic feedback devices include gloves, joysticks and exoskeletons that simulate the feel of forces, surfaces and textures as users interact with virtual objects. For example, the Cybergrasp system is a force-reflecting exoskeleton that can apply forces of various temporal profiles to allow individual finger movements. The system has shown to be a safe and feasible device for the training of hand function with hemiparetic patients (Adamovich et al. 2009; Merians et al. 2011).

13.2.3 Disadvantages of VR Rehabilitation

Over the past 20 years several threats and disadvantages to VR technology have been reported in the literature. Rizzo and Kim (2005) summarized several potential threats and weaknesses that could prevent widespread adoption of VR applications in a comprehensive SWOT analysis. One of the main disadvantages of VR as a viable rehabilitation solution is the lack of standards, frameworks and compatibility amongst the many different available technologies. Drivers, operating systems, hardware, databases and the actual VR content all have to be compatible and operate on a range of different system configurations. In addition, adverse side effects, lack of cost-benefit analyses and the fear of clinicians that they will be replaced by VR applications have been brought up as potential barriers to the use of this technology. Some studies reported transient side effects after using VR such as dizziness, headache (Crosbie et al. 2012) and pain (Sucar et al. 2009). Simulation/cyber sickness can be a serious concern for the widespread adoption of VR in clinical settings as the systems need to be used with brain-injured users over extended periods of time (Bohil et al. 2011). However, reports of cyber sickness incidents have been mixed, as Holden's review (2005) reports no occurrences of adverse side effects in experiments where VR has been used to train motor abilities.

In addition, high cost has always had a negative impact on the widespread use of VR rehabilitation tools. Even though the cost of displays and PC hardware has been rapidly decreasing over the past years, fully immersive systems are still expensive. Especially complex projection screens (e.g. CAVE systems or projection domes) and wide-field-of-view HMDs are not affordable for everyday clinical use. On the contrary, handheld devices and gaming peripherals such as the Microsoft Kinect, Nintendo Wii, Razer Hydra and PlayStation Move have provided access to low-cost tracking interfaces which make VR experiences accessible to a large audience.

Lastly, legal aspects of VR use in neurorehabilitation have to be considered. According to the Medical Device Directive (2007) a medical device is defined "a*s any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purpose*" (Medical Device Directive 2007, p. 5). If systems are used for rehabilitation purposes, they are per definition medical devices and have to be certified accordingly. This could potentially increase the costs of using these products, and has to be considered as one of the potential risks using VR systems in neurorehabilitation.

13.2.4 Application to Neurorehabilitation

Rehabilitation is a complex and *"active process by which those affected by injury or disease achieve a full recovery or, if a full recovery is not possible, realize their optimal physical, mental and social potential and are integrated into their most appropriate environment."* (World Health Organization 2001). Rehabilitation includes a wide range of activities and services aimed at reducing the impact of injuries and disabilities by applying coordinated problem-solving processes across many disciplines. Many patients attending rehabilitation services have multi-factorial, complex problems that often require several interventions to be given by different health care professionals. It is unlikely that VR interventions will be appropriate in all cases as a sole one-size-fits-all solution. At this point it is difficult for clinicians to choose an appropriate VR intervention from the large number of available technologies. While the previously discussed reviews give an overview of available interventions and VR systems, most systems are in prototypical stages and have only been employed in preliminary trials or laboratory settings. Comprehensive comparisons of usability and efficacy across all interventions for motor rehabilitation are still lacking.

When choosing a VR task for neurorehabilitation, clinicians should consider the difficulty level (Can I challenge the patient appropriately throughout the rehabilitation process?), task complexity (Can the task be broken down into individual components?), task content (Is the task relevant and motivating for the patient?), available feedback (Is the feedback direct and understandable for the patient?) and the potential for transfer of skills (Can the task content be gradually changed to promote transfer to real life?).

Moreover, it should be considered whether each intervention is grounded in a model of health and disability like the International Classification of Functioning, Disability and Health (ICF)(World Health Organization 2001). It is important to work with such models when developing or applying VR tools in order to standardize and classify interventions from a clinical perspective regardless of software and hardware components. For example, it is possible to design a VR intervention that solely focuses on basic body functions (e.g. balance using the WiiFit Balance Board) in which the user is only asked to shift balance according to some basic instructions. This same application can also target the ICF level of activities by integrating the balance task as part of a snowboarding or similar balance game. Lastly, VR interventions also can target the level of participation by placing a functional task (e.g. balance training) in a relevant context such as shopping, cooking or other activities that are essential for each individual to participate in daily life.

13.3 Conclusion and Future Challenges

The findings of the reviews discussed in this chapter suggest that the application of VR in rehabilitation seems promising. However, the studies so far are too few and too small to draw strong conclusions. The advantages of motivation, task relevance, structured feedback and tailored tasks with appropriate difficulty level have been described as advantages of VR by nearly all authors. Pricing and availability of VR hardware, software and gaming peripherals such as the Microsoft Kinect, Nintendo Wii and PlayStation Move have seen much improvement over the past years. However, expensive one-off VR systems still exist and compatibility of different hardware, software, drivers and development protocols is still a problem. Furthermore, consistent evidence for the usability and efficacy of VR interventions across clinical domains does not exist yet. Clinical trials are sparse, uncontrolled, of small sample sizes and lack consistent methodology across trials and VR systems. The development of clinical, methodological and technical standards is needed before VR interventions can become a widespread alternative to traditional therapies.

Through the review of the existing literature and state of the art in VR technology, one is left with several key questions which are of high relevance to the use of VR interventions in neurorehabilitation:

- There are many differences between a realistic, functional VR task and its real-world counterpart. Which aspects of the VR task contribute to its success?

Which are key elements that help users engage with and benefit from the rehabilitation task?

- VR technology can be intimidating and overwhelming for some users. Which patients and therapists can benefit most from VR interventions? Which patient characteristics, motor and cognitive deficits are best suited for VR rehabilitation protocols? Are there cases in which VR interventions can be detrimental to rehabilitation progress?
- Which training tasks, gaming aspects, hardware and user feedback are the most immersive? How can motivation to exercise be maintained over extended periods of time?
- At which point throughout the rehabilitation process should VR interventions be applied? Are different applications required for acute, sub-acute and chronic disorders?
- How can the use of VR technology in neurorehabilitation be justified with cost-benefit analyzes?

Based on the previous reviews and key questions, the following challenges and goals are expected to be of particular value to the VR neurorehabilitation field:

- Cost-effective hardware was one of the main barriers that prevented VR from becoming a mainstream technology over the past 20 years. However, tracking devices and HMDs are finally evolving towards high-quality affordable products. The goal should be for VR systems to not only be affordable by a clinic, but also for the patient to continue rehabilitation after being discharged from the inpatient or outpatient program.
- Naturalistic user interfaces are starting to emerge in the form of gaming peripherals. The current generation of these devices already provides great opportunities for clinicians and researchers to integrate full-body tracking into rehabilitation applications and games. In the future, these devices need to accurately and reliably detect the full human body including face, fingers and voice at a level that is currently reserved to prohibitively expensive research-grade tracking systems.
- The answer to most of the previously stated key questions lies in a series of sufficiently-powered randomized controlled trials. These trials need to validate a set of the most promising VR interventions across several patient populations. Replication of studies is also needed.
- The VRPN peripheral standard has already set an example of how VR devices can work together. However, more industry standards for device drivers, VR hardware, software and the VR development and validation process are needed.

VR technology is a promising tool in the clinician's and researcher's toolkit. With a coordinated effort between VR developers, engineers, clinicians and researchers, VR interventions have the potential to provide a safe, customized and motivating rehabilitation experience to patients across all spectrums of neurological injury.

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Chapter 14
Surface EMG in Neurorehabilitation and Ergonomics: State of the Art and Future Perspectives

Filipe Barroso, Diana Ruiz Bueno, Juan Álvaro Gallego, Paola Jaramillo and Atilla Kilicarslan

Abstract Electromyography is a valuable technique that can be used for several purposes, including the comprehension and assessment of the motor system as well as the diagnosis of some pathologies and rehabilitation. Given the drawbacks of traditional surface electromyography recordings with two electrodes, a new approach called high-density surface electromyography enables implementation of spatial information to the temporal information content of the electromyographic signal. The following review describes the rationale for the use of high-density recordings, the state of the art techniques, and technologies for its detection and conditioning. Some examples are showcased providing new insights on muscle physiology, ergonomics (for the assessment and prevention of musculoskeletal disorders), as well as training and rehabilitation treatments.

Keywords High-density surface electromyography · Motor units · Muscle physiology · Ergonomics · Work-related disorders

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14.1 Introduction

It is hard to imagine life without movement. Muscle control and movement are a prerequisite to perform daily activities. Hence, the development of mechanisms to control muscle-brain interaction, monitor force and fatigue, prevent work-related disorders and avoid pelvic floor lesions, just to mention a few, are some of the applications that could benefit from the implementation of high-density surface electromyography.

In the human body, central commands are projected to the motoneurons innervating the muscles through a number of descending pathways, both direct and indirect. Motor units, defined as a motoneuron and the muscle fibers it innervates, constitute the smallest element that can be controlled to regulate muscle contraction, and ultimately movement (Soderberg 1992). When a motoneuron is activated, its action potential reaches the neuromuscular junctions, where it propagates in both directions of the muscle fibers towards the tendons. The sum of these muscle fiber action potentials is referred to as a motor unit action potential (MUAP).

MUAPs can be detected on the skin surface by using, for that purpose, sets of electrodes, a technique known as surface electromyography (sEMG). Surface EMG detects an interference signal constituted by the sum of electrical signals coming from several motor units (Farina et al. 2004). Some questions do arise when analyzing this technique: for instance, is it possible to decompose sEMG signal into the individual discharge patterns of each motor unit? Can sEMG features give us information concerning brain motor control strategies or muscle fatigue? Can they be used to monitor disorders, treatments or sport training? After decades of research, the answers to these questions begin to emerge.

The traditional approach when employing sEMG is to use a bipolar configuration (consisting of two electrodes for each targeted muscle). In this case, the detected signal is composed by the potentials from many motor units. Since it is not possible to extract information about individual motor units from this recording configuration, sEMG is normally considered a global indicator of muscle activity. In addition, the interpretation of bipolar sEMG recordings is often prone to errors due to its dependency on appropriate electrode placement (Farina et al. 2004). To overcome drawbacks of bipolar configuration, high-density sEMG represents a reliable alternative to handle large numbers of spatially arranged electrodes, which facilitates a wide arrange of applications when compared to traditional sEMG (Merletti et al. 2008).

This chapter is divided into four sections. First, a description of electromyography (EMG) is presented, as well as different recording techniques (intramuscular and surface), limitations of traditional bipolar sEMG, and advantages on using high-density sEMG as the best approach available. Next, a thorough review of the technology for the detection and processing of high-density sEMG is conducted. This is followed by a review of applications, e.g., in ergonomics and rehabilitation. Finally, major remarks and conclusions are presented regarding this novel technique.

14.2 Background

Motor units are the smallest functional units that the central nervous system can control (Soderberg 1992). Each motor unit is constituted by a motoneuron and the muscle fibers it innervates (see Fig. 14.1), which spread over the so-called motor unit territory. When a motoneuron is activated, its action potential travels until the neuromuscular junctions, where it propagates in both directions of the muscle fibers towards the tendons. As mentioned above, the sum of these muscle fiber action potentials is referred to as MUAP. Although each muscle fiber just receives input from only one motor unit, different motor units overlap their territories spatially.

The central nervous system controls muscle force by concurrently regulating the recruitment and firing rate of the population of motoneurons innervating the muscle (Adrian and Bronk 1929). Due to the one-to-one association between the action potentials fired by the spinal motoneurons and its innervated muscle fibers, it is possible to infer motor strategies from EMG recordings (Merletti et al. 2008). The ensemble of action potentials fired by the spinal motor neurons constitutes the neural drive to muscles (Farina et al. 2010).

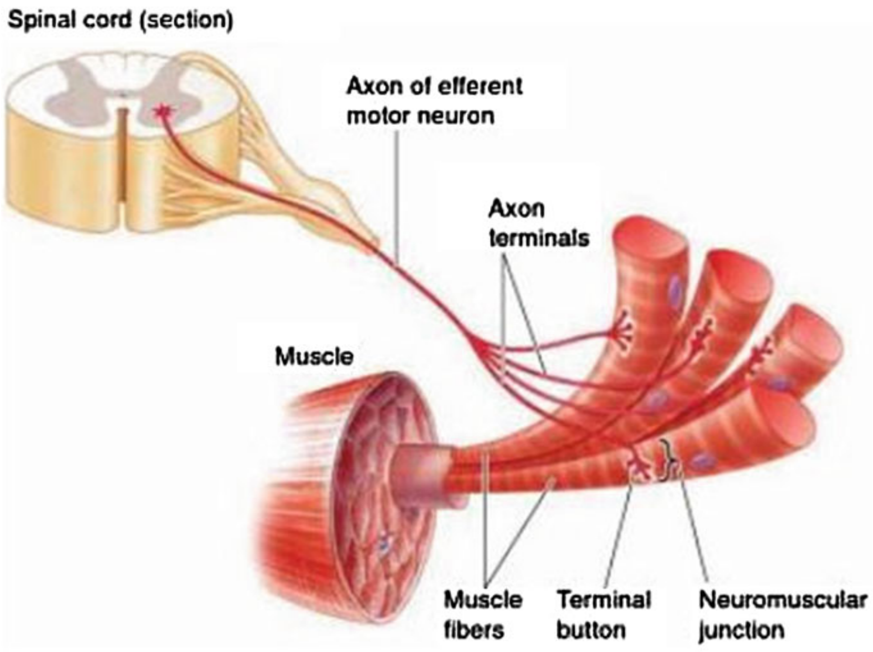

Fig. 14.1 A portion of the spinal cord showing a motoneuron, and how it innervates a number of muscle fibers (connected at the neuromuscular junction). The action potential travels from the axon of the motoneuron to the neuromuscular junction, where it propagates towards the tendons in both directions. Taken from Sherwood (2008)

The information that can be extracted from the EMG depends greatly on the recording technique employed (see Fig. 14.2), which depends highly on the volume conductor. The volume conductor is the ensemble of muscle, fat and skin layers that behaves as a (spatial) low pass filter. EMG activity may be recorded from the vicinity of the motor units through intramuscular electrodes, typically 5–6 electrodes are used (Stashuk et al. 2004). Conversely, sEMG signals are heavily influenced by the low pass filter separating the muscle fibers from the detection point (Lindstrom and Magnusson 1977), which causes limitations. This poses a challenge since small MUAPs signals are hardly captured via surface electrodes hindering detection of individual motor unit spike trains. Furthermore, sEMG technology only registers activity from large or superficial motor units, typically at a maximum depth of 1–2 cm (Merletti et al. 2008).

The conventional approach to analyze sEMG data is to consider it as a non-stationary[1] interference signal composed by the potentials from many motor units. Since it is not possible to extract information about individual motor units from the classical recording configuration consisting of two electrodes, sEMG is normally considered a global measure of muscle motor unit activity (Farina et al. 2004). However, physiological and non-physiological factors can enable misguided interpretation of bipolar sEMG recordings (Merletti et al. 2008). Hence, electrode placement is a significant factor to consider when implementing sEMG (Farina et al. 2004, see the example in Fig. 14.2b). Physiological factors deal with fiber membrane properties, such as conduction velocity (CV), configuration of intracellular action potentials, as well as issues regarding motor unit properties, such as number of recruited motor units, distribution of discharge patterns, and firing rate synchronization. Alternatively, the term non-physiological factors relates to inter-electrode distance, inclination of the detection system relative to muscle fiber orientation, and relative displacement of the muscle with respect to the recording point. Moreover, crosstalk, understood as recording of a signal over one muscle that is actually generated by a nearby muscle is another important non-physiological component, which is not easily identified (Farina et al. 2004).

High-density sEMG recordings, performed through matrices comprising a large number of spatially arranged electrodes, represent a technique able to overcome the limitations of traditional EMG recording and processing, and broaden their potential and applicability. Large electrode arrays enable sampling muscle activity at multiple locations—referred to as spatial sampling (Merletti et al. 2008), which in turn provides concurrent information of motor unit recruitment in time and space (Fig. 14.3a shows an example of data acquired with high-density EMG). Furthermore, these arrays assess motor activity of their constituent motor unit spike trains via decomposition algorithms (see, e.g., Holobar and Zazula 2007).

Bidimensional (or linear) high-density sEMG electrode arrays, if correctly aligned with the fibers (see Fig. 14.3), offer the possibility of directly observing the

[1] In a broad sense, a signal is defined as stationary if its statistical parameters (e.g., mean and variance) do not change over time.

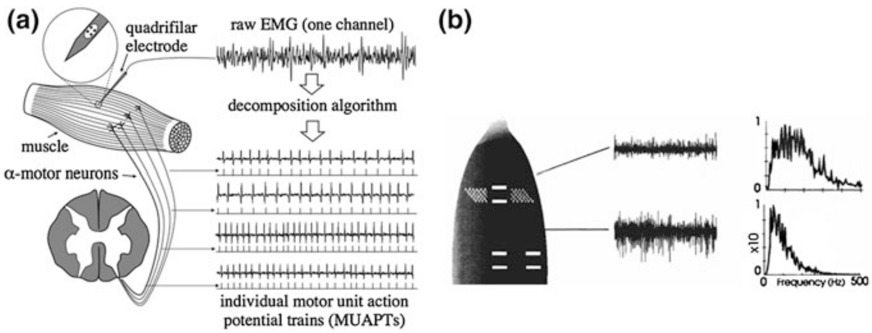

Fig. 14.2 Example of intramuscular and surface EMG signals. **a** Shows an example of intramuscular EMG recording, in which a quadrifilar intramuscular electrode (Basmajian and De Luca 1985) is inserted into the muscle. The raw intramuscular EMG signals (see example) are commonly decomposed into constituent individual motor unit action potential trains using one of the existing algorithms (see Merletti and Farina 2009 for a review). **b** Shows an example of sEMG signals recorded with the classical two electrode configuration. The figure illustrates how electrode placement influences the recorded signal, by representing the data recorded at two different locations (locations are shown in an idealized muscle drawing, raw signals recorded over the selected areas are shown in the *middle column*) and their corresponding amplitude spectra (*right column*); notice the change in the scale, illustrating how electrode placement influences significantly the amplitude of the signal recorded. Therefore, it can be observed how the preferred location is between the neuromuscular junction (in the middle of the muscle), and the tendon (upper and lower extrema). **a** Reprinted from Merletti and Farina (2009), **b** From De Luca (1997)

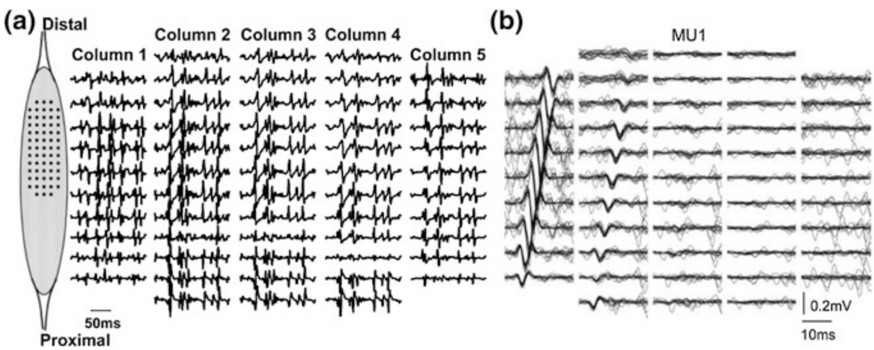

Fig. 14.3 An example of data acquired using a bidimensional EMG electrode array, and its partial decomposition. **a** Shows the raw data acquired with a grid comprising 61 electrodes (inter-electrode distance of 5 mm) applied at the biceps brachii of a healthy subject who performed a voluntary contraction at 5 % of the maximum voluntary force. **b** Represents the potentials of a single motor unit obtained from single differential signals in order to increase spatial resolution. Potentials in the same column of the electrode grid are aligned with fiber detection, and allow for the observation of the propagation of the action potential from the innervation zone to the tendon. More motor unit potentials were obtained. Reprinted from Farina et al. (2004)

propagation of single MUAPs. In addition, these arrays also enable the study of the topographical distribution of muscle activation level (see, e.g., Merletti et al. 2010). However, there are some limiting factors, such as the cancellation of positive and negative phases of MUAPs (Keenan et al. 2005), the estimation of CV, muscle fiber length and orientation, and the localization of the innervation zone(s) (Barbero et al. 2012) and tendon endings, which could be estimated through identification of individual motor units.

The analysis of individual motor units from the sEMG is constrained by the number of recorded contact points, with the exception of a few cases (Farina et al. 2008a). That is, it requires concurrent recording of motor unit activities to effectively implement high-density sEMG. A spatial filter[2] is firstly applied when analyzing high-density sEMG recordings. Spatial filters improve selectivity by decreasing the number of motor units contributing to the recorded signal, thus facilitating their identification (Merletti et al. 2008). Hence, decomposition of sEMG output is on the shapes of MUAPs.

Through high-density sEMG, a few representative motor units can be identified without extracting complete discharge patterns (see the example in Fig. 14.3b). This approach, referred to as incomplete decomposition, allows for the characterization of certain properties of individual motor units, such as fiber orientation, CV, and the location of innervation zones (Vieira et al. 2011; Lapatki et al. 2006).

Complete EMG decomposition, on the contrary, identifies motor units whose action potentials are added to the recorded signal, providing a complete overview of motor unit behavior. The first approaches for decomposition of the high-density sEMG relied on template matching techniques. These are limited by poor selectivity when MUAPs overlap; therefore, blind source separation algorithms[3] were developed. Such algorithms rely either on linear instantaneous mixing models or convolutive mixing models. The latter is preferable since it allows variations of MUAP shapes in different recording locations (Merletti et al. 2008). Among the methods assuming convolutive mixing models, the convolution kernel compensation (CKC) technique (Holobar and Zazula 2007; Holobar et al. 2009) estimates the discharge patterns of individual motor units without estimating the underlying mixing process, enhancing computational time. Validation through moderate contractions in a muscle group showed that its accuracy is comparable to that of intramuscular EMG. Although the initial version of the algorithm assumed motor unit firings were statistically independent, it has been recently shown that a gradient descent version of CKC successfully separates motor unit activity in pathological tremor patients (Holobar et al. 2012), exhibiting highly synchronized firing (Fig. 14.4).

[2] In EMG analysis, a spatial filter is an operation where the signal at each channel in the electrode array is changed by a function of the signals in the neighboring electrodes.

[3] Blind source separation is the separation of a set of source signals from a set of mixed signals, which is carried out without the aid of information about the source signals, or the mixing process. To this end, blind source separation algorithms typically assume that the signals are statistically independent or uncorrelated.

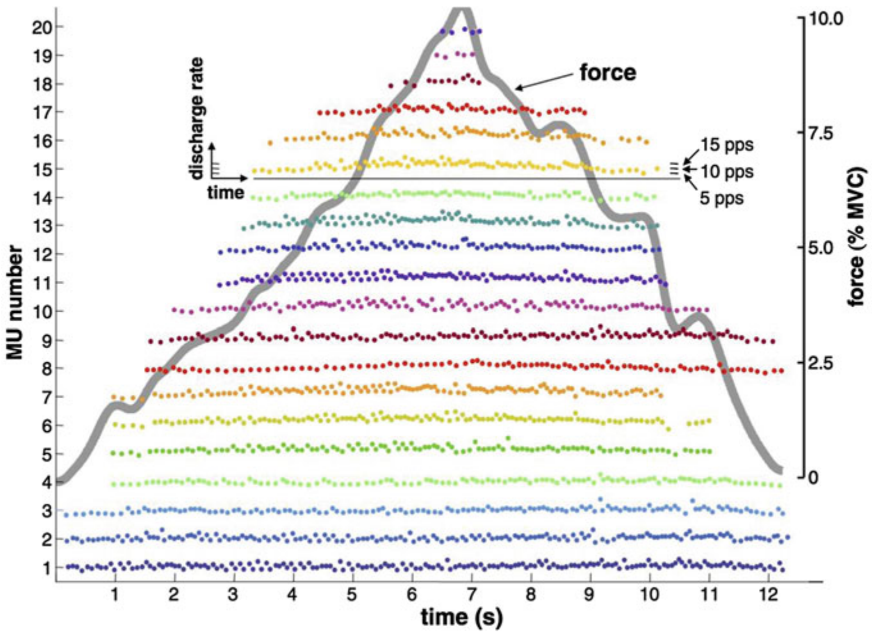

Fig. 14.4 Example of complete EMG decomposition with the CKC technique. The plot shows the individual motor unit discharge patterns (20 motor units) identified during an increasing and decreasing isometric contraction of the abductor pollicis brevis muscle. Motor unit discharge patterns were obtained after the decomposition of high-density EMG recordings (13 × 5 electrode grid). Each *dot* indicates a motor unit discharge at a certain instant, and the height at which the *dot* is represented, the instantaneous firing rate. Reprinted from Merletti et al. (2008)

Interestingly, the combination of properties extracted from bidimensional maps and motor unit spike trains allows for a detailed analysis of muscular and neural adjustments in motor unit properties (Merletti et al. 2008). Therefore, there is a wide range of applicability regarding current and potential applications of high-density sEMG as explained in the next section of the chapter.

14.3 Technology for the Detection and Processing of High-Density Surface Electromyography

Several factors, as described in the previous section, encourage the use of high-density electrode arrays as a solution to the problems that are non-physiological in nature, such as (but not limited to) cross-talk, muscle motion during a measurement, and problems associated with the correlation of the data measured at different recording sessions due to the change in the location of the electrode.

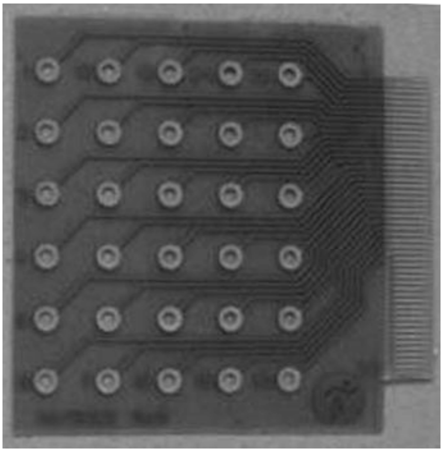

Fig. 14.5 Example of a high density sEMG electrode grid (Merletti et al. 2009)

High-density electrode arrays can be described as two dimensional array systems consisting of multiple small sized, closely spaced electrodes. When compared to single electrode pairs, high-density electrode arrays provide a comprehensive measurement interface of muscle activity due to higher sampling sensitivity of surface potentials. The first designs of high-density electrodes were linear arrays (Broman et al. 1985; Masuda et al. 1985). These arrays were applied along the muscle fiber direction for detection of propagating action potentials, which can be in turn used to estimate the CV, and to determine the location of the innervation zones and tendons (Farina et al. 2000; Merletti et al. 2003). High-density array systems provide not only temporal information but also distribution of the electrical activity at the targeted area. Figure 14.5 shows an example of a high density electrode array.

Some important topics should be considered when designing high-density electrode arrays, including spatial filtering, configuration and geometry of the detection system and amplifier design. A widely used, optimal configuration for sEMG measurements is the monopolar configuration. Moreover, different linear combinations of recorded signals can be captured within electrode arrays. For instance, the single differential configuration, which records the difference of the potentials detected by two electrodes at a fixed distance. In the case of wavelengths much larger than the interelectrode distance, spatial filtering is introduced. Through spatial filtering reduces detection volume and improves spatial selectivity (Farina and Cescon 2001). One of the most important types of spatial filters is the Laplacian filter, which is applied both for linear and bi-dimensional arrays. Figure 14.6 represents the single MUAP measurement of the abductor hallucis muscle using a two dimensional electrode grid (13 $\times$ 5 electrodes, of 2 mm in diameter, and 8 mm inter-electrode distance).

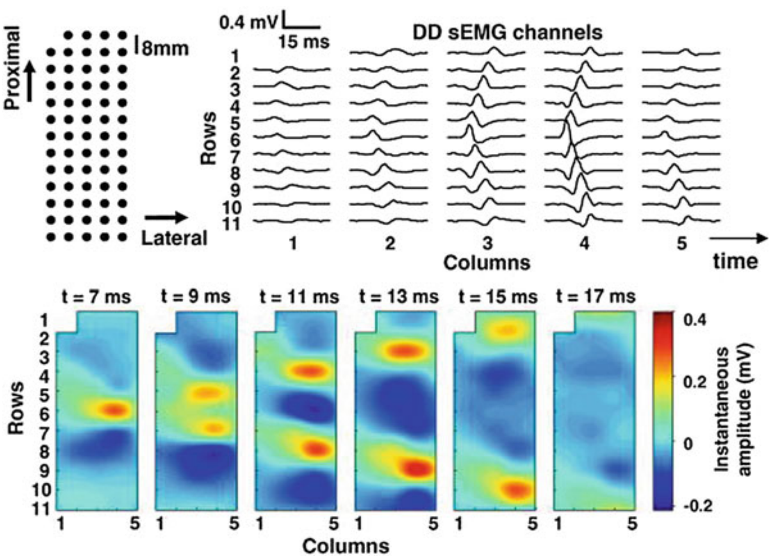

Fig. 14.6 Example of a single MUAP and instantaneous EMG potential maps (interpolated with bicubic spatial interpolation). The *top plot* shows the representation of the motor unit action potential in each position of the electrode grid (shown in the *top left*)

When building an EMG amplifier, a number of design criteria needs to be considered. High input impedance, high common mode rejection ratio[4] (CMRR) and low noise are mandatory characteristics. These parameters are affected by different configurations of circuits. Knowing that the input impedance must be at least two orders of magnitude greater than the electrode–skin interface impedance, three configurations of amplifiers are the most suitable: operational amplifiers (OAs) in voltage follower conditions, two OA instrumentation amplifiers and the three OA instrumentation amplifiers. There are variations that have been developed more recently for multichannel detections (Merletti and Parker 2004).

It is important to account for noise effects generated from the amplifier. For instance, voltage noise exists within an OA with "flicker noise" contributions below 10–20 Hz. Another source of noise is the input current noise flowing into the equivalent impedance of the generator. If such impedance is high, the current noise may be comparable to the voltage noise density and cannot be neglected. These two sources are uncorrelated thus the total input noise power is linearly dependent on the bandwidth of the amplifier. A simple solution is limiting the amplifier bandwidth reduces the total noise and reduces disturbances.

[4] CMRR is the ability of the amplifier to reject the input signals that are common to both inputs.

14.4 Applications of High-Density Surface Electromyography

14.4.1 Applications in Physiology

The use of high-density sEMG allows researchers and practitioners to obtain detailed information about muscle physiology. High-density sEMG can be used, among other applications, to provide information about motor unit physiology, namely the location of their innervation zones, their anatomical features, and also to estimate the mechanisms that underlie fatigue. For example, it is known that in the gastrocnemius medialis (GM) muscle of cats, motor units are distributed extensively throughout the longitudinal axis of the muscle. However, in the case of humans, this distribution was unknown until analyzed with high-density sEMG (Vieira et al. 2011). Vieira et al. focused on whether the area occupied by motor units is relatively large when compared with the size of the muscle, as it occurs in cats or if it is more localized (see Fig. 14.7). Due to the pennation angle of GM

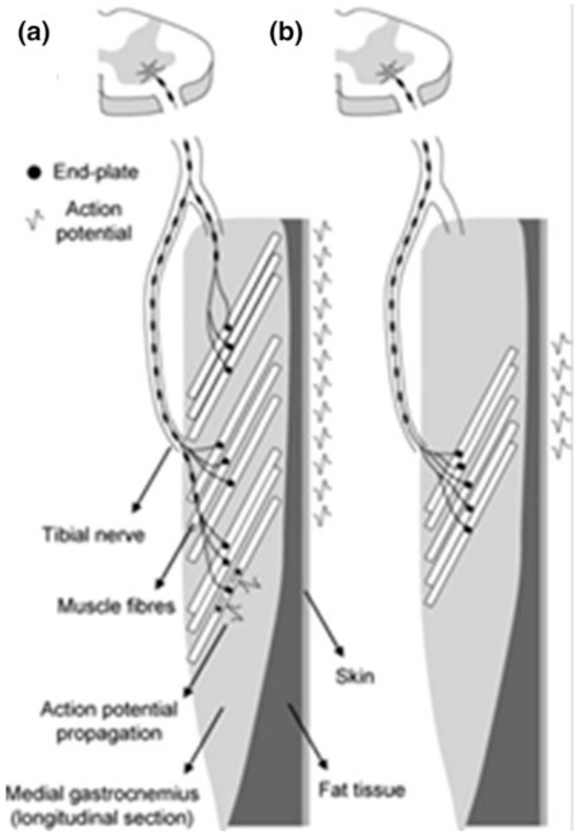

Fig. 14.7 **a** Representation of the hypothesis that motor units extend widely along human gastrocnemius medialis. **b** Representation of the hypothesis of spatially localized muscle units. Reprinted from Vieira et al. (2011)

fibers, motoneurons supply fibers dispersed throughout the GM. Therefore, it is expected that action potentials of single motor units distribute along the skin surface showing mostly the fiber-end-effect.

Using a linear array of 16 silver electrodes (10×1 mm size), with 10 mm inter-electrode distance, Vieira et al. identified 55 motor units, the majority of which were detected in the most distal sites. The group also detected single motor unit potentials throughout five consecutive surface electrodes, which indicate that motor units are less extended in the longitudinal axis of human GM when compared to cats.

Therefore, the study presented in Vieira et al. (2011) observed that motor units of GM are localized, when compared to the total size of the muscle. This arrangement can have implications for the regional control of muscle activity, i.e., the central nervous system may be able to activate sub-volumes of the GM muscle, taking advantage of local variations in muscle architecture (Vieira et al. 2011). Furthermore, this finding indicates that when using bipolar recordings of sEMG, the location of motor units in GM must be considered.

14.4.2 Applications in Ergonomics

Ergonomics, a scientific discipline that focuses on the interaction of a human with the environment, provides applications of high-density sEMG since this technique reveals information regarding muscle activity and fatigue (Barbero et al. 2012). Musculoskeletal injuries in the upper limb and neck represent common disorders in the general population, but mainly in manual workers. Carpal tunnel syndrome (CTS) is a disorder caused by repetitive hand tasks, forceful movement executions and awkward postures. To assess CTS, modifications in the activation of the abductor pollicis brevis muscle were detected with multiple sEMG electrodes (Barbero et al. 2012) (see Fig. 14.8), and some parameters of the signal were compared between non-manual and manual workers to find correlations: the normalized rate of change, the average rectified value of the sEMG, the mean frequency of power spectrum, muscle fiber CV and the kurtosis[5] of the signal amplitude distribution. Among the mentioned parameters, kurtosis was the most suitable to monitor CTS. Troubles in neck and shoulder zones are also usual. An attempt to assess disorders in these regions with sEMG (Sjøgaard et al. 2006) has been reported. Despite the fact that lower than maximal voluntary contractions and the activation of the muscles involved were successfully detected in affected subjects, no robust quantitative factor for assessment was found.

When dealing with ergonomics and rehabilitation, muscle activation and fatigue must be assessed under dynamic conditions. Myoelectric indicators of fatigue are caused by two main physiological phenomena: (1) the reduction of muscle fiber

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[5] Kurtosis is a feature of a probabilistic density function that describes its shape.

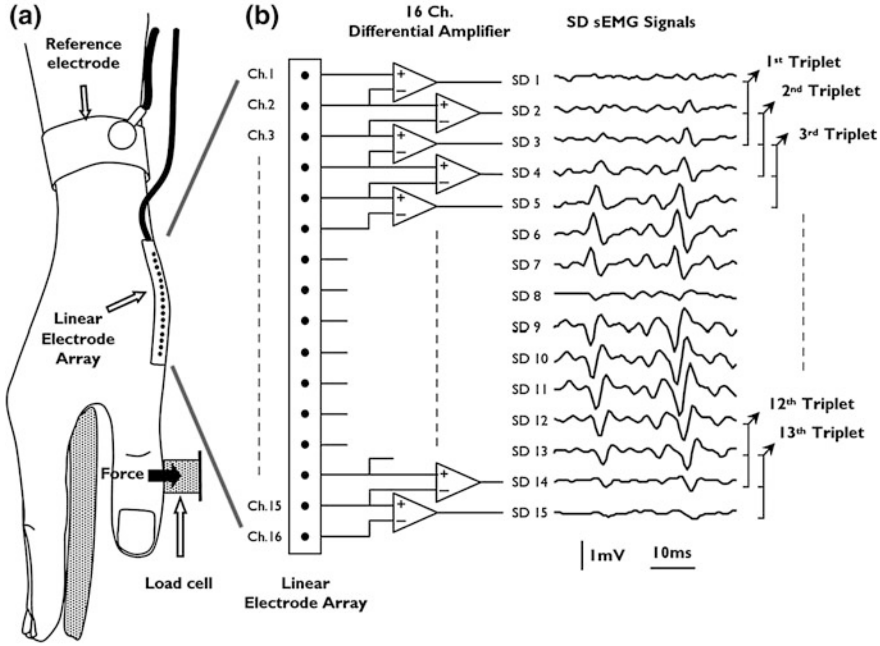

Fig. 14.8 **a** Experimental setup to measure the abductor pollicis brevis muscle, the placement of the electrodes and the load cell to collect the isometric force. **b** Differential amplifier and a set of EMG signals where innervation zones can be observed. Reprinted from Bonfiglioli et al. (2012)

CV and (2) the increased motor unit synchronization as a means for the central nervous system to try to increase muscle force. Interpretation of the sEMG signals under dynamic contractions poses a challenge due to its complexity, since changes in the sEMG signals are related to the changes in force output, muscle fiber length, and relative position of surface electrodes and sources.

In Gazzoni (2010) three different case studies related to these issues were reviewed. Case 1 investigated the myoelectric manifestations of fatigue in the biceps brachii during dynamic elbow flexion/extension. It was shown that sEMG signals displayed the shift of muscle fibers under the skin during movement, and how, through adequate channel selection, it is possible to study fatigue of simple repetitive motion and distinguish among responses to different loads. Case 2 was a laboratory study that focused on the myoelectric manifestations of fatigue in arm and trunk muscles during a repetitive lifting task. Results showed that the amplitude of the sEMG decreased during task repetitions. A decline of CV was correlated with the drop of sEMG amplitude. The author speculated that the reduction of sEMG amplitude was due to the central motor control optimization, since the subject learns how to perform the task with lower muscle activation. Case 3 was a field test during welding of a car door, with the objective of assessing the physical stress of the subject. The study determined that the most reliable way to study myoelectric manifestations of fatigue is to measure isometric contractions before, during, and after the working task, due to high variability observed among subjects during muscle activation intervals and sEMG signal envelopes.

Overall, the authors concluded that signal non-stationarity, electrode shift with respect to muscle fibers, and changes in CV are especially important in the case of ergonomics. All the case studies showed that multichannel sEMG technique helped to compensate (to a certain extent) for the confounding factors due to dynamic contractions.

14.4.3 Applications in Pelvic Floor Analysis and Rehabilitation

Pelvic floor trauma arising from child delivery in females, and from surgery or ageing in males is the most common cause of urinary and fecal incontinence, which leads to a severe loss of quality of life. Through a better understanding of the anatomy of the external anal sphincter (EAS), puborectalis (PB), and urethral sphincter (US) muscles it is expected to develop better treatments for incontinence.

There are several setups to assess the activity of the EAS and PB muscles. These range from needle electrodes to non-invasive methods such as surface or intra-anal monopolar, bipolar or multichannel sEMG recordings. Due to the constraints of the invasive techniques, and limitations on bipolar recordings, high-density sEMG emerges as the most adequate method to record EAS and PB activity. By using this technique, it has been proven that anatomical and physiological information of EAS can be extracted; otherwise, not attainable using a classic setup consisting in a pair of electrodes. Multichannel sEMG allows the identification of single motor units (see Fig. 14.9 and previous figures), the localization of innervations zones, the estimation of EMG amplitude, muscle fiber length, and CV (Merletti et al. 2004), or even of the geometry of the fibers (Cescon et al. 2011). These high density sensors can be reusable, after sterilization, or disposable, and consist of one or more circumferential arrays of 16 electrodes placed on an anal probe, designed specifically to follow the muscle fiber orientation (Merletti et al. 2004) (see Fig. 14.9).

Histogram distribution of innervations zones have been obtained for both genders, through the visual analysis of the EMG signals at three depth levels (Enck et al. 2004). It has been concluded that there is no standard pattern of innervation. Moreover, sphincter injuries and trauma during delivery (e.g. due to episiotomy) are accompanied by incontinence, which makes women more likely to suffer from incontinence. There have been some efforts to develop methods for the automatic localization of EAS innervations zones with high-resolution sEMG, based on a segmentation-classification approach with a matching filter algorithm for real time applications (Mesin et al. 2009). Research on the distribution of innervation zones in EAS muscles has shown high inter-individual variability. Therefore, there is a need to assess innervation for each pregnant woman before delivery to provide indications about the least damaging direction of episiotomy.

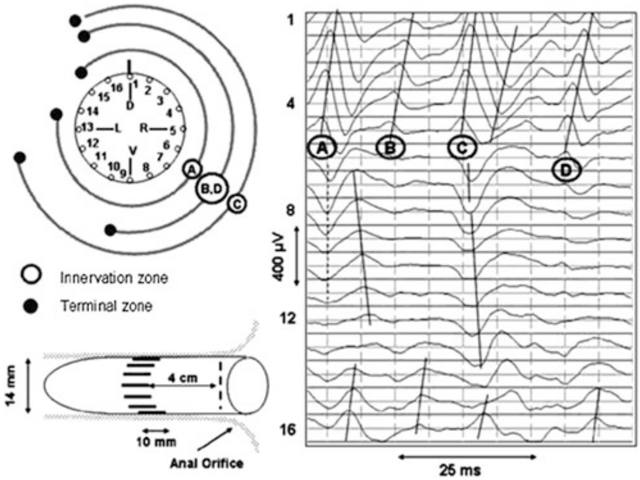

Fig. 14.9 The figure shows the 16 channels array, and four motor unit action potentials identified from the sEMG signals detected along the array (*circles* containing *A*, *B*, *C*, *D*). The electrode probe and its placement along the anal canal is also shown (Merletti et al. 2004)

Concerning the PB muscle, with similar techniques it is possible to extract anatomical information about the innervation zone and individual motor units through minimally invasive multichannel EMG recordings (Cescon et al. 2008). Estimation of MUAP amplitude, its direction of propagation, and CV were studied in healthy and incontinent patients to identify the differences among them, contributing to the elucidation of the mechanisms of incontinence.

Regarding urinary incontinence, it is necessary to know the activation level of the US when voiding and storing urine for functional diagnosis. Several methods are normally used for this purpose, such as sEMG analysis (Heesakkers and Gerrestsen 2004). Surface EMG can be recorded with circular arrays of sEMG electrodes placed around a small probe. Although the methodology has been tested in women, more studies are needed in males. Advances in the quantification of US muscle activity, are expected via biofeedback.

In summary, the continuous progress in this application is expected to achieve some degree of prevention and earlier detection of fecal and urinary incontinence, and also to contribute to limit interventions that might create asymmetry of pelvic floor innervations.

14.5 Conclusions and Future Challenges

This chapter presented the rationale for using high-density EMG recordings when studying muscle function. We have highlighted that it is possible to minimize the disadvantages presented in traditional bipolar recordings through electrode arrays.

This technology enables a wide range of analysis, such as, muscle function in the spatial domain, muscle properties including localization of the innervation zone, or the extraction of motor unit spike trains. We also review some applications of high-density sEMG in the areas of basic physiology, motor control, the assessment and prevention of neuromuscular disorders, and rehabilitation, in order to further stress the potential of this approach.

The development of algorithms that extract motor unit activities from the high-density sEMG is the most significant advance in the field of EMG in decades. The characterization of the neural drive to muscle by means of motor unit spike trains provides a realistic representation of how supraspinal and spinal factors influence muscle function. This information generates detailed information about muscle function not available beforehand. So far, we are only beginning to explore this technique, which needs to be improved in some areas, such as dynamic muscle contractions.

Due to the properties of the volume conductor, the algorithms for the decomposition of the sEMG can only detect the activities of motor units located relatively in the surface. Therefore, it is expected that the combination of this approach with high-density intramuscular EMG recordings (e.g. Farina et al. 2008b) will constitute the means to characterize muscle motor units firing properties.

This chapter also discusses some applications of high-density sEMG in the areas of basic physiology, motor control, prevention and assessment of neuromuscular disorders, and rehabilitation. Of great importance is the identification of motor unit territories in different muscles, or assessment of the back, shoulder and upper arm muscles to study optimization of task performance through minimal effort. Notice the latter is extremely important so as to reduce the cost of work-related musculoskeletal disorders. Another important application of high-density sEMG reviewed here is the prevention of episiotomy-related cases of incontinence, and the development of interventions for rehabilitation. A large number of other applications, such as the control of robotic exoskeletons and neuroprostheses, the assessment of the effects of muscle training, and the investigation of the mechanisms underlying various neurological disorders, are currently under investigation. The potential applications of high-density sEMG as a form of human–machine interface are currently evolving to facilitate strategies in rehabilitation engineering.

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Part IV
Hands-on Guides

Chapter 15
Introduction to Low-Cost Motion-Tracking for Virtual Rehabilitation

Sebastian Koenig, Aitor Ardanza, Camilo Cortes, Alessandro De Mauro and Belinda Lange

Abstract Low-cost motion sensors have seen tremendous increase in popularity in the past few years. Accelerometers, gyroscopes or cameras can be found in most available smart phones and gaming controllers. The Apple® iPhone, Nintendo® Wii™ and the PlayStatio® EyeToy™ are just a few examples where such technology is used to provide a more natural interaction for the user. Depth-sensing cameras by companies such as Microsoft, PrimeSense and Asus can enhance the user experience even further by enabling full-body interaction. This chapter will specifically discuss the use of the Microsoft® Kinect™ depth-sensing camera (Kinect) for rehabilitation of patients with motor disabilities. In addition, examples will be provided of how the Kinect can be used with off-the-shelf computer games or utilized in conjunction with modern game development tools such as the game engine Unity. The examples will outline concepts and required resources in order to enable the reader to use low-cost depth-sensing cameras for rehabilitation.

Keywords Video games · Middleware · Virtual Reality · Interactive technologies

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15.1 Virtual Reality and Video Games for Rehabilitation

Virtual reality (VR) based rehabilitation of motor disorders is a very promising area of research and development. Virtual reality systems can range from high-cost platform systems and robotics to low-cost off-the-shelf video gaming technologies. There has been growing recognition of the potential value of VR and video game technology for creating a new generation of tools for advancing rehabilitation, training and exercise activities. Research in the area of VR and rehabilitation suggests that VR game-based technology can be used effectively to improve motor skill rehabilitation of a range of functional deficits (Boian et al. 2002; Chuang et al. 2002; Adamovich et al. 2004; Dvorkin et al. 2006; Fung et al. 2004; Fulk et al. 2005; Fung et al. 2006; Subramanian et al. 2007; Holden et al. 1999; Merians et al. 2002, 2009; You et al. 2005; Jack et al. 2001; Mirelman et al. 2009). Virtual Reality has also been integrated with robotics to provide motivation and feedback within rehabilitation with robotic devices that control and/or assist the user to move (De Mauro et al. 2011, 2012; Deutsch et al. 2004).

Part of the excitement in this area has grown from the well-known concept in motor learning that by providing a stimulating environment in which to practice repetitive, targeted movements with appropriate feedback can improve rehabilitation outcomes. Providing people with the opportunity to practice physical exercises within a digital game simulation has the potential to motivate the user to perform a higher number of repetitions in a more engaging environment (Rizzo and Kim 2005). Virtual reality systems demand focus and attention because the user is interacting within a situation that depends on their input. Game-based interactions can motivate the user to move and provide the user with a sense of achievement, even if they cannot perform that task in the 'real world'. Researchers have shown that the movements performed during VR rehabilitation can be similar to those used in traditional therapy, however, this is dependent on the specific VR system (Antonin et al. 2004).

The recent release of physically interactive video game systems has increased the interest and accessibility of the use of VR technologies within the rehabilitation setting. Some researchers have treated neurological impairments by implementing off-the-shelf game consoles, such as the Sony Playstation®2 EyeToy™ (Flynn et al. 2007; Rand et al. 2008) and Nintendo® Wii™ (Deutsch et al. 2008), with promising results. The underlying motion-sensing and 3D graphic technologies that are used in these commercial game systems allow the user to engage in entertaining motor games using gross body movements that are not bound by the limits of a mouse, joystick or game-pad interface. Yet whilst these systems have enjoyed wide adoption by millions of users and are generally stimulating and entertaining, clinicians and patients cannot easily alter the hard coded stimulus parameters of the game system as is needed to optimally rehabilitate precise motor skills in a controlled, clinically relevant way (Lange et al. 2009). In addition to the limited options for the systematic control of stimulus parameters needed to customize interaction challenges to the needs of the user, these video games provide limited capacity for the recording of meaningful performance data (Lange et al. 2009, 2010). Therefore, while it is noted that these interactive video games are fun and motivating, such out-of-the-box systems do not consistently meet the clinical requirements for delivering precise motor interventions in a systematic fashion that can be customized to the needs of a target user group. However, the potential does exist that these systems can be creatively repurposed for useful rehabilitation purposes.

Many researchers are beginning to explore the potential of the Microsoft Kinect technology for rehabilitation. The solution to the challenge of using VR and video games in rehabilitation can be approached in two different ways: (1) the use of a middleware that allows tailored movements to be programmed so a patient can play an existing game with individualized movements or (2) the development of software specifically designed for the purpose of customized rehabilitation that is compatible for use with off-the-shelf interactive and video game hardware. This chapter will provide an overview of the tools that can be used to customize existing games, provide a tutorial to allow the reader to begin to explore the use of these tools, and provide a brief introduction to some of the tools that can be used to develop specific rehabilitation software.

15.2 Advances in Low-Cost Tracking Technology

Recent advances in video game technology have made available a large number of low-cost devices that can track the user's motion. These range in capability from handheld controllers that can be used for gesture-based control, such as the Nintendo® Wiimote™ and the Playstation® Move™, to cameras that use computer vision techniques to sense the user's body poses such as the Playstation® EyeToy™ and the Microsoft® Kinect™.

Depth-sensing cameras provide developers and clinicians with the most natural, but also the most flexible way to interact with rehabilitation applications. The user is not required to wear any markers, carry any additional devices or use specific limbs to interact with a system. Full-body tracking provides the opportunity to select any combination of gestures and limbs for interaction with a software application. Such flexibility can be used to tailor the user interaction towards the specific rehabilitation goals of the user (Lange et al. 2011a, b).

15.2.1 Depth-Sensing Frameworks

For the purpose of this chapter the Microsoft® Kinect™ has been used to demonstrate how depth-sensing cameras can be used with off-the-shelf computer games and customized applications within a game engine such as Unity. The Kinect was chosen because of its wide availability and the existing integration within several development tools that facilitate its use in rehabilitation. There are multiple options for using the Kinect as an input device for games. Originally, the Kinect was released as a peripheral for the Xbox360 gaming console. However, Kinect-enabled games for the Xbox360 system do not give clinicians the freedom to choose gestures and movements that fit the therapeutic goals of the patient. Once the user input has been decided by the developer of the game, it cannot be adapted easily to fit the needs of users with disabilities. Alternatively, the Kinect can be used with a Windows PC through third-party software from OpenNI or the Kinect for Windows Software Developers Kit (SDK). Both options provide more freedom for leveraging the Kinect's tracking capabilities to control games for the purpose of rehabilitation and social reintegration of users with disabilities. The Kinect for Windows SDK enables developers to access the Kinect's data to enhance existing or newly developed games with gesture control and full-body tracking.

OpenNI™ (DotNetNuke Corporation) is an industry-led not-for-profit organization promoting the standardization of natural interaction devices. OpenNI provides an open-source framework for developers to leverage these devices for their own applications. The framework provides integration for the Microsoft® Kinect™ camera, PrimeSense camera and Asus Xtion Pro camera through an API for the sensor devices and an API for additional high-level middleware packages.

There are several other solutions for depth-tracking available that provide similar features to OpenNI's and Microsoft's development kits. Omek's Beckon SDK (Omek Interactive, Israel) is a comprehensive development suite that supports any commercially available 3D camera. Omek also offers a range of tools to enable developers to author gestures or integrate full-body tracking into the Unity game engine. SoftKinetic's iisu SDK (SoftKinetic, Belgium) offers a similar set of comprehensive 3D gesture recognition tools that support a range of different depth-sensing cameras. Lastly, PrimeSense offers a depth-sensing camera and sensing framework NITE which can be used with the OpenNI framework. For each of the available software suites it is important to consider which sensors are supported, how gestures are detected and implemented, which distances to the camera are leveraged (e.g. close-range tracking for hand-detection) and which licensing options are available.

15.2.2 Flexible Action and Articulated Skeleton Toolkit (FAAST)

FAAST (Institute for Creative Technologies, CA; Suma et al. 2011) is a middleware that facilitates the integration of full-body control with VR applications and video games using OpenNI-compliant depth sensors (Fig. 15.1). It interfaces directly with OpenNI/NITE or the Microsoft Kinect for Windows SDK to access pose information and perform additional high-level gesture recognition for generating events based on the user's movements.

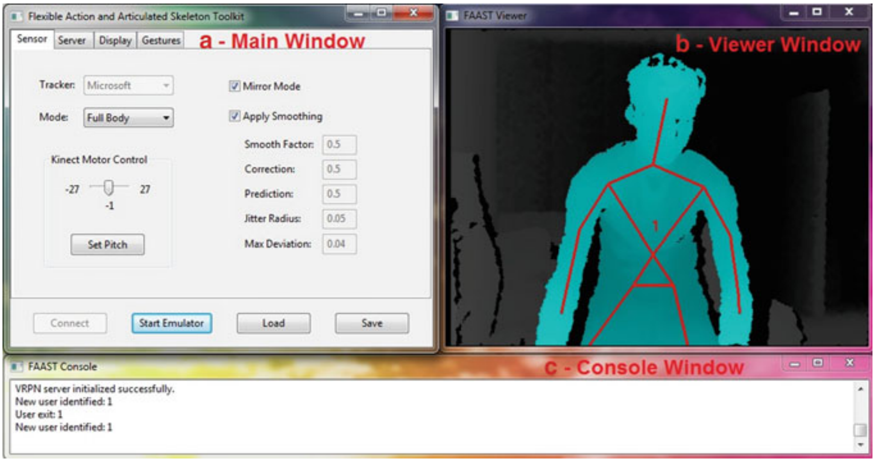

Fig. 15.1 FAAST user interface

FAAST considers two broad categories of information from the sensor: actions and articulated skeletons. Articulated skeletons consist of the positions and orientations for each joint in a human figure and are useful for VR and video game applications in allowing direct control of a virtual avatar through body movements. FAAST retrieves these skeleton joints from the OpenNI/NITE or Kinect for Windows SDK drivers and transmits them to the end-user application using the Virtual Reality Peripheral Network (VRPN), a popular software package in the VR community for interfacing with VR peripherals (Taylor et al. 2001). FAAST includes a custom VRPN server that streams each joint's skeleton data as a six degree-of-freedom tracker, allowing applications to interface with the sensor as they would with any other motion-tracking device.

FAAST enables these custom sensors to provide input to a wide range of applications. It can be used to emulate keyboard and mouse input for standalone PC applications as well as web-based games. Users can customize the key-bindings and sensitivity for triggered actions at run-time, thus providing flexible input that can easily be adjusted according to the individual user's preferences and therapeutic goals. Exemplarily, the same game can be played with different gestures and ranges of motion to allow players with different levels of ability and different therapy goals to play with or against each other. Figure 15.2 shows a player using FAAST to control an online game with different sets of gestures.

15.2.3 MiddleVR

MiddleVR (IminVR, France) is a middleware that facilitates the integration of virtual reality hardware in a wide range of applications. A standalone version of MiddleVR and a Unity implementation are offered for developers to enhance user

Fig. 15.2 Using FAAST to control a game (Suma et al. 2011)

interaction though VR hardware. MiddleVR can be utilized to display immersive content with complex projection solutions such as Head-Mounted Displays, Powerwalls, VR Walls, Workbenches, Holobenches, HoloStages, Caves and 3D Televisions. Active and passive stereoscopic displays are supported. MiddleVR is also able to integrate VR peripherals, enabling the user to interact with the virtual world in a more natural way. For example, 3D trackers, haptic devices, joysticks, 3D mice, depth-sensing cameras and several other devices can be used to interact with immersive virtual content. Most of these devices are supported through the VRPN library. However, it is also possible to use other drivers to integrate devices such as the Microsoft Kinect. This allows developers to use the VR peripherals to perform actions in the 3D application instead of using traditional input devices. For instance, the position and orientation of the viewport of a virtual scene can be modified according to the measurements obtained from a 3D tracker installed on the head of the user. This can be a meaningful interface when the users are expected to orient themselves in the environment or observe a virtual scene or object from different perspectives.

Alternatively, MiddleVR can be used to interact with virtual objects via alternative input devices such as a haptic glove. Users can perform different gestures to reach, pick up and release virtual items which can be a useful training scenario for motor rehabilitation. Integration of the Microsoft Kinect depth camera gives the developer the freedom to use any of the user's tracked joints to interact with a virtual environment.

MiddleVR is set up through a graphical configuration tool which allows the developer to select the supported hardware and decide how the hardware input is mapped to user actions. For example, the head position of the Microsoft Kinect can be mapped to the position of the scene's main camera, allowing the user to look around a virtual scene naturally. In addition to the configuration tool MiddleVR also provides a C# interface and a C++ API for direct integration in applications (Fig 15.3).

15.2.4 Unity

Unity (Unity Technologies, San Francisco, CA) is a development platform for games and general 3D content that allows the developer to publish applications for

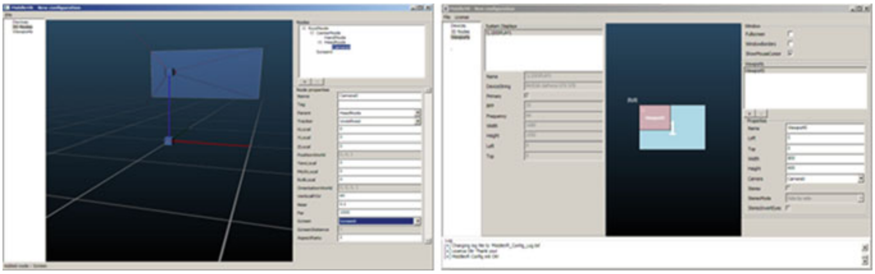

Fig. 15.3 MiddleVR interface

PC, Mac, mobile devices, web, Flash and gaming consoles (Wii, PS3, Xbox360). As a so-called game engine it integrates a wide range of tools that can be used to create interactive virtual environments. Unity's toolset encompasses the rendering of 3D models, animations, shading and lighting, input and output operations, user interfaces, physics simulations, audio, network integration, scripting of game logic and other features that are needed to develop games and interactive applications. There are many free and paid online tutorials available to explain each of the engine's features in detail. Of particular importance is Unity's ability to communicate with external applications via the use of plugins. This allows developers to import data from the Kinect via OpenNI or the Kinect for Windows SDK into Unity. The information can then be used within Unity to control virtual avatars, trigger events or allow the user to interact with a virtual environment. Further, external applications such as MiddleVR can act as a middleware to exchange data between Unity and a wide range of sensors or display solutions.

15.3 Tutorial

15.3.1 Using FAAST to Define Gestures that can be Used to Play Existing Games

The FAAST middleware can be used to define a range of gestures. These gestures can be assigned to key strokes, such as the up, down, left and right arrows or the space bar and 'w', 's', 'a' and 'd' keys. A FAAST keyboard emulation feature can be used so that the gestures assigned to the different keys can be used to play any existing game that uses those keys. This provides an opportunity for clinicians to assign customized gestures for their patients to play games that are engaging and low-cost (or free) for therapeutic exercise. The following section will provide a basic overview of how to define and save gestures.

15.3.1.1 FAAST User Guide

In order to use FAAST, a Microsoft Kinect camera needs to be installed and connected to the PC. Both versions of the Kinect sensor, the Xbox360 version and the Kinect for Windows version, are supported. Further, Microsoft's Kinect for Windows SDK or OpenNI/NITE drivers are needed to use FAAST. The driver packages can be downloaded and installed from the respective websites listed in the reference list (Microsoft Kinect for Windows, FAAST). Once these driver packages are installed, open FAAST by double clicking on the FAAST application icon in the FAAST folder.

FAAST consists of three different windows: main window (Fig. 15.1a), viewer window (Fig. 15.1b) and console window (Fig. 15.1c). The main window consists of four tabs: the sensor tab, the server tab, the display tab and the gesture tab. The sensor tab (Fig. 15.1a) allows the user to specify the installed drivers (Microsoft SDK or OpenNI), the tracking mode (full-body or seated), and sensor angle and provides several options to control tracking characteristics such as mirror mode and smoothing parameters. The server tab (Fig. 15.4a) provides choices for the tracked skeletons and the coordinate system in which the user's joints are being calculated. For any standard application in which only one user is tracked to control an application, no changes of these options are required. The display tab (Fig. 15.4b) allows the user to change the appearance of the FAAST viewer window by switching between RGB image and depth image for foreground and background of the tracked scene. It also provides options for changing the text size of the console window and moving all FAAST windows as well as saving the window configuration. The gesture tab (Fig. 15.4c) can be used to define gestures by providing sets of input conditions and specifying the output of each gesture.

To add a gesture, click on 'New gesture' in the gesture tab. A new window will open (Fig. 15.4d). Type a gesture name and define timings for input and output. Timeouts are used to limit the frequency at which gestures can be recognized (input timeout) or how often outputs are triggered when a gesture output is set to continuous looping (e.g. pressing a mouse button 10 times per second while the gesture is being maintained). Timeouts are displayed in seconds.

Once the new gesture is added, Input and Output conditions must be assigned to the gesture. Input relates to the gesture that must be performed and Output is the keyboard press, mouse-click or mouse movement that the gesture will be assigned

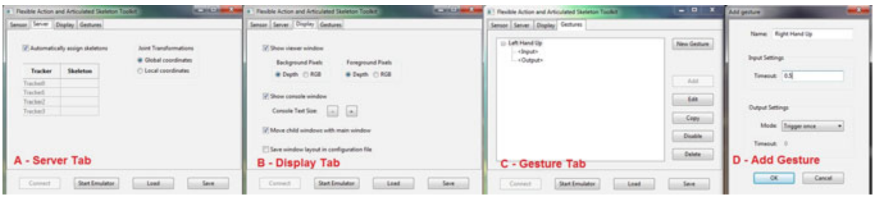

Fig. 15.4 FAAST interface: main window, viewer window and console window

to within the game or interaction. Input and Output conditions can be defined by clicking on each gesture's input and output node (Fig. 15.5a) in the gesture tab and selecting the "Add"-button on the right-hand side of the window (Fig. 15.5b). FAAST offers a wide variety of input constraints to define the user movement that is expected to trigger an output action. Selecting a constraint type opens a new window to add and define the parameters of a gesture (Fig. 15.5c). Exemplarily, body constraints can be customized to detect any leaning, turning or jumping movement in any direction and magnitude/distance. Multiple input and output nodes can be combined to create more complex gesture sequences which have to be satisfied before an action is triggered. Time constraints also provide the ability for temporal sequences of inputs and outputs for even greater customizability of the FAAST tool.

Gestures can be enabled and disabled separately to experiment with different combinations of gestures. This can be especially helpful when individual gestures are tested with patients with motor deficits. By sequentially combining different gestures, the complexity of the user interface can be increased gradually.

All settings can be saved to the local hard drive by selecting the "Save" button in the FAAST main window. Previously saved configurations can be loaded by clicking the "Load" button and selecting the saved configurations file (file ending.xml). Once all gestures have been defined and the Kinect has been successfully started ("Connect" button), pressing the "Start Emulator" button will enable gesture recognition. The FAAST console window will display whenever defined gestures are triggered and users enter or exit the scene. When a gesture is recognized the assigned output (e.g. keyboard or mouse button press) is triggered. The output is sent to the currently active application. As such, FAAST can run alongside standalone or web-based applications to provide the needed user input, effectively replacing keyboard or mouse inputs. The gesture recognition can be stopped by pressing the "Stop Emulator" button in the main window.

When defining gestures for existing applications the developer or clinician needs to consider the number of gestures that are required to control all aspects of

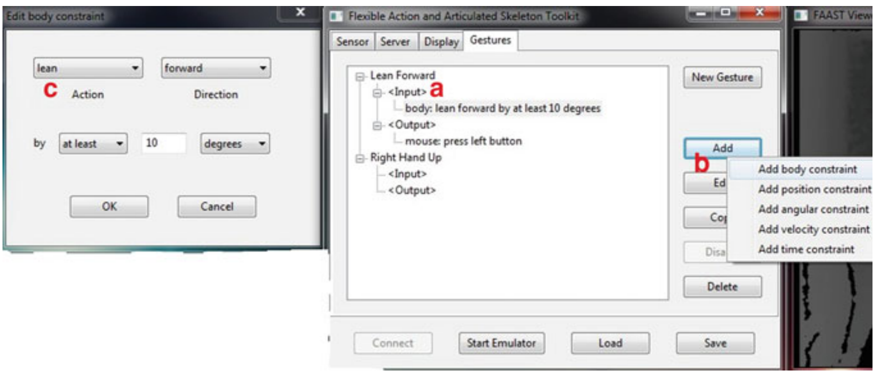

Fig. 15.5 FAAST interface: defining gestures

the game or application. Any application that requires a large number of keystrokes or mouse commands will place high demands on the user to remember and combine the assigned gestures. This problem becomes even more apparent with motor-impaired patients who only have limited range of motion or limited control over parts of their body. Furthermore, games that require precise timings of button presses or use mouse movements as primary control scheme are difficult to master with FAAST. Specific clinical considerations also include the goal of the interaction. The games and gestures must be chosen carefully so as to not encourage sequences of movements that could be inappropriate or unsafe for the patient.

15.3.2 Using MiddleVR to Interact Within a Unity3D Application

MiddleVR can be used to integrate VR input and display devices into existing game development workflows. Developers can utilize VR hardware to make their rehabilitation applications more engaging and customizable for the users. The following section will provide a basic overview of how to configure MiddleVR and a Microsoft Kinect within the game engine Unity in order to start developing customized rehabilitation applications.

15.3.2.1 MiddleVR User Guide

Working with MiddleVR requires several configuration steps that will be described in Sects. 15.3.2.1 and 15.3.2.2. For the purpose of this guide, MiddleVR's integration with the Unity game engine was used. The goal of this guide is to control an avatar within Unity by mapping simple cubes to the location of each of the Kinect's joints.

Firstly, MiddleVR needs to be configured to specify input and output devices that are used with the final application. The configuration is saved in a file (file format.vrx) which is then used in conjunction with the actual application that is being controlled by the user. The initial configuration process is performed in MiddleVR's main window. The window consists of the windows for "Devices", "3D Nodes", "Viewports" and "Cluster".

By default Middle VR has selected keyboard and mouse as input devices (Fig. 15.6). To add or delete any device we will use the "+" and "−" buttons. In the list of "3DTrackers": we have the option to select "Tracker Kinect (Microsoft SDK)".

After defining all needed input devices we need to map the device input to objects or actions in the application (Fig. 15.7). Through the 3D Nodes window the user can define scene objects (i.e. nodes) to be controlled by the input of any Kinect joint. Nodes are placed in a hierarchy with the "VRRootNode" (Fig. 15.7a)

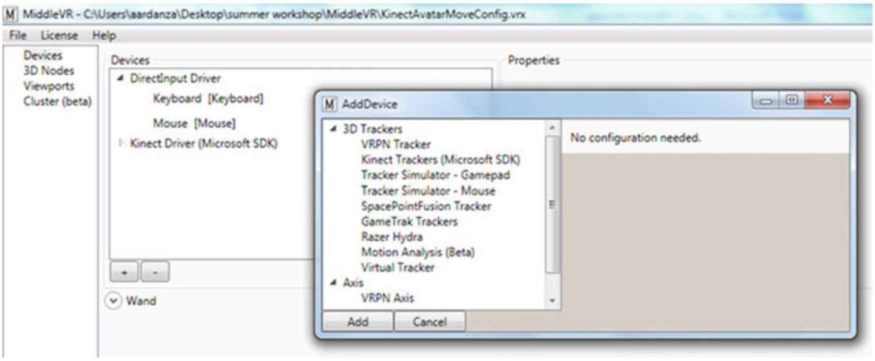

Fig. 15.6 MiddleVR: device selection interface

being the highest node in this hierarchy under which all other nodes are being arranged. While creating mappings between user input and nodes one needs to be aware that each created node will correspond to an object in the actual application.

For example, if the goal of the final application is to control the scene camera through the Kinect's head joint and to control two virtual hands by the Kinect's two hand joints, a total of five nodes are needed. The "VRRootNode" is at the very top of the hierarchy, a "Kinect0.RootNode" (Fig. 15.7b) contains all remaining nodes associated with the tracked skeleton of the active Kinect camera. Underneath the "Kinect0.RootNode" the three nodes for the user's head and both hands are placed. Each of these nodes needs to be assigned a Kinect joint that is controlling the node's position. The available Kinect joints can be selected in the dropdown list "Tracker" (Fig. 15.7c). The name of each created node should follow a consistent naming convention, because the node names and the objects

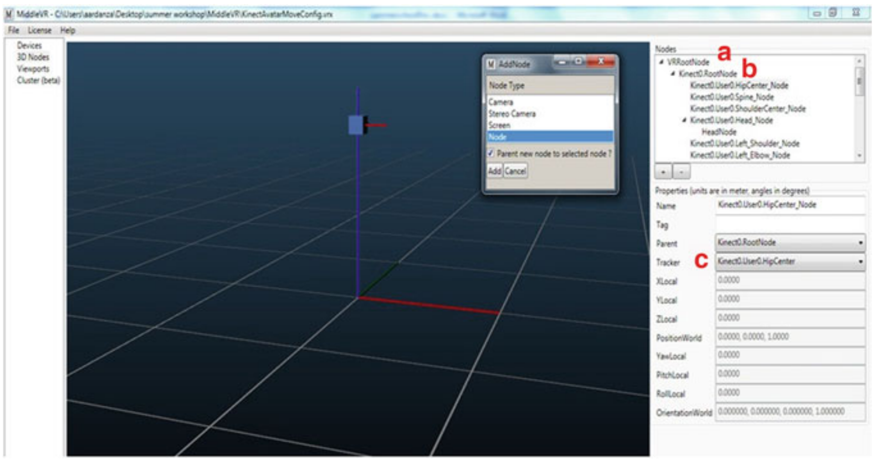

Fig. 15.7 MiddleVR: scene objects interface

being controlled by the Kinect within the game engine Unity need to match. For example, one of the “Kinect0.User0.Head_Node” in Fig. 15.8 is connected to the Kinect tracker “Kinect0.User0.Head”. When the application is set up within the game engine Unity, the object being controlled by the Kinect’s head joint needs to be named “Kinect0.User0.Head_Node”.

MiddleVR also provides the option of controlling a camera to manipulate the player’s view during the game. This can be achieved by creating a “camera” object instead of a node and linking it to the Kinect’s head joint. However, for the purpose of this tutorial a default Unity camera will be used instead of a head-tracked viewpoint.

Once all nodes and trackers have been configured, a configuration file is saved to the local hard drive. This file contains the information of the nodes and trackers which needs to be accessed from the application within Unity.

15.3.2.2 Unity3D User Guide

In order to import MiddleVR’s tracking information into Unity a downloadable Unity-package is available on MiddleVR’s website (see reference list). After launching Unity and creating a new scene (select “File—New Scene”; Fig. 15.8a), the MiddleVR package needs to be imported into Unity. This can be achieved by clicking “Assets—Import Package—Custom Package”.

- After selecting the previously downloaded Unity package (MiddleVR.unity-package) and importing the asset, a new folder named “MiddleVR” will be available in the Project View (Fig. 15.8b).

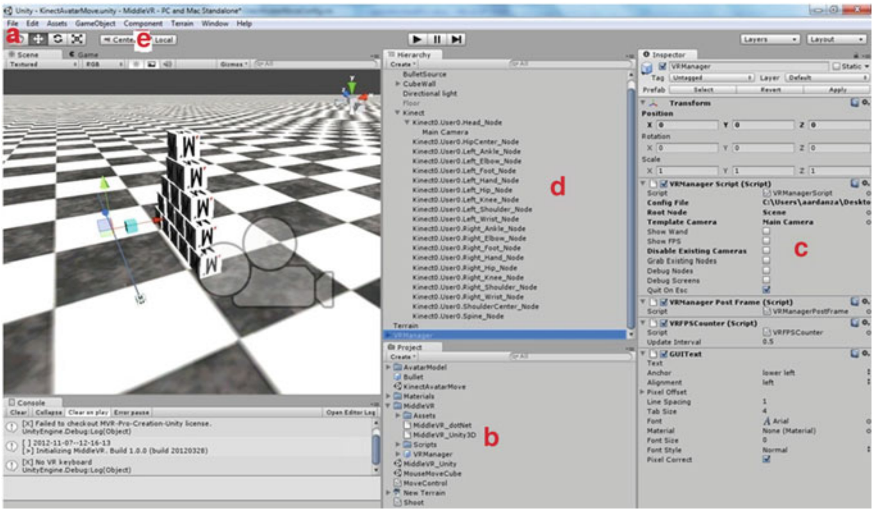

Fig. 15.8 Unity3D Main interface

- The folder contains a so-called prefab named "VRManager". The "VRManager" needs to be dragged and dropped into the Hierarchy View (Fig. 15.8d).
- When clicking on the "VRManager" in the Hierarchy View, the properties of the "VRManager" Script become available in the Inspector (Figs. 15.8c, 15.9).
- The "Config File" needs to be set to the location of the previously created MiddleVR configuration file (Fig. 15.9).
- The Root Node needs to be set to the game object that contains all of the Kinect-controlled objects. In this example the root node that contains all relevant objects is the game object "Kinect" in the Hierarchy View (Fig. 15.8d).
- In order to control all objects correctly, game objects for each of the previously created nodes are required. These game objects need to be placed underneath the root node and renamed to the names we assigned to the nodes in MiddleVR.
- For this example, simple cubes or spheres are sufficient to simulate an avatar (Select "Game Object—Create Other—Cube/Sphere" in Unity). In a complete game each of these nodes could be part of a more sophisticated rigged character that contains joints and limbs created in 3D modeling applications such as Blender, Autodesk Max or Maya.
- Figure 15.8d shows a list of 20 cubes that correspond to 20 nodes representing the whole skeleton that the Kinect is able to track. If the original configuration within MiddleVR contains more or less nodes (e.g. only head and two hands as previously described), the number of game objects in the hierarchy needs to be adjusted accordingly.
- If all objects and scripts are set up, the play button in the top center of the Unity application will attempt to run the application. If a Kinect is connected and the Microsoft Kinect for Windows SDK is installed, the created cubes will follow each joint of the tracked skeleton. The virtual avatar comes alive.
- In order to enable the avatar to interact with the virtual environment, a physics simulation can detect whenever the avatar collides with virtual objects. For this purpose physics components need to be added to each avatar game object. This can be achieved by selecting each avatar object and adding a box collider (or

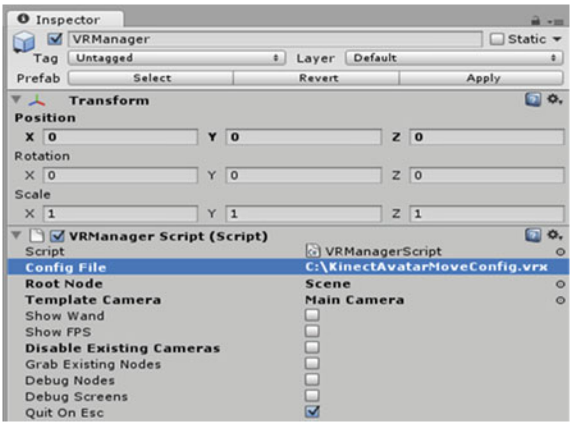

Fig. 15.9 Unity3D VR manager properties

sphere collider if spheres were selected as body parts, Fig. 15.8e "Component—Physics—Box Collider/Sphere Collider").

- The example in Fig. 15.8 shows a stack of boxes in the scene view. For collisions to take place, these boxes also need box colliders and a rigidbody. Rigidbody components (Fig. 15.8e "Component—Physics—Rigidbody") allow the object to be affected by gravity.
- Once all objects are set up properly, the avatar can interact with the stack of boxes by simply colliding with the placed objects.
- Be advised that attempting to punch or kick the stack of boxes can lead to injuries as the player can easily collide with real-world obstacles while interacting with the immersive virtual environment.

15.4 Conclusion

Many researchers are beginning to explore the potential of the Microsoft Kinect technology for rehabilitation. This chapter provided an overview of the tools that can be used to customize existing games or to develop games that use VR hardware. Two potential examples for the development of rehabilitation applications using the Kinect were outlined in this chapter: (1) the use of a middleware (FAAST) that allows tailored gestures to be programmed so a patient can play an existing game with individualized movements and (2) the use of MiddleVR middleware for the development of software specifically designed for customized rehabilitation. The use of FAAST (or similar middleware applications mentioned in this chapter) is perhaps more accessible and user-friendly for clinicians and non-programmers to practice and use with patients in the clinical setting. However, gestures and game choices must be given careful consideration in order to maintain rehabilitation goals and avoid the risks of frustration or injury to the patient. The development of specifically tailored rehabilitation applications using low-cost hardware such as the Kinect requires more technical and programming skills. While this chapter provided a brief introduction to some of the technical components, the development of game-based rehabilitation applications is an iterative process that requires the collaborative effort and involvement of clinicians, patients, designers, programmers and engineers.

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Chapter 16
Human Movement Analysis with Inertial Sensors

Stefan Lambrecht and Antonio J. del-Ama

Abstract Present-day systems for human movement analysis are not portable, have a limited capture volume and require a trained technician to analyze the data. To extend the use and benefits to non-laboratory settings the acquisition should be robust, reliable and easy to perform. Ideally, data collection and analysis would be automated to the point where no trained technicians are required. Over the last decade several inertial sensor approaches have been put forward that address most of the aforementioned limitations. Advancements in micro-electro-mechanical sensors (MEMS) and orientation estimation algorithms are boosting the use of inertial sensors in motion capture applications. These sensors currently are the most promising opportunity for non-restricted human motion analysis. In this chapter we will describe the types of sensors used, followed by an overview of their use in the biomechanics community (Sect. 16.1); provide the necessary background of basic mathematics for those that want to refresh the basics of kinematics (case studies and appendix). The limitations of traditional systems can be dealt with due to the redundant information available to obtain orientation estimates. There are several different methods to derive orientation from sensor information; we will highlight the main groups of algorithms and the various ways in which they use the available data (Sect. 16.3). The chapter furthermore contains two hands-on examples to derive orientation (case study 1) and extract joint angles (case study 2, Sect. 16.4).).

Keywords Inertial sensors · Motion analysis · Signal processing · Kinematics · Orientation

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16.1 Introduction

Human movement analysis can be defined as the interdisciplinary field that describes, analyzes, and assesses human movement. Movement analysis has become a valuable tool in clinical practice, e.g. instrumental gait analysis for children with cerebral palsy (see also Chap. 2). The data obtained from measuring and analyzing limb movement enables clinicians to assess the impaired function and prescribe surgical or rehabilitation interventions. Despite the recognized potential of human movement analysis for diagnosis of neurological movement disorders, rehabilitation from trauma, and performance enhancement its use is restricted to limited specialized medical or rehabilitation centers. The lack of existing applications is mainly due to limitations associated with current motion capture equipment.

The currently available motion capture systems can be divided into vision based and sensor based systems (Zhou and Hu 2007). The vision based systems can be further divided into marker based systems and markerless systems. The former are considered as the gold standard, providing with the most accurate measurements. However, these systems present additional limitations on top of the high financial investment required. Present-day marker based systems are not portable, have a limited capture volume and require a trained technician to analyze the data. The latter is due to a need for a pre-calibration procedure to convert the marker data to a model representing the subject.

Markerless vision based systems, such as the Kinect are not as costly but still suffer from occlusion and illumination problems and a limited capture volume. Furthermore, the repeatability of their measurements is often limited. Traditional sensor based systems (e.g. acoustic or magnetic motion capture systems) also have a restricted capture volume and are sensitive to environmental conditions such as illumination and air flow (depending on the type of sensor used).

To extend the use and benefits of human motion analysis to non-laboratory settings the acquisition should be robust, reliable and easy to perform. Cluttered scenes, changing environmental conditions and non-limited capture volumes are common outside of the laboratory. Ideally, data collection and analysis would be automated to the point where no trained technicians are required. Over the last decade several inertial sensor approaches have been put forward that address most of the aforementioned limitations. Advancements in micro-electro-mechanical sensors (MEMS) and orientation estimation algorithms are boosting the use of inertial sensors in motion capture applications.

Use of magnetic and inertial measurement units (MIMU) is growing in ambulatory human movement analysis. A MIMU consists of a variety of sensors; generally these are three accelerometers, three gyroscopes and three magnetometers. Data fusion of these sensors provides orientation of the MIMU and therefore can provide orientation of the segments to which they are attached. The popularity of MIMU stems from their low cost, light weight and sourceless orientation. MIMU obtain a reference orientation by using the earth gravitational force and the geomagnetic north. Therefore, MIMU do not need a fixed spatial reference in the lab (usually defined at a forceplate center/corner). MIMU are starting to demonstrate their potential in motion analysis applications in robotics, rehabilitation and clinical settings. In addition to being less obtrusive and relatively inexpensive, the main advantage of MIMU is that they are not restricted to a defined capture volume and relatively easy to use.

The objective of this chapter is to provide an outline on the potential of MIMU in human movement analysis (see Fig. 16.1). To accomplish this objective, the chapter is organized in four main sections. Section 16.1 provides a short overview of inertial sensing approaches used to obtain orientation. This overview is by no means a complete review of the literature on orientation estimation using inertial sensors, but rather an overview of sensor alternatives that preceded the current popular approach. In Sect. 16.2 you can refresh your knowledge on 3D kinematics and mathematics. The reader is considered to have prior knowledge in this area. References are provided for those in search of a more complete introduction to 3D kinematics. In Sect. 16.3 an introduction to orientation estimation algorithms is provided, including a first case study. The case study addresses extracting orientation from inertial and magnetic sensor data. Section 16.4 is dedicated to a case study on human movement analysis with MIMU. A theoretical basis for human movement analysis with MIMU is provided, followed by a practical example: estimation of 3D knee joint angles during overground walking. This last case study

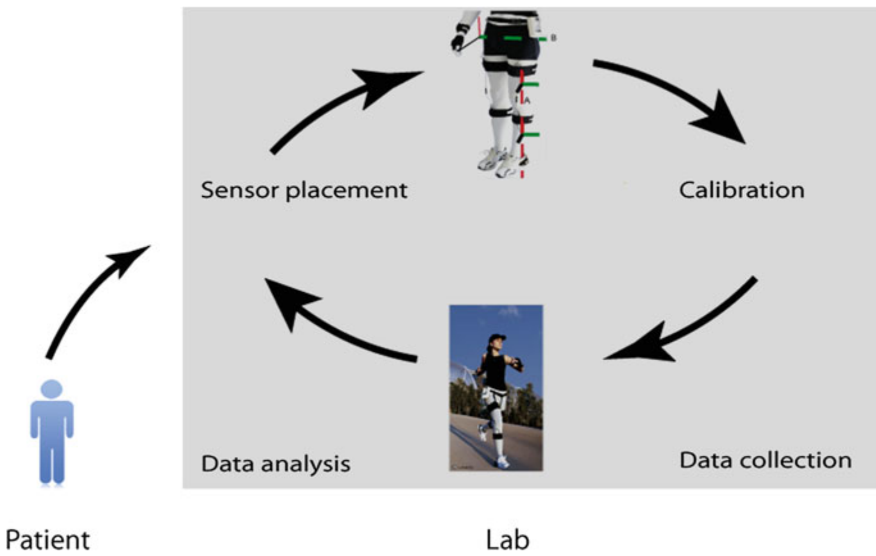


Fig. 16.1 Flow diagram of human motion analysis with inertial sensors. When the patient enters the lab he/she is equipped with inertial sensors (one on each body segment adjacent to a joint subjected to investigation). A two-phased calibration procedure (static and dynamic) precedes the actual data collection and analysis. The last step is to interpret the data

contains all the information provided earlier in this chapter and can be used as a guide to perform human movement analysis outside of a specialized laboratory.

A summary in layman terms is provided in text boxes before each technical section in an attempt to improve readability for those lacking a strong mathematical background.

16.2 Inertial Sensing Approaches

Currently three different sensors are often combined to obtain more accurate and robust orientation estimates. The strengths of accelerometers, gyroscopes, and magnetometers are combined in an attempt to address their individual weaknesses. In this section the type of sensors are described, followed by an overview of their use in the biomechanics community. A case study estimating orientation from accelerometer and magnetometer data concludes this section.

16.2.1 Type of Sensors

Accelerometers measure linear accelerations, originating either from the earth gravitational field or inertial movement. Time mathematical integration of the acceleration signal yields the momentary velocity of the point to which the device is attached, and a second integration yields a spatial displacement of that point, potentially providing an alternative measurement to that generated by a more expensive position measurement system. Under static and quasi-static conditions the accelerometer can be used as an inclinometer. However, under more dynamic conditions it becomes very hard to impossible to accurately decompose the signal into inertial and gravitational components.

Gyroscopes measure angular velocity. Integrating the angular velocity provides us with the angular change over time. A tri-axial gyroscope setup can, given initial conditions, thus track changes in orientation. However, gyroscopes are prone to unbiased drift after integration, limiting their use in time. This error occurs upon integration of the gyroscope signal with the inherent small temperature related spikes. Over time, the integration of these spikes causes the gyroscope signal to drift further and further away from the actual tilt angle. This drift error is strongly affected by temperature, and much less by velocity or acceleration; gyroscopes can thus be applied in highly dynamic conditions, but only for short periods of time.

Magnetometers measure the geomagnetic field, and as such indicate the earth north direction in the absence of other ferromagnetic sources. Magnetometers are often combined with accelerometers, where the former provide the heading of the coordinate system.

16.2.2 Historical Overview

Inertial technology was introduced in biomechanics for impact analysis in the 60–70s. The first studies were done with uni-axial accelerometers, but quickly configurations with three, six, and nine accelerometers were considered (Morris 1973). The initial results indicated that there were severe restrictions in time duration. Giansanti et al. more recently investigated the feasibility to reconstruct position and orientation (pose) data based on configurations containing respectively six and nine accelerometers. They concluded that neither of these configurations was suitable for body segment pose estimation (Giansanti et al. 2003).

In the following decade inertial sensors made their way into motion analysis, in particular in the clinical assessment of gait. Accelerometers were still the preferred sensor type. Willemsen et al. (1991) performed an error and sensitivity analysis to examine the applicability of accelerometers to gait analysis. They concluded that the model assumptions and the limitations due to sensor to body attachment were the main sources of error. The model used was a planar (sagittal plane) lower extremity model consisting of rigid links coupled by perfect mechanical joints (i.e. hinge joint representing the knee). Willemsen et al. (1990) used this two-dimensional model to avoid integrating and thus avoid the troublesome integration drift. They placed four uni-axial accelerometers organized in two pairs on each segment. This method was deemed acceptable for slow movements but considerable errors were reported for higher frequencies (faster movements). Still without additional sensors, Luinge and Veltink applied a Kalman filter (more information on Kalman filters is provided later) to the accelerometer data to improve the orientation estimate (Luinge and Veltink 2004). Luinge and Veltink estimated the contribution to acceleration due to gravity and due to inertial acceleration and used these estimates in their subsequent calculations to derive orientation. Previously low pass filters (only letting that part of the signal through that has low frequency, in this case gravity) were used to eliminate as much as possible the unwanted inertial acceleration signal from the accelerometer data. The filter designed by Luinge and Veltink outperformed these low-pass filters, especially under more dynamic conditions, and might be one of the bases of the popularity of Kalman filters in current orientation estimation algorithms.

By the start of this century, both the cost and size of micro-electro-mechanical sensors (MEMS) had dropped severely. This led to an influx of their application in biomechanics and research in general, and allowed for novel methods in orientation estimation. In particular, it allowed researchers to combine various sensors and thus exploit their individual strengths. Initially accelerometers and gyroscopes were combined (Williamson and Andrews 2001), and later magnetometers were added (Bachmann 2004). Currently the most popular fusion method is based on a Kalman Filter where the information from all three sensors is taken into account. Accelerometers and magnetometers combined act as an electronic 3D compass. This information can be used to provide the initial condition and correct the drift error present in the gyroscope estimation. The gyroscopes in turn are used to smooth the previous estimate, which is especially valuable under dynamic conditions. More information on fusion algorithms is provided in Sect. 16.3. Despite the improvements realized by sensor fusion, there is still room and need for improvement. Additional sensors [GPS, Kinect, magnetic sources and sensors] and anatomical constraints (Luinge et al. 2007) are some of the approaches that have been put forward as potential solutions. Most efforts however are directed to improve the fusion and filtering algorithms.

> Prior to start to work with the MIMU, an introduction to human movement analysis related algebra is given in the appendix. Readers that are already familiarized with this knowledge can go to the first practical example at the end of this section. For those in need for more basic or in depth information, we refer to the following publications (Winter 2004; Vaughan et al. 1999).

16.2.3 Case Study: Electronic Compass by Fusion of Accelerometer and Magnetometer Data

Kinematic technology allows measuring spatial segment movement. The type and format of data obtained depends on both the movement under investigation as well as on the technology used to record this movement. The type of sensors used and the way in which the information from these sensors is exploited determines the accuracy, reliability, and potential field of application.

> This case study exists in determining three unit vectors (a vector is a representation of direction and magnitude of the quantity represented by its data (e.g. Gravity, voltage…); a unit vector is a vector that has a magnitude of 1, and can be obtained by normalizing or taking out the effect of magnitude by dividing a vector by its absolute value) that are perpendicular to each other (for three vectors A, B, C: A to B, A to C, and B to C). These three unit vectors together form a coordinate system from which we can extract orientation. We will make use of sensor data to provide us with two of the three desired vectors, and use a mathematical trick to obtain the third (cross product).

In the absence of motion it is assumed that the only acceleration measured by the accelerometers is gravity. Accelerometer data can thus be used to obtain a reference ($\vec{Y}$) of the global vertical axis, the gravity vector (Kemp et al. 1998). In the absence of ferromagnetic perturbations we can use a similar construct to obtain a horizontal vector based on the magnetometer data ($\vec{H}$). Since both gravity and the geomagnetic field are earth bound, it should be clear that we are obtaining sensor orientation with respect to the global or earth reference frame. Data from the accelerometers and magnetometers has to be normalized in order to obtain unit vectors. Taking the cross product of the unit vectors $\vec{H}$ and $\vec{Y}$ gives us a third unit vector ($\vec{Z}$), normal to both $\vec{H}$ and $\overrightarrow{Y}$. Consecutive cross products ensure that the obtained system is orthogonal. We can thus obtain $\vec{X}$ by taking the cross product of $\vec{Z}$ and $\vec{Y}$. The obtained vectors can be organized in matrix format to obtain the rotation matrix (see appendix for more information on matrix and vectors). From this matrix we can then extract the Euler angles using the X–Y′–Z″ rotation sequence (see appendix: How to extract rotation angles using Euler convention). A pseudo-code version and numerical example are provided to further clarify this process. A pseudo-code is an easy way to give a steps sequence to achieve a given goal. The name pseudo-code comes from computer programming science, where "pseudo" is given since the code is not written in any computer language but in a sequence of steps.

Solving this for a numerical example gives us:

Get raw data

Sensor data of the individual sensors the TechMCS (Technaid, S.L.) consists of: accelerometer data is displayed in m/s^2, gyroscope data in rad/s, magnetometer data in uT, and temperature in degrees Celsius.

AcceX	**AcceY**	**AcceZ**	**Temp**
9.66E + 00	1.67E + 00	3.48E – 01	3.40E + 01
GyroX	**GyroY**	**GyroZ**	
−1.10E − 02	6.73E − 03	1.55E − 03	
MagnX	**MagnY**	**MagnZ**	
−3.18E + 01	−7.91E + 00	−1.83E + 01	

Get unit vectors

$$\vec{Y} = [9.85E-01 \quad 1.70E-01 \quad 3.55E-02]$$
$$\vec{H} = [-8.47E-01 \quad -2.10E-01 \quad -4.88E-01]$$

Get sensor orientation

$$\overrightarrow{X'} = \mathrm{cross}(\vec{Y},\vec{H}) = [-7.57E-02 \quad 4.50E-01 \quad -6.28E-02]$$
$$\vec{X} = \mathrm{norm}\left(\overrightarrow{X'}\right) = [-1.64E-01 \quad 9.77E-01 \quad -1.36E-01]$$
$$\vec{Z} = \mathrm{cross}\left(\vec{X},\vec{Y}\right) = [5.79E-02 \quad -1.28E-01 \quad -9.90E-01]$$

The obtained vectors can be organized in matrix format; from this rotation matrix we can then extract the Euler angles (see Sect. 16.2).

Get rotation matrix

$$^{G}R_s = \quad [^{G}X_s \, ^{G}Y_s \, ^{G}Z_s]_{3\times3}$$

$$^{G}R_s = \begin{matrix} X\cdot x & Y\cdot x & Z\cdot x \\ X\cdot y & Y\cdot y & Z\cdot y \\ X\cdot z & Y\cdot z & Z\cdot z \end{matrix} = \begin{matrix} -1.64E-01 & 9.85E-01 & 5.79E-02 \\ 9.77E-01 & 1.70E-01 & -1.28E-01 \\ -1.36E-01 & 3.55E-02 & -9.90E-01 \end{matrix}$$

Get Euler angles

$$\theta_1 = 177.947^\circ$$

$$\theta_2 = -7.830^\circ$$

$$\theta_3 = 99.538^\circ$$

As mentioned earlier, the method explained above is only valid in static or quasi-static situations. In motion trials, such as gait analysis, we can no longer assume that the acceleration due to movement is insignificantly small compared to gravity. Therefore, the accelerometer can no longer be used as a standalone inclinometer (providing with an attitude reference) and a more elaborate method should be used to obtain orientation with respect to the global reference system.

16.3 Orientation Estimation Algorithms

If, as is the case with the MIMU used in our case studies (Technaid 2013), sensor production is not fully automatic then axis misalignment and cross axis sensitivity have to be accounted for, on top of the sensor noise. One of the types of noise that is to be expected is drift error in the gyroscope signal. This error occurs upon integration of the gyroscope signal with the inherent small temperature related spikes. Over time the integration of these spikes causes the gyroscope signal to drift further and further away from the actual tilt angle.

Sensor fusion can be defined as "the conjoint use of various sensors to improve the accuracy of the measurements under situations where one or more sensors of the network are not behaving properly" (Olivares et al. 2011).

The listed difficulties can be dealt with due to the redundant information available to obtain orientation estimates. Orientation can either be obtained by integrating the gyroscope data or by combining the accelerometer and magnetometer data into an electronic compass.

> There are several different methods to derive orientation from sensor information; in the following we briefly highlight the main groups of algorithms and the various ways in which they use the available data. A survey of all published methods would be too technical and lengthy to strive for in this section. We will therefore highlight the two main approaches and briefly explain (one of) the most popular solutions within each approach.

The *deterministic approach* is based on vector matching. To derive orientation three independent parameters are needed. Two, non-parallel, vector measurements are sufficient to generate these three parameters. This approach has been demonstrated earlier when we derived orientation from magnetometer (local magnetic field vector) and accelerometer (gravity vector) data. The example given closely corresponds to the TRIAD (tri-axial attitude determination) method. Other least-squares approaches are the QUEST (Quaternion estimation) methods, factorized quaternion methods and the q-method (Cheng and Shuster 2005; Shuster 2006). All aforementioned methods are single-frame methods, i.e. they rely on the data from the current frame to derive orientation in that same time frame. The TRIAD method has several limitations: it only allows 2 input vectors and is sensitive to the order in which they are presented; using only data from one time frame it is more sensitive to random error.

Sequential approaches, the most well-known being the Kalman filters, are able to attain better results by taking advantage of more data and thus reducing the sensitivity to random error. The Kalman filter is a recursive filter, meaning that it reuses data to improve the estimate of the state of the system and to moderate the noise present in the measurement data. It is since long the most commonly used orientation estimation algorithm (Yun and Bachmann 2006; Sabatini 2006; Roetenberg 2006; Park 2009). The most used version is the extended Kalman filter (EKF). The extended KF accounts for a certain degree of non-linearity by linearizing about the current best estimate. If the non-linearity is high then a different filter type, better fit to cope with non-linearity (e.g. Particle filter methods), should be chosen instead. The EKF is also the filter type used to obtain the orientation data in the second case study.

The equations behind the EKF can be separated into two groups: time update or predictor equations and measurement update or corrector equations (see Fig. 16.2). To be able to remove the drift error present after integrating the gyroscope data we have to estimate it. Upon removal of this drift the gyroscope signal will be closer to the actual rotations and changes in orientation. We furthermore need a reference to help us identify the drift in the gyroscope signal. We are using orientation data as input into our EKF, thus the reference will be provided by combining the data from the accelerometers and magnetometers (see case study 1). The filter parameters are altered depending on the movement or activity under investigation. The gains of each parameter are calculated continuously to indicate the importance (level of trust to be given to) of each input for the estimation. The initial tuning of the parameters has a strong impact on the performance of the filter. It is hard to impossible to find a configuration that is suitable for both static or slow movements and highly dynamic activities.

The EKF thus balances the strengths and weaknesses of the various sensors to achieve a compromise of orientation estimation with higher accuracy and reliability. The most important limitation of the EKF is that, being an adaptive filter, its behavior depends on the tuning of the parameters and the motion being analyzed. The data provided and analyzed in this chapter was obtained using the on-board algorithm from the TechMCS MIMU (Technaid, S.L.).

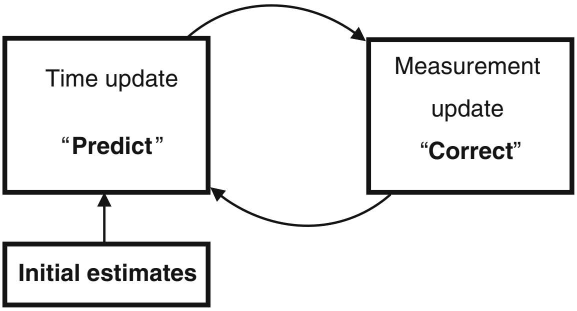


Fig. 16.2 Scheme of a Kalman filtering algorithm. Stochastic filters such as the EKF use a model of the sensor measurements (measurement model) to produce an estimate of the system state. Stochastic filtering thus exist of two stages in a loop, a prediction stage of the new state (time update) and an update stage where this prediction is verified by the new measurements (measurement update)

16.4 Human Movement Analysis with MIMUs

In this section we will start from both raw and orientation data provided by the TechMCS sensors, but you can apply the following to any sensor or system providing this data. The orientation estimation was obtained using the on-board algorithm from the TechMCS MIMU (Technaid, S.L.). The raw sensor data will be used in the sensor-to-body calibration. We will use the sensor orientation data to derive anatomical joint angles. In particular we will look at the right knee joint during normal over-ground walking. Two sensors are placed in an elastic strap and tightened with velcro on the lateral side of the right leg; one on the thigh (1/3 up from the knee joint) and the other on the shank (1/3 down from the knee joint) (see Fig. 16.3). It is important to create a significant, but not uncomfortable, pre-load while attaching the straps to avoid excessive motion artifacts during data collection. The same principles hold for other joints in the human body, as well as other movements. Starting from sensor orientation, we have to obtain anatomical segment orientation. Once we have the orientation of all of the segments involved we can calculate the rotation matrix between two adjacent segments and extract the relevant joint angles.

16.4.1 Sensor-to-Body Calibration

To obtain anatomical segment orientation a sensor-to-body calibration is required (see Fig. 16.3). The purpose of the calibration is to identify, for each sensor attached to a segment, a constant rotation matrix relating the sensor frame to the anatomical frame of the segment to which it is attached. The ISB

Fig. 16.3 Two-step calibration procedure to calibrate the MIMU to their respective body segments of the lower limb. The first step (*A*) consists of maintaining an upright posture with the leg fully extended. In this posture the segment length is aligned with the earth gravity vector (vertical axis, in *red*). The second step (*B*) determines the second vector (*green*). We have opted for a planar movement around the hip joint (hip flexion–extension) with a straight leg. During the movement, both shank and thigh move in the same plane with a common flexion–extension axis (*dotted green line* at the hip). The third calibration axis (*black*) is then obtained by taking the cross product from the vectors measured in A and B. To correct for any misalignments due to measurement error (e.g. poor execution of the flexion–extension movement), one of the measurement axis is subsequently corrected by taking the cross-product between the third axis and the other measurement axis

recommendations (see appendix) to quantify joint motion are based on systems providing position data (Grood and Suntay 1983; Wu et al. 2002). However, current IMUs and MIMU are unable to provide position data. When only orientations of body segments are available, positions have to be determined by linking segments to each other, using a linked-segment model based on segment orientation and fixed segment lengths (Faber et al. 2010; Van den Noort et al. 2012). Therefore, several calibration methods have been proposed that do not rely on or require position data of bony anatomical landmarks (Favre et al. 2009; O'Donovan et al. 2007; Picerno et al. 2008). Three main groups can be distinguished: reference posture or static methods, functional methods, and those requiring additional equipment. The static methods rely on one or several predefined postures and predominantly use accelerometer and magnetometer data. Functional uni-articular joint movements are added in the functional methods. The functional joint axis of rotation is derived from the gyroscope data (Luinge et al. 2007; Jovanov et al. 2005). The calibration method used here belongs to the latter category and can be divided into two parts, the first being static. The participant, equipped with a sensor on the thigh and shank, is required to stand still with both legs parallel and knees extended. It is assumed that the longitudinal axis of the segment ($\vec{Y}$) coincides with the gravity vector. To obtain this unit vector, the accelerometer data during a specific frame is extracted. It is recommended to verify the absence of motion artifact of amplitude spikes during the chosen frame, or alternatively average the accelerometer data over a short interval. After doing so, we have obtained the first axis of the anatomical coordinate system (ACS).

Get raw data

$$\text{raw}\left(\overrightarrow{Accel}\right) = raw(XYZ\, accelerometer\, signal)$$

$$\text{norm}\left(\overrightarrow{Accel}\right) = \text{raw}\left(\overrightarrow{Accel}\right)/|\text{raw}\left(\overrightarrow{Accel}\right)|$$

Get unit vector

$$\vec{Y} = \text{norm}\left(\overrightarrow{Accel}\right)$$

For the data provided in the previous section this gives us:

$$\overrightarrow{Y\_thigh} = [\,0.99580.0821 \quad -0.0416\,]$$

$$\overrightarrow{Y\_shank} = [\,0.98740.0877 \quad -0.1317\,]$$

Subsequently a functional motion is executed; we have opted for a pure hip flexion without bending the knee (see Fig. 16.3). During this movement, thigh and shank are assumed to move strictly in the sagittal plane, perpendicular to the direction of rotation. Assuming a pure hip flexion–extension motion, for which the flexion–extension axis would be in the same plane as the knee flexion–extension axis. Other movements can also be executed, such as knee flexion–extension or leg adduction-abduction. Here, the mean value is taken over a single hip flexion motion.

Get raw data

$$\text{mean}\left(\overrightarrow{Gyro}\right) = mean(XYZ\, gyroscope\, signal)$$

$$\text{norm}\left(\overrightarrow{Gyro}\right) = \text{mean}\left(\overrightarrow{Gyro}\right)/|\text{mean}\left(\overrightarrow{Gyro}\right)|$$

Get unit vector

$$\vec{H} = \text{norm}\left(\overrightarrow{Gyro}\right)$$

Applied to the dataset provided,[1] the vectors derived from the dynamic calibration trials are:

$$\overrightarrow{H_{thigh}} = [0.1750 \quad -0.1676 \quad 0.9702]$$

$$\overrightarrow{H\_shank} = [0.5033 \quad 0.0398 \quad 0.8632]$$

The two obtained vectors, $\vec{Y}$ and $\vec{H}$, both originate from measurements and can thus be non-perpendicular due to measurement error. In patient populations performing a pure motion can be a demanding task, therefore the longitudinal vector (derived from the static trial) is chosen as the base of our calculations. Taking the cross product between ($\vec{Y}$) and ($\vec{H}$), we obtain a third vector ($\vec{X}$) that is orthogonal to the two original vectors. To ensure an orthogonal coordinate system we then compute the cross product between ($\vec{Y}$) and ($\vec{X}$), and obtain ($\vec{Z}$). ($\vec{H}$) is thus a temporary vector that is later corrected, resulting in ($\vec{Z}$) (see Fig. 16.4).

Get unit vectors

$$\overrightarrow{Y\_segment} = \text{norm}\left(\overrightarrow{Accel}\right)$$

$$\overrightarrow{H\_segment} = \text{norm}\left(\overrightarrow{Gyro}\right)$$

Get sensor orientation

$$\overrightarrow{Z\_segment} = \text{cross}(\overrightarrow{Y\_segment}, \overrightarrow{H\_segment})$$

$$\overrightarrow{X\_segment} = \text{cross}(\overrightarrow{Z\_segment}, \overrightarrow{Y\_segment})$$

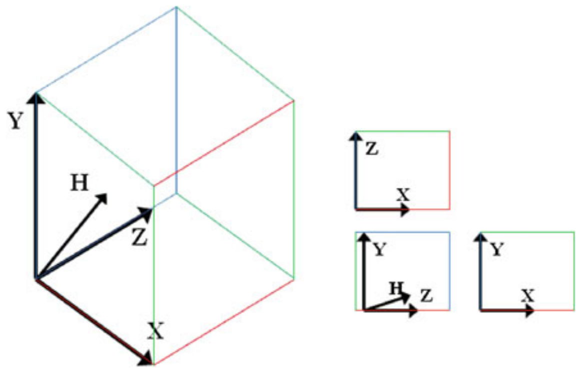


Fig. 16.4 Double cross-product to ensure mutually perpendicular vectors

[1] The flexion cycle we have identified resides in the interval between frames 431 and 450 in the datasheet provided.

Get calibration matrix

$$
\begin{aligned}
{}^{G}R_{s\_segment} &= \left[{}^{G}X_{s}\,{}^{G}Y_{s}\,{}^{G}Z_{s}\right]_{3\times 3}\\
{}^{G}R_{s\_segment} &= \left[\overrightarrow{X\_segment}\overrightarrow{Y\_segment}\overrightarrow{Z\_segment}\right]_{3\times 3}
\end{aligned}
$$

In the numerical example we obtain the following matrices for the thigh and shank:

$$
{}^{G}R_{s\_thigh} = \begin{matrix} 0.0732 & -0.9805 & -0.1826 \\ 0.9958 & 0.0821 & -0.0416 \\ 0.0558 & -0.1787 & 0.9823 \end{matrix}
$$

$$
{}^{G}R_{s\_shank} = \begin{matrix} 0.0878 & -0.9961 & -0.0053 \\ 0.9874 & 0.0877 & -0.1317 \\ 0.1317 & 0.0063 & 0.9913 \end{matrix}
$$

The matrix ${}^{G}R_{segment}$ allows us to represent the sensor orientation data provided by the TechMCS in the local coordinate system of the segment to which it is attached. This is done by multiplying the constant calibration matrix ${}^{G}R_{s\_segment}$ by the inverse of the sensor data matrix $R_{s\_segment}$ at each frame. The CS in which the sensor data is obtained, is not conform the ISB guidelines. The output of the TechMCS is a measure of its orientation with respect to a reference frame fixed to the earth; we therefore need to multiply the data by an ISB_conversion matrix to comply with the ISB recommendations (Grood and Suntay 1983; Wu et al. 2002). It was deemed easier to correct this mathematically post-data collection, and prioritize optimal IMU to segment attachment during trials.

Get data

$$
\begin{aligned}
{}^{G}R_{S\_segment} &= \text{ calibration matrix to transfer from sensor to anatomical frame (constant)}\\
R_{S\_segment} &= \text{ sensor orientation data, updated each frame}
\end{aligned}
$$

Get ISB_conversion

$$
R_{ISB} = \begin{matrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{matrix}
$$

Get segment orientation

$$
\begin{aligned}
{}^{G}R_{thigh} &= {}^{G}R_{S\_thigh} * \ \text{inverse}\left(R_{S\_thigh*}R_{ISB}\right)\\
{}^{G}R_{shank} &= {}^{G}R_{S\_shank} * \ \text{inverse}\left(R_{S\_shank*}R_{ISB}\right)
\end{aligned}
$$

Get joint orientation

$$
{}^{G}R_{knee} = {}^{G}R_{thigh} * \ \text{transpose}\ \left({}^{G}R_{shank}\right)
$$

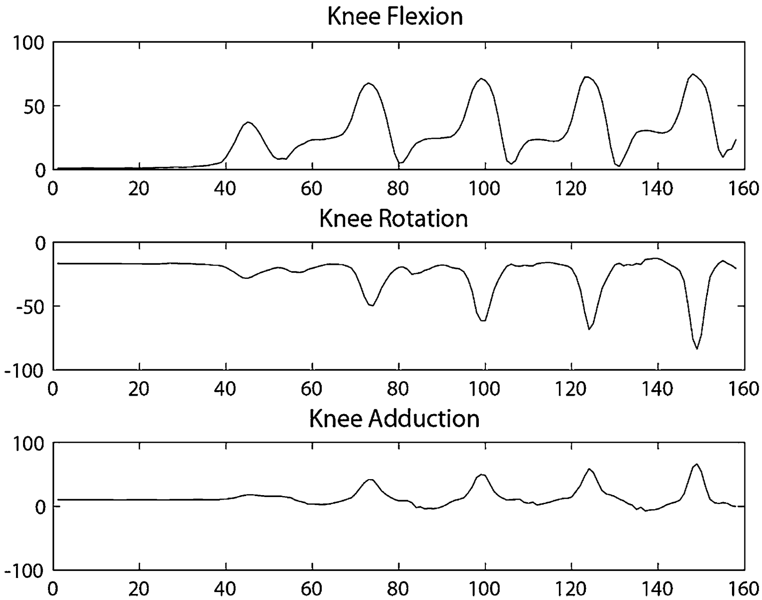


Fig. 16.5 Three dimensional knee joint angles during an unrestricted walking trial performed at self-selected speed by a healthy subject. Data representing right knee movement

Get Euler angles

$$(\mathit{Shorthand\ notation}{:}\ c1 = cos\theta_1,\ s2 = sin\theta_2)$$

$$(\mathit{ISB\ recommended\ Euler\ sequence}{:}\ X - Y' - Z'')$$

$$^{G}R_s = \begin{array}{ccc} \boldsymbol{c}2\boldsymbol{c}3 & s3c1 + s1s2c3 & s1s3 - c1s2c3 \\ -c2c3 & c1c3 - s1s2s3 & s1c3 + c1s2s3 \\ \boldsymbol{s}2 & -s1c2 & \boldsymbol{c}1\boldsymbol{c}2 \end{array}$$

$$\begin{aligned} \theta_2 &= \text{asin}\ ({}^{G}R_s(3,1)) \\ \theta_1 &= \text{acos}\ ({}^{G}R_s(3,3)/\cos(\theta_2)) \\ \theta_3 &= \text{acos}\ ({}^{G}R_s(1,1)/\cos(\theta_2)) \end{aligned}$$

Applying this to the full data-set gives us the following knee joint angles (see Fig. 16.5)

16.5 Conclusion

Inertial/magnetic sensors are relatively robust to environmental factors, which is one of the drawbacks of traditional technologies for movement analysis. Fusion algorithms allow perform 3D movement analysis, but two main concerns must be taken into account. First, sensor performance and data reliability depends on the appropriate selection of filter parameters, depending on the nature of the movement under analysis. Second, the compatibility with position-based systems through ISB standards is not guaranteed yet, although novel methods for anatomical calibration are being proposed.

MIMU thus offer valuable opportunities to almost restriction-less motion capture and monitoring of health state and activities of daily living, for example in a telemedicine application (Jovanov et al. 2005).

Appendix: Theoretical Basis for Human Movement Analysis with Inertial Sensors

Kinematics is the branch of mechanics that describes the motion of points, bodies (objects) and systems of bodies (groups of objects) without consideration of the causes of motion. Therefore, kinematics is not concerned with the forces, either external or internal, that cause the movement. It includes the description of linear and angular displacements and its time-derivatives: velocities and accelerations. A complete and accurate quantitative description of the simplest movement requires a huge volume of data and a large number of calculations, resulting in an enormous number of graphic plots. Therefore, it should be kept in mind that any given analysis may use only a small fraction of the available kinematic variables.

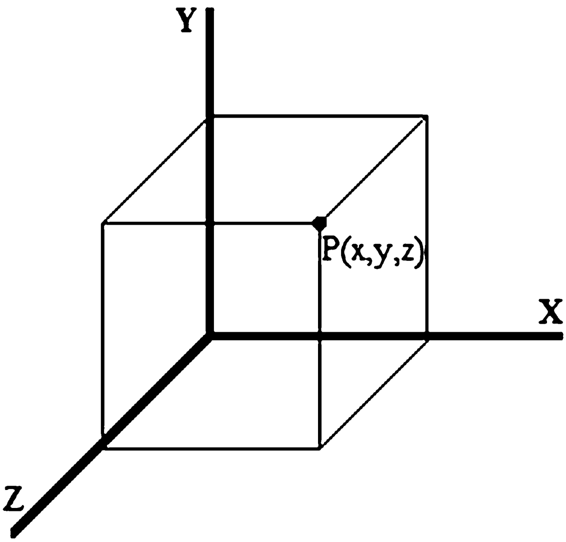
Cartesian Reference Systems

A reference system is an adequate and arbitrary system where the position of any point (or solid) is referenced. A Cartesian reference system is formed by three perpendicular axes, which origin is located at the common intersection of the axes, determining the 3 dimensions of the space. Any point in the space is therefore located with respect to this reference system by three coordinates, one by each axis: (x, y, z) (Fig. 16.6).

Two types of reference systems are commonly defined for human movement analysis:

- Fixed reference system, also called absolute or inertial, which is a Cartesian reference frame fixed to the world, coincident with the view of the external observer. In this reference system magnitudes related with global body movements are defined, as the movement of the body center of mass or trunk bending and rotations.
- Relative reference system, also called segment reference system, is a Cartesian reference frame fixed to the moving segment. A common variable measured on this reference system is joint movement.

Fig. 16.6 Cartesian reference system



The relative system commonly defined for human movement analysis has its origin coincident with the body center of mass, whose directions axis $(X - Y - Z)$ are coincident with the main body axis as follows: X is the anterior axis (also called direction), pointing forward, Y is the vertical axis (also called direction), pointing upwards, and Z is the medial–lateral axis (also called direction), pointing right.

This body-centered reference system also contains the main body planes:

- Sagittal plane: divides any part of the body into right and left portions. It is perpendicular to z (medial–lateral) axis. Flexion and extension takes place in the sagittal plane.
- Frontal plane: divides any part of the body into front and back portions. It is perpendicular to x (anterior) axis. Abduction and adduction take place in the frontal plane.
- Transverse plane divides any part of the body into upper and lower portions. It is perpendicular to y (vertical) axis. Internal and external rotation takes place in the transverse plane. Also called medial and lateral rotation.

Three-Dimensional Kinematics

Matrix Notation for Reference Systems

The human musculoskeletal system is composed of a series of jointed links, which are commonly approximated as rigid bodies. Six independent parameters, the degrees of freedom, DOF, are needed to describe the location $((x, y, z)$ coordinates

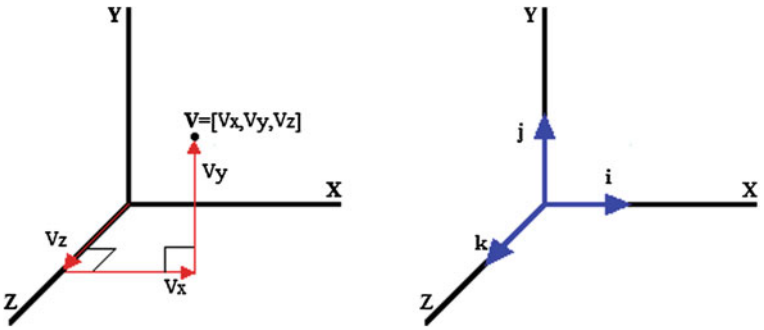


Fig. 16.7 Vector coordinates (*left*). Unitary vectors that define a reference system (*right*)

with respect to reference system axes) and orientation ((α, β, γ) angles with respect to reference system planes) of a segment in space. Those six coordinates $(x, y, z, \alpha, \beta, \gamma)$constitute the degrees of freedom of a segment, and therefore uniquely define its spatial location and orientation at any time instant.

Most of the mechanical quantities one has to deal with in motion analysis, such as linear and angular position, velocity and acceleration of the markers and segments, are vectors. Because a vector has both magnitude and direction, one can describe the same vector in several different perspectives, depending on the intention or objective of the analysis. Describing a vector in a particular perspective is in essence equivalent to computing its components based on the coordinate system of the particular perspective.

Matrices are a form of mathematical notation suitable for operations among coordinate systems and vectors. A reference system can be defined using three vectors that represent each system's axes, whose length is the unity. Therefore, the unit vector of the axes reference system, hence unit coordinate vectors (Fig. 16.7 right), can be expressed follows, where $\boldsymbol{i}$,$\boldsymbol{j}$,$\boldsymbol{k}$ are the unit vectors of the $X-Y-Z$ respectively: $\boldsymbol{i} = [1, 0, 0]$, $\boldsymbol{j} = [0, 1, 0]$, $\boldsymbol{k} = [0, 0, 1]$. Using this notation, the global coordinate system can be expressed by sorting $\boldsymbol{i}$,$\boldsymbol{j}$,$\boldsymbol{k}$ vectors into a matrix as follows:

$$[\boldsymbol{i}, \boldsymbol{j}, \boldsymbol{k}] = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

Rotation Matrix

As shown in Fig. 16.7 left, a vector can be expressed as the sum of the component vectors projected over the i, j, k vectors:

$$\boldsymbol{V}_x = v_x \cdot \boldsymbol{i}; \quad \boldsymbol{V}_y = \boldsymbol{v}_y \cdot \boldsymbol{j}; \quad \boldsymbol{V}_z = \boldsymbol{v}_z \cdot \boldsymbol{k};$$

$$\boldsymbol{V} = \left[\boldsymbol{v_x}, \boldsymbol{v_y}, \boldsymbol{v_z}\right] = \boldsymbol{i} \cdot v_x + \boldsymbol{j} \cdot v_y + \boldsymbol{k} \cdot v_z$$

In other words, one can not only describe the same vector in several different perspectives, but also change the perspective from one to another depending on the situation and needs. This changing perspective of describing a vector is called vector transformation or axis transformation, and it is done through rotation matrices. A rotation matrix is the mathematical form for expressing in a compact way the orientation of a reference system, usually a mobile one, with respect to another, usually fixed reference system.

To transform a vector from one reference frame to another is equivalent to changing the perspective of describing the vector from one to another. A transformation alters not the vector, but the components as follows:

$$v'_x = \boldsymbol{v} \cdot \boldsymbol{i}' = \left(v_x \cdot \boldsymbol{i} + \boldsymbol{v_y} \cdot \boldsymbol{j} + \boldsymbol{v_z} \cdot \boldsymbol{k}\right) \cdot \boldsymbol{i}' = \boldsymbol{v_x} \cdot \boldsymbol{i} \cdot \boldsymbol{i}' + \boldsymbol{v_y} \cdot \boldsymbol{j} \cdot \boldsymbol{i}' + \boldsymbol{v_z} \cdot \boldsymbol{k} \cdot \boldsymbol{i}'$$

$$\boldsymbol{v'_y} = \boldsymbol{v} \cdot \boldsymbol{j}' = \left(\boldsymbol{v_x} \cdot \boldsymbol{i} + \boldsymbol{v_y} \cdot \boldsymbol{j} + \boldsymbol{v_z} \cdot \boldsymbol{k}\right) \cdot \boldsymbol{j} = \boldsymbol{v_x} \cdot \boldsymbol{i} \cdot \boldsymbol{j}' + \boldsymbol{v_y} \cdot \boldsymbol{j} \cdot \boldsymbol{j} + \boldsymbol{v_z} \cdot \boldsymbol{k} \cdot \boldsymbol{j}'$$

$$\boldsymbol{v'_z} = \boldsymbol{v} \cdot \boldsymbol{k}' = \left(\boldsymbol{v_x} \cdot \boldsymbol{i} + \boldsymbol{v_y} \cdot \boldsymbol{j} + \boldsymbol{v_z} \cdot \boldsymbol{k}\right) \cdot \boldsymbol{k}' = \boldsymbol{v_x} \cdot \boldsymbol{i} \cdot \boldsymbol{k}' + \boldsymbol{v_y} \cdot \boldsymbol{j} \cdot \boldsymbol{k}' + \boldsymbol{v_z} \cdot \boldsymbol{k} \cdot \boldsymbol{k}'$$

$$\begin{bmatrix} v'_x \\ v'_y \\ v'_z \end{bmatrix} = \begin{bmatrix} \boldsymbol{i} \cdot \boldsymbol{i}' & \boldsymbol{j} \cdot \boldsymbol{i}' & \boldsymbol{k} \cdot \boldsymbol{i}' \\ \boldsymbol{i} \cdot \boldsymbol{j}' & \boldsymbol{j} \cdot \boldsymbol{j}' & \boldsymbol{k} \cdot \boldsymbol{j}' \\ \boldsymbol{i} \cdot \boldsymbol{k}' & \boldsymbol{j} \cdot \boldsymbol{k}' & \boldsymbol{k} \cdot \boldsymbol{k}' \end{bmatrix} \cdot \begin{bmatrix} v_x \\ v_y \\ v_z \end{bmatrix}$$

In those transformations, $\boldsymbol{i},\boldsymbol{j},\boldsymbol{k}$ are the unit vectors of the $X-Y-Z$ system, and $\boldsymbol{i}',\boldsymbol{j}',\boldsymbol{k}'$ are the unit vectors of the $X-Y-Z$ system. Therefore, the transformation matrix from the global reference frame (frame G) to a particular local reference frame (frame L) can be written as:

$$\begin{bmatrix} v'_x \\ v'_y \\ v'_z \end{bmatrix} = {}^{L}\boldsymbol{T}_G \cdot \begin{bmatrix} v_x \\ v_y \\ v_z \end{bmatrix}$$

$${}^{L}\boldsymbol{T}_G = \begin{bmatrix} \boldsymbol{i} \cdot \boldsymbol{i}' & \boldsymbol{j} \cdot \boldsymbol{i}' & \boldsymbol{k} \cdot \boldsymbol{i}' \\ \boldsymbol{i} \cdot \boldsymbol{j}' & \boldsymbol{j} \cdot \boldsymbol{j}' & \boldsymbol{k} \cdot \boldsymbol{j}' \\ \boldsymbol{i} \cdot \boldsymbol{k}' & \boldsymbol{j} \cdot \boldsymbol{k}' & \boldsymbol{k} \cdot \boldsymbol{k}' \end{bmatrix}$$

Obviously, in human movement analysis the local reference frame is typically fixed to a segment or a body part, whereas the global reference system is reference system fixed to the laboratory, the global reference system.

Similarly, ${}^{G}\boldsymbol{T}_L$ is the inverse rotation matrix of ${}^{L}\boldsymbol{T}_G$ which can also be derived as:

$${}^{G}\boldsymbol{T}_L = \begin{bmatrix} \boldsymbol{i}' \cdot \boldsymbol{i} & \boldsymbol{j}' \cdot \boldsymbol{i} & \boldsymbol{k}' \cdot \boldsymbol{i} \\ \boldsymbol{i}' \cdot \boldsymbol{j} & \boldsymbol{j}' \cdot \boldsymbol{j} & \boldsymbol{k}' \cdot \boldsymbol{j} \\ \boldsymbol{i}' \cdot \boldsymbol{k} & \boldsymbol{j}' \cdot \boldsymbol{k} & \boldsymbol{k}' \cdot \boldsymbol{k} \end{bmatrix}$$

However, a special feature of the rotation matrices is that they are *orthonormal*, that is, the vectors $\boldsymbol{i}, \boldsymbol{j}, \boldsymbol{k}$ are *orthogonal* and *unitary*. Therefore, the inverse of those matrices are in fact their transpose, so the change is straightforward:

$$^{G}\boldsymbol{T}_{L} = \left(^{L}\boldsymbol{T}_{G}\right)^{-1} = \left(^{L}\boldsymbol{T}_{G}\right)^{T}$$

A series of transformations can be performed through successive multiplication of the transformation matrices from the right to the left. Once the transformation matrices from the global reference frame to the local reference frames are known, computation of the transformation matrices among the local reference frames is simply a matter of transposition and multiplication of the transformation matrices. Hence the transformation matrix from one local reference frame (A) to another (B) can be easily obtained through cascading of the transformation matrices:

$$^{B}\boldsymbol{T}_{A} = {}^{B}\boldsymbol{T}_{G} \cdot {}^{G}\boldsymbol{T}_{A} = {}^{B}\boldsymbol{T}_{G} \cdot \left(^{A}\boldsymbol{T}_{G}\right)^{-1} = {}^{B}\boldsymbol{T}_{G} \cdot \left(^{A}\boldsymbol{T}_{G}\right)^{T}$$

How to Extract Rotation Angles Using Euler Convention

As shown above, the components of a free vector change as the reference frame changes. Figure 16.8 shows two different reference frames: the $X - Y$ system and the $X' - Y'$ system. Vector $\boldsymbol{v}$ can be expressed as $\boldsymbol{v}(x, y)$ in the $X - Y$ system, $\boldsymbol{v}(x', y')$ in the $X' - Y'$ system. The relationships between $X - Y$ and $X' - Y'$ can be obtained from the geometric relationships:

$$x' = x \cdot cos(\Phi) + y \cdot sin(\Phi)$$

$$y' = y \cdot cos(\Phi) - x \cdot sin(\Phi)$$

In matrix form:

$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} cos(\Phi) & sin(\Phi) \\ -sin(\Phi) & cos(\Phi) \end{bmatrix} \cdot \begin{bmatrix} x \\ y \end{bmatrix}$$

It is straightforward to expand these manipulations between axes to the three-dimensional space:

$$x' = x \cdot cos(\Phi) + y \cdot sin(\Phi)$$

$$y' = y \cdot cos(\Phi) - x \cdot sin(\Phi)$$

$$z' = z$$

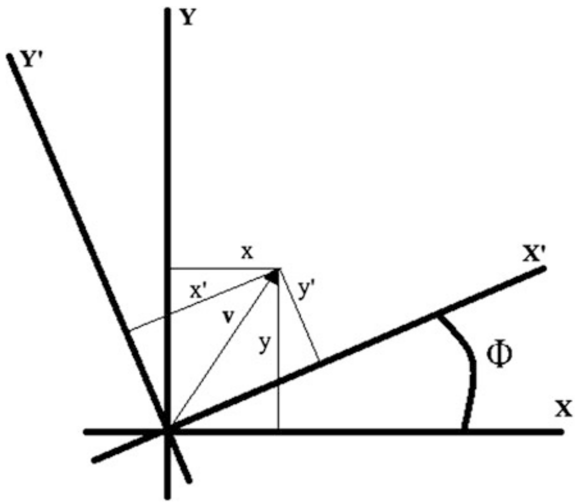


Fig. 16.8 Two-dimensional vector transformation between two coincident reference frames

In matrix form:

$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = \begin{bmatrix} cos(\Phi) & sin(\Phi) & 0 \\ -sin(\Phi) & cos(\Phi) & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} x \\ y \\ z \end{bmatrix}$$

Therefore, the rotation around the z axis from $X - Y - Z$ reference system to $X' - Y' - Z'$ is expressed as follows:

$$\boldsymbol{R}_z(\Phi) = \begin{bmatrix} cos(\Phi) & sin(\Phi) & 0 \\ -sin(\Phi) & cos(\Phi) & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

Rotation around the X and Y axis can be obtained in a similar procedure:

$$\boldsymbol{R}_x(\Phi) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & cos(\Phi) & sin(\Phi) \\ 0 & -sin(\Phi) & cos(\Phi) \end{bmatrix}$$

$$\boldsymbol{R}_y(\Phi) = \begin{bmatrix} cos(\Phi) & 0 & -sin(\Phi) \\ 0 & 1 & 0 \\ -sin(\Phi) & 0 & cos(\Phi) \end{bmatrix}$$

Once rotation around each of the three reference system axis is defined, an arbitrary rotation, which is usually composed by rotations around all three axes, can be seen as a composition of three sequential rotations, which is actually what the Euler theorem states.

Using Euler theorem, any arbitrary rotation can be de-composed into three sequential rotations. For example, consider the sequence $X - Y' - Z''$. This means that we rotate about X axis first, θ_1 degrees. As result we get the new orientation, given by $X' - Y' - Z'$. Then a rotation around the new Y' axis θ_2 degrees is made, resulting in the new orientation $X'' - Y'' - Z''$. A final rotation around the new Z'' axis θ_3 degrees is made, resulting in the resulting final orientation $X''' - Y''' - Z'''$.

Taking each rotation matrix, any point $\boldsymbol{p}(x, y, z)$expressed in the $X - Y - Z$ reference system (local) can be transformed (expressed) in the global reference system $X''' - Y''' - Z'''$ as follows:

$$\begin{bmatrix} p_{x'''} \\ p_{y'''} \\ p_{z'''} \end{bmatrix} = [\boldsymbol{R}_z(\theta_3)] \cdot \left[\boldsymbol{R}_y(\theta_2)\right] \cdot [\boldsymbol{R}_x(\theta_1)] \cdot \begin{bmatrix} p_x \\ p_y \\ p_z \end{bmatrix} = {}^{L}\boldsymbol{R}_G$$

Expanding the former, and using shorthand notation where $c1 = cos(\theta_1)$ and $s2 = sin(\theta_2)$

$$\begin{bmatrix} p_{x'''} \\ p_{y'''} \\ p_{z'''} \end{bmatrix} = \begin{bmatrix} c2 \cdot c3 & s3 \cdot c1 + s1 \cdot s2 \cdot c3 & s1 \cdot s2 - c1 \cdot s2 \cdot c3 \\ -c2 \cdot c3 & c1 \cdot c3 - s1 \cdot s2 \cdot s3 & s1\text{c}3 + \text{c}1s2 \cdot s3 \\ s2 & -s2 \cdot c2 & c1 \cdot c2 \end{bmatrix} \cdot \begin{bmatrix} p_x \\ p_y \\ p_z \end{bmatrix}$$

From the above matrix, θ_1, θ_2 and θ_3 angles can be obtained as follows:

$$\theta_2 = arcsin\left({}^{L}\boldsymbol{R}_G(3,1)\right)$$

$$\theta_1 = arcos\left(\frac{{}^{L}\boldsymbol{R}_G(3,3)}{cos(\theta_2)}\right)$$

$$\theta_3 = arcos\left(\frac{{}^{L}\boldsymbol{R}_G(1,1)}{cos(\theta_2)}\right)$$

This example corresponds to a rotation sequence around $X - Y' - Z'$ axes. However, any other rotating sequence can be used. In theory, there are 12 possible correct rotation sequences, by the combination of the $X - Y - Z$ rotations.

International Society of Biomechanics Standards

One of the characteristics of Euler theorem, is that the value of θ_1, θ_2 and θ_3 angles depend on the rotation sequence assumed, this makes the comparison of data among various studies difficult, if not impossible. On the other hand, some rotation sequences are closer to representing joint rotations in clinically relevant terms, which makes the application and interpretation of biomechanical findings easier and more welcoming to clinicians.

The international society of biomechanics has made recommendations for the definitions of segment coordinate systems as well as for rotation sequences for reporting joint movement (Grood and Suntay 1983; Wu et al. 2002). The purpose was to present these definitions to the biomechanics community so as to encourage the use of these recommendations, to provide first hand feedback, and to facilitate the revisions. It was hoped that this process will help the biomechanics community to move towards the development and use of a set of widely acceptable standards for better communication among various research groups, and among biomechanists, physicians, physical therapists, and other related interest groups. Those recommendations include the definitions for major human joints as ankle, hip, spine, shoulder, elbow, wrist and hand.

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Chapter 17
Design of Experiments for Bioengineers in Clinical Settings

Juan-Manuel Belda-Lois and Helios De Rosario Martínez

Abstract This chapter is an introduction for the design of experiments involving human beings. This is a very common scenario in bioengineer practice. The usual problem we are facing is understanding the effects of a new development in the target population. The development could be a new device, a new algorithm, or a piece of software. Facing this problem implies taking a number of decision such as the hypotheses of different factors that can influence the outcome, the analysis of the data to achieve the conclusions, the number of subjects participating in the experiment and the number and definition of the set of measurements to be applied to each subject. This approach is slightly different from a clinical trial. The approach presented in this paper is focussed on understanding the effects of an intervention in a small number of subjects. A clinical trial usually aims at quantifying the effects in the general population. The view we will adopt will be a frequentist approach (opposite to a Bayesian approach) (Fienberg 2005). This is especially important for aspects related with the analysis and almost negligible in the aspects that are related with the experimental design. Besides, for all the examples, we will take into consideration a general linear model, but the conclusions could be extended to a generalized linear model. Again, the impact of our restriction is more important in the part related with the analysis than with the design of the experiment. Although there are many pieces of software devoted to the design of experiments, the examples shown in this chapter have been made using R (R Development Core Team 2012). There are many reasons for this decision: R provides the tools required for advanced statistics, it is widely distributed and it is free. All the examples, have been made using 3 packages: **car** (Fox and Weisberg (2011)) and **phia** (de Rosario-Martinez (2012)) for analysis and **AlgDesign** (Wheeler (2011)) for the design of the experiments.

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17.1 Intoduction: General Linear Model

A general linear model is a least squares regression. Therefore, an analysis of an experiment for an analysis based on a general linear model consistsof the selection of the minimum number of trials that allows the identification of the model and the correct estimation of the errors of fitting.

The output of the general linear model is one (or more) real valued variable while the input could be a set of categorical and real valued variables. The real valued variables are called *covariates* and the categorical values are *factors*. Besides, each possible value of the categories is called a *level*.

For instance, if we intend to investigate the effects of 3 different training methodologies to improve rehabilitation time, we can create a model with the output *time* (a real-valued variable) and the input would be the training strategy. In this case it is a factor (*strategy*) with 3 levels one per strategy. If age can influence the outcome (the time for rehabilitation) we can include *age* as a covariate in the model.

Generally speaking, when the general linear model is fitted, the researcher aims to know if the effect of each level of the factor produces a measurable effect in the output of the model. The complexity of the model increases as long we include in the analysis cross-relationships of the levels of the different factors or if we add more factors.

This is usually tested by means of *ANOVA* (analysis of variance), from a model fitted with observations that are assumed to be independent from each other. The easiest way to ensure the independence of observations is to perform each measurement with a different user, but when the experiment allows it, researchers often prefer "re-using" the subjects for different experimental conditions, due to several reasons: the cost of recruiting different subjects, difficulty of instrumentation and calibration, etc.

This requires using specific techniques for *repeated-measures ANOVA* (Girden (1991)), which will not be discussed in detail here, although one of the methods is discussed in an example below. A (positive) side effect of this approach, is that the variability in the measures due to individual differences in the subjects is singled out of other sources of variability, and this leads to a better fit (with lower residual errors), with the same number of measurements.

Models that are too complex imply a much higher number of measurements for a proper fitting. However, oversimplified models can lead to wrong inferences. Generally speaking it is always worthy to build the models as simply as possible based on our prior knowledge or based on the state of the art.

Therefore, the needs for an experiment can be summarized as:

1. Defining the model.
2. Determining the number of measurements required.
3. Analyzing the fitted model.

An example will clarify the theoretical explanation. We want to analyze the sensitivity to FES[1] of a number of users that will experience FES at the forearm for the first time in their life. In particular, we are willing to know what the maximum tolerated electrical intensity (*Intensity*) for the users is, taking into account the frequency of stimulation (*Freq*), the size of the electrodes (*Size*), and the side of stimulation (*Side*).

For our purposes, we will treat *Freq*, *Size* and *Side* as factors. *Side* is a factor with 2 levels *palmar* and *dorsal*. *Freq* and *Size* are real valued variables, but we can treat them as factors, dividing each into a limited set of levels. Electrical intensity is the output of the model, and will be kept as a real valued variable. The benefit of considering *Freq* and *Size* as factors within multiple levels is the possibility to gather non-linear relationships. Including them as covariates will only take into consideration the trend of the stimulus.

A model incorporating all the possible relationships of the factors is called a "full factorial" model. In a full factorial model, we consider all the possible interactions between factors, at the expense of a more complex model. A model that considers just the levels of each factor, dismissing the cross-relationships between factors, is called a "main effects" model.

17.2 Design of Experiments

The objective of the design of experiments can be synthesized in being able to determine what the measures required to fit a statistical model are. The key aspect that distinguishes an experiment and a study is that in a *study* we take a representative sample from the population, in order to learn about some of their characteristics, whereas in an *experiment* we control some aspects of the population sample, and we want to know how the different factors influence the outcomes.

The safest, but most expensive experiment, includes all the possible combinations of factors in a balanced way, meaning that each combination is measured the same number of times. This is called a *full factorial design*.

A full factorial model (Table 17.1) requires a minimum of 18 measures to be fitted, coinciding with the number of parameters. But a fit from only those 18 observations would lead to an exact solution; this is called a perfect fit. To be able to perform a statistical analysis of the model, we need to have an estimation of the

[1] FES: Functional Electrical Stimulation

Table 17.1 Full factorial design for the FES experiment

	Freq (Hz)	Size (cm^2)	Side
1	20	2	Palmar
2	30	2	Palmar
3	40	2	Palmar
4	20	3	Palmar
5	30	3	Palmar
6	40	3	Palmar
7	20	4	Palmar
8	30	4	Palmar
9	40	4	Palmar
10	20	2	Dorsal
11	30	2	Dorsal
12	40	2	Dorsal
13	20	3	Dorsal
14	30	3	Dorsal
15	40	3	Dorsal
16	20	4	Dorsal
17	30	4	Dorsal
18	40	4	Dorsal

errors and this is only possible by doing more measurements. The obvious solution is to repeat these 18 measures a number of times.

Very often, when dealing with experiments including humans we perform different measurements in the same subject and then analyze how the different inputs affect the output through the pool of subjects. An experiment of this kind is called a *repeated-measures* experiment. In this case we can think of applying the whole set of measurments for the full factorial design in each participating subject. But, we could be interested in reducing the number of measurements per subject without losing too much information.

Therefore, we need a measurement of the degree of information lost when the number of measurements is reduced. This can be done comparing one parameter obtained from the design of experiments. This parameter is the "determinant of the covariance matrix" Wheeler (2011), Wheeler (2004). We can compare an experiment using a smaller number of measurements per subject with respect the full factorial design comparing the ratio of this parameter.

In our case, if we reduce the number of measurements per subject to 7 properly chosen measurements, the efficiency of the experiment is 92 % (Table 17.2). There are a number of optimal designs already published in the scientific literature, but for general purposes we can use an algorithmic approach such as Federov (Federov (1972))

Table 17.2 Suboptimal design for the main effects model

	Freq (Hz)	Size (cm^2)	Side
1	20	2	Palmar
6	40	3	Palmar
7	20	4	Palmar
8	30	4	Palmar
11	30	2	Dorsal
13	20	3	Dorsal
18	40	4	Dorsal

Measuring this combinations for a set of subjects has an efficiency of 92 % with respect the full factorial design for a main effects model

17.2.1 Blocked Designs

In the previous examples, we have defined optimal sets of factor combinations, that may be repeated several times during the experimentation in order to reduce the residual error and obtain better fits. However, repeating all the combinations may be unacceptable due to many reasons. In a repeated measures experiment, if each subject had to repeat all the chosen combinations, the sessions could be too long, and the experiment could be affected by accommodation effects, and fatigue of the user, etc. In such cases, it is possible to select a smaller number of combinations applied to each subject, in such a manner that the aggregated data could still be used to fit the model. We refer to those designs as "blocked designs".

For instance, in the example of the electrical stimulation experiment, even 7 measurements could be too much for a single subject. In this case, we can assess the availability of using a blocked design for 4 measurements and 20 subjects.

17.3 Analysis

In a context of general linear model analysis, the ANOVA approach we are considering provides information on the differences between the levels of a factor or a combination of factors. However, many times this information is not enough, because we want to know between which the levels or the combination of levels we found the differences. This is, very often, analyzed by post-hoc analysis.

Let us take, for this and later sections, an example data set based on R.J. Boik's hypothetical data (Boik 1979), which he used for demonstrating how to analyze interaction contrasts, although it will be used here for a larger variety of interaction analyses. It represents a hypothetical experiment, where people affected by hemophobia were treated with different fear reduction therapies and different doses of antianxiety medication, in a balanced factorial design, and the effect of these

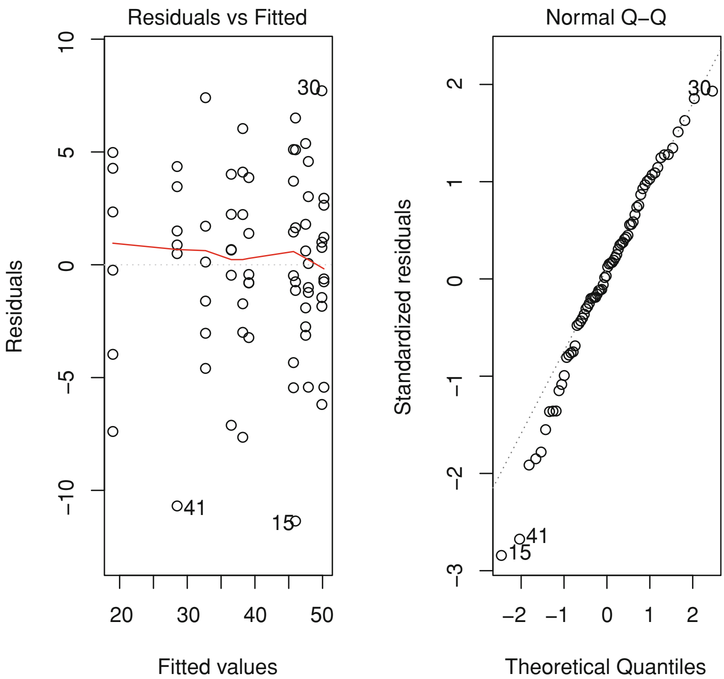

Fig. 17.1 Residuals versus fitted values and Q-Q plot of `mod.boik`

Table 17.3 Anova table (type II tests). Response: edr

	Sum Sq	Df	F value	Pr(> F)
Therapy	2444.1	2	63.813	< 0.01
Medication	2370.9	3	41.269	< 0.01
Therapy:medication	1376.4	6	11.979	< 0.01
Residuals	1149.0	60		

combined treatments was measured by their electrodermal response in an experimental session[2].

Before proceeding with detailed analyses of the interactions, we should first check if the model is coherent with the data, and if the interaction between both factors is actually significant. We can do this by examining the residuals of the model (see Fig. 17.1) and the ANOVA (Table 17.3).

Although the plots of Fig. 17.1 show a minor departure of normality for the residuals, specially due to a couple of extremely low observations, for the sake of

[2] The data set is based on the results reported in Boik's paper for the different tests, but not directly copied from his original work (that actually gives no data set). Thus, the residual plots are irrespective of Boik's paper, and due to rounding inaccuracies, the last decimals of the tables in that paper are not exactly the same as those reported here.

balance we will keep all data, and assume that the model assumptions hold. Then we see in the ANOVA table that the interaction between *therapy* and *medication* is significant, so it does makes sense to investigate this effect.

In factorial experiments like this one, the dependency between factor levels and the response variable is usually represented in a contingency table, where the rows and columns are related to the different levels of both treatments, and each cell contains the adjusted mean of the response ($\widehat{Y}$) for the corresponding interaction of factors. When there is an interaction effect, the cell means are taken as the most straightforward way of representing this effect. These values are obtained from the model coefficients of the fitted model (Table 17.4).

We can plot these means, as in Fig. 17.2. The off-diagonal panels are the typical interaction plots, the lack of parallelism between lines reveals how one factor changes the effect of the other one. In this case, we see that the control group hardly obtains any benefit from the medication, whereas with the other therapies (`T1` and `T2`) the fear to blood is reduced proportionally to the medication dose, more markedly for the former. On the other hand, the diagonal panels represent the marginal means of each factor.

17.3.1 Testing Simple Effects

The tabulation or graphical representation of cell means may give us a hint of the underlying structure of main effects and interactions, but they do not suffice to assure whether a specific change in the factors plays a significant role in the variation of the dependent variable. In many cases the researcher does not even have a preliminary hypothesis that can be tested, and must fall back to *post-hoc* methods.

Table 17.4 Differences between the means levels of the factors of therapy and medication

	Therapy	Medication	Adjusted mean
1	Control	Placebo	50.20043
2	T1	Placebo	49.89963
3	T2	Placebo	45.69925
4	Control	D1	47.49899
5	T1	D1	38.20065
6	T2	D1	39.09930
7	Control	D2	45.99989
8	T1	D2	28.50055
9	T2	D2	36.50036
10	Control	D3	47.89981
11	T1	D3	18.99962
12	T2	D3	32.69961

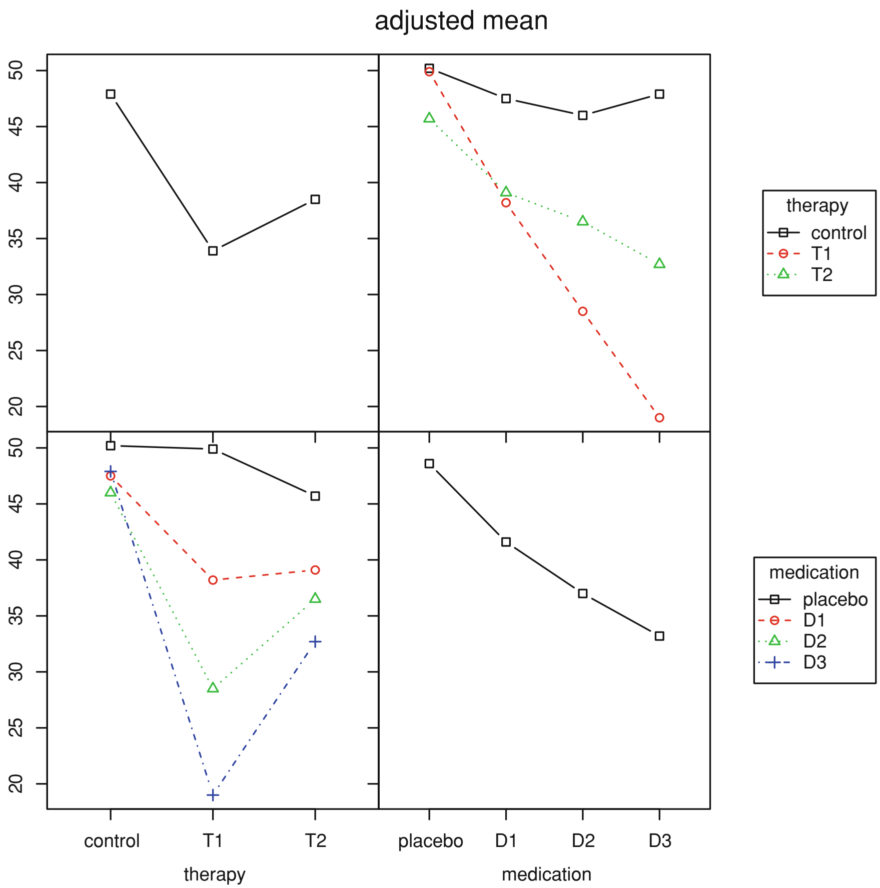

Fig. 17.2 Result of `plot(boik.means)`

The available methods for the *post-hoc* analysis of main effects are manifold. Most procedures consist in evaluating multiple contrasts between factor levels, possibly with corrections of the *p*-value in order to protect the family-wise error rate. "Contrasts" are comparisons of the expected values of the model's dependent variable, for different cases of the predictors that should yield the same results if the null hypothesis were true. For instance, a contrast related to the effect of medication in Boik's example could be the comparision of the value of EDR between the placebo group and the average of the three doses, or between the highest and lowest dose, etc. Such comparisons may be coded as linear combinations of the factor levels, whose coefficents add up to zero, like "$placebo - \frac{1}{3}(D1 + D2 + D3)$", or "$D3 - D1$", for the previous examples. Ordered factors are often tested with "polynomial contrasts", associated to polynomial patterns of variation; e.g. a linear pattern would be an increment (or decrease) of EDR when the medication dose increases, a quadratic pattern would be a greater (or lower) effect of the medium dose in comparison with the highest and lowest ones, etc.

Pairwise comparisons between any couple of levels are usually the default strategy when the researcher has no previous plan, although this is inefficient when the factor has many levels. Tukey's method for testing pairwise contrasts, and Scheffé's method for all possible contrasts within a factor, are probably the most popular ones. Many statistics textbooks and software packages include detailed explanations and facilities for doing those tests, and they will not be treated here.

On the other hand, the post-hoc analysis of interactions is less known for many researchers, since it is a controversial matter without a clear consensus about the "best practices". The analysis of simple main effects is the most straightforward technique, and also the most used one, although it is very criticized by the experts in statistics (Rosnow and Rosenthal (1989); Ottenbacher (1991); Pardo et al. (2007)). Broadly speaking, analyzing simple main effects consists in testing the effect of one factor, when the values of all the other interacting factors are fixed at a certain combination of levels. Such a test is then repeated at other fixed levels, and the results are compared.

For instance, we could compare the global effect of medication for different therapies, as done in Table 17.5. Such global effect can may represented by any full set of orthogonal contrasts. [3] In this case, the columns *medication1*, *medication2*, *medication3* of the table contain the values of the linear, quadratic, and cubic contrasts across ordered medication doses for each therapy group. The rest of columns show the results of a multivariate Pillai test applied to those contrasts (which would be the same for any set of three orthogonal contrasts). These tests just quantify the qualitative interpretation that was made from the plots: the dose of medication does not have a significant effect for the control therapy group, but its effect is remarkable for the other groups (at $\alpha = 0.05$).

The criticism often posed to this method is that interactions are mixed with main effects (or lower order interactions within), so the tests are not really related

Table 17.5 ANOVA table simple main effects of medication at fixed therapies, with *p*-values adjusted by Holm correction.

	Medication1	Medication2	Medication3	df	SS	F	*p*-value
control	2.3006	−0.4008	−1.8999	3	54.38	0.9465	0.4239
T1	30.9000	19.2010	9.5009	3	3153.95	54.8985	0.0000
T2	12.9996	6.3997	3.8007	3	538.99	9.3818	0.0001
Residuals				60	1149.01		

[3] A full set of orthogonal contrasts are independent of each other, and can be combined to create any possible contrast for that factor. The coefficients of the linear combinations associated to such contrasts form an orthogonal basis, i.e. their dot product is zero.

to the term that is supposedly under investigation. Using this example, the *post-hoc* analysis of the interaction between therapy and medication is being performed because the first ANOVA told us that it is significant; and this means that the model coefficients related to this term are unlikely to be null. However, the tests of simple effects that have just been described do not only involve those coefficients, but also the coefficients related to the lower-order terms *therapy* and *medication*.

On the other hand, many researchers like simple effects for their relatively straightforward interpretation. Moreover, the interference of lower-order coefficients may be regarded a lesser issue when the marginality principle is considered. In this theoretical framework, the presence of a high-order interaction makes lower order terms meaningless, so that their effects are absorbed by the interaction. Therefore, the coefficients of lower-order terms would partially be related to the interaction effect as well.

17.4 Interaction Contrasts

Another alternative to simple effects is the study of interaction contrasts, which were in fact the subject of the paper where our working data is derived from, although Boik used a slightly different procedure for their analysis. The theoretical advantage of this technique is that it is not affected by the coefficients of main effects, unlike the analysis of simple main effects. Interaction contrasts are defined as "differential effects", or more descriptively as "differences of differences", or "contrasts between contrasts". They basically consist in calculating one or more contrasts across a factor, and then iterating on the results of that operation across the remaining factors.

For instance, the test of simple effects calculated in the previous section could be transformed into a test of interaction contrasts, if instead of fixing the levels of *therapy* for evaluating the contrasts across medications, we consider pairwise contrasts between therapy groups. The results of this analysis are shown in Table 17.6

These tests show how the contrasts across medication doses differ between pairs of therapy groups. We can see that the effect of therapy *T1* differs from the controls and the other therapy, even more than *T2* from the controls. This was not so clear from the simple effects tests. Moreover, these results are not disturbed by the main

Table 17.6 ANOVA table of the interaction contrasts between medication and therapy, with *p*-values adjusted by Holm correction.

	Medication1	Medication2	Medication3	df	SS	F	*p*-value
control versus T1	−28.5999	−19.6019	−11.4008	3	1332.10	23.1869	0.0000
control versus T2	−10.6999	−6.8005	−5.7007	3	175.95	3.0627	0.0348
T1 versus T2	17.9000	12.8013	5.7002	3	556.55	9.6874	0.0001
Residuals				60	1149.01		

effects of factors at all, because the calculation of contrasts has removed them for both factors, without having defined them explicitly.

In the absence of a previous plan for testing effects, the researcher may be tempted to explore all the possible crossing between pairwise contrasts, as done in Table 17.7. If all the factors of the model had 2 levels, this would have been an optimal strategy for analysing the interaction, since the result would have been reduced to one test, corresponding to the single d.o.f. of such an interaction. But the factors with more levels heavily increase the number of tests, so that for our 3×4 factorial design, with $2 \times 3 = 6$ d.o.f., we obtain 18 overredundant tests. Such a high number of tests is difficult to interpret, let aside the lack of reliability of the p-values (with or without corrections). A more sensible strategy consists in defining a small number of meaningful contrasts that can be of interest for the researcher. For instance, we might be interested in knowing the effect of crossing the following contrasts for each factor

1. For *therapy*: controls versus the average of *T1* and *T2*, and *T1* versus *T2*.
2. For *medication*: placebo versus the average of all real doses, the minimum dose versus the maximum, and the medium dose versus the average of all doses.

Table 17.8 shows the results of this test plan, that is much clearer than Table 17.7. Moreover, all these contrasts are orthogonal to each other (none of them can be obtained by combination of the others), so the tests are independent, and the adjustment of p-values is reliable. Taking some care about the meaning of

Table 17.7 Full set of pairwise interaction contrasts for Boik's model, with p-values adjusted by Holm correction.

Therapy contrast	Medication contrast	EDR difference	df	SS	F	p-value
control versus T1	placebo versus D1	−8.9975	1	121.43	6.341	0.1448
control versus T2	placebo versus D1	−3.8985	1	22.80	1.191	0.6952
T1 versus T2	placebo versus D1	5.099	1	39.00	2.036	0.6952
control versus T1	placebo versus D2	−17.1985	1	443.68	23.169	0.0002
control versus T2	placebo versus D2	−4.9984	1	37.48	1.957	0.6952
T1 versus T2	placebo versus D2	12.2002	1	223.27	11.659	0.0150
control versus T1	placebo versus D3	−28.5994	1	1226.89	64.067	0.0000
control versus T2	placebo versus D3	−10.699	1	171.70	8.966	0.0439
T1 versus T2	placebo versus D3	17.9004	1	480.63	25.098	0.0001
control versus T1	D1 versus D2	−8.201	1	100.88	5.268	0.2271
control versus T2	D1 versus D2	−1.0999	1	1.81	0.095	0.7593
T1 versus T2	D1 versus D2	7.1012	1	75.64	3.949	0.4116
control versus T1	D1 versus D3	−19.6019	1	576.35	30.096	0.0000
control versus T2	D1 versus D3	−6.8005	1	69.37	3.622	0.4326
T1 versus T2	D1 versus D3	12.8013	1	245.81	12.836	0.0096
control versus T1	D2 versus D3	−11.4008	1	194.97	10.181	0.0271
control versus T2	D2 versus D3	−5.7007	1	48.75	2.545	0.6952
T1 versus T2	D2 versus D3	5.7002	1	48.74	2.545	0.6952
Residuals			60	1149.01		

Table 17.8 Orthogonal interaction contrasts for Boik's model, with *p*-values adjusted by Holm's correction

therapy contrast	medication contrast	EDR difference	df	SS	F	*p*-value
control versus T1, T2	placebo versus D1, D2, D3	−8.7671	1	461.17	24.082	0.0000
T1 versus T2	placebo versus D1, D2, D3	7.1851	1	309.75	16.175	0.0007
control versus T1, T2	D1 versus D3	−7.6217	1	348.54	18.201	0.0004
T1 versus T2	D1 versus D3	6.4007	1	245.81	12.836	0.0020
control versus T1, T2	D2 versus D1, D2, D3	−1.3001	1	10.14	0.530	0.9392
T1 versus T2	D2 versus D1, D2, D3	−0.4044	1	0.98	0.051	0.9392
Residuals			60	1149.01		

positive and negative figures of the column "EDR difference", we can conclude the following:

1. According to the first two tests, the benefit of taking medication (pooling over the three doses) is greater if the subject also receives some therapy, and this effect is specially marked for therapy T1.
2. And according to the second two tests, the therapies interact in the same manner with the benefit of increasing the medication from the minimum to the maximum. On the other hand, we cannot say that the therapy influences the difference between the medium dose and the average of all doses.

17.5 Multivariate Approach for Repeated-Measures

Repeated-measures experiments are common in many disciplines, including psychology and agriculture, although in the latter they are usually found with the specific strucutre and name of "split-plot" designs. The classical approach for analysing this kind of experiments is via multi-strata ANOVA or univariate mixed-effects models, where the subjects or plots are introduced as factors with random effects, added to the error term. However, when the design is balanced and adequately sized, the multivariate approach is recommended, since it does not depend on the sphericity assumption and the results are more robust (Keselman 1998).

To illustrate this approach, we can use the invented data set used by O'Brien's and Kaiser's seminal paper on the method (O'Brien and Kaiser (1985)). Those data may represent the control measures of 16 subjects (8 male and 8 female) that were classified into three groups (5 control subjects, 4 taking treatment "A", and 7 taking treatment "B"), and were observed in 5 consecutive hours, at 3 different sessions (prior to the treatment, after receiving the treatment, and in a follow-up session).

In the multivariate analysis of repeated-measures experiments, each repeated measure is treated as a different variable (hence in this example we would have $3 \times 5 = 15$ variables, for the different observations of each subject). The analysis consists in doing various multivariate ANOVA to "response transformations" of those variables, which are associated to orthogonal contrasts of the "within-subjects" factors. For instance, to test the "session" factor (with the three levels: "pre", "post", and "followup"), we should define two pairwise orthogonal contrasts (e.g. "pre versus followup", and "post versus followup"). Table 17.9 shows the response transformation coefficents associated to those contrasts, for the 15 repeated measures.

Thus, to test the effect of the session (and its interactions with the "between-subjects" factors, i.e. "treatment" and "gender"), the 15 original variables would be transformed into 2 response transformations (one per row of Table 17.9), and a multivariate ANOVA would be done to them. To test the effects of between-subjects factors alone, the response transformation would be the average of the original variables. Table 17.10 shows the results of these ANOVA for all the interactions between "within-subjects" and "between-subjects" factors.

Besides the intercept, the only significant effects at $\alpha = 0.05$ are the main effects of session and hour. Nevertheless, let us suppose that we have reasons to be more liberal, and want to investigate the interaction between session and treatment, which is near the α level of significance ($p = 0.062$). First we may explore and plot the cell means of this interaction.

Table 17.9 Response transformations for the "session" within-subjects factor

Session hour	Pre					Post					Followup				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
pre versus followup	1	1	1	1	1	0	0	0	0	0	−1	−1	−1	−1	−1
post versus followup	0	0	0	0	0	1	1	1	1	1	−1	−1	−1	−1	−1

Table 17.10 Repeated-measures ANOVA of O'Brien & Kaiser data (Pillai statistic)

		Pillai stat.	F	Df1	Df2	p-value
—	(Intercept)	0.9674	296.389	1	10	0.0000
—	Treatment	0.4408	3.940	2	10	0.0547
—	Gender	0.2679	3.659	1	10	0.0848
—	Treatment × Gender	0.3635	2.855	2	10	0.1044
Session ×	(Intercept)	0.8136	19.645	2	9	0.0005
Session ×	Treatment	0.6962	2.670	4	20	0.0621
Session ×	Gender	0.0661	0.319	2	9	0.7350
Session ×	Treatment × Gender	0.3106	0.919	4	20	0.4721
Hour ×	(Intercept)	0.9329	24.315	4	7	0.0003
Hour ×	Treatment	0.3163	0.376	8	16	0.9183
Hour ×	Gender	0.3392	0.898	4	7	0.5130
Hour ×	Treatment × Gender	0.5702	0.798	8	16	0.6132
Session × Hour ×	(Intercept)	0.5604	0.478	8	3	0.8203
Session × Hour ×	Treatment	0.6624	0.248	16	8	0.9916
Session × Hour ×	Gender	0.7115	0.925	8	3	0.5895
Session × Hour ×	Treatment × Gender	0.7928	0.328	16	8	0.9724

The plot of Fig. 17.3 shows that in the post-test and follow-up phases, the response of the control group more or less remains at the same level as in the pre-test phase, whereas the response for the other treatments increases. But the plot does not tell if those differences are really significant. This information is reported in Table 17.11. The tests show that the only significant contrast at $\alpha = 0.05$ is

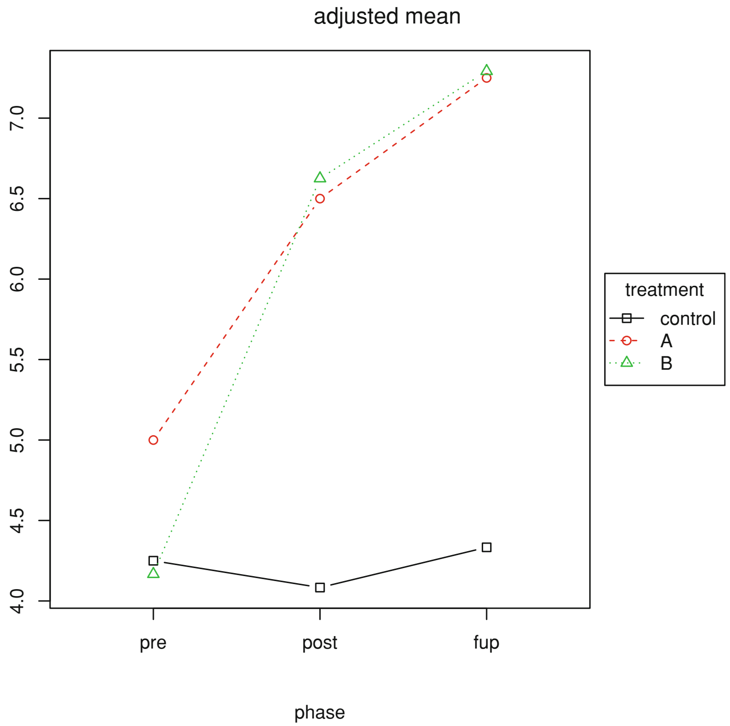

Fig. 17.3 Means of the `treatment:phase` interaction for the O'Brien and Kaiser model

Table 17.11 Orthogonal interaction contrasts for Boik's model, with *p*-values adjusted by Holm's correction

Treatment contrast	Session contrast	Value	Pillai stat.	F	Df1	Df2	*p*-value
Control versus A	Pre versus post	1.6667	0.2011	2.517	1	10	0.8625
Control versus B	Pre versus post	2.6250	0.4469	8.079	1	10	0.1329
A versus B	Pre versus post	0.9583	0.0879	0.963	1	10	1.0000
Control versus A	Pre versus followup	2.1667	0.4520	8.249	1	10	0.1329
Control versus B	Pre versus followup	3.0417	0.6778	21.038	1	10	0.0090
A versus B	Pre versus followup	0.8750	0.1348	1.558	1	10	1.0000
Control versus A	Post versus followup	0.5000	0.0447	0.468	1	10	1.0000
Control versus B	Post versus followup	0.4167	0.0403	0.420	1	10	1.0000
A versus B	Post versus followup	−0.0833	0.0015	0.015	1	10	1.0000

between the pre-test and follow-up sessions, when compared between the control group and treatment B. Given the similarity betwen the means of treatments A and B, we could have expected a significant difference between controls and treatment A as well, but the test does not reject the null hypothesis in that case, because the number of observations for treatment A is lower, and therefore the size of the effect is relatively smaller.

17.6 Models with Covariates

Data sets may include numeric predictors. When combined with factors, they are called *covariates* and ANOVA is called ANCOVA (Analysis of Covariance). Let aside their interactions, each covariate contributes one degree of freedom in linear models, i.e. there is only one coefficient per covariate in the model formula. For instance, a pure linear regression with one covariate and no factors would be:

$$Y_i = \beta_0 + \beta_1 X_i + \varepsilon_i \tag{17.1}$$

In that formula, the coefficient β_1 associated to the covariate is obviously the slope of Y along X, although it can also be seen as an infinitesimal abstraction of the concept of "contrast" used for factorial models. Such models have a finite number of factor combinations where the adjusted mean of the response can be evaluated, and therefore a finite number of possible contrasts across factor levels. On the other hand, the possible values of a covariate are infinite, and so are the possible pairs of values $X_a \neq X_b$ for which we could estimate a contrast. However, in a linear model the expected value of such contrasts would always be proportional to the difference between X_a and X_b, and it is straightforward to see that the ratio between both differences would be equal to the slope represented by the model coefficient for X:

$$\frac{\Delta E(Y)}{\Delta X} = \frac{\partial E(Y)}{\partial X} = \beta_1 \tag{17.2}$$

Carrying on with that analogy, if interactions between factors were represented as "differences of differences", the interaction between factors and covariates can be seen as "differences of slopes". Let us illustrate that concept with an example using the data from (Cartwright et al. (1968)), a two-year experiment about the effectiveness of stannuous fluoride (SF) and acid-phosphate flouoride (APF) in dental caries reduction. 69 female children completed that study, 22 of them treated with SF, 27 with APF, and the remaining 20 were a control group treated with distilled water (W). At the beginning and the end of the study, the number of decayed, missing or filled teeth (DMFT) was measured for each child. Table 17.12 shows the result of the ANCOVA of a model fitted to those data, where the dependent variable is the increase of DMFT after the two-year period, and the effect of the treatment has been crossed with the linear effect of the age at the beginning of the study.

Table 17.12 ANCOVA table of the crossed effect of age and dental treatment on caries reduction

	SS	Df	F	p-value
Age	0.103	1	0.0694	0.7931
Treatment	32.243	2	10.9011	0.0001
Age×treatment	13.459	2	4.5550	0.0143
Residuals	93.169	63		

The ANCOVA reveals that the treatment had an important effect, not only on the average increment of DMFT, but also in its interaction with age. The first row of the table does not show a significant effect of age alone although this is only a consequence of pooling the results over all three groups. The differences represented by these effects may be seen in the plots of Fig. 17.4: the increment of DMFT had the lowest average and a negative slope along age (tooth decay was reduced with age); the highest average was for the control group, which moreover had a positive slope along age; and the SF group had an intermediate increment of DFMT, which was more or less constant along age.

The analysis of the interaction between treatment and age is very similar to the one performed in factorial models. The only practical differences is that contrasts are not done for the expected values of the independent variable (increment of DMFT in this case), but for the slopes of that variable along the covariate (age). This can be seen, for instance, in the values of Table 17.13. Since the slope along age was the lowest for APF, and the highest for W, the three "slope" differences were negative, although the only significant one was the difference between those extreme values.

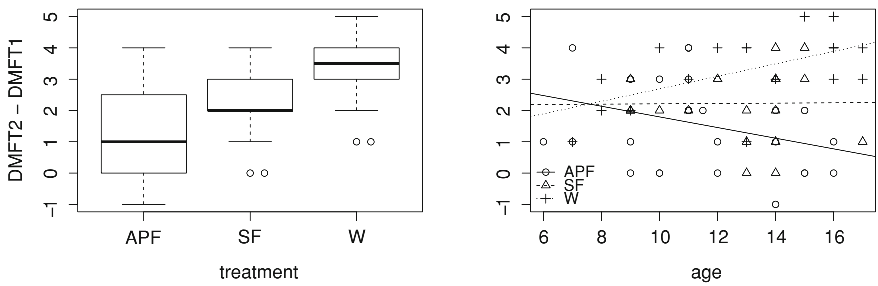

Fig. 17.4 Differences of DMFT versus age and linear trends, for each treatment group

Table 17.13 Test of an interaction between a factor and a covariate (slope contrasts)

	Slope difference	Df	SS	F	p-value
APF versus SF	−0.176	1	2.152	1.4555	0.3710
APF versus W	−0.370	1	13.448	9.0934	0.0111
SF versus W	−0.194	1	2.650	1.7918	0.3710
Residuals		63	93.169		

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