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Neurorehabilitation Technology

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Foreword

Physical therapy is hard work. For the person undergoing neurorehabilitation, many factors, including frustration and the seemingly slow pace of visible improvement, stand in the way of neuromuscular recovery and functional gain. But what are the most effective rehabilitation strategies? What combination of these strategies provides the best overall outcome? What clinical scales offer the most accurate representation of functional change and quality of life? And, perhaps most important for the forward-looking clinician, is healthcare research addressing and funding this complex domain adequately? How could we develop effective techniques faster and deploy them with more confidence? If therapy is hard work for the patient, then navigating therapy research is similarly challenging to the practitioner. Then there is the infuriating corollary to the inherently slow pace of neurologic recovery: rehabilitation research studies depend on human-subjects testing, which is rate-limited, of course, by that same, slow pace of neural system recovery. We can't win!

Or can we? Three factors stand in our favor. First, the value of effective rehabilitation to society is increasingly being acknowledged, from a quality of life perspective, as the sheer number of people with disabilities is increasing in most of the world's cultures today and as medical advances in, for example, acute-phase stroke management and spinal cord injury repair are thankfully saving lives yet increasing the number of people living with a disability. Secondly, on par with global warming, the economics of healthcare are frightening futurists (and our children) to consider seriously the long-term prognosis of our species. These two factors are the "push" to drive toward better solutions. The third is a "pull": mechatronics technology. As the costs of computational power and MEMS-based sensing/actuating/control components decrease, we can focus more on effective, robust therapy and less on flaky, bulky, expensive hardware. The end result is that rehabilitation research has been significantly empowered in recent years to expand its horizons. In the past decade, as a result, robots have for the first time actually been deployed in the clinic, not just in surgery, but in rehabilitation as well. Whereas in the past, researchers were focused on replicating therapist interventions with robot assistants, today we are moving on to envisioning interventions that therapists can design and guide, but that only robots can perform, due to the complex adaptive control interactions between sensors, the interface, and actuators. We have come a long way in the past 30 pioneering years of rehabilitation robotics.

This book illustrates admirably how the state of the art in using robots in rehabilitation has advanced, from basic human neuromuscular systems modeling and therapy interventions to the development of the technology itself. Robotics is proving its value in both upper-limb manipulation and lower-limb gait therapy, and with functional systems in between as well. We have seen the knowledge translation imperative progress, even if slowly, to connect research labs with clinical practice. Now, with the first products in this niche on the market, the future for therapy robotics is looking promising. As you will read in the chapters of this book, so is the future of rehabilitation robotics research.

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Preface

The aim of this book is to provide a current overview of rehabilitation technology with a strong emphasis on current and future clinical applications. Rehabilitation technology is a rapidly developing and expanding field, which involves a broad range of therapeutic robotics, assistive devices, and related supporting technologies such as functional electrical stimulation. This field also covers several facets of rehabilitation, such as clinical/functional assessments, monitoring systems, assistive devices, and reinforcement approaches including feedback of performance data and virtual reality tools.

The target audience for this book is clinicians and therapists involved in neurorehabilitation of disorders of the central nervous and neuromuscular systems. Therefore, the book focuses on the practical and theoretical significance of new technologies in a clinical setting and critically discusses advantages, limits, and shortcomings, as well as further developments. Given the scope of this book, technical systems without clinical data are not covered. All chapters are written by experts either involved in the development of technology in rehabilitation or those applying new technologies in rehabilitation centers. In several instances a close interaction between engineers and medical personnel allowed development and introduction of well-designed robots for application in human subjects suffering a movement disorder. After a period of rapidly expanding rehabilitation technology, we are now at a stage where problems and limits of neurorehabilitation technologies warrant critical review. This aspect is also covered in several chapters of the book. In such a rapidly evolving field it could hardly be avoided that some important issues regarding optimal use of neurotechnology will be controversial and that different opinions emerge in different chapters. Nevertheless, there is little doubt that such technology will play an essential role in future rehabilitation approaches. Intense cooperation between technologists and medical researchers is required to achieve optimal solutions for further successful developments in this field.

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Contents

Introduction: Rationale for Robot Use

Neurorehabilitation technology, which includes robotics, is a rapidly expanding field in research and clinical applications. This book discusses the state of art in this field and also examines evolving developments in related basic research and in therapeutic applications. A key question we seek to answer is "What is the rationale for robot use in neurorehabilitation?"

During the last 15 years, it has become evident that conventional physiotherapy applied during neurorehabilitation of stroke and spinal-cord-injured (SCI) subjects has demonstrated limited efficacy, as assessed in the context of evidence-based medicine. This physiotherapy has usually been conducted on limited populations, with little objective measurement of its effects on outcomes, and with few standardized assessments over the course of rehabilitation. In addition, conventional physiotherapy has focused on repetitive training of limbs with sensory motor deficits, usually without a sound scientific basis.

In Europe, different therapeutic "schools" (Bobath/Vojta) have emerged based on individual therapist experiences – but again, the intervention is not based on a rational approach driven by knowledge of the pathophysiological basis of impairment. Few studies have been performed to evaluate the effects of a given therapy, or to compare the effects of different therapeutic interventions. Of course, in neurorehabilitation, the optimal approaches, such as the use of full randomized controlled trials (RCT), are very difficult to implement rigorously, because of the confounding effects of spontaneous recovery of function. Thus, the quantitative effects of conventional physical therapies still remain an open question. Some investigators have even argued that therapy provides no real benefit beyond that offered by spontaneous recovery alone [1, 2].

From Basic Research to Clinical Application

From the late 1980s to the early 1990s, two basic-research developments have led to profound changes in neurorehabilitation interventions.

First, research performed in cats with a transected spinal cord showed that a locomotor training approach was effective in promoting gait restoration.

Here, a spinalized cat has been shown to walk very effectively on a moving treadmill with body weight support [3]. This finding renewed interest in the notion of locomotion pattern generators in the mammalian spinal cord, and indicated that they could be potentially harnessed for restoration of locomotion in the injured human as well. Since this approach to functional training appeared to be successful in re-establishing locomotor function in animal models, it has been translated to SCI locomotion and to gait recovery in stroke subjects as well [4, 5].

Second, several approaches have been introduced to successfully induce axonal regeneration in animals with damaged spinal cords, using antibodies to block the effects of myelin products on neuronal growth [6]. Although these interventions hold great promise, in order to translate these approaches into practical therapies for humans, a standardization of assessments and conventional therapies is now required [7]. These developments have forced rehabilitation centers in Europe and in the United States to build collaborative research networks, to introduce and establish standardized clinical and functional assessments, and to monitor therapeutic effects over the course of rehabilitation.

Locomotor Training

The use of body-weight-supported, treadmill-based manual locomotor training of stroke/SCI subjects began in the early 1990s, relying on the aforementioned observations in the spinalized cat as motivation [3]. This training, primarily applied in SCI subjects, was associated with considerable additional costs. In severely affected SCI subjects, two physiotherapists are required to assist the leg movements on both sides during the step cycle [8], and there are often additional therapists required to substitute for the treating therapists, because the intervention was very demanding on both therapist and patients. In addition, experience with this intervention is needed for the therapist to induce appropriate timing of movements between the two sides of the patient, and for the amount of assistance to be applied. As a consequence greater costs were incurred, resulting in the need to provide relatively short training periods, i.e., the training was usually limited to about 30 min per day. This limited training duration, which appears to be suboptimal in length, and the cyclic nature of repetitive movements to be assisted over longer time periods, led to the idea that a robotic device could serve as an alternative to manual training, and that such a device could take over the physically demanding functional training [9].

Requirements for a Robotic Device

For the successful construction and implementation of the first robotic devices providing locomotor training of SCI/stroke subjects, several factors had to be

identified and verified. Safety constraints had to be established, mainly related to the forces that could be safely applied to the legs. There were also concerns about skin integrity and the prevention of skin ulcers.

In the beginning, position-controlled fixed physiological stepping movements, which have been pre-recorded from healthy subjects, were imposed on the legs of SCI subjects using an exoskeleton robot [9]. Despite the non-interactive and simple control paradigm, the first training sessions using such a position-controlled robotic device provided an excellent experience for the patient and the therapists, and showed promise for long term beneficial impact on locomotion.

In subsequent years, it has become evident that merely imposing fixed movements on paretic limbs is not sufficient to achieve optimal training effects. In the analogous cat experiments, for example, the moving treadmill triggered the hind limbs to generate a physiological movement pattern while the body was supported. Correspondingly, for optimal results in human training, with the assistance of therapists, leg movements should only be assisted insofar as it is required by the severity of paresis of an individual subject. Therefore, ongoing developmental advances in robotic devices have taken into account these findings to enhance training effects.

Later versions of these robotic gait trainers have assisted leg movements only to the extent required by the motor deficit of the individual subject. Feedback information has been provided to both the patient and therapists about the patient's contribution to the locomotor movements [10]. This technology considerably enhanced training motivation and presumably also training effects, although this is currently under continuing study. In addition, different assessments (e.g., muscle tone, locomotor ability) have been introduced and the devices have provided standardized measures of impairment and of functional outcomes (for review see [11]).

What Is Needed for a Successful Training?

In light of the above history, it is now reasonable to ask, what is the rationale for applying a robotic device in stroke/SCI subjects?

The main potential advantages are:

- The robot allows standardized training sessions that simultaneously provide objective measures about the physical aspects of the training performed (e.g., applied forces, velocity, duration of training, leg excursions) and about the training effects, (i.e., the progress of recovery can be monitored).
- Robots enable longer training times.
- The robots relieve therapists from physically demanding work allowing them to optimize other aspects of the individual therapy and to focus on actual requirements and care.

However, there are remaining questions that require answers before the field can effectively advance:

- What are the essential cues to optimize the training by a robotic device? We know, for example, that load- and hip-joint-related input is essential for an appropriate leg muscle activation during a locomotor training [12]. Thus body re-loading as much as possible during the course of training and extensive hip joint excursion movements are essential to achieving an appropriate leg muscle activation and, consequently, to strengthen training effects. Certainly other as yet unknown receptor inputs might also be relevant.
- What is the best type of feedback information for the patient during a functional training episode, and how should it best be delivered to reinforce training effects?
- With a robotic device, longer training sessions become feasible. How long should a training session last per day to achieve optimal effects? (In a recent study on stroke subjects, for example, 1-h training sessions resulted in better effects than shorter ones [13]. A corresponding study in SCI subjects is underway.) Regardless of potentially optimal requirements, training time might be limited by the individual's health condition.
- What walking speed is appropriate to achieve the best effects, or should speed be varied during a training session?
- How "physiological" must the locomotor training conditions be? Is it, for example, required to assist the lateral shifts of the pelvis during the locomotor training within a robotic device? Despite "optimal" training conditions, it can hardly be expected that normal stepping movements can be achieved after a SCI or brain damage. The goal should always be to achieve the optimum level of locomotor ability suited for an individual subject.
- How much and how early after a SCI or brain damage should a patient be challenged during the locomotor training? Should the patient not only move his legs with the minimal assistance needed but also maintain body equilibrium as much and as early as possible?
- How much can virtual reality (VR) interventions enhance the effectiveness of training? Do only certain patient subgroups, e.g., children or elderly patients, profit from such an approach? Or can VR make the training just more attractive to the patient?

Evidence of Therapy Effectiveness

As outlined above, there is a lack of high-quality evidence regarding the effectiveness of most conventional therapeutic approaches in neurorehabilitation. Robotic devices make it possible to test specific therapeutic approaches using standardized measurements. Nevertheless, the "open questions" indicate that many studies are necessary to answer all questions satisfactorily. It is also obvious that different therapeutic approaches should be compared with each other, and the effects of spontaneous recovery of function should also be factored into the trial design. Nevertheless, until now, few such studies exist, for example, to compare conventional with functional training. In a recent study [14] the locomotor training in SCI subjects was compared using

a treadmill with body weight support with over ground stepping on parallel bars and/or with external physical assistance. No significant difference in outcome was found. This is perhaps not so surprising since, in both cases, a functional locomotor training was performed. It would be of greater interest to investigate if severely affected SCI/stroke subjects benefit more from an early-onset training with body weight support and assistive devices than conventional physiotherapy over the course of the early rehabilitation phase.

The effectiveness of a rehabilitation approach in stroke/SCI subjects can hardly be compared with the spontaneous outcome in function, i.e., by a group of control subjects without therapy. Therefore, novel therapies have to be compared for their superiority in multicenter trials either with conventional or other new therapeutic approaches. Robotic devices might help to monitor the development of function over the course of rehabilitation.

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Part I

Basic Framework

Multisystem Neurorehabilitation in Rodents with Spinal Cord Injury

1

Grégoire Courtine, Rubia van den Brand, Roland R. Roy, and V. Reggie Edgerton

Abstract

A number of neurorehabilitative strategies have demonstrated efficacy in enhancing the recovery of sensorimotor function after a spinal cord injury (SCI). Combinations of task-specific motor training, epidural electrical stimulation of the spinal cord, and pharmacological interventions such as the administration of serotonergic agonists have resulted in remarkable improvements of locomotor and/or postural functions in rats with a complete SCI. Similar results are emerging in human patients with severe spinal cord damage. Synergistic amelioration of the loss of sensorimotor function through combinatorial approaches, i.e., the use of two or more interventions simultaneously, indicates that individual interventions can have both specific and complementary influences. For example, electrical stimulation applied at distinct rostrocaudal locations or agonists to specific receptor subtypes administered systemically tune unique aspects of locomotor movements. When administered simultaneously, the effects of these interventions can combine synergistically and result in significantly greater improvements in locomotor performance than either intervention alone. In addition, the use of robotic assistance during motor training, in particular in an "assist-as-needed" mode that allows a normal amount of variability in performing the task as opposed to a repetitive rigid training mode, can strongly enhance the effect of locomotor rehabilitation. We suggest that all

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of these interventions are enabling factors. They enable spinal neural circuitries to interpret task-specific sensory input and use this information in a feedforward manner to produce appropriate motor responses. Continued advancement in the development and refinement of such neurorehabilitative interventions will ensure progress towards improving the quality of life of individuals with a SCI or other severe sensorimotor dysfunctions.

Keywords
Spinal cord injury • Epidural electrical stimulation (EES) • Monoamine administration • Robotic training • Rehabilitation

1.1 Introduction

Severe spinal cord injury (SCI) significantly impacts the ability of affected individuals to generate functional standing and walking movements. A century of research on the organization of the neural processes that control movements in mammals, however, has demonstrated that the basic neuronal circuitries sufficient to generate efficient stepping patterns and independent standing are embedded within the lumbosacral segments of the spinal cord [1–3], i.e., caudal to the level of most human SCI. Indeed, current views on motor control suggest that the descending systems provide excitatory and modulatory drives to spinal circuits, but the operations underlying the elaboration of motor patterns for walking and standing are essentially achieved by the neuronal networks in the spinal cord. Therefore, the question becomes: how can we transform nonfunctional spinal motor circuitries into highly functional and adaptive networks after a severe SCI to enable motor control during neurorehabilitation and thus restore functional capacities in paralyzed subjects?

In this chapter, we briefly summarize the basic historical concepts underlying the control of locomotion and the plasticity of spinal neuronal networks with neurorehabilitation. We then show how this fundamental knowledge can be exploited to design enabling multisystem interventions after a severe SCI, i.e., combinations of electrical and pharmacological stimulation paradigms, robotic devices, and sensory-based motor training that are capable of restoring motor control abilities after the loss of descending input (Fig. 1.1). We describe recent experiments in animal models of SCI that demonstrate the impressive capacity of this multisystem approach to improve motor functions after the complete interruption of supraspinal information. Next, we describe current efforts for the development of technologies to optimize this approach. Finally, we discuss the potential of this technologically intensive but physiology-based neurorehabilitation approach to crystallize into fully operative neuroprosthetic systems and robotically assisted training procedures capable of restoring useful functional capacities in humans with severe spinal cord damage.

1.2 Experimental Concepts Underlying Activity-Dependent Plasticity After a SCI

At the beginning of the past century, Philippson [2] and Sherrington [1] reported unexpected observations that revolutionized our conception of the neural control of movements. They showed that after a complete transection of the thoracic spinal cord in cats and dogs, the hindlimbs could still exhibit a range of motor patterns in response to changing sensory inputs. These observations led Sherrington to conceive the production of locomotor movements as “a train of motor acts resulting from a train of successive external situations.” [1] Sherrington aimed to emphasize the crucial importance of afferent information in

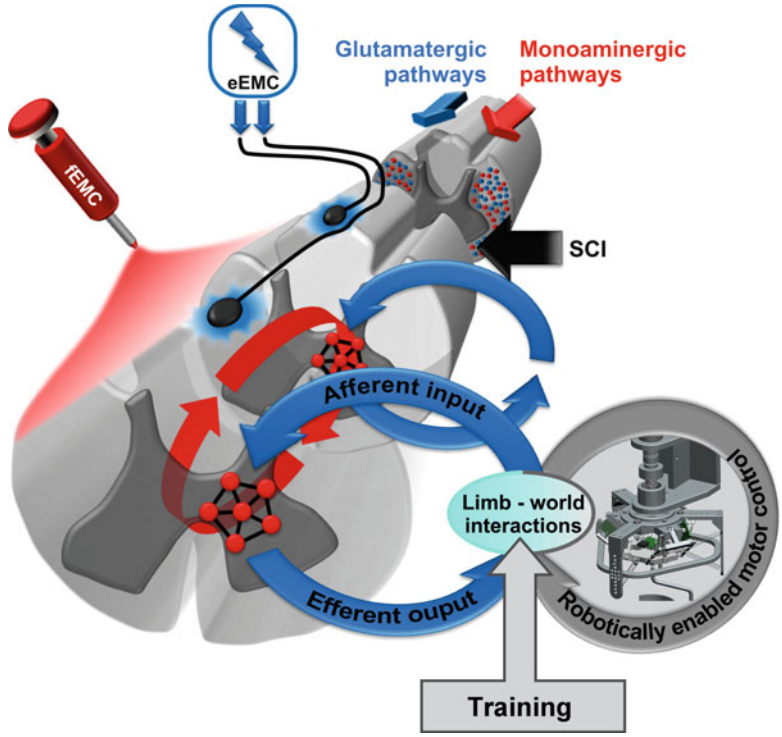

Fig. 1.1 Multisystem neurorehabilitation to restore motor functions after a severe SCI. Schematic drawings of locomotor circuits are shown after a SCI at the thoracic level that interrupts both glutamatergic (*blue*) and monoaminergic (*red*) descending pathways originating from various brainstem areas. The combination of monoamine receptor agonists and epidural electrical stimulation at the L2 and S1 levels can tune the physiological state of the spinal circuits to a level sufficient for motor control to occur. Therefore, these interventions are termed pharmacologically (*fEMC*) and electrically (*eEMC*) enabled motor control. The generation of efficient locomotor movements under their combined influences, termed e*fEMC*, results from the ability of spinal circuitries to ensure a continuous match between afferent input and efferent output defining optimal motor states. To ensure appropriate interactions between the locomotor system and the external world during training, robotic interfaces can be interposed to provide robotically enabled motor control conditions. Such robotic systems can assist limb movements for propulsion as well as trunk motion for balance. Finally, these various *motor control-enabling systems* can be used in combination to facilitate neurorehabilitation

allowing, selecting, and controlling spinal motor outputs after the loss of supraspinal influences (see discussions in [4]). How can this conceptual view be exploited to improve functional capacities after a SCI?

In the early 1980s, Edgerton and Rossignol reasoned that if sensory input can access and control spinal circuits deprived of brain input, the repetitive exposure to organized patterns of sensory input with training might promote beneficial functional changes in the activated neuronal networks. Their work clearly demonstrated the potential utility of intense daily exercise on a treadmill for improving the stepping capacities of adult cats with a complete spinal cord transection at the thoracic level. They further reported that after several months of daily step training, the spinal cats regained an impressive ability to produce full weight-bearing locomotion for extended periods of time [5, 6]. Fueled by these findings, Edgerton and his team evaluated the potential of rehabilitative training and weight-bearing afferent input to improve function after a SCI by evaluating the ability of spinal cats to develop the capacity to stand [7]. They discovered a surprising property of spinal circuitries: cats that had been trained intensely to stand, developed the remarkable ability to support their entire body weight for up to 1 h, but they stepped very poorly on the treadmill, i.e., the spinal cord learned the sensorimotor task

that was specifically practiced and trained [8, 9]. These results led to the concept of spinal learning via activity-dependent plasticity: as repetitive activation of a synapse can change its properties within a timeframe that ranges from milliseconds to months [10], the repetitive and simultaneous activation of certain sensory and motor pathways with task-specific training can select and reinforce those circuits and connections in a way that significantly improves their ability to perform the practiced movement successfully [11, 12]. This Hebbian-type plasticity at a systems level predicts that the outcome of a neurorehabilitative program will strongly depend upon the type and quality of the motor function that is trained. Moreover, this concept emphasizes the crucial importance of concurrent sensory information in shaping the functional remodeling of spinal circuitries with training.

Following these observations, there has been substantial success in translating activity-based rehabilitation therapies from cats to humans with a partial SCI [13, 14]. Improvements of ambulatory function in response to locomotor training in patients with an incomplete SCI have been reported in several studies from different laboratories [15–18]. A clinical trial demonstrated that with weight-bearing training, 92% of subjects with an incomplete SCI (ASIA C or D) regained the ability to walk at a functional speed within 3 months [19]. In contrast, in individuals with a severe SCI classified as ASIA A, B, and most Cs with low lower limb motor scores [20], locomotor training has not resulted in successful overground walking, even with the aid of any walking device. Why does locomotor training fail to significantly ameliorate motor functions in severely affected individuals?

The answer may be deceptively simple: robust neural activity needs to be present for activity-dependent plasticity to occur, i.e., some critical level of excitability must be present within the locomotor networks to respond to proprioceptive input. In contrast to individuals with an incomplete SCI who progressively regain basic walking capacities after recovering from the initial spinal shock, patients with a severe SCI exhibit limited or no residual function to be trained [18], and locomotor rehabilitation thus fails to promote useful plasticity in the sensorimotor pathways [21]. Therefore, given the assumption that the locomotor networks remain functional in the lumbosacral spinal cord after these severe injuries, the next logical step was to develop interventions to gain access to the dormant spinal locomotor circuitries after a SCI, with the aim of enabling motor control during rehabilitation to mediate use-dependent plasticity in the trained neuronal networks.

1.3 Motor Control–Enabling Systems After a SCI

A severe lesion of the spinal cord significantly compromises the degree of sustainable excitability in the lumbosacral circuitries. Thus, the inability to produce standing and stepping patterns after a severe SCI is not due only to the interruption of the descending motor commands, but also, and above all, to the markedly depressed state of the spinal neuronal networks [21]. Consequently, in the past decade, much effort has been focused on developing paradigms to tune the physiological state of the spinal circuits to a level sufficient for stepping and standing to occur. Various strategies including electrical stimulation of the muscles [22, 23] or dorsal roots [24], epidural [25–27] or intraspinal [22, 24] electrical spinal cord stimulation, administration of a variety of pharmacological agents [28–32], and smart robotic systems [33, 34] have shown the capacity to facilitate standing and/or stepping after a severe SCI. Since these interventions are not used to induce but rather to allow the production of movements, we term these paradigms *motor control–enabling systems* (Fig. 1.1).

1.3.1 Electrically Enabled Motor Control (*eEMC*)

Weight-bearing locomotion and standing have been induced in complete spinal mammals by electrical stimulation, using both penetrating electrodes inserted into the spinal cord tissue and electrodes placed on the surface of the dura. Using penetrating microelectrodes, Shik and colleagues [35] originally observed that stimulation of the dorsolateral funiculi at the cervical and thoracic spinal cord levels initiates stepping in decerebrate cats via activation of intraspinal

fibers. More recently, the Mushahwar, Prochazka, and Rossignol research teams have developed systems of intraspinal stimulating microelectrodes for rats and cats whereby a set of penetrating electrodes is inserted in the ventral horn to facilitate the activity of the neuronal networks that control stepping [36–38]. Using a less invasive technique, Garcia-Rill and colleagues [39] reported that epidural electrical stimulation of both the cervical and lumbar enlargements with plate electrodes induces locomotion in decerebrate cats. Since then, tonic *eEMC* applied over the dorsal surface of virtually any lumbar or sacral segment [40] has shown the ability to facilitate stepping on a treadmill as well as standing in rats [29, 41], rabbits [42], cats [42], and humans with a severe SCI [43, 44].

While intraspinal microstimulation offers the advantage of closer juxtaposition of the electrode to motoneurons and interneurons in the intermediate and ventral laminae, the insertion of multiple penetrating electrodes into the spinal cord is a complex procedure [22] that can inflict significant tissue damage [45]. Their placement may be difficult to maintain in ambulatory individuals, particularly for very long periods. In addition, recent evidence suggests that many of the beneficial effects of intraspinal microstimulation may rely on the same mechanisms as epidural electrical stimulation (EES) [46]. While the direct stimulation of muscles using computer-controlled patterns of activation has had some success in the recovery of hand control [47], acceptability by individuals with a SCI has not been high. One limitation is the absence of feedback mechanisms for maintaining adaptive control. We therefore focus this section on the principles of and mechanisms through which EES enables motor control after a SCI while retaining some adaptive features.

The mechanisms underlying the facilitation of motor activities with *eEMC* are not yet fully understood [48]. Electrophysiological recordings [49] and computer simulations [46, 50] suggest that EES can directly engage spinal circuits primarily by recruiting posterior root fibers at their entry into the spinal cord, as well as along the longitudinal portions of the fiber trajectories. When the stimulation is used to actually induce evoked potentials during quiet standing, 3–4 well-defined motor responses in lower limb muscles can be classified based on their respective latencies and threshold (Fig. 1.2). The early response (ER), which only

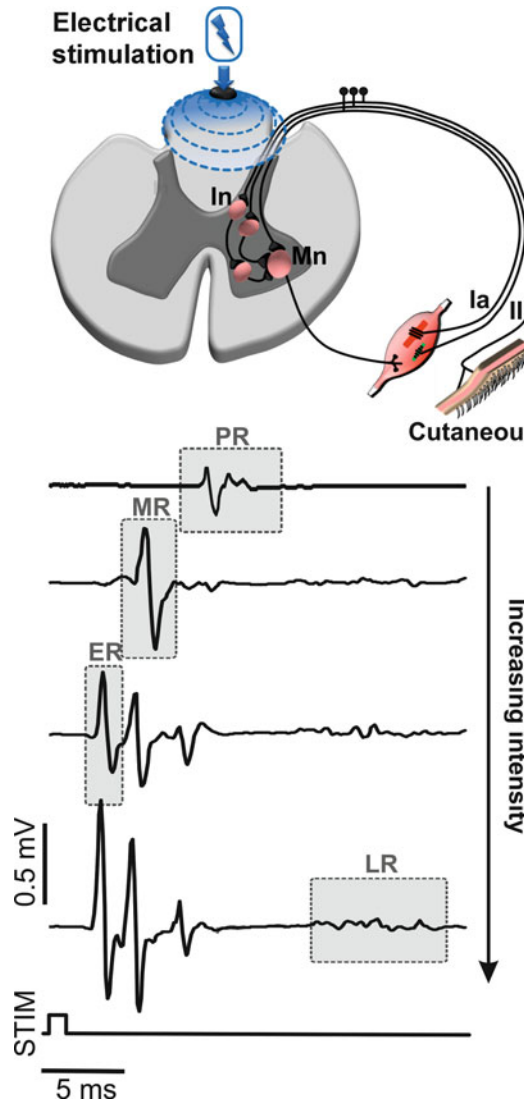

Fig. 1.2 EES elicits distinct motor responses through the recruitment of specific pathways. Schematic illustration of the afferent systems putatively recruited when delivering single-pulse EES over spinal segment S1. When applied over the dorsal aspect of the spinal cord, the electrical stimulus typically elicits three or four responses in all hindlimb muscles. The responses are termed early response (*ER*), middle response (*MR*), polysynaptic response (*PR*), and late response (*LR*) based on their respective latencies and thresholds (see text for details). *In* interneuron, *Mn* motoneuron

appears at higher intensities when stimulating the more caudal segments, results from the direct stimulation of motoneurons and/or motor nerves. The middle (MR) response is essentially mediated by the monosynaptic connections between Ia fibers and motoneurons, i.e., a response equivalent to the H-reflex [49, 51] (Fig. 1.2). The neural elements associated with the polysynaptic response (PR) and long latency response (LR) remain undetermined but are likely to rely on multiple afferent systems. Based on the electrophysiological signature of these responses, we argue that the PR relies in part on the disynaptic and/or oligosynaptic connections between group II fibers and motoneurons [25, 49] (Fig. 1.2). We also surmise that EES recruits large-diameter cutaneous afferent fibers that contact multisensorial interneurons (Fig. 1.2), facilitate transmission in group Ib and II pathways [52], and can elicit coordinated bilateral motor responses in flexor and extensor muscles [53]. Cutaneous sensory systems may contribute to both PR and LR responses. It is worth noting, however, that this intuitive explanation is not clearly applicable to the "enabling" mode of stimulation whereby modest stimulation levels induce little or no measurable evoked potentials. At this intensity, the stimulation instead modifies the physiological state of the locomotor circuitry via the activation of proprioceptive input associated with standing and stepping [54].

How do electrically induced motor responses translate into functional patterns of electromyographic (EMG) activity during stepping and standing? When a spinal rat is positioned bipedally on a stationary treadmill belt, continuous EES applied at the sacral level (S1) induces tonic levels of EMG activity in extensor muscles, which enables the maintenance of a continuous standing posture (Fig. 1.3) [28]. A close inspection of muscle EMG traces reveals that the sustained EMG activity in extensors is composed of a succession of motor responses that are closely linked to the electrical stimulation (Fig. 1.3). When treadmill belt motion is initiated, all hindlimb joints undergo changes toward extension (limb moving backward), creating dynamic proprioceptive input that immediately transforms the motor patterns from a tonic to a rhythmic state (Fig. 1.3). Under such locomotor states, we found that EMG bursts are essentially built from a sequence of MR responses in extensor muscles and MR and PR responses in flexor muscles (Fig. 1.3) [25]. Both responses are markedly modulated in amplitude throughout the gait cycle according to the phase of the movement [25, 49, 51] (Fig. 1.3). This phase-dependent modulation of electrically evoked motor responses in flexor and extensor muscles creates rhythmic and alternating bursts of EMG activity sufficient to sustain continuous hindlimb locomotion on a treadmill [25]. MR and PR motor components show similar behaviors when eliciting step-like patterns with epidural stimulation in the paralyzed legs of human subjects [43]. Together, these data indicate that central mechanisms dynamically update the level of excitability in motor pools and strictly tune the gain in afferent pathways based on the current sensory and motor states of the locomotor apparatus [55]. Although experimental evidence is still incomplete, *eEMC* seems to play a crucial role in augmenting the excitability of the spinal circuitries that underlie and control postural and locomotor tasks.

Analysis of EMG activity during standing and stepping showed that EES engages motor pools through the recruitment of afferent pathways, which follow a strict muscle-specific architecture along the rostrocaudal extent of the spinal cord [56], consequently, it is plausible to determine whether *eEMC* delivered at specific locations elicits distinct patterns of motor responses in lower limb muscles. To address this issue, we applied *eEMC* over lumbar (L2) versus sacral (S1) segments during both standing and stepping in spinal rats [28]. Consistent with the rostrocaudal anatomical gradient of flexor and extensor motor pools, we observed a facilitation of flexion with lumbar EES, whereas stimulation applied at the sacral level primarily facilitated extension, both during standing (Fig. 1.4a) and stepping (Fig. 1.4b). Moreover, the combination of two [28], and even more efficiently three [41], sites of *eEMC* promoted

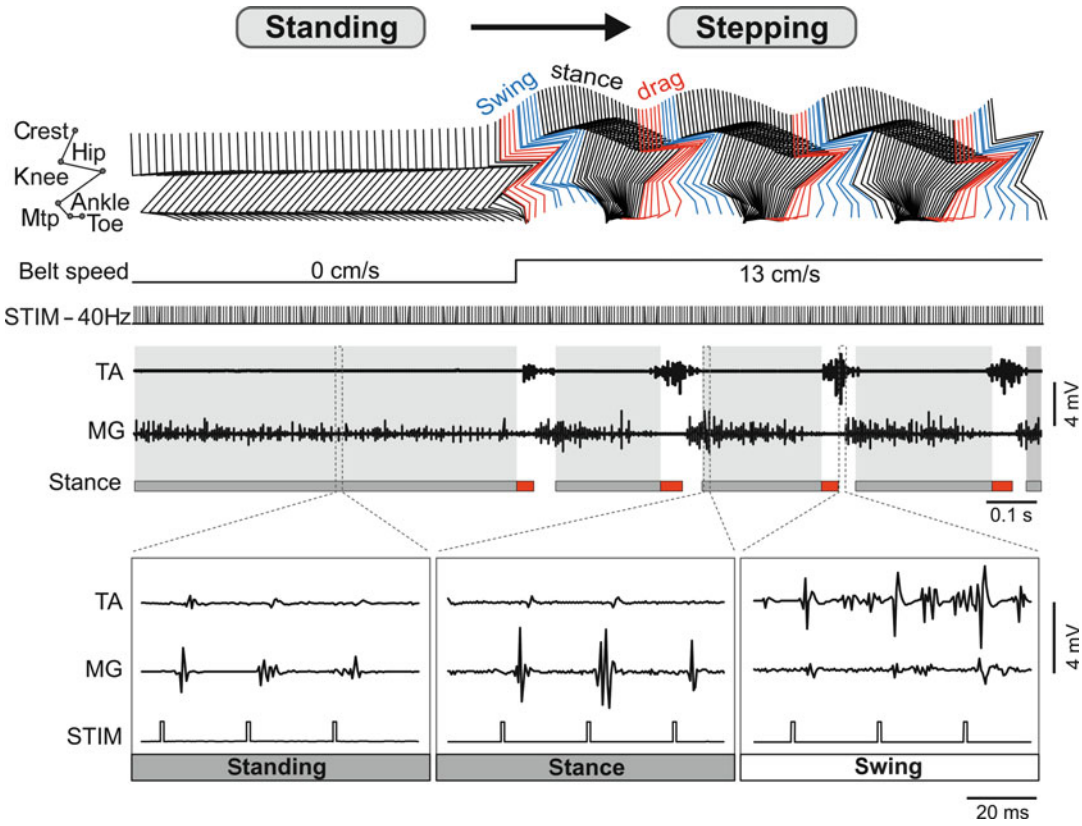

Fig. 1.3 Modulation of spinal circuits with EES during stepping in spinal rats. Hindlimb kinematics and EMG activity from tibialis anterior (*TA*) and medial gastrocnemius (*MG*) muscles are shown for a spinal rat receiving continuous (40 Hz) EES at the sacral (S1) level. During the represented sequence, the treadmill belt abruptly switches from static (no motion) to a dynamic (13 cm/s) condition. The lower insets display the responses occurring during the highlighted region of the EMG recordings. During standing, the sustained EMG activity in extensor muscles (*left inset*) is composed of a succession of MR responses that are locked to the stimulation. The emergence of the dynamic state (belt motion) induces the immediate modulation of motor evoked responses whereby the MR in the MG is facilitated during stance (*middle inset*) and inhibited during swing (*right inset*), whereas the MR and LR are suppressed in flexor muscles during stance, but substantially facilitated during swing

clear synergistic facilitation of stepping which was evident in the increased consistency of hindlimb kinematics and enhanced weight-bearing capacities.

Under normal conditions, glutamatergic reticulospinal neurons provide the tonic excitatory drive to engage spinal locomotor networks [57]. Here, we summarize results from various studies that collectively demonstrate the powerful ability of basic spinal cord electrical stimulation to replace the descending source of tonic excitation to enable standing and stepping in paralyzed subjects with a severe SCI. We therefore term this intervention *electrically enabled motor control* or *eEMC* (Fig. 1.1). In the complete absence of monoaminergic input, however, *eEMC* alone fails to promote substantial levels of weight bearing with plantar placement of the feet on the treadmill belt [28]. Similarly, descending glutamatergic input alone fails to elicit long-lasting step-like patterns in mice without the presence of monoamines [57]. We show in the next section that to attain robust stepping capacities after a severe SCI, *eEMC* needs to be combined with pharmacological agents that replace the lost modulatory monoaminergic input.

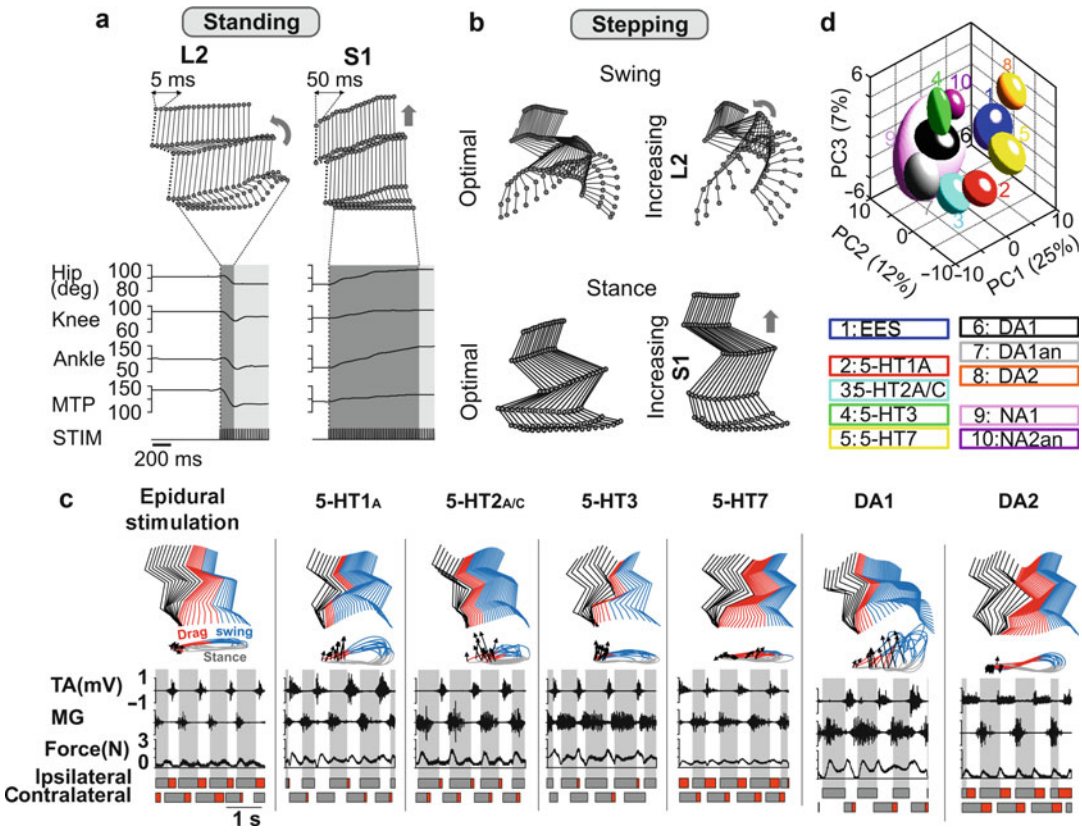

Fig. 1.4 Specific modulation of hindlimb movements mediated by EES and monoaminergic agonists during standing and stepping. (**a**) Stick diagram decomposition of hindlimb movements and associated time course of changes in hindlimb joint angles (increase toward extension) when delivering EES at L2 (*left*) or S1 (*right*) during standing. (**b**) Effects of increasing stimulation intensity at L2 during swing (*top*) and at S1 during stance (*bottom*) on hindlimb stepping movements enabled by dual-site EES and serotonin agonists. (**c**) Representative features of locomotion recorded in spinal rats under EES at L2 + S1 and agonists to various monoaminergic receptors (*indicated above*). A representative stick diagram decomposition of hindlimb motion during swing is shown for each condition with the successive color-coded trajectories of limb endpoint. Vectors represent the direction and intensity of the limb endpoint velocity at swing onset. A sequence of raw EMG activity from TA and MG muscles is displayed at the bottom. Gray and red bars indicate the duration of stance and drag phases, respectively. (**d**) Three-dimensional statistical representation of locomotor patterns based on principal component analysis applied on a large number of gait parameters ($n = 135$). Gaits associated with a given monoaminergic receptor clustered in a distinct location, revealing that each receptor promoted unique stepping patterns [61]

1.3.2 Pharmacologically Enabled Motor Control (*fEMC*)

Spontaneous locomotor activity is associated with a substantial release of monoamines within most laminae of the lumbosacral segments [58]. These monoaminergic inputs are not restricted to the classical, hardwired synaptic communication but primarily operate perisynaptically through three-dimensional chemical diffusion, i.e., volume transmission [59]. Monoaminergic neurotransmitters easily escape the synaptic cleft, enter the extracellular space, and reach extrasynaptic G-protein–coupled receptors located on the surface membrane of neighboring cells. This signaling transduction pathway profoundly alters cell properties over timescales that span from minutes to hours [59]. Volume transmission communication suggests that pharmacological agents mimicking the action of monoamines

could act in concert with EES to orchestrate the functional tuning of spinal circuitries in SCI subjects [60].

We directly tested this hypothesis in adult rats with a complete SCI [28]. We selected agonists to 5-HT_{1A} and 5-HT_7 (8-OHDPAT) and 5-$HT_{2A/C}$ (quipazine) receptors since these pharmacological agents have previously shown the ability to facilitate locomotion in rodents with a SCI [29, 30]. In the subacute phase after the injury, the functional state of the spinal circuitries is markedly depressed. Accordingly, neither electrical stimulation nor serotonin agonists could induce functional states that would enable stepping movements on the treadmill at 1 week post-injury. In striking contrast, the combination of dual-site EES and serotonin agonists promoted coordinated locomotion with plantar placement and substantial levels of weight bearing on the treadmill. Detailed statistical analyses revealed that each pharmacological or electrical intervention modulates distinct aspects of the locomotor movements, suggesting a fine-tuning of selective functional circuits (Fig. 1.4d). For example, 5-$HT_{2A/C}$ receptors primarily facilitated extension and weight-bearing capacities, whereas 5-HT_{1A} and 5-HT_7 receptors facilitated rhythmic components and promoted stepping patterns biased towards flexion (Fig. 1.4c). The functional specificities of electrical and pharmacological stimulations, in turn, provided the means for the exquisite synergy between the two paradigms, such that only a combination of serotonin agonists and EES was able to engage spinal locomotor networks as early as 1 week after a complete SCI. We recently investigated whether this receptor-specific functional tuning of gait could apply to a broader range of monoaminergic receptors. Using advanced neurobiomechanical analyses (Fig. 1.4c), we demonstrated the intriguing ability of serotonergic, dopaminergic, and noradrenergic receptor subtypes to modulate stepping behavior in qualitatively unique ways in adult spinal rats [61]. Thus, stimulation of spinal monoaminergic receptors pharmacologically and recruitment of spinal circuits electrically can modulate recognizable qualitative features of locomotion independently as well as collectively in rats deprived of any supraspinal influences. Since the beneficial influences of *fEMC* and *eEMC* do not simply sum algebraically but actually enable novel and specific motor control states, we term this synergistic combination *efEMC* for *electropharmacologically enabled motor control* (Fig. 1.1).

1.3.3 Robotically Enabled Motor Control (*rEMC*)

There are various lessons to be learned on the advantages of developing the engineering aspects of robotic technologies in coordination with input from neurophysiologists and rehabilitative specialists [62]. One example of this multidisciplinary perspective is the importance of the type of control that is designed to operate a robot when attempting to assist in the recovery of stepping after a SCI [11, 12, 33, 34, 54, 63]. More specifically, we first observed that adult mice with a complete mid-thoracic SCI could learn to step more successfully when there was no continuous and rigid control of the movements of the limbs by the robotic arms, i.e., the mice were allowed to step independently at intervals throughout a given robotically controlled training session [34]. Subsequently, a similar experiment was performed with spinal mice in which the control of the robotic arm was programmed to "assist-as-needed." The robotic arm would move the limb within a preselected window size to accommodate the variation that is intrinsic to every movement of the gait cycle [33]. Those mice that were trained with the robotic arms controlled in an "assist-as-needed" mode learned to step better than those trained with rigid control of the trajectory of the legs during stepping. Further investigation identified the probable reason for this improved stepping with the "assist-as-needed" control algorithms [64]. Detailed analysis of the EMG patterns revealed that the rigid control scheme intermittently interrupts the alternate recruitment of flexor and extensor muscles; the neural control system operates in a continuous correction mode. In contrast, by enabling variability in the limb trajectory, the "assist-as-needed" control mode does not constrain the timing of the movement, thereby allowing the appropriate recruitment of flexor muscles during swing and extensor

muscles during stance, as required to produce a coordinated stepping pattern [64].

Collectively, these data emphasize the importance of designing smart robotic interfaces to enable the spinal locomotor system to generate appropriate stepping movements as opposed to building robots that move the limb along fixed trajectories. Consequently, we term this concept *robotically enabled motor control* or *rEMC* (Fig. 1.1). There is growing evidence that *rEMC* not only applies to limb movements but also to the trunk–limb system for the control of balance and weight bearing [65].

1.3.4 Sensory-Enabled Motor Control (*sEMC*)

Under normal conditions, the descending systems control the general features of locomotor movements, i.e., gait initiation, speed of progression, and direction of walking. A key issue for the design of clinically relevant neurorehabilitation procedures is the identification of an alternative source of adaptive control for stepping when these pathways are interrupted by a SCI. As summarized in the first section of this chapter, Sherrington originally introduced the idea that sensory ensembles dictate the properties of spinal locomotion *in vivo* [1]. This viewpoint, historically reduced to the "chain of reflex" hypothesis, predicts that the succession of external situations detected by afferent systems allows, determines, and actually controls the characteristics of centrally generated motor outputs. Currently, sensory input is instead regarded as part of reflex subsystems that modulate, but are under the control of, central pattern generator (CPG) networks [53, 66]. Here, we provide a few examples that illustrate the ability of multisensory information to control spinal motor outputs with an astonishing degree of precision, a capacity that can be exploited to produce flexible and adaptive patterns of locomotion after a SCI.

In the absence of treadmill motion, but under weight-bearing conditions, electrical and pharmacological stimulations allow spinal rats to maintain a tonic posture behaviorally visible as standing (Fig. 1.5a). When the treadmill belt motion is initiated, however, the spinal circuits detect the emergence of dynamic conditions and immediately transform the motor patterns from a tonic to a rhythmic state [28]. Likewise, spinal locomotor systems can accommodate limb kinematics and EMG patterns to changing treadmill belt speeds within a single step, even at running velocities (Fig. 1.5a). Strikingly, while spinal rats are running on the treadmill, the sudden stop of the belt abruptly terminates flexor bursting and results in sustained tonic activity of extensor muscles [28]. Spinal sensorimotor systems are thus capable of recognizing a deviation from expected task-specific patterns of proprioceptive input within milliseconds, hence allowing the immediate switch from a running to a standing state without any supraspinal influence. Similar modulation of locomotor patterns can be found in decerebrate and spinal cats [42] as well as humans with a severe SCI during manually assisted stepping on a treadmill [67, 68]. Along the same line, spinal rats show the remarkable ability to adjust limb movements to a sudden change in the direction of the treadmill belt from forward to backward, or to a progressive rotation of the body in a sideward direction (Fig. 1.5b). In both situations, spinal circuitries respond to changing external conditions with a complete reorganization of hindlimb kinematics and muscle activity patterns to produce continuous locomotion in virtually any direction in space [28].

During the execution of these various motor tasks, we found that there was often a continuous match between the spatiotemporal patterns of sensory inputs (external situations) and the characteristics of the motor outputs [28] (Fig. 1.5b). The precision and versatility of these complex tuning patterns cannot be explained by any of the spinal reflex responses that have been described to date. Together, these data suggest that the ensemble of afferent systems sensitive to load, direction, and velocity collectively contribute to elaborate a detailed representation of the locomotor state that allows for the continuous selection of the combination of motor circuits appropriate to perform the current task successfully. These observations imply that after the loss of brain input, sensory information is instructive in a functional, primarily feedforward manner [12].

The recovery of hindlimb locomotion in animals with a SCI is usually attributed to the

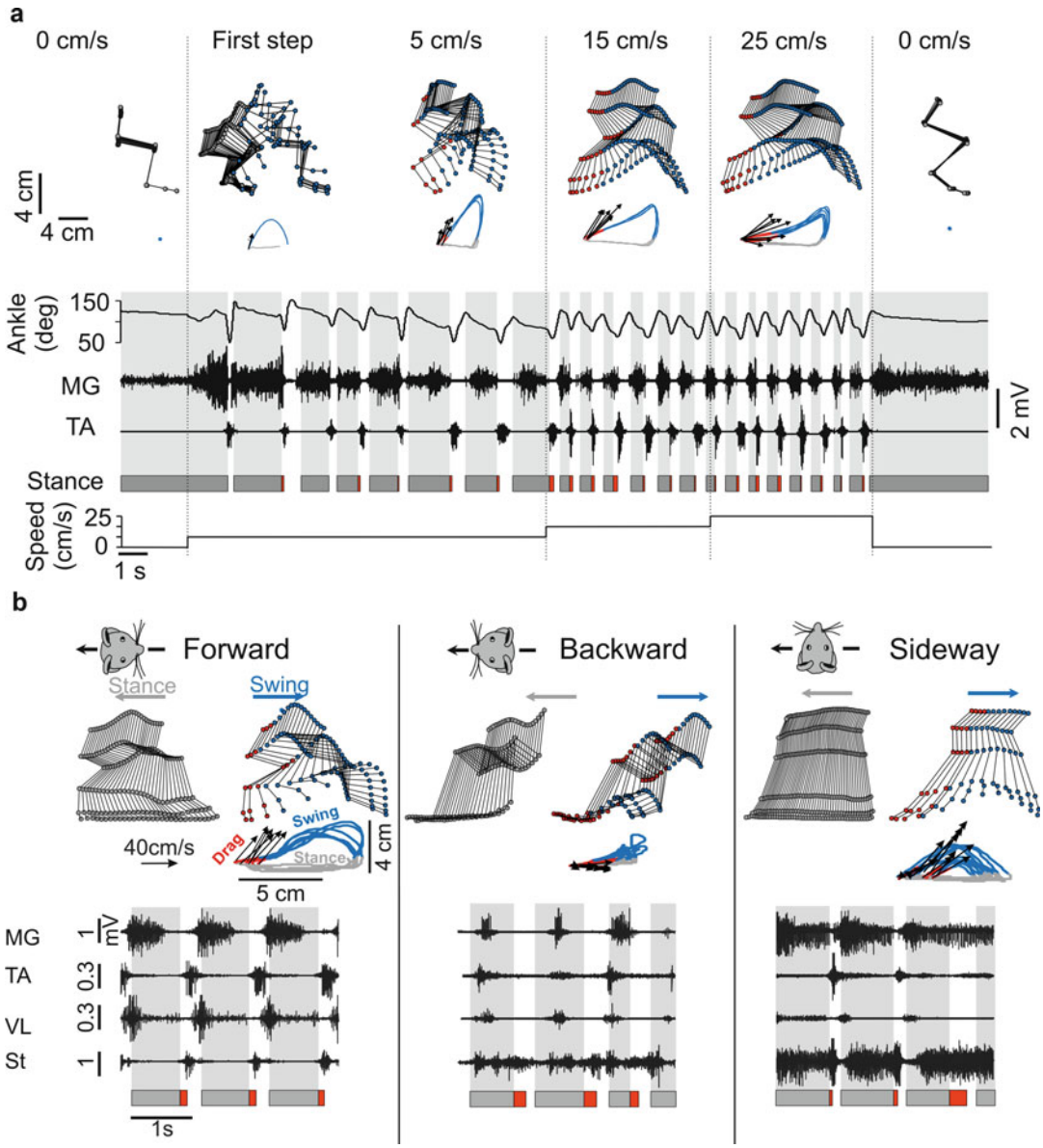

Fig. 1.5 Effects of velocity- and direction-sensitive afferent input on the characteristics of hindlimb movements in spinal rats. (**a**) Representative example of hindlimb kinematics and EMG activity recorded from a continuous sequence of steps during a gradual increase of treadmill belt speed including running velocities. Stick diagram decomposition of the first step shows the smooth transition from standing to stepping. Conventions are the same as in Fig. 1.3. (**b**) Representative example of hindlimb kinematics and EMG activity recorded during continuous locomotion in the forward (*left*), backward (*middle*) and sideway (*right*) direction. The same limb from the same rat corresponding to the leading (*front*) limb during sideway stepping is shown for the three conditions. Data are represented as in Fig. 1.3, except that stick diagrams are shown in three dimensions, with the main plane oriented with the direction of treadmill belt motion. *VL* vastus lateralis, *St* semitendinosus muscles [28]

recovery of neuronal networks responsible for central pattern generation, i.e., CPG networks [69, 70]. Even in humans, the recovery of locomotor function after a severe SCI is still thought to heavily rely on CPGs present in the human spinal cord [71]. We instead argue that the recovery of impressive locomotor capacities with step training (see Sect. 1.5) under the presence of

electrical and/or pharmacological stimulation relies on the ability of the spinal circuitries to utilize sensory ensembles as a continuing source of motor control and as a substrate for learning [12, 72]. Indeed, the data presented in this review show that the spinal cord acts as a smart processing interface that continuously integrates multisensory input to control its motor output, both acutely and chronically. Thus, beyond representing an automated machinery that produces stereotyped reflexes and CPG-like activity, we argue that evolutionary pressures engineered the spinal brain to process complex patterns of afferent input and utilize this information to make decisions about how to maintain successful locomotion. Moreover, repetitive exposure to specific sensory patterns with practice allows for the significant optimization of these sensori-motor processes whereby spinal circuitries can learn to produce optimal motor states in the total absence of brain input.

Here, the concept of optimal motor states is not restricted to stereotyped stepping patterns with alternation between extensor and flexor muscles, but instead it encapsulates the rich repertoire of motor behaviors underlying activities of daily living. In fact, even when deprived of any supraspinal influence, spinal circuitries can recognize task-specific sensory input and instantly modulate or transform the patterns of muscle activity to execute a variety of motor tasks ranging from standing, walking, running, stepping backward, or even stepping in a sideward direction [28]. Currently, the power of *sEMC* for the production and training of motor functions after SCI is not well recognized or exploited to the level of its potential [44] (Fig. 1.1).

1.4 Impact of Chronic SCI on the Function of Spinal Circuitries

What is the impact of the chronic absence of weight-bearing and normal activation patterns on the functional capacities of spinal locomotor systems? In general, it is thought that severe spinal cord damage induces a short period of complete paralysis, which is followed by a slow and incomplete recovery of function that eventually reaches a plateau in the chronic state of the injury. Overwhelming evidence against this oversimplified view, however, has accumulated in recent years. A large number of detrimental changes in cell properties and circuit connectivity have been described in the chronic state of SCI. For example, Vinay and his coworkers [73] found that a complete SCI leads to a downregulation of the potassium-chloride co-transporter-2 (KCC2) in motoneuron membranes, which, in turn, results in a substantial positive shift in the membrane equilibrium potential of chloride. This shift has a dramatic impact on neuronal function by changing the effect of inhibitory input into excitatory input, which could contribute to the development of spasticity [74].

At the network level, a series of anatomical and neurophysiological observations in animals [75–77] and humans [78, 79] suggest that after a severe SCI the spinal circuitries responsible for the control of stepping and standing undergo a major remodeling, a process that continues to evolve for years after the SCI [80]. After the interruption of descending pathways, the severed axonal fibers degenerate, creating vacant synaptic territories that become partially reoccupied by sprouting intraspinal fibers [75, 77]. These new synaptic connections likely lead to the formation of aberrant circuits that may misdirect neural information towards inappropriate motor networks during movement [54, 81]. Indeed, we observed that rats with a complete SCI show a significant deterioration of stepping capacities in the chronic state of the injury [28]. Whereas the combination of electrical and pharmacological stimulations enabled coordinated locomotion with plantar placements at 1 week after the injury, the same rats exhibited poorly coordinated stepping patterns with large variability when tested at 9 weeks post-lesion (Fig. 1.6a, b). Compared to noninjured rats, these animals displayed a large increase in the expression pattern of the activity-dependent neuronal marker c-fos in all lumbar and sacral segments (Fig. 1.6b, d) [28]. This marked increase in the number of cells contributing to stepping in chronic spinal animals suggests that new nonfunctional circuits progressively form after a severe SCI, and that these abnormal connections engage inappropriate circuits to produce locomotor

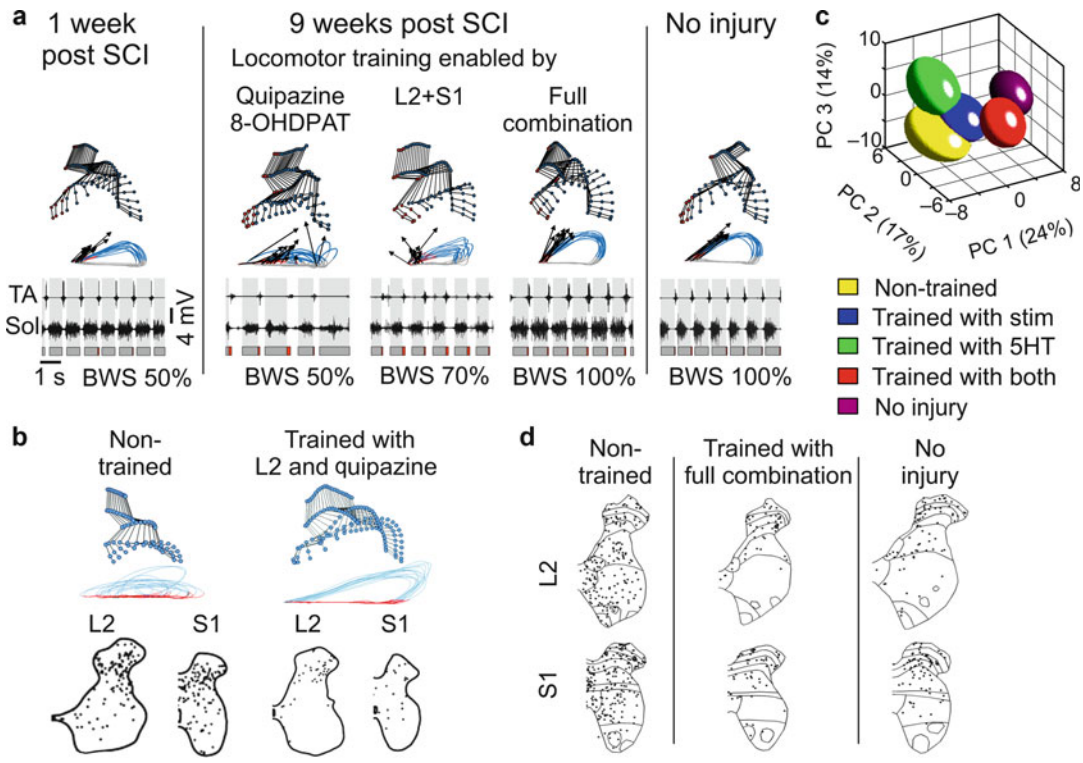

Fig. 1.6 Locomotor training enabled by selective pharmacological and/or electrical stimulation paradigms promotes the recovery of intervention-specific gait patterns in rats deprived of supraspinal input. (**a**) Representative illustrations of EMG and kinematic features during stepping under the full combination (stimulation at S1 plus L2 and quipazine plus 8-OHDPAT) 1 week post-injury (before training; *left*) and after 8 weeks of training enabled by pharmacological and/or electrical stimulation (*middle*). A similar representation is shown for a noninjured rat (*right*). Conventions are the same as in Fig. 1.3. (**b**) Representative illustrations of kinematic features during stepping in nontrained rats and rats trained with EES at L2 and quipazine administration. Below representative camera lucida drawings of FOS-positive neurons in spinal segments L2 and S1 of a nontrained SCI rat and a SCI rat trained with stimulation at L2 and quipazine administration. (**c**) Three-dimensional statistical representation of locomotor patterns based on principal component analysis applied on a large number of gait parameters ($n=135$). Each group ($n=5$–7 rats) clustered in distinct locations, revealing that each locomotor training paradigm promoted the recovery of unique stepping patterns. (**d**) Representative camera lucida drawings of FOS-positive neurons in spinal segments L2 and S1 of a nontrained SCI rat (*left*), a SCI rat trained with the full combination (*middle*) and a noninjured rat (*right*) [28]

patterns when pharmacological and/or electrical interventions are administered. These results are compatible with the emergence of abnormal reflexes [78, 79], unintended movements [81] and spasticity [82] in the chronic state of the injury in humans. Together, these results show that spared neuronal circuitries below a complete SCI do not remain unchanged. Instead, major plastic changes progressively take place post-lesion, which lead to a deterioration of the neuronal function in the chronic state of the injury.

In light of these changes, can step training enabled by locomotor permissive interventions direct the chaos of plasticity that spontaneously occurs after a SCI and can this use-dependent plasticity lead to useful changes associated with improved functional capacities?

1.5 Neurorehabilitation with Motor Control–Enabling Systems

Intensive rehabilitative training has shown the capacity to prevent deterioration of function and improve stepping and standing capacities in cats

with a complete SCI [83]. Similar activity-based approaches alone, however, failed to promote similar improvements in rats [84] and humans [21] with a severe SCI. As mentioned in the first section of this chapter, we surmised that the absence of robust activity during locomotor training is largely responsible for the poor effects of rehabilitation. We directly tested this hypothesis by training spinal rats on a treadmill under the presence of *efEMC* interventions, which encourage coordinated patterns of locomotion in the paralyzed hindlimbs.

In our first attempts, we only used a combination of lumbar (L2) EES and 5-$HT_{2A/C}$ agonist (quipazine) administration to facilitate locomotion during the training of spinal animals [85]. As mentioned above, each locomotor permissive system modulates distinct features of stepping behaviors. Accordingly, this specific combination promotes unique patterns of locomotion including enhanced extension components, in particular, in the distal extremities [29]. After 2 months of training, the rats displayed improved locomotor movements characterized by a low variability in kinematics features and the capacity to step for an extended period of time on the treadmill under the presence of pharmacological and electrical interventions. The rats, however, developed exaggerated stance phases with marked extension of the foot and toes during swing (Fig. 1.6b). The chronic repetition of a certain type of movement thus reinforced and indeed amplified the specifically trained stepping behavior. More recently, we tested the therapeutic potential of locomotor training enabled by lumbar (L2) plus sacral (S1) EES and agonists to 5-HT_{1A}, 5-$HT_{2A/C}$, and 5-HT_7 receptors (quipazine and 8-OHDPAT) [28]. Compared to lumbar stimulation and quipazine alone [85] (Fig. 1.6b), this combination enabled more normal stepping patterns and effectively promoted locomotion as early as 1 week post-injury (Fig. 1.6a). In contrast, the combination of lumbar stimulation and quipazine was not effective in encouraging locomotion until 2–3 weeks post-SCI [86]. After 9 weeks of neurorehabilitation, the spinal rats recovered the impressive capacity to perform full weight-bearing locomotion with features that were nearly indistinguishable from those underlying walking patterns of the same rats recorded before the injury (Fig. 1.6b, c). Rats trained with electrical stimulation alone or serotonin agonists alone developed specific patterns of locomotion, but these interventions failed to prevent the deterioration of functional capacities at the chronic state of the injury (Fig. 1.6a–c). Collectively, these results suggest that the repetitive activation of unique combinations of sensorimotor circuits under the influence of distinct electrical and pharmacological stimulations and through task-specific sensory patterns lead to the selection and reinforcement of those neuronal networks in an activity-dependent manner [12]. As exemplified in cats [7–9, 87], the rodent spinal motor circuitries deprived of any supraspinal influences can learn the task that is trained and practiced.

This concept of Hebbian plasticity among spinal sensorimotor pathways is consistent with the changes in c-fos expression patterns underlying continuous locomotion of trained rats. Regardless of the intervention used to facilitate stepping, we found that rats exposed to locomotor rehabilitation exhibited a substantial decrease in the number of c-fos positive neurons compared to nontrained animals [28, 85] (Fig. 1.6b–d). However, the detailed features of c-fos expression patterns in the lumbar and sacral segments depended significantly on the selective intervention provided during training, i.e., each neurorehabilitation procedure promoted specific gait patterns that were presumably produced by unique combinations of neuronal networks (Fig. 1.6c). These results demonstrate that the recovery of stepping ability after a complete SCI does not result from the activation of an ontogenetically defined hardwired circuitry that persists and recovers post-injury. Instead, specific combinations of locomotor training, pharmacological, and electrical stimulation interventions induce novel activity-dependent anatomical states that reflect the ability of spinal circuits to learn and that can promote high levels of functional recovery without any supraspinal input in adult rats.

1.6 Development of Operative Neuroprosthetic Systems

As described above, different stimulation parameters and sites of EES can modulate specific aspects of the spinal locomotor output. In addition, with varying levels of activation of specific pharmacological receptors, *fEMC* strategies can be used to selectively activate different combinations of locomotor circuits within the lumbosacral spinal cord. For an individual to take full advantage of this modularity, however, semiautomated control systems including feedback loops will be necessary [88]. The flexible manipulation of *eEMC* and *fEMC* to modulate movements will further require the development of a device that can receive mechanical and/or biological signals that, in turn, can modulate an output of chronically implanted epidural electrode arrays capable of achieving the desired movement. There are multiple solutions with varying degrees of complexity and sophistication that can be utilized to achieve this goal. As a starting point, we have developed an on–off system that can detect the intent of a rat with a complete thoracic spinal cord transection to step based on EMG signals from the forelimbs [89]. Once the criterion EMG pattern from multiple forelimb muscles is recognized, an output signal is sent to a stimulator that activates the lumbosacral spinal cord epidurally with a preselected frequency and voltage level. This approach needs further development so that different combinations of electrodes from the chronically implanted epidural electrode array can be activated at a selective stimulation intensity and frequency to achieve the most effective standing or stepping in a subject at any given time during the recovery from injury. In humans, the neural interface must be able to accommodate differing levels and types of dysfunction within and across subjects. Thus, this interface must have different degrees of automaticity in the interpretation of feedback signals. For human subjects, a hand-controlled "joystick" could be designed so that the user could manually control the stimulation parameters (with predefined limits for safety) when the person intends to stand, walk, or perform other sensorimotor tasks.

A more advanced but complex and invasive approach could capitalize on established concepts from brain–machine interface systems. Neural states can be readily extracted from the modulation of cortical ensembles to detect the intent to perform a range of tasks [90–92]. In turn, these neural states can be readily exploited to modulate the patterns of stimulation in a neuroprosthetic epidural electrode array to stand, walk, or adjust locomotor movements to the requirements of the external world, e.g., cross an obstacle or, climb stairs.

In the technical development of interventions to facilitate motor recovery after a SCI and many other degenerative neuromotor disorders, there will inevitably be the need for a paradigm shift in the ability to monitor and quantify a wide range of motor tasks, including postural control, locomotion, and fine motor skills. Although the technical capability and expertise to accomplish such assessments is well established in basic research laboratories, realization of these technical capabilities in clinical rehabilitation settings is minimal. This limitation, in itself, has minimized advances that could be made from a research, and also a patient's, perspective. For example, it is clear that the technical capabilities exist to quantify all of these types of movements and to provide immediate feedback to the patient that can serve as a major motivational stimulus and also immediate knowledge of whether a certain intervention has any impact on the ability to perform a given motor task. This type of information is equally available to the researcher, clinician, and patient. A key to capitalize on this type of technology will involve the design of smart robotic interfaces to enable the performance of movements in severely affected individuals (see Sect. 1.3.3).

1.7 Perspectives for Viable Clinical Applications

We are approaching a new and exciting era for the capability to recover significant levels of motor control after a severe SCI and the onset of a variety of degenerative motor diseases. This optimism is based on years of progression of the

evolution of new perspectives and concepts related to how the nervous system controls movement. These new fundamental concepts provide the basis for developing new strategies that combine biological and technical breakthroughs. For example, we know that very complicated and detailed motor tasks can be performed with little or no supraspinal control due to the fact that most of the neurophysiological details are embedded and accomplished within the circuits of the spinal cord [93]. Furthermore, we now understand that these neural circuits remain functional after most spinal cord injuries and that they can be revived with appropriate activity-dependent interventions [28, 83]. In this chapter, we have documented various observations supporting these positions, and we have demonstrated that access to this surviving circuitry can be gained by electrically stimulating the lumbosacral spinal cord epidurally and by facilitating the spinal circuitry pharmacologically. Most importantly, however, a central component in realizing improved motor control using these *motor control–enabling strategies* is the potent activation of the circuitries underlying the motor task that is being relearned. Specifically, the strategies will have minimal or no positive effect in relearning a motor skill if the circuitry that generates that motor skill is not recruited in the presence of EES and/or pharmacological facilitation. Our challenge in the near future is to develop procedures that will improve the efficacy of these interventions by understanding in more detail the basic biology of these enabling techniques. Which circuits within the spinal cord are being activated to perform a given task and what neurotransmitter systems are critical for these circuits to successfully generate the desired movement with the patient having the control and confidence necessary to execute the strategies in day-to-day activities? The application of these strategies with further developments in robotics will have to occur to fully realize the impending, remarkable potential that remains after even some of the most severe injuries to the neuromotor system.

Conclusions

Spinal cord damage severely impacts sensorimotor function and thus the quality of life of affected individuals. After a SCI, improvement in sensorimotor functions can be achieved via a number of activity-dependent rehabilitative strategies, e.g., task-specific sensorimotor training, robotic interface systems, pharmacological facilitation of the spinal neural circuitries, and spinal cord epidural stimulation. Although each of these interventions can have a positive impact on the recovery process after a SCI, the efficacy of these interventions can increase tremendously when they are administered in combination. Consequently, future efforts should consider a multidimensional approach in developing and refining neurorehabilitative approaches for individuals with severe sensorimotor dysfunctions after a SCI or other debilitating conditions.

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Application Issues for Robotics

2

Markus Wirz and Ruediger Rupp

Abstract

This chapter covers the various aspects related to the application of rehabilitation robots. The starting point for developing any novel therapeutic device should be the specific requirements of the users. Users in this case are patients with neurological conditions but also therapists. Both claim different requirements, which need to be united. Modern neurorehabilitation is grounded in the premise that activity is beneficial. Robots are valuable tools to apply intensive active training in terms of the number of repetitions and task specificity. The complexity of robotic devices is mainly determined by the residual functions of the patient. In patients with muscular weakness, a simple weight support system might be sufficient, whereas in patients with severe paralysis, actively driven exoskeletons with multiple degrees of freedom are necessary. Robots must comply with general regulatory and safety standards. Robotic devices have to be adjustable to a wide range of anthropometric properties and to the amount and the characteristics of their impairment. The user-friendliness of the robot's human–machine interface consisting of the mechanical, the control, and the feedback interfaces determines whether a device becomes integrated in the rehabilitation program or not. An inherent advantage of the more complex rehabilitation robots is their ability to use angular and force sensor signals for assessment and documentation. These are important to objectively control the course of the training, to legitimate and shape the training, and to document progresses or deteriorations. In the future, devices

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which allow the continuation of a robotic therapy at home will further enlarge the range of applications.

Keywords
Patient and therapeutic requirements • Complexity vs. usability • Customization • Regulatory and safety issues • Human–machine interfaces • Robotic assessments • Home application

2.1 Introduction

This chapter focuses on aspects which need to be considered when technologies are applied to subjects. Technical devices are developed in order to support humans in many ways. Tower cranes are able to lift and manipulate heavy loads. Submarine robots work in an environment which is not compatible with human life. Smart controllers inflate airbags within split seconds in order to protect the driver of a car. There is also a long list of technical devices which have been applied in medicine, e.g., infusion pumps, blood pressure measuring devices, or electric stimulators for the treatment of pain. One kind of machines is driven by the force of the person using it, e.g., strengthening apparatus. These are considered as passive devices. Other systems include electric drives or other actuators, e.g., pneumatic devices, and can apply supporting, assisting, or resistance forces. Such actuated devices are referred to as active systems. Devices can act on their own by means of a controller which follows predefined algorithms, e.g., for the surveillance of vital functions such as heart rate monitors. Not only in daily life is the technology becomes smarter but also in the field of treatment and rehabilitation. After an accident or a disease, highly sophisticated devices are applied. These devices help the human physician to draw meaningful conclusions out of a number of figures or to eliminate muscle trembling during a subtle surgical intervention. The focus of this chapter is set on rehabilitation technologies including robotic devices which became established within the last decade for patients with neurological conditions, e.g., spinal cord injury or stroke. These robotic assistive devices enable to start a functional and goal-oriented training earlier as compared to the conventional approaches. In addition, an intensive application of adequate afferent feedback and a high number of repetitions of functional movements support the rehabilitation of function such as walking or arm use. Robots not only perform movements repeatedly, but they allow the introduction of task variation and provide feedback in order to maintain an adequate level of challenge for the patient. The issues discussed may partially also be valid for other types of rehabilitation and assistive technologies.

The starting point for developing any new device should be the specific requirements of subjects. Subjects in this case are patients with neurological conditions, and it is intended that they will profit from a more effective way of training, meaning that they achieve their individual goals within a shorter period of time. Subjects are also therapists who, by using robotic devices, experience physical relief and can use assessment systems – which are less prone to subjective influence – for quantification of functional improvements. Patients and therapists claim different requirements which need to be united in a meaningful way. Those requirements should be in the focus as opposed to technical feasibility which does not always comply with a rehabilitative demand. This may be different if robots are in the developmental stage; however, the potential clinical application has to be borne in mind throughout the whole developmental process.

Besides the specifications which are framed by patients and therapists, there are several technological issues and principles regarding the clinical application of therapeutic robots. Both aspects will be covered in the next sections.

2.2 Human Issues

2.2.1 Patient

The clinical presentation of a spinal cord injury (SCI) or a stroke comprises motor weakness or complete paresis, complete or partial loss of sensory function, and a more or less pronounced derailment of the vegetative functions [1–3]. The latter include lack of bladder and bowel voiding function, lack of blood pressure adaptation as a response to upright position (orthostatic hypotension), etc. Patients in the early stage after such an event generally have a poor condition which needs to recover to a certain extent before intensive rehabilitation can be initiated. Beside the vegetative symptoms, patients have a reduced vital capacity which may become evident in upright standing and during exercise. Also in the acute phase after stroke, patients' stability in terms of circulation, mood, and motivation is impaired. Robotic devices should account for those instable situations in such a way that subjects can be evacuated from the device within a short period of time. Fittings must be designed that they can be removed quickly, and the whole device must be removable in order to get access to the patient or to transport an unconscious patient from the device without constraints. Patients with SCI have a marked propensity to faint once they are elevated in an upright position. The possibility to position patients horizontally when the blood pressure starts to drop is therefore crucial. After a traumatic SCI, the spine becomes instable in most cases. In addition, extremity fractures can occur. Rehabilitation therapists must make sure that the musculoskeletal system is stable enough to tolerate the applied load and forces, as with robotic devices which are used to train walking function. This holds also true in cases where fractures and instabilities have been treated surgically. The partial lack of sensibility has to be taken into account when a patient with a neurological condition is trained. After every training session, the spots where forces are exchanged between the robotic device and the patient have to be inspected visually. Any sign of strain must be documented and carefully controlled. Robotic devices enable intensive and long training sessions with a large number of repetitions. Some patients may react to that amount of workload with signs of overload, e.g., joint swelling, increased spasticity, or pain. In older patients with a known history of osteoporosis, the training intensity has to be set carefully. The repeated stress on bony structures may result in a fatigue fracture.

Patients who experience an impairment of their cognitive function, e.g., distorted self-perception, might not be able to cooperate with a robotic device. Even though some devices use virtual environments which are very like the real world and the control of these environments is intuitive, patients still require the ability to abstract. In order to completely cope with robotic devices and to make use of the numerous ways of training modalities, patients need to have no more than mild cognitive deficits.

The population experiencing a SCI is becoming older [4]. Patients with stroke are typically of advanced age. These subjects are generally not used to working with new information technologies and may be reluctant to train in a robotic device. Without complete confidence in a training device, the success of the intervention is endangered. It is therefore important that patients are able to acknowledge robotic training as an important component on the way to their maximum possible independence. For future generations, who are much more used to computers and robots from their lives before the neurological incident, this item might be less an issue.

2.2.2 Therapist

Usually, the usage of robotic devices is not a subject in basic physiotherapy training. The reason for that is that the field of rehabilitation robotics is growing rapidly, and a large number of new devices are being developed every year. Different robots are available, and to date no standard devices are established. However, the proper use of robotic devices is critical for the success of the

training. A sufficient period of time should be scheduled for the instruction of therapists. It is important that every therapist does as many one-to-one trainings under supervision of an expert user as needed until she or he is able to apply the device accurately and safely. It is recommended that in a given institution, special safety procedures become defined. It must be ensured that every person who trains with a robotic device has been instructed properly beforehand. The emergency procedures should be trained practically. Liability issues in case of an accident must be clarified. Some devices are easy to use, and a basic instruction is sufficient. However, other devices require extensive training and experience in order to respond to variations and irregularities. It must be evaluated if multiple or only few therapists are assigned to use a device. In the case of a large number of users, a single therapist will never become confident with the device. On the other hand, when only few staff members know how to run the device, experience can be accumulated in a shorter period of time. Additionally, knowledge exchange is easier among a smaller group of users. There are also mixed models where an experienced user does the setup for a given patient during an initial training session. The subsequent trainings will then be performed by a therapist with less specific knowledge, usually the therapist who trains the patient with non-robotic interventions. If required, the more experienced colleague provides supervision in that phase. The advantage of such a model is that a therapist who knows a patient from the conventional therapy can also perform the robotic training as opposed to a therapist who is skilled using the robot but does not know the peculiarities of the patient.

2.2.3 Principles of Robotic Training

At the current stage, robots do not introduce completely new rehabilitation strategies [5]. Robotic devices rather enhance and amend existing approaches. Electromechanical devices can generate and apply greater forces for a longer period of time and follow more precisely predefined trajectories. In addition, robots can measure far more accurately and free from subjective perception than human therapists. However, robotic devices usually measure forces only in one plane or degree of freedom. A human therapist is able to perceive forces acting in multiple directions, in particular rotational forces. There are also approaches where a patient can train on a robotic device at home without direct supervision of a therapist. In that case, patient and therapist are connected through the internet, allowing the therapist to monitor the progress of the patient and adapt the training protocol [6].

The question pertaining to the principles behind robotic training is the question regarding the principles of neurological rehabilitation. In recent years, there have been many reports on the principles and strategies on which neurological rehabilitation is based [7–13]. Most reports which have been published regarding this topic relate to the stroke population since this is one of the most common conditions for acquired neurological disability. Nevertheless, from an empiric point of view, most of the described principles can be transferred to other groups of patients, e.g., SCI, multiple sclerosis, or Parkinson disease. One major and persistent principle of neurological rehabilitation is that of motor learning [11, 12, 14]. During rehabilitation, patients have to relearn motor tasks in order to overcome disability and limitations in the completion of daily activities. These processes are initiated by task-specific training which supports either true recovery of lesioned areas within damaged neural structures or compensation [11, 15]. Regardless the underlying mechanism, the principles of motor learning apply in both cases [12, 16]. These principles comprise among others: task specificity, goal orientation, meaningfulness, and most importantly, a high amount of practice. Rehabilitation robots allow task-specific training early after a neurological incident. For the training of gait function, robotic devices are applied which support the patient to perform leg movements during walking. At such an early stage, patients cannot stand up independently and are not or only partially able to perform leg movements on their own. Studies have shown that adequate proprioceptive afferent input is critical for training functional tasks, e.g., walking in patients with SCI [17–20]. The reciprocal

unloading and loading of the legs as well as hip extension seem to be task-specific afferents for the appropriate facilitation of neural structures which are involved in the control of walking.

Also, devices for the training of upper limb functions are most valuable for the rehabilitation. These robots assist patients to follow task-specific trajectories. There are upper extremity robots which are designed for the use in a very early stage when the patient still lies in his bed for most of the time [21]. A number of devices work in conjunction with a display on which the patient completes meaningful tasks of daily living within a virtual environment [22]. An advantage of such a training using virtual environment is that patients do not focus on the learning of specific movements itself but on the effects of these movements. This so-called external focus is beneficial for the learning of task automatism [23, 24]. Other approaches aim at minimizing the lack of coordination between shoulder and elbow joint during reaching movements [25].

Without the support of electromechanical devices, patients would not be able to start these exercises at an early stage or may get exhausted after a short while and few repetitions. Compared to the human therapist, who might get tired while providing extensive amount of support to patients who are dependent on help for completing task-oriented exercises, robotic devices allow longer training durations and a higher number of repetitions. Studies have shown that augmented exercise results in an improved outcome [26]. However, it seems not sufficient just to repeat a specific movement or completion of a task. Task variability improves the acquisition of that task [14]. Robotic devices which have been developed so far offer numerous ways to adapt and vary training. The introduction of virtual environments wherein the patients take over control enables multiple ways of tasks and task variation within the same robotic setup. Further possibilities to adapt tasks are the number of degrees of freedom which are under control of the patient. The amount of support to control a given degree of freedom, e.g., hip flexion or extension, could be adapted according to the patient's abilities. Robots may not only provide assisting forces but in later stages also resisting forces. Increased resistance perpendicular to a defined trajectory helps to guide a patient through a desired movement path. The changes of movement velocity entail a different level of challenge. Walking within a robotic device allows dynamic walking at a nearly normal walking speed as opposed to walking within parallel bars or other walking aids where speed is markedly slowed down. Walking speed during training is considered important to warrant further improvements [27].

In order to control movements and for safety reasons, robots are equipped with sensors. These sensors measure positions, velocities, and accelerations on one hand and torques and forces on the other. These signals can be used for a specific feedback for both patients and therapists. Feedback can be provided using various cues such as auditory, visual, or haptic. Based on the forces patients exert on the machine selected actions occur in the virtual environment, e.g., an avatar walks left or right or a virtual hand grasps an object. In such a way, robotic devices act as an interface between the real and a virtual world. The raw signals, however, serve the therapist to survey the level of activity of the patient and to document the progression within a training series. However, to date, only little is known how these figures translate to unsupported activities without a robot.

After all, it is the skill of the human therapist to integrate various signals and expressions and hence to perceive the actual state of the patient. Based on those findings, therapists will shape exercises and set up conditions in a way that patients are challenged and motivated without being overstrained. For therapists and patients, robotic devices offer a useful tool to implement the principles of neurological rehabilitation from the very beginning of rehabilitation and to measure and control the progress.

2.3 Technical Issues

2.3.1 Complexity of Robotic Devices

The main goal of a task-oriented neurorehabilitative training is to enhance neuroplasticity by enabling patients with neurological impairments

to perform movements of activities of daily living. A key factor for the success of the training is the number of repetitions and the generation of physiological afferent stimuli [28]. For achieving a meaningful improvement of motor functions by mass practice therapy regimes, supportive devices are beneficial and valuable tools. The complexity of these devices is mainly determined by the residual functions of the patient group in the focus. In patients with minor to moderate impairments, passive devices may be sufficient to enable the execution of relevant tasks. This is especially true for the upper extremity, where passive devices like the Swedish Help Arm (also known as Helparm, Swedish Sling, Deltoid Aide, or OB Helparm), the Freebal device, or the recently commercialized ARMON orthosis (Microgravity Products BV, Rotterdam, Netherlands) are used to reduce or eliminate the effects of gravity and thereby allowing the user to effectively use his weak muscles for performing functional tasks like eating, drinking, or grooming. These devices may also help the patient retain or reestablish important proprioceptive information about the achievable workspace that the impaired limb should be able to reach as recovery progresses. Since the purely passive devices are relatively simple in their construction, they are affordable also for the patients themselves and are easy to use. The main disadvantage of these simple passive devices, which are mainly based on springs or counterweights, is that they basically provide a constant amount of weight reduction regardless of the position of the extremity. Even in positions of the arm, where less or no support is necessary, the patient is supported. Additionally, the desired movement trajectory cannot be predefined, and therefore the user may train a wrong, unphysiological movement pattern. In the worst case, the patient cannot complete a desired movement at all. To overcome this limitation, passive devices are often used during occupational therapy sessions under supervision of a therapist, who actively supports the movements to ensure that a physiological movement trajectory is achieved.

To free the therapist from this physically exhausting and mechanistic work of manually guiding the movements and to perform a therapy in a more standardized way, active robotic devices with integrated actuators have been introduced. The active components of the robots consist nowadays mainly of electric motors or pneumatically driven actuators in combination with spindles, gears or bowden cables. Within the class of active devices, there are technically more simple devices, which are mainly based on an end-effector approach, and complex devices, in which several degrees of freedom (DOF) of several joints are actively driven independently.

The end-effector-based systems use dedicated hand grips or footplates and guide the movements of the hand or foot in space [29–31] (Fig. 2.1). Their main advantage is their easy setup since no technical joints of the device have to be aligned with the anatomical joints of the human body. Furthermore, they only use one or two drives per extremity to generate a two-dimensional planar motion. However, the movements originate from the most distal segment of the extremity, and therefore – though the kinematic movement pattern looks similar to the physiological situation – the kinetics of the generated movements may not be perfectly physiological [32]. However, this seems to be crucial for the success of the therapy [20]. Additionally, in end-effector-based robots, only information about forces and/or position of the most distal part of the extremity is available, which may be too unspecific for control of a physiological kinetic and kinematic movement trajectory. Examples of machines based on the end-effector approach for the upper extremity are the MIT Manus [33] approach and for the lower extremity the gait trainer [34] (Fig. 2.1).

A physiological movement of all joints of an extremity can only be achieved by the use of active drives, which support the movements of every DOF of a dedicated joint. Additionally, an individualized setup of a joint and movement phase–related resistance is only possible with actively driven exoskeletons. Locomotion robots are often constructed as actuated exoskeletons which operate in conjunction with a system for partial body weight unloading and a moving treadmill [35–38]. Since active components form the most expensive parts of a robotic device, usually a compromise between costs and functionality in terms of

Fig. 2.1 The gait trainer GT I assists the patient during gait training using an end-effector-based approach combined with a system for partial unloading of the body weight (Photo courtesy Reha-Stim, Berlin, Germany. Used with permission)

perfectly following a given trajectory has to be made. Therefore, robotic locomotion training machines are mainly generating movements in the sagittal plane, whereas movements in the frontal or transversal plane are restricted to passive movements. A general challenge of the application of exoskeletons is their proper adjustment and alignment to the anatomical constraints of the different types of joints. Due to their mechanical complexity, the exoskeletons are often time-consuming in their initial setup and in everyday applications. Examples for actively driven exoskeletons are the Lokomat and Lopes devices for the lower extremity [18, 19] and the ARMIN and RUPERT devices for the upper extremity [39, 40].

Though actively driven, exoskeletons represent the state of the art of robotics technology they still leave room for improvement. Most of the systems are operating in an open-loop position control mode, which means that the actively driven joints follow predefined reference trajectories. Hence, the patient's movements are supported even during phases where the voluntary force of the patient would be sufficient. In these cases, the robotic device does not help, but hinders a patient to perform a movement task. Therefore a closed-loop "assist-as-needed" control scheme should be implemented into the active devices to challenge the patient as much as possible and to provide support, when and where it is needed [41]. Special focus should be put on the fact that a physiological movement does not consist of a highly reproductive movement pattern, but contains some variability [42]. Therefore, robotic devices should also incorporate a control scheme that does allow for small deviations from

the reference trajectory, e.g., like the nonlinear control scheme of the "force fields" implemented in the T-/Pneu-WREX device [43] or an impedance control scheme of the Lokomat [44]. In this way, a true cooperative robot-assisted therapy will become reality.

Nevertheless, all motor-driven orthotic devices only generate muscle movements in a passive way. However, from the results of pilot studies, it may be concluded that an additional activation of muscles by externally applied electrical currents leads to a better outcome [45, 46]. Therefore, the combination of functional electrical stimulation and an actively driven exoskeleton may enhance neurorehabilitation in the future. From a technical viewpoint, this combinatorial approach causes additional problems since two force generating systems – the muscles and the external drives – contribute to the same movement, and appropriate, robust control schemes have to be developed and tested.

However, such hybrid systems offer the possibility that not only a training of restricted or lost motor function can be performed but that the same system can also be used for substitution of permanently lost motor functions [47]. To achieve this functionality novel, lightweight drives and multichannel, dry electrode concepts have to be introduced.

2.3.2 Regulatory and Safety Issues

Robotic training devices and all of their subsystems including software are medical products and therefore have to comply with the International Standard IEC 60601–1, which has become the global benchmark for medical electrical equipment. Compliance with the IEC 60601–1 International Standard and/or the relevant national versions does not equal medical device approval. However, it is a recognized step towards medical device approval in nearly all markets across the world. As a result, many companies view compliance with IEC 60601–1 as a de facto requirement in most markets for product registration, "CE" "UL" "CSA" marking, contract tenders, and defense against claims in the event of problems, etc. The biggest upgrade in the third edition of the standard published in 2005 [48] is that it requires a manufacturer to have a formal risk management process in place which complies with ISO 14971. The following, not exhaustive list summarizes the most important standards that apply in particular to therapeutic robotic systems:

- IEC 60601–1–1: Medical electrical equipment – general requirements for basic safety and essential performance
- IEC 60601–1–2: Medical electrical equipment – electromagnetic compatibility
- IEC 60601–1–4: Medical electrical equipment – programmable electrical medical systems
- IEC 60601–1–6: Medical electrical equipment – usability
- ISO 13485: Medical devices – quality management system
- ISO 14971: Medical devices – application of risk management to medical devices

In parts, also the "ISO 9241: Ergonomics of human-system interaction," which contains substandards for user-centered design, applies to the design of robotic devices. It has to be emphasized that devices used in clinical applications do not necessarily need to be certified. However, if these noncertified machines are intended to be used in human applications, then in additional to the application to an ethical committee, a special insurance has to be procured, which covers the risks of adverse events caused by the application. By all means, a risk analysis according to ISO 14971 is mandatory to obtain ethical approval. In addition to the safety, manufacturers have to prove in clinical testing that the device is efficient in order to introduce the device in the European and American market. Since therapeutic robots are highly innovative products, in most cases, no data can be taken from literature which prove their efficiency. Therefore, clinical trials, preferably with a controlled and randomized study design, have to be performed. This fact has to be considered especially by small- or medium-sized companies, because a proper efficacy study may cause additional costs in the range of the device development before the introduction of the novel device to the market.

Within the framework of the IEC 60601, no dedicated substandard for robotic training devices has yet been introduced. Thus, the potential risks of harming the patient by the robotic training or the device itself have carefully to be considered. In general, active orthotic devices inherently bury the risk of causing severe injuries to the musculoskeletal system, e.g., bone fractures, capsule injuries, ruptures of muscle fibers, etc. This risk has to be minimized by a joint-related limitation of the maximum torque, which may be generated by the drives. Since a model-based estimation of the drives' torques is often not precise, enough redundant force or torque sensors have to be foreseen to ensure that the applied forces in every DOF stay in a safe range. In case the reference trajectory cannot be followed with maximum torque, the robot may either switch off, halt the movement, or limit the applied torque to a safe amount. In case of end-effector-based robotic systems, only the net force of several joints can be measured, which may lead to false-switch-off episodes of the machine or in the worst case to an exceeding of safe torque limits.

The most apparent adverse events of robotic devices in particular of active exoskeletons for locomotion training are skin erythema [49]. Though skin erythema is not a life-threatening condition, it may severely affect the compliance of the patient since the training may be interrupted a few days to allow for healing. Therefore, the main focus of the mechanical design of robotic devices has to be put on the parts that are in direct contact with the patient. It is highly recommendable to avoid the occurrence of shear forces in the orthotic components with direct skin contact by design, in order to minimize the risk for skin erythema in case of misalignment of the human and the machines joint centers.

Depending on the onset of training after a CNS lesion and the cardiovascular status of the patient, episodes of presyncopes or syncopes may occur during verticalization for locomotor training. For adequate handling of a patient in this case of a medical emergency, safety mechanisms for quick evacuation of an uncooperative patient are necessary.

Despite the automatic deactivation of the device in case of excessive torques, several emergency stops or enabling mechanisms have to be foreseen [50]. This will allow to check for attendance of the therapist or to give the patient the opportunity to stop the training at will. The latter is especially important if the patient performs the training on his own without supervision of a therapist.

Finally, the best safety concept of a machine is useless if it does not work properly due to defective mechanical or electrical components. Thus, highly qualified technical support has to be available to perform regular checkups and maintenance of the device.

2.3.3 Customization

Human beings vary to a great degree in their anthropometric data like size and weight and body proportions like length or widths of extremities. In order to perform the training in 95% of the population with one device, the machine has to be adjustable to a large degree and in many ways. This means that, e.g., in a locomotion exoskeleton, the length of the shank and thigh, the width of the pelvis, and the position of the trunk in all three directions must be adaptable to the individual patient. Also the continuous increase of the body mass index of the population of industrial countries represents a challenge for the level of adaptability of orthotic and robotic devices.

In addition to the differences in the properties of the body segments, the amount of impairment of neurological patients varies to a high degree. This applies not only to individuals within the same patient group but also between different patient groups. For example in incomplete SCI persons, the individual motor deficits may vary between subjects to a high degree, ranging from an isolated drop foot on one side to an almost complete loss of motor function in both legs. In stroke survivors, an increased spastic muscle tone may restrict the successful application of a robotic training. In traumatic brain injury, cognitive restrictions may occur additionally to

the physical impairments, which reduce the cooperativeness of the patient to a minimum. All these patient-related factors require an individualized setup of either the mechanical components of the machine or the training paradigms including feedback modalities. Since a regular therapy session is for personnel resources reasons limited to 45–60 min, every effort has to be made to keep the changeover time at a minimum. In reality, it takes one therapist about 5 min to prepare an end-effector-based robotic system to a patient and about 10–15 min in case of an exoskeleton. Much more time has to be reserved when the system is initially being set up.

Ideally, a machine would automatically adapt to different patients or not need any type of adjustment, since technical solutions have been provided which do not need manual interventions. Surprisingly, up to now, not a lot of effort has been made into this direction.

Also, the machine has to provide the possibility for setup of a large variety of training paradigms in order to broaden its fields of application. Most importantly, the function that is trained has to be the same as the one which should be improved. Recent developments in robotics for the lower extremities take this prerequisite into account and offer the possibility for training of stair climbing [22].

Nevertheless, it has to be kept in mind that practically none of the robotic devices are able to generate a fully physiological movement since not every DOF is equipped with an actuator and therefore cannot be controlled independently.

2.4 Human–Machine Interface

The user interface is a crucial part of a robotic therapy system since it determines to a large degree whether a device is regularly integrated in the rehabilitation program of neurological patients or not. Since the robotic systems are designed by research and development engineers, the user interfaces they design tend to be complicated and are not intuitive to understand. This is a general problem of the human–machine interface in almost every technical product intended to be operated by users with different technical expertise and non-technical professional background. Therefore, the ISO 9241–210 standard, which refers to "Ergonomics of human-system interaction – Part 210: Human-centred design for interactive systems" may be a good starting point to continuously improve the human–machine interface of a technical system. The ISO 9241–210 standard defines the framework of an iterative approach to involve end users during all stages of development of a product and explicitly includes parts which are important for any type of assistive technology.

It has to be emphasized that in rehabilitation robotics the term "end user" includes therapists as well as patients. Therefore, their feedback should be addressed very carefully by developers and implemented into novel designs for increasing the acceptance.

2.4.1 Mechanical Interfaces

Special attention must be paid to the mechanical interfaces between robot and patient. At the points where the robot is attached to the patient, high forces are transmitted depending on the mode of operation, i.e., either a robot assists the performance of movements or applies resistance forces. Force vectors have to be in accordance to the joint axes to allow pure rotational moments. The fixations of the robot have to be soft and mold to fit the respective part of the body in order to prevent the occurrence of pressure lesions or abrasions of the skin. In contrast to that requirement, the interfaces must transmit the forces without loss, e.g., by deformation or loose fit. This will ensure appropriate monitoring and modeling of the forces which exert on the patient. This is especially important pertaining to the assessment features of robotic devices. Fixations have to be adaptable to a wide range of anthropometrics. The usage has to be unambiguous and easy. This is of importance in the case when a patient has to be removed from the device quickly.

2.4.2 Control and Feedback Interfaces

An important component of the robotic system is the control interface, which is used by the therapist to set and adapt the most important therapy parameters like speed, amount of support or range of motion, and the feedback interface, which is used to provide the patient with information about the current status and the progress of the training. The control interface has to provide a very intuitive graphical user interface, which can be handled by an operator during the therapy. Special focus has to be put on the limitation of the number and the selection of an appropriate size of the control elements on the screen or on the operator panel to avoid faulty parameter settings. A general requirement of the robotic device often demanded by therapists is a high degree of "transparency," i.e., all of the machine parameters and options are accessible. However, a balance has to be found between maximal adjustability and easy handling. A possible way to meet both claims could be the common implementation of a standard and an expert mode together with the possibility for individualization of the graphical user interface.

Additionally to the graphical user interface, the input device is of crucial importance, since keyboards and mice are not easy to handle while having the patient in the focus, which often results in mismatch of parameter settings. Therefore, touch panel-based interface systems are a proper choice, in particular if the system is operated by a patient without supervision.

Since most of the robotic machines are equipped with sensors, which provide feedback about the current state and performance of the patient, the implementation of an automated adaptation scheme would free the therapist from continuously adjusting the relevant parameters of the therapy. In some cases, such an adaptation scheme may allow a robotic therapy without the need for continuous supervision by a therapist. However, in this condition, an adequate feedback has to be provided to the therapist and the patient so that both are informed what the machine is doing and to give them the confidence that both have the machine under control and not vice versa.

At the current stage of knowledge, the benefit of any neurorehabilitative approach seems to be based on the enhancement of spinal as well as supraspinal neuroplasticity. In order to enhance the supraspinal neuroplasticity, the patient has to be provided with an adequate feedback of his current performance, in particular in patients with sensory deficits. This is also most important for increasing motivation. Comparable to the situation in the control interface, the number of dynamic feedback parameters presented to a patient at a time has to be carefully chosen, since a patient is only capable to influence one or two parameters simultaneously. The feedback parameters have to be individualized, chosen according to the main functional deficit and the most severe impairment respectively. In case of the lower extremities, this might be a joint angle of a dedicated gait phase like swing or stance phase. The feedback should be provided in an absolute scale so that patients are able to compare their current status to their status at the end of the last therapy session. Also, feedback modalities other than visual may provide a more effective way to enhance the perception of the patient [51].

2.4.3 Assessment and Documentation

Rehabilitation robots are not only equipped with motors but also with multiple sensors. The signals deriving from these sensors are used to control the operation of the robots but can also serve as feedback and to measure certain biomechanical properties. Angular sensors can measure range of movement, force, or torque transducers' voluntary strength of muscle groups (Fig. 2.2).

Combined signals can assess resistance against passive movements and where in the movement arc resistance occurs. Changes in resistance can be attributed to impaired muscular tone or spasticity. Assessments are important to control the course of the training, to legitimate training and to document progresses or deteriorations. Measurement results can be used to monitor the

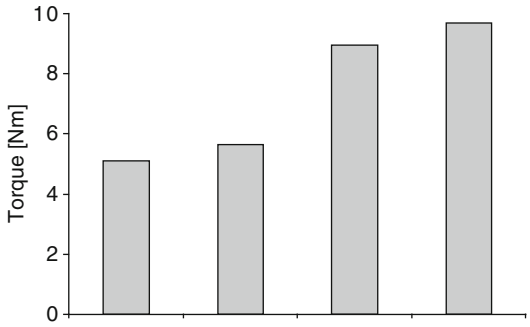

Fig. 2.2 Example of a series of force measurements recorded with the Lokomat system. The columns represent the maximum force in direction of unilateral hip flexion during successive sessions from a patient recovering from a Guillain–Barré syndrome (The respective value of healthy volunteers amounts to 74 Nm)

actual state of the patient and to shape the training accordingly. Some improvements may not be perceived by the patient but are accessible for the sensors. Prove of gains are important factors to generate motivation [52]. However, for any assessment, there are basic requirements which have to be met in order to be useful. Assessments have to be practical, reliable, valid, and responsive to changes. The measurement within a robotic device is easy to perform since it can be performed along with training or as a part of the training. Nevertheless, the assessment within a robotic device is restricted to that particular situation; for example, a robot is able to measure the range of motion in the sagittal plane, but its mechanical construction does not allow measuring in the other planes. Appropriate software can record and compare the results to previous measurements or normative values. On the first sight, it seems obvious that a mechanical sensor has a higher accuracy than a human examiner. A reduction of error leads to increased reliability. Still, there are more sources for error, e.g., the instruction of the therapist or pain may influence measurements. Few studies pertaining to this issue affirmed feasibility and reliability [53–55]. The concept of validity states that a given testing procedure aims at measuring a specified property. Regarding range of movement and voluntary muscle strength, there are no controversies as opposed to the measurement of spasticity. Even widely used tests such as the manual Ashworth scale (MAS) are under debate and may be improved if tested using a robot [56].

Although only few studies addressed the issue of the quality of assessment recorded by rehabilitation training robots, it can be stated that these devices measure practically and reliably. Appropriate measurements whose results can be transferred into daily functions need to be defined.

2.4.4 Continuation of a Robotic Therapy at Home

Due to increasing economical restrictions in the health care system, the length of primary rehabilitation is getting shorter, i.e., in the US Model Spinal Cord Injury System, the mean initial rehabilitation period of incomplete patients was 89 days in 1975, which continuously decreased to 28 days in 2005 [57]. It can be expected that this trend will continue in the future and lead to even shorter rehabilitation periods.

With the help of robotic locomotion, the sufficient intensity of task-oriented gait training can be sustained in the clinical setting, whereas a dramatic reduction of the quantity and quality of the training occurs after the discharge from the rehabilitation unit. This is especially true if patients return to their home in rural areas.

Though systematic experimental investigations are missing, it may be concluded from review of the literature that long-term, mid-intensity locomotion training over several months is more effective than the application of training protocols with high intensity for only a few weeks [58, 59]. However, up to now, only a few robotic training devices exist for home-based locomotion training. A simple transfer of the existing robotic devices to the patients' homes is not possible since most of them are mainly restricted to the application in a clinical setting due to their size, weight, and price. Furthermore, most of the devices have to be operated by skilled therapist.

The main challenges of therapy devices for application in the home environment are safety issues and the self-operation of the device by the users. This is especially true for the use of

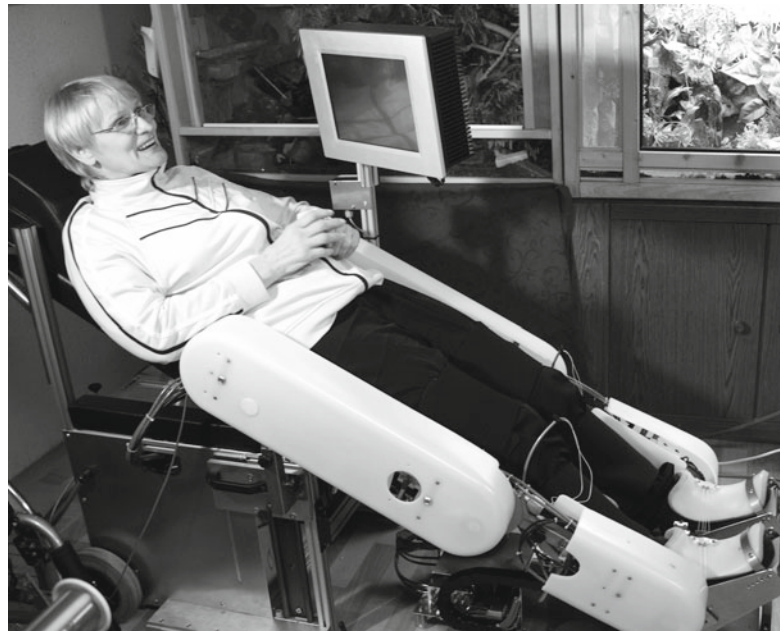

Fig. 2.3 The MoreGait is a pneumatically actuated robot for the training of ambulatory function. The device allows the use at the patient's home

locomotion training devices. Whereas in the clinical environment, the therapy is supervised by trained therapists, in the home environment, a safe operation without the need for supervision has to be guaranteed.

Only a few studies exist which describe the development and application of dedicated home-based robotic training systems [6, 60]. In locomotion robotics, a key method to minimize the risk of injuries is to put the user in a safe training position, like a semirecumbent position of the body in the MoreGait device (Fig. 2.3).

From the available results of real home-based training, it may be concluded that a safe application without a high risk for serious adverse events is feasible and that the outcomes of the training are in the same range than of systems used in clinics.

Nevertheless, a certain amount of supervision is necessary to assess the current status of the patient, to individually adjust therapy parameters to the patient's progress, and to help patients in solving small hardware problems. Here, internet-based telemonitoring methods are a cheap and effective tool for transfer of sensor data and diagnostic trouble codes of the machine to a centralized location, e.g., a large rehabilitation center or an outpatient clinic. Personal video conferences between a therapist and users or among different users are very valuable to keep patients motivated and to share experiences.

A very promising way of performing a home-based therapy, especially in patients with minor motor and cognitive deficits, is the use of conventional gaming consoles like Nintendo's Wii or Microsoft's Xbox in particular with the kinect option. The latter allows for full body movement analysis, and therefore a joint-specific therapy without the need for dedicated markers or sensors fixed to the body. The main advantage of using such type of technology is the nonlimited availability and the low price.

The gaming console–based training relies mainly on the feedback principles of the external focus, which is beneficial for the learning of task automatism. This form of training is motivating and provides the possibility for giving feedback about the current state of the functional impairment and the improvement over time to the user. However, up to now, only a few studies exist which evaluate the effect of a console-based training [61]. Furthermore, it has to be investigated in the future if the already implemented option for an internet-based multiplayer mode may be used for supervision of home-based training by a qualified therapist.

2.4.5 Financial Aspects

In the long run, every novel therapeutic or diagnostic procedure will only become a standard if a financial benefit for the health care or the welfare system can be achieved. This does not necessarily mean that the novel method has to be inexpensive; the maybe most prominent counterexample is MRI, which is a cost-intensive diagnostic method but which saves a lot of money by providing the basis for a major improvement in clinical decision-making.

The costs for the application of a robotic training device are composed of the device's costs, costs for personnel and their training, cost for infrastructural alterations, and cost for technical support. The costs of the device are mainly based on its complexity: the more complex, the more expensive. The price of a system is, to a large degree, dependent on the number of actuators it contains, since not only actuators but also sensors for safety issues have to be foreseen. Most of the people outside the neurorobotics field believe that – like in industrial robots – fewer personnel are necessary to perform a given therapy regime. This may be true for the lower extremities, where up to three therapists are needed to perform conventional body-weight-supported treadmill training. However, this does not apply to upper extremity training settings, where only one therapist is needed to perform manual training. By any means, one therapist is necessary to supervise the robotic training therapy.

The justification for implementing robotic training machines into clinical routine is mainly based on the fact that, in the given time frame for primary rehabilitation, the patient achieves a higher level of independence by the use of robotic therapies [62], which, in turn, may save costs for care and prevent secondary complications.

Nevertheless, in most countries, the robotic training sessions are not regularly compensated by insurance companies or sickness funds. Here, additional efforts are needed in the future from industry as well as from health care providers to give every patient with a motor disorder the chance to profit from such training.

2.5 Conclusion

For the successful development, application, and integration of robotic systems, engineers, clinicians, and end users have to work closely together. The devices' specifications should be founded on rehabilitative goals and neurophysiological knowledge. The characteristics of robotic devices should comply with the demands of patients and therapists. In order to justify the costs of rehabilitation robots, they should allow for adaptation to a wide range of patients with respect to anthropometrics but also with respect to different grades of capabilities reflecting the actual state of rehabilitation. In the beginning, supporting forces are required; in later stages, a device may apply resisting forces in order to challenge patients appropriately at every level. The setup and operation of robots should fit in a clinical setting. Signals from sensors enable sophisticated feedback modalities and the surveillance of training progression.

Robotic devices are very useful enhancements of rehabilitation interventions, offering additional training as well as measurement options. Studies suggest that an advantage of therapy by robotic devices, compared with conventional therapies, may be an increase in repetitions during training. Robot-assistive training devices therefore allow a massed practice therapy paradigm, which is intensive, frequent, and repetitive and accords with the principles of motor learning. They offer, for the first time, the possibility to systematically investigate dose–outcome relationships since the variability and the physical constraints of therapists and their limitations in terms of guiding movements of several joints simultaneously can be overcome.

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The Human in the Loop

3

Alexander C. Koenig and Robert Riener

Abstract

In classical man-machine interfaces applied to rehabilitation, the primary goal is to control the (bio)mechanical interaction between the human and the machine or environment. However, integrating the human into the loop can be considered not only from a biomechanical view but also with regard to psychophysiological aspects. Biomechanical integration involves ensuring that the system to be used is ergonomically acceptable and "user cooperative." Psychophysiological integration involves recording and controlling the patient's physiological reactions so that the patient receives appropriate stimuli and is challenged in a moderate but engaging way without causing undue stress or harm. In this chapter, we present examples of biomechanical and psychophysiological integration of patients that have been verified with the gait robot Lokomat.

Keywords

Human in the loop • Rehabilitation • Stroke • Gait training • Gait robot • Lokomat • Bio-cooperative control

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3.1 Introduction: Multimodal Interactions of the Human in the Loop

The use of conventional rehabilitation devices can be unsatisfactory because an efficient interaction between the technical system and the patient is often limited or impossible. Many advanced rehabilitation systems that include novel actuation and digital processing capabilities work in a "master–slave" relationship, thus tending to force the user only to follow predetermined reference trajectories without taking into account individual properties, spontaneous intentions, or voluntary

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efforts of that particular person. For instance, many actuated orthoses imply to patient's legs a predetermined motion pattern but do not react to the patient's voluntary effort.

A common problem of these conventional mechatronic solutions is that they are applied in an open-loop manner, not incorporating the human in a natural way. The patient or therapist just presses a button or moves a joystick, and a primitive "if-then" algorithm executes a predefined unidirectional (unilateral) action on the human. This action can be the simple execution of a fixed reference movement with the support of a machine, e.g., an orthosis or wheelchair, where the patient remains passive and his or her intentions and needs are ignored rather than involving the patient's complete sensorimotor system in an orchestrated manner. This action can also involve the display of other modalities, e.g., the presentation of visual or auditory instructions without taking into account the person-specific or task-specific context. During such unidirectional communication, biomechanical and psychophysiological effects on the human are usually not taken into account. Thus, the loop is not closed via the human in order to fit the device to the biomechanical or physiological state of the human, the human's behavior or intention, and environmental factors. The possibilities of the user to intervene are limited to "initiation" and "perturbation."

In contrast, novel rehabilitation technologies offer a new approach by placing the human into the loop, where the human is more than just a sender of the command to a device or the passive receiver of a device action. The human closes the loop by feeding back the biomechanical and physiological information to a processing unit. The interaction becomes bidirectional and the technical rehabilitation system takes into account the user's properties, intentions, and actions, as well as environmental factors. For example, an actuated orthosis should be able to detect the patient's effort and engagement in order to optimize participation and support the patient only as little as needed, or the audiovisual display signals of a training system should adjust to the alertness of the patient in order to optimize engagement and maximize motivation.

Integrating the human into the loop can be considered from biomechanical, physiological, and even psychological viewpoints (see Fig. 3.1) [1]. Biomechanical integration makes the rehabilitation system safe, ergonomically acceptable, and "user cooperative." Thus, with respect to rehabilitation robotics, the robot assists the human in a compliant way, with just as much force as needed so that the patient can contribute to the movement with his own voluntary effort. Psychophysiological integration involves recording and controlling the patient's physiological reactions so that the patient receives appropriate stimuli and is challenged in a moderate but engaging and motivating way without causing undue stress or harm. Including physiological or psychological interpretations into the loop makes the system "bio-cooperative."

In the following sections, we will discuss how patients during rehabilitation can be integrated into the control loop. We present examples for biomechanical, physiological, and psychological closed-loop controllers applied to the gait robot Lokomat (Fig. 3.2) [2]. In principle, all examples of human-in-the-loop control can be translated to other gait rehabilitation robots, such as the AutoAmbulator (www.healthsouth.com), the LOPES [3], the WalkTrainer [4], and the GaitTrainer [5], or even to rehabilitation robots used for the upper limbs, such as the ARMin [6, 7], the HapticMaster [8], or the MIT Manus [9].

3.2 Human Biomechanics in the Loop: User-Cooperative Control of Motion

3.2.1 Rationale

In early clinical applications, the Lokomat was only used in a position control mode and did not systematically allow for deviation from the predefined gait pattern. In position control mode, the measured hip and knee joint angles are fed into a conventional PD controller that determines a reaction to the current error value (amplified by a factor P). Another reaction to the derivative error (amplified by a factor D) is based upon the rate at

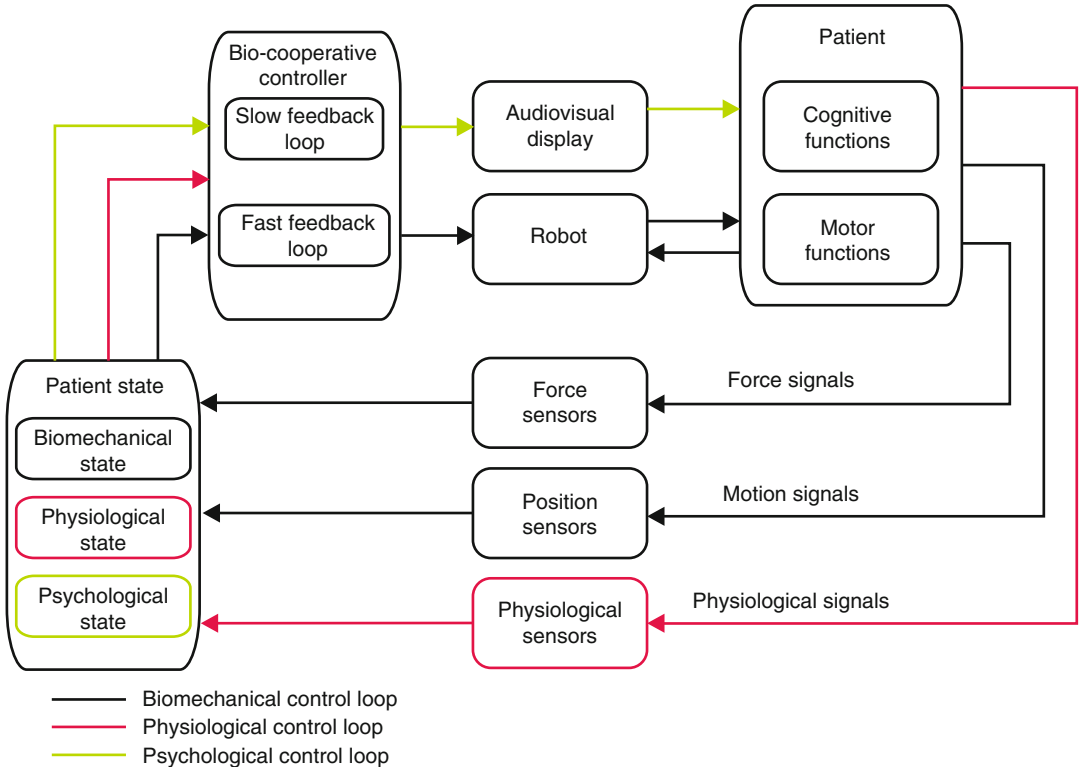

Fig. 3.1 The human is in the loop with respect to biomechanical (*black*), physiological (*red*), and psychological aspects (*green*). A fast feedback loop with update frequencies in the millisecond range controls the robot. A slow feedback loop adapts robot and audiovisual display with an updating frequency of several seconds (Adapted from Riener and Munih [1], (© 2010, IEEE); used with permission)

which the error has been changing. Controlling human biomechanics, i.e., human body limb motion, therefore, requires measurement of positions. Additional force sensing may be advantageous using more advanced control strategies (Fig. 3.3).

However, rigid execution and repetition of the same pattern do disregard the activity of the human subject or may even cause complete passivity, which is not optimal for learning. In contrast, variability and the possibility to make errors are considered as essential components of practice for motor learning. Bernstein's demand that training should be "repetition without repetition" [10] is considered to be a crucial requirement and is also supported by recent advances in computational models describing motor learning [11]. More specifically, a recent study by [12] demonstrated that intralimb coordination after stroke was improved by manual training, which enabled kinematic variability, but was not improved by position-controlled Lokomat training, which reduced kinematic variability to a minimum.

In response to this important finding, "patient-cooperative" control strategies were developed that "recognize" the patient's movement intention and motor abilities by monitoring muscular efforts and adapt the robotic assistance to the patient's contribution, thus giving the patient more movement freedom and variability than during position control [13, 14]. It is recommended that the control and feedback strategies should do the same as a qualified human therapist, i.e., they assist the patient's movement only as much as needed and inform the patient how to optimize voluntary muscle efforts and coordination in order to achieve and improve a particular movement.

Fig. 3.2 Patient exercising with the Lokomat® (Courtesy Hocoma AG, Switzerland, www.hocoma.com; used with permission)

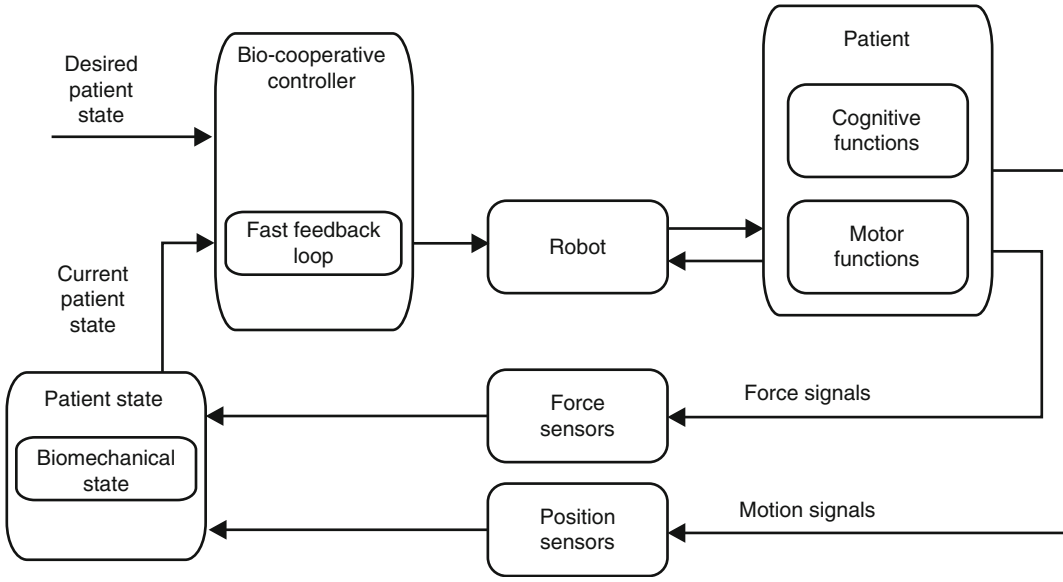

Fig. 3.3 The human in the biomechanical control loop. The user-cooperative controller provides a training environment where the human can actively control his/her movements. A visual display provides feedback about the quality of the movement (deviation between desired and actual one)

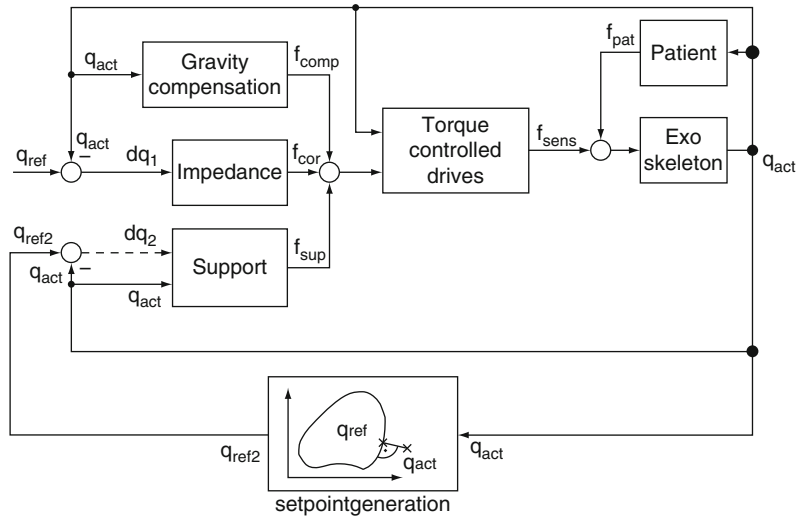

Fig. 3.4 Path-control strategy as derived by Duschau-Wicke et al. [14]: q is the vector of generalized joint angles; F is the vector of joint forces (From Duschau-Wicke et al. [14], (© 2010, IEEE); used with permission)

The first step in incorporating a variable deviation from a predefined leg trajectory into the system, thus, giving the patient more freedom, may be achieved using an impedance control strategy. The deviation depends upon the patient's effort and behavior. An adjustable torque is applied at each joint, depending on the deviation of the current joint position from the desired trajectory. This torque is usually defined as a zero order (elastic) or higher order (usually first or second order) function of angular position and its derivatives. This torque is more generally called mechanical impedance [15]. Figure 3.4 depicts a block diagram of an impedance controller.

The impedance controller was initially tested in several healthy subjects with no known neurological deficits and also in several subjects with incomplete paraplegia [13]. In the impedance control mode, angular deviations increased with increasing robot compliance (decreasing impedance) as the robot applied a smaller force to guide the human legs along a given trajectory. Inappropriate muscle activation produced by high muscle tone, spasms, or reflexes can affect the movement and may yield a physiologically incorrect gait pattern, depending on the magnitude of the impedance chosen. In contrast, several subjects who used the system with the impedance controller stated that the gentle behavior of the robot feels good and comfortable (personal experience of subjects told to the authors).

The disadvantage of a standard impedance controller is that the patient needs sufficient voluntary effort to move along a physiologically correct trajectory, which limits the range of application to patients with only mild lesions. In addition, the underlying gait trajectory allows no flexibility in time, i.e., leg position can deviate only orthogonally but not tangentially to the given trajectory.

3.2.2 The Path-Controller Implementation

Therefore, the features of the impedance controller have been extended into a novel "path controller" [14] in which the time-dependent walking trajectories are converted to walking paths with user-determined free timing (Fig. 3.4). In this manner, the controller enables the impedance along the path to vary in order to obtain satisfactory movement, particularly at critical phases of gait (e.g., before heel contact, see [14]). This is comparable to fixing the patient's feet to soft rails, thus limiting the accessible domain of foot positions calculated as functions of hip and knee angles. The patients are free to move along these "virtual rails." In order to supplement these corrective actions of the Lokomat, a supportive force field of adjustable magnitude can be added. Depending on the actual position

of the patient's legs, the supportive forces act in the direction of the desired path. The support is derived from the desired angular velocities of the predefined trajectory at the current path location. Supportive forces make it possible to move along the path with reduced effort. Compared to the impedance controller, the path controller gives the patient more freedom in timing while he or she can still be guided through critical phases of the gait, providing a safe and variable repetitive gait therapy.

The reference trajectory has been recorded from healthy subjects [2] and is used as set point for the impedance controller. The treadmill speed is selected by the therapist. A dynamic set point generation algorithm is used to minimize the Euclidean distance between the reference trajectory and the actual trajectory. An adjustable zero band of a predefined width creates a virtual tunnel around the reference trajectory. The width of the zero band has been designed heuristically based upon the evidence and experience from pretrials. The width was computed to permit larger spatial variation during late swing and early stance phase to account for the large variability of knee flexion at heel strike. Additionally, the reference trajectory has been adapted to a less pronounced loading response and more knee flexion during swing phase so that the desired zero band spreads symmetrically around the reference. In this way, a common tunnel was obtained that could accommodate all subjects and enable additional variability and support. Within the tunnel, the controller is in so-called free run mode; that is, the output of the impedance is zero, and gravity and friction torques of the robot are compensated. Therefore, subjects can move freely and with their own timing as long as they stay within the tunnel. Leg postures outside the tunnel are corrected by the impedance controller. The spring constant of the virtual impedance is chosen as a function of the distance to the tunnel wall. These measurements were experimentally determined such that the wall of the tunnel felt comfortably soft to the subjects. A nonlinear stiffness function is implemented to allow for a compromise between soft contact with the wall and strong corrections for larger deviations. An additional damping constant was determined as a function of the stiffness such that the system is critically damped. Adjustable supportive torques can be superimposed to the controller output. To determine the direction of support, a torque vector is calculated by differentiating the reference trajectory with respect to the relative position in the gait cycle. Thus, the direction of the torque vector is tangential to the movement path in joint space. The supportive torques not only are important in helping a patient to overcome weaknesses but also reduce the effect of the uncompensated inertia of the robot. More details and data regarding the path controller may be found in [14].

3.2.3 Evaluation of the Path Controller

The path-control strategy was tested on 12 subjects with incomplete spinal cord injury. The subjects were actively trying to match desired movements presented to them via a visual display. Additionally, subjects performed the same task with the classical position control mode of the Lokomat. The angles of the hip and knee were recorded by the position sensors of the Lokomat. Data were cut into single strides and normalized in time to 0–100% of the gait cycle. For each instant of the gait cycle, the mean and the standard deviation of the joint angles were calculated. After walking under the different conditions, subjects rated the influence they had on their movements and the effort they had to make on a visual analog scale ranging from 0 to 10. The ratings for the two different conditions were compared using a Kruskal-Wallis nonparametric analysis of variance (ANOVA) at a 5% significance level [16]. The subjects produced walking trajectories that qualitatively match the spatial path of the desired walking pattern. During stance phase (0–60% of the gait cycle), subjects systematically showed more knee flexion than the desired pattern. Largest variance occurred during swing phase and load response. The subjects had the impression to have significantly more influence on their leg movements and to train with significantly more effort with

the path control strategy than with position control. Measurements of muscle activity and heart rate also indicated that the patient participated stronger to the movement when using the path controller as compared with the position controller (for further results, see [14, 17]).

The results show that the subjects were able to freely influence their movements within the spatial constraints of the desired walking pattern. Although the controller leaves maximum freedom, it still ensures functional gait in critical situations. Particularly during stance phase, where subjects were not able to keep their knee joints extended, the controller assisted the subjects by keeping them within the region around the spatial path of the desired walking pattern. Thus, the user-cooperative path control strategy provides a safe training environment and makes the human an active agent in the biomechanical control loop of the gait rehabilitation robot Lokomat.

3.3 Human Physiology in the Loop

3.3.1 Rationale

Neurological patients in need of gait rehabilitation can greatly benefit from cardiovascular training, i.e., of performing exercises in which their heart rate is controlled to a desired level [18]. Depending on the degree of the impairment caused by the lesion, this training is performed either on treadmills for less severe cases or on stationary bicycles in severely affected patients. Particularly, nonambulatory patients cannot exercise on treadmills but have to use stationary bicycles, where the problems of coordination and balance during walking do not need to be taken into consideration.

Besides cardiovascular training, coordinative gait training plays a major role in rehabilitation of stroke survivors [19]. Gait robots, such as the Lokomat [2], the WalkTrainer [4], the LOPES robot [3], and the AutoAmbulator (www.autoambulator.com), allow even nonambulatory patients to exercise walking by guiding the legs of the patient on a walking trajectory. These robotic devices were shown to cause significant improvement of gait function in patients suffering from stroke [20, 21].

Integration of cardiovascular training into gait therapy, therefore, combines the benefits of both trainings and has the potential to improve gait rehabilitation. While treadmill-based heart rate control is well established in healthy subjects [22–24], cardiovascular gait training with robotic assistance has not been used with neurological patients as patients can be too impaired to walk on a treadmill at speeds that would permit control of heart rate.

Three major challenges of treadmill walking with a gait robot compared to standard treadmill walking need to be considered. First, for patient safety, treadmill speed during robot-assisted rehabilitation training is typically limited to very slow walking speeds and does not allow fast walking or running. The Lokomat gait orthosis, for example, is limited to 3.2 km/h, which is low compared to previous approaches where heart rate control was performed with walking speeds greater than 3.6 km/h [25]. Second, for facilitation of stance, the patient can be body weight–supported, which will decrease heart rate with increasing body weight support (BWS) [26]. And third, all gait robots use actuators to provide supportive guidance force in order to enable the walking movement in patients with little leg force or little coordinative capabilities. This guidance force can be expected to alter heart rate as it decreases the energy required by the subject to perform the walking movement (Fig. 3.5).

3.3.2 Model-Based Heart Rate Control

A model that predicts the changes in heart rate that can be expected from changing the robotic therapy can be used to predict situations that might become harmful to the patient. Additionally, it can be used as a basis for controlling heart rate to a desired level, depending on the current settings of the gait robot.

During robot-assisted gait training, the robot can exert large forces onto the patient's legs to guide them on a reference trajectory. This power exchange between the device and the patient has a major effect on heart rate. At high guidance forces with a stiff impedance controller, the

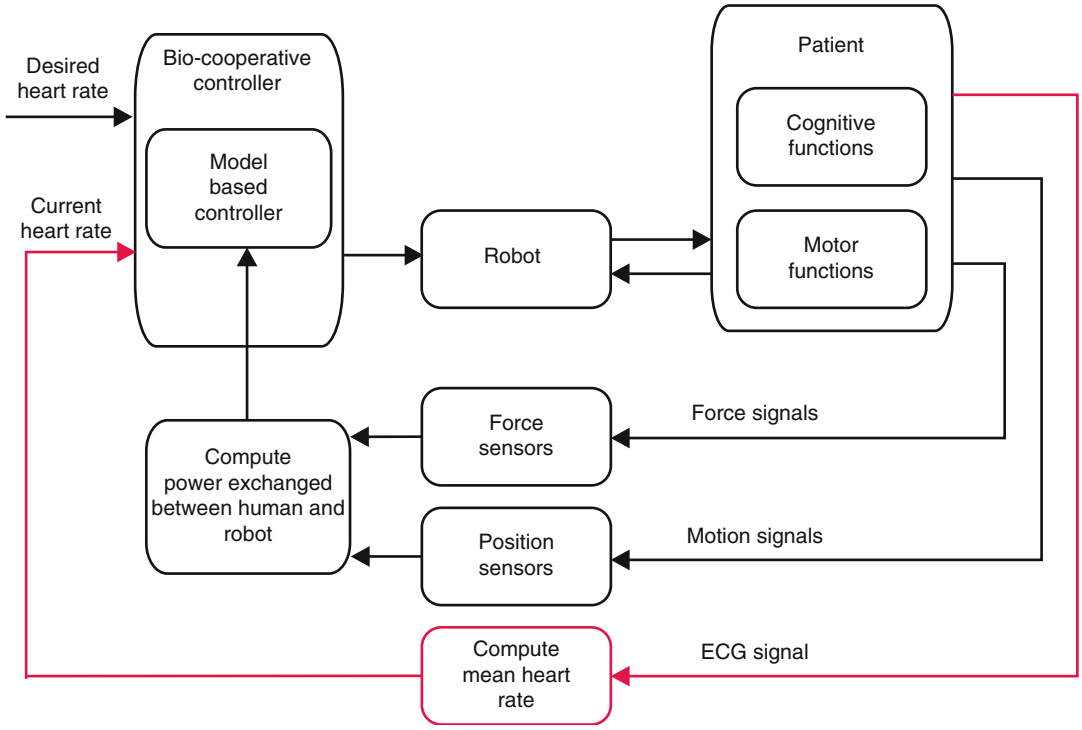

Fig. 3.5 Model-based control of heart rate as derived by [38]. Heart rate control is performed based on a model by taking power exchange between patient and robot into account

patients have the possibility to walk actively, i.e., pushing into the orthosis with high forces, or behave passively, letting the robot move their legs. The torques exchanged between human and orthosis can be considered as the dominant port for power exchange in the Lokomat system (Fig. 3.2). The power during walking P_{Lokomat} can be computed as the product of interaction torques between human and Lokomat with the angular velocity of the robot joints.

In an experimental study with eight chronic stroke patients, we evaluated the effects of BWS, treadmill speed, and guidance force on the patient's heart rate. It was found that changes in guidance force did not significantly alter heart rate. BWS, on the other hand, had a major impact on heart rate. Increased BWS reduces the loading the patient has to carry during walking, which will increase heart rate. High loading of the patient during treadmill training was, however, shown to be a key factor for a successful rehabilitation outcome [27, 28]. In order to maximize the quality of coordinative training, BWS is usually adjusted to the individual patient to a fixed minimal value.

Treadmill speed and power exchanged between robot and human were identified as major factors that influenced heart rate during Lokomat walking. The dependency between gait speed and heart rate of healthy subjects has been previously investigated. Increases in treadmill speed were shown to linearly increase heart rate [29–31]. This can be interpreted as low-pass reaction to a sudden increase of oxygen demand, which we modeled as a first order delay (PT1) element. Treadmill acceleration and deceleration resulted in an overshoot, respectively, and undershoot of heart rate before steady state was reached [30, 32], which we modeled as a second order derivative (DT2) element. Holmgren reported a drop in arterial pressure that reached its minimum 10 s after onset of exercise [33]. The heart rate overshoot might be caused by a first overreaction of the cardiovascular system to compensate for the blood pressure

drop. Feroldi et al. argued that the overshoot might be a result of changes in the balance between sympathetic and parasympathetic activities [34]. The power expenditure of a subject during exercise on a bicycle ergometer [35] and during arm cranking [36] was reported to correlate linearly with heart rate. Therefore, the power expenditure of the human was taken as a linear input parameter modeled as a first order PT element. After longer training durations, a fatigue effect, which resulted in increased resting heart rate, was observed and described by several researchers [30, 37]. We modeled this as a first order low-pass element. This resulted in a model with five scaling factors and six parameters.

Using the model described above, model predictive control can be employed to perform heart rate control of neurological patients while walking in a robotic gait orthosis. Heart rate control has been successfully demonstrated using other control techniques such as PID or H_∞ control in healthy subjects using Hammerstein models [25]. However, a model-based approach differs from the approaches above in its usability with severely affected stroke patients as power exchange between human and robot could be taken explicitly into account. In this model, the power exchange with the Lokomat accounted for up to 75% of the predicted increases in heart rate. Compared to PID control, model predictive control enabled the use in a straightforward way, including the influence of power expenditure as external disturbance in the controller.

3.3.3 Evaluation of Model-Based Heart Rate Control

The model setup was verified with five healthy subjects and eight chronic stroke patients (three females and five males, all hemiparetic). Patients taking beta-blocking medicine, which was shown to decrease adaptation of heart rate to physical stress, were excluded from the study. The model reached an average coefficient of determination r^2 of 79%. The model depended upon four subject-individual parameters and six subject-independent parameters. The independent parameters were the overshoot and undershoot dynamics for treadmill acceleration and deceleration, respectively [38].

Model-based heart rate control was evaluated with three healthy subjects as well as with three stroke patients by controlling heart rate to 70, 80, and 90 beats/min. In healthy subjects, the controller could stabilize heart rate within 1 bpm ± 3 bpm. To mimic the training situation in which patients exercise, we limited the treadmill speed of the Lokomat to 3 km/h. When trying to control the subjects' heart rate to 90 bpm, treadmill speed saturated. In patients, heart rate control depended upon the baseline heart rate during standing as resting heart rate of stroke was shown to be increased compared to the resting heart rate of healthy subjects [39]. However, it was possible to control heart rate of stroke patients in a range between resting heart rate and plus 10 beats/min.

3.4 Human Psychology in the Loop

3.4.1 Rationale

In several therapeutic training applications, there is the desire to identify the actual cognitive load in order to assess whether the patient is bored, engaged, or even stressed and frustrated. We thereby defined cognitive load as a mental state that reflects the level of mental engagement the patient is directing toward the rehabilitation task. It is a unitless one-dimensional variable that ranges from underchallenged or bored via challenged and motivated to overstressed and frustrated.

Controlling cognitive load would be desirable because it is known that a challenging cognitive load, i.e., high motivation and active participation during a difficult but feasible task, can enhance motor learning and thus further increase the rehabilitation outcome [40]. During robot-assisted gait rehabilitation, control over the mental state of subjects is made possible via virtual environments, which were shown to increase patient motivation [41]. However, control of the mental state requires obtaining objective assessments of the current cognitive load of patients. Questionnaires only provide information at discrete points in time after

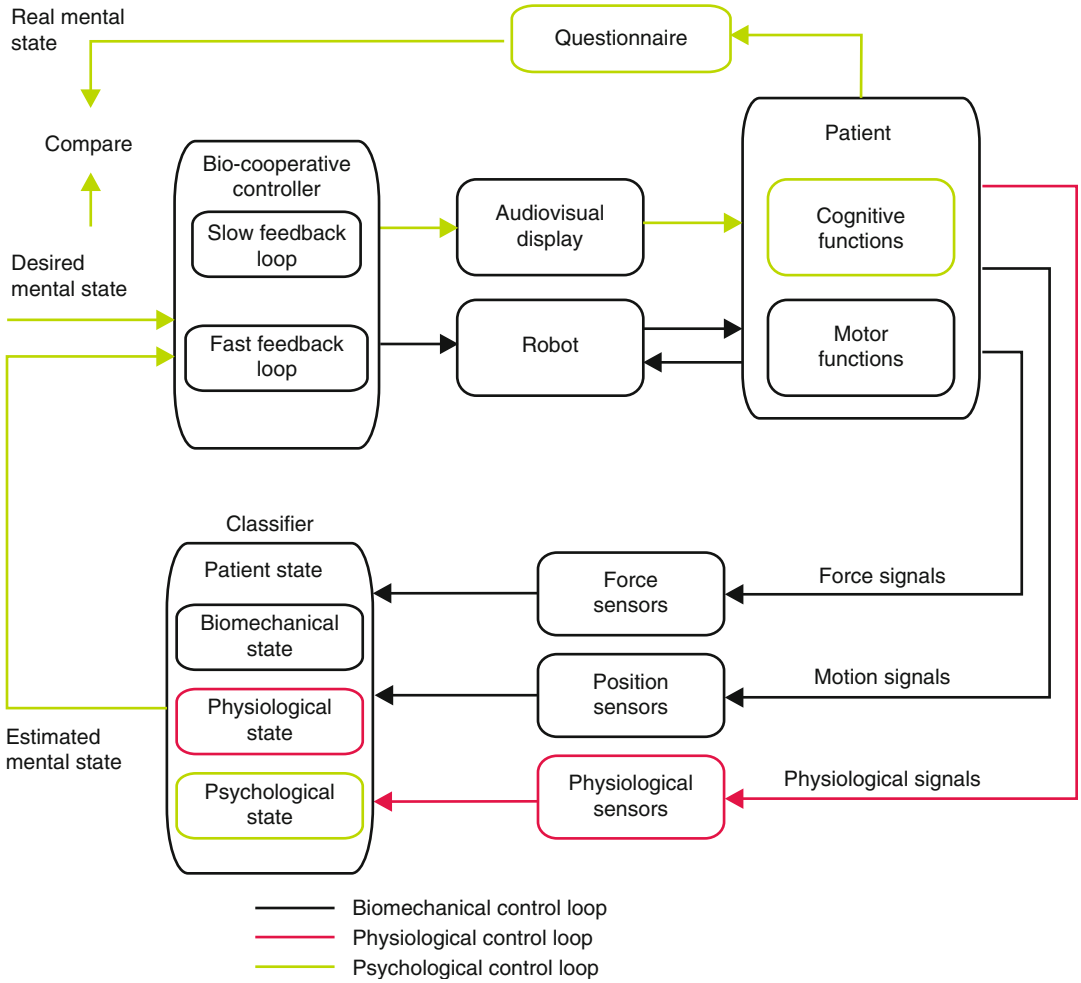

Fig. 3.6 Closed-loop control scheme for automated control of cognitive load during robot-assisted gait training. Questionnaires can be used to ensure that the desired mental state can really be established in the subject

training has ceased and cannot be used in real time. Also, neurological patients, particularly stroke survivors, might suffer from cognitive deficits such as aphasia or limited self-perception capabilities. Even patients who do not suffer from cognitive deficits might not be able to objectively assess what kind of training might be most beneficial for their rehabilitation.

In our approach, we try to control the cognitive load to a level in which the subject is motivated and challenged but not bored or overstressed or frustrated (Fig. 3.6). We can modulate the cognitive load in the subject by adapting the audiovisual display and the settings of the robot. By monitoring and controlling physiological quantities during robotic gait training, we obtain an objective quantification of cognitive load.

Input signals are stimuli that are presented to the human during the training intervention. They include motor aspects (e.g., treadmill speed and body weight support) as well as audiovisual stimuli provided by auditory and visual displays. The audiovisual display presented a virtual task that the subject has to fulfill. The task can be controlled by the motor output of the legs measured via forces applied to the Lokomat. By increasing or decreasing the difficulty of the robotic training and the virtual task, the mental state of the subject can be altered, which causes a psychological reaction.

Table 3.1 Overview of physiological signals recorded for determination of psychological states

Signal	ECG		SCR	Skin temperature	Breathing	Joint torques
	Time	Frequency				
Quantity	Mean heart rate	Spectral power of HRV				
Psychological interpretation	Physical effort, arousal [42]	Arousal [43]	Cognitive load, arousal [44, 45]	Valence [46, 47]	Physical effort, arousal [48]	Physical effort

Changes in the mental state, particularly arousal and valence of a subject, are reflected in numerous physiological signals, as summarized in Table 3.1 [42–48]. These human "output" signals are affected by the autonomic nervous system [49]. We selected heart rate and heart rate variability (HRV) obtained by electrocardiogram (ECG) recordings [50], skin conductance response (SCR) [51], skin temperature, breathing frequency, and joint torques (Table 3.1). Other physiological signals (EEG, EMG, spirometry, and eye movements) were tested but later omitted as recording turned out to not bear relevant information in relation to the experimental effort or could not be recorded in a reliable manner. We extracted features from the physiological data, took the mean standard deviation over 30 s, and fused the data into one feature vector. All signal processing software was written in MATLAB 2008b (The MathWorks, Natick, MA, USA, www.mathworks.com).

The electrocardiogram was measured by three surface electrodes. Heart rate was computed from the electrocardiogram recordings using a real-time R wave detection algorithm [52]. Heart rate variability was computed as a discrete time series of consecutive RR intervals. Using a thermistor flow sensor placed underneath the nose, we recorded the breathing of subjects and computed breathing frequency and its derivative using a peak detection algorithm. Changes in galvanic skin response were measured using two electrodes attached to the hand. Skin conductance response events were detected from the skin conductance signal when signal amplitude changed by at least 0.05 mS in less than 5 s [45]. Skin temperature was measured on the fifth finger. Signals were sampled at 512 Hz according to the recommendations of Malik [50]. Force data from the Lokomat were weighted and summed for each step such that it reflected the current physical effort of the subjects [53].

We first established how physiological signals would react to increased physical and mental stress and designed a classifier that would estimate the current psychological state from physiological recordings. We then performed experiments in which we put the human in a closed control loop and performed control of cognitive load to a desired state.

3.4.2 Physiological Signals as Markers for Psychological States

Understanding the effects of physical and mental stress on the physiological signals is the first step toward control of psychological aspects of the human. We provoked different physical and cognitive stress situations by providing external stimuli and observed physiological outputs in seven healthy subjects (Fig. 3.7) [68]. Mild physical stress was produced by walking in the Lokomat without any additional audiovisual display and by walking in the Lokomat while playing a virtual soccer game against a virtual opponent. Mental stress was produced by letting the subject perform mental arithmetic tasks. Data were recorded at these five randomized conditions:

- Standing
- Walking
- Walking and soccer
- Standing with arithmetic task
- Walking with arithmetic task

Results are summarized in Table 3.2; they showed that the number of SCR events increased significantly when subjects had to perform mental arithmetic tasks [54], whereas skin temperature decreased significantly during mental arithmetic

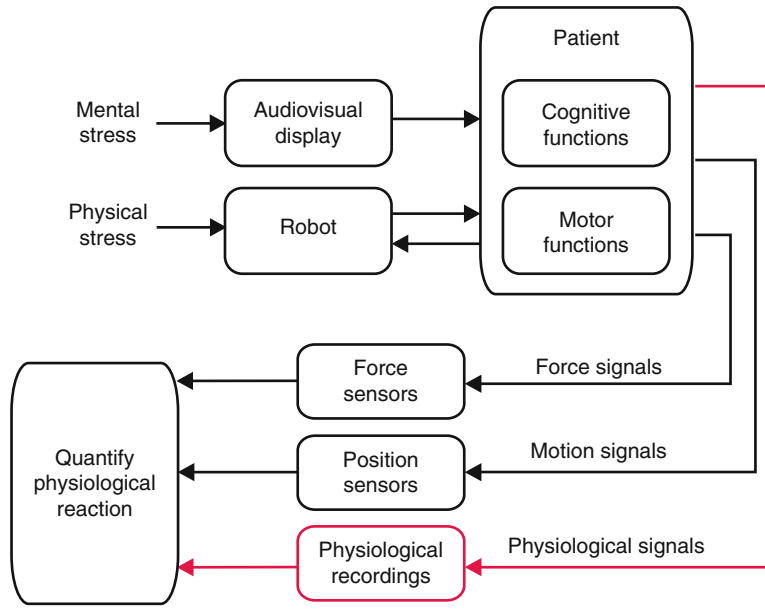

Fig. 3.7 Quantifying the effects of mental and physical stress on physiological signals (From Riener et al. [68], (copyright IEEE), used with permission)

Table 3.2 Effects of mental and physical load on physiological parameters

	Heart rate [1/min]	SCR events [–]	Skin temperature [°C]	Breathing frequency [1/min]
Standing (baseline)	74 ± 12.1	2 ± 1.3	28.7 ± 3.9	12 ± 3.9
Walking	89 ± 17.4	8 ± 7.0	28.5 ± 1.5	20 ± 3.8
Walking and virtual task	109 ± 17.6	20 ± 13.4	27.7 ± 2.1	26 ± 6.0
Standing and arithmetic task	100 ± 24.4	25 ± 7.5	26.8 ± 3.0	–
Walking and arithmetic task	91 ± 19.4	25 ± 10.8	26.6 ± 2.6	–

SCR skin conductance responses, *Skin temp* skin temperature. Breathing frequency during arithmetic tasks could not be recorded as subjects had to talk, which prevented analysis of the thermistor signal [68]. From Riener et al., (copyright IEEE), used with permission)

tasks. Heart rate increased with physical load, but it also increased with mental workload [55].

The isolated findings are congruent with the literature. An increase in heart rate was found due to negative emotions or stress [56, 57]. The number of SCRs increased for all scenarios compared to baseline. This was expected as the change in skin conductance is induced by external virtual reality stimuli [44, 57].The highest increase in the number of SCRs was found for the arithmetic task condition, which presented the situation with the highest cognitive load. Skin temperature is influenced by vasoconstriction, which is controlled by the sympathetic part of the autonomous nervous system [57]. An increase of sympathetic activity, and therefore a decrease in skin temperature, was found in the study of Ohsuga et al. [58] as reaction to cognitive load. Our results show that skin temperature decreased during cognitive stress induced by a virtual or arithmetic task. Different studies have found a relationship between negative emotions and increasing respiratory activity [59]. An increase in breathing frequency was also found in different studies during excitement or during pleasant attentive states [59, 60]. However, the literature for respiration and emotions is not very clear, and not all studies found an increase in breathing frequency due to positive or negative stimuli [59].

The interesting observation is that physical activity in the Lokomat does not occlude the

Table 3.3 Characteristics of patients of open-loop identification experiments (From Koenig et al. [69], (copyright IEEE), used with permission)

Subject	Gender	Age [year]	Time since incident [min]	Lesion	Beta-blocker
1	F	52	29	Left ischemic infarct	No
2	M	43	5	Right hemorrhagic infarct	No
3	F	37	22	Left hemorrhagic infarct	No
4	M	66	29	Left ischemic infarct	No

Abbreviations: *F* Female; *M* Male

effects of mental workload. However, many results on single measures (e.g., heart rate, breathing frequency) of these preliminary tests were not significant enough mainly, because the virtual scenarios were partially not immersive enough and provided too weak stimuli.

3.4.3 Real-Time Classification of Cognitive Load

After we established a first understanding of physiological reactions to cognitive load, we investigated the possibility to automatically classify cognitive load physiological recordings [69]. Using data from open-loop experiments in nine healthy subjects and four neurological patients, we set up a linear classifier that would objectively estimate the cognitive load from physiological signals, biomechanical recordings from the robot, and information from the virtual environment. We compared the output of the automatic classifier with questionnaires' answers of the subjects to evaluate how well the classifier predicted the actual cognitive load (Table 3.3).

A virtual reality task with adjustable difficulty level was used to modulate cognitive load and effort during training sessions. In the virtual task, subjects had to collect and avoid objects, which were placed on a straight line and disappeared slowly in front of them. The walking speed in the scenario was controlled via the subject's voluntary effort performed in the Lokomat. An increase in effort leads to an increase in virtual walking speed; a decrease in effort leads to a decrease in virtual walking speed. While the subject could influence the virtual walking speed in the scenario, the real walking speed in the Lokomat was kept constant. In addition to the appearing objects, questions were displayed in a box on the screen, which the subjects had to answer while performing the walking task. If the statement was correct (e.g., $1+1=2$), the subject had to collect the box before it disappeared. If the statement was false (e.g., $1+1=3$), the subject had to avoid a collision by decreasing the walking speed until the box disappeared. From the virtual environment, we obtained the success rate of correctly avoided and collected objects and correctly answered questions.

We investigated a Kalman adaptive linear discriminant analysis (KALDA) classifier that was developed for EEG analysis [61] and adapted to rehabilitation [62]. We trained the KALDA to classify cognitive load from the recorded physiological variables. All data recorded in the "no task" condition, regardless of the level of physical effort, were labeled as baseline to the classifier. This ensured that the classifier estimated only cognitive load and not physical effort.

The task difficulty could be increased by posing difficult questions, by decreasing the time available to read and answer the question, by decreasing the distance between objects, and by increasing the time until the objects disappear. Conversely, the difficulty could be decreased by posing easy questions, allowing more time to read and react to the question, by increasing the distance between objects, and by decreasing the time until the objects disappeared.

Results show that off-line classification was possible with an average of 87% correctly classified in healthy subjects and 75% correctly classified in neurological patients (Tables 3.4 and 3.5).

Table 3.4 Classification results of healthy subjects with a Kalman adaptive linear discriminant analysis (KALDA) classifier (From Koenig et al. [69], (copyright IEEE), used with permission)

Subject	1	2	3	4	5	6	7	8	9	Mean
Classification result [% correct]	86	71	100	86	71	100	86	100	86	87

Table 3.5 Classification results of neurological patients with a Kalman adaptive linear discriminant analysis (KALDA) classifier (From Koenig et al. [69], (copyright IEEE), used with permission)

Patient	1	2	3	4	Mean
Classification result [% correct]	80	60	80	80	75

3.4.4 Evaluation of Psychological Closed-Loop Control

Using the open-loop classifier trained with data of nine healthy subjects and four stroke patients, we closed the loop around the human in the gait robot and controlled cognitive load to a desired, optimal state. The audiovisual display was adapted such that the subject in the Lokomat would be optimally challenged, avoiding training situations where the subject was bored, overstressed, or frustrated.

If the classifier detected a suboptimal mental state, the virtual environment described above was adapted accordingly: If the subject showed a tendency to become bored, the task was automatically set to be more difficult; if the classifier detected that the task became too difficult for the subject, the training environment was automatically adapted to be easier and less stressful for the subject.

Five healthy subjects walked in the Lokomat and started at a task that was either too easy or too difficult for their abilities. Inputs to the classifier were physiological signals, biomechanical recordings, and task success (Fig. 3.8). Every 60 s, the classifier adapted the virtual environment based on its internal evaluation of the current cognitive load of the subject. Ten adaptation steps were performed for each subject. Validation of the classifier's decision was done at each adaptation step by asking the subjects if they would prefer the task to be easier or more difficult. The subject's answer was recorded but only used for comparison to the decision of the classifier.

The adaptation of task difficulty could have been based solely on the task success in the virtual environment. We investigated the necessity of physiological signals by performing a second experiment in which the classifier only received task success as input. Again, subjects were asked whether they wanted the task to be easier or more difficult. The controller adapted the task difficulty ten times, once every 60 s. The correct classification results are summarized in Table 3.6.

The physiological signals improved the classification results by 24% compared to a control system that would only take the current task success into account. The classifier that could access physiological, biomechanical, as well as task success data was superior in the amount of correct decisions compared to the classifier that only received task success as input (Table 3.6).

Therefore, we conclude that cognitive control is indeed possible in subjects during robot-assisted gait training. Future studies on neurological patients will have to evaluate if the method can be used in a clinical setting.

3.5 General Discussion and Conclusion

Placing the human into the loop can be considered from various viewpoints and realized for different applications. It can integrate controlling biomechanical, physiological, as well as psychological aspects of the human, who then represents the plant within the control system.

Integration of healthy subjects in a biomechanical or physiological control loop is commonly

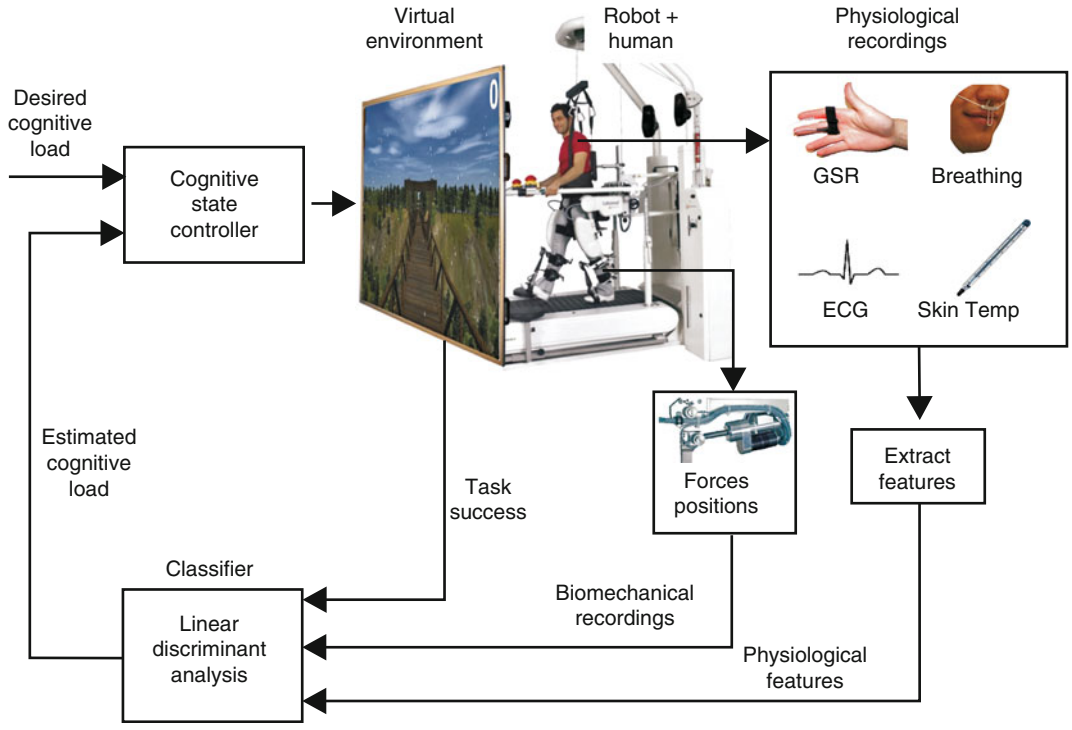

Fig. 3.8 System setup for control of cognitive load (Adapted from Koenig et al. [69], (copyright IEEE), used with permission)

Table 3.6 Classification results in % correctly classified decisions of five healthy subjects (From Koenig et al. [69], (copyright IEEE), used with permission)

		Subject					
		1	2	3	4	5	Mean
Classification result [% correct]	All input data	80	80	90	90	100	88 ± 8
	Only task success	50	70	60	60	80	64 ± 11

In two consecutive experiments, the classifier input was altered. In the first experiment, the classifier obtained physiological signals, biomechanical data, and score information from the virtual environment (All input data). In the second experiment, the classifier only obtained the task success information from the virtual environment (Only task success)

performed during heart rate control on exercise treadmills. Online detection of psychological states of healthy subjects has also been previously performed by Rani et al. [63], who determined the stress level of test subjects in real time from analysis of heart rate variability. However, their approach was nonadaptive and did not take physical activity induced by walking nor the challenges of treating neurological patients into account.

In neurorehabilitation, active biomechanical participation was shown to increase motor learning [40]. Control of biomechanical participation was exemplarily shown in the path-controller paradigm. The positive effect of active physical participation on rehabilitation was confirmed by studies that connected cardiovascular training with a positive effect on the recovery after neurological injury [18], exemplarily implemented in closed-loop heart rate control. Heart rate control in the Lokomat thereby allows cardiovascular training of nonambulatory patients; meanwhile, our applications guarantee that the patient is training in a safe region by keeping relevant physiological values, such as heart rate, in an

appropriate range. Besides closed-loop physiology control, the role of motivation is known to be important in the success of neurorehabilitation [64, 65]. The human-in-the-loop structure allows optimization of mental engagement of the subject, thus increasing motivation. Controlling cognitive engagement in neurorehabilitation as implemented in closed-loop control of psychology, therefore, has the potential to increase motor learning and thereby the training efficiency and therapeutic outcome of neurological rehabilitation [66, 67].

Detection and control of physiological and psychological states is thereby neither limited to a particular gait orthosis nor to rehabilitation of the lower limbs. In robot-assisted arm rehabilitation, as performed with the ARMin [6], the HapticMaster [8], or the MIT Manus [9], the lower level of physical effort as compared to walking might even improve the accuracy of the algorithms described above.

It can be concluded that closed-loop control of mental states has the potential to improve robot-assisted rehabilitation by enabling clinicians to provide patient-centered rehabilitation therapy. In the future, human-in-the-loop strategies will break with the classical master–slave paradigm that requires the user to adapt to the robotic system. Focusing on integrating mental states in the control loop will make the patient the master and the robot the slave. By using auto-adaptive algorithms such as intelligent machine learning as described above, the robot will learn how to automatically adapt to the specific needs and demands of the patient.

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Learning in the Damaged Brain/Spinal Cord: Neuroplasticity

4

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Abstract

Neuroplasticity refers to the ability of the central nervous system (CNS) to undergo persistent or lasting modifications to the function or structure of its elements. Neuroplasticity is a CNS mechanism that enables successful learning. Likely, it is also the mechanism by which recovery after CNS lesioning is possible. The chapter gives an overview of the phenomena that constitute plasticity and the cellular events leading to them. Evidence for neural plasticity in different regions of the brain and in the spinal cord is summarized in the contexts of learning, recovery, and rehabilitation therapy.

Keywords

Recovery • Rehabilitation • Stroke • Spinal cord injury • Brain lesion • Plasticity

4.1 Learning in the CNS

Rehabilitation technologies that support movement recovery make use of different brain and body mechanisms, one of which is the brain's ability to learn. Likely, the learning of the damaged central nervous system that mediates partial or complete recovery of function is different from learning in the healthy state. But it is thought that recovery after stroke shares certain cellular and system mechanisms of neuroplasticity with healthy learning. Clearly, the main behavioral determinants of healthy learning of novel movements, activity and repetition, are also important in recovery.

Motor learning is a general term that encompasses many different processes. Distinct behavioral and neural mechanisms are engaged depending on the level of complexity of the movement to be learned and the stimulus driving learning. A few different forms of motor learning are briefly reviewed.

Motor adaptation is a type of motor learning that acts on a time scale of minutes to hours in

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order to account for predictable perturbations to a movement [1]. Adaptation occurs on a trial-by-trial basis, correcting a given movement from one trial to the next. It is driven by sensory prediction errors, which represent the difference between the brain's estimate of the sensory consequences of movement and the actual sensory feedback [2]. Once a movement has been adapted, it must actively be de-adapted (i.e., actively unlearned) when the predictable perturbation is removed.

Associative learning can also occur on a time scale of minutes to hours. Classical conditioning is perhaps the most commonly studied form of associative learning. It acts to link two previously unrelated phenomena in order to improve behavior. For example, in eyeblink conditioning, a "conditioned" stimulus like a sound or tone can be repeatedly paired with a second, slightly delayed "unconditioned" stimulus like a puff of air to the eye [3]. Early in the learning process, the eye blinks in response to the puff of air (i.e., unconditioned response). However, with repeated exposure, the eye begins to blink when the tone is sounded, therefore anticipating the air puff by closing the eye (i.e., conditioned response). This type of conditioning can be used to make associations between many types of behaviors.

Motor learning can also be driven by feedback, either positive in the form of reward-based learning [4] or negative in the form of avoidance learning [5]. These learning processes can occur on short or long time scales depending on the type and complexity of the movement. Motor skills can also be learned via implicit processes [6]. Small improvements after repeating a novel movement, e.g., when learning to play a piano piece, are often not obvious or consciously perceived. Indeed, the reward of playing the piece well is typically late and temporally unrelated to each training trial (e.g., the audience applauds). Thus, implicit motor learning may depend on use-dependent or Hebbian-like plasticity rather than reward-based mechanisms.

All of these forms of motor learning rely on networks of neural structures rather than single areas, but there are some key regions that seem to play especially important roles in each. Adaptation is known to be cerebellum dependent. Classical conditioning can involve the cerebellum and hippocampus depending on the specific timing between stimuli. Reward and avoidance learning are dependent on basal ganglia circuitry. Use-dependent learning likely occurs at many levels of the nervous system, including spinal cord, brain stem, and cerebral structures. Importantly, all forms of motor learning are dependent on cellular mechanisms of plasticity including long-term potentiation and long-term depression. As such, these mechanisms are reviewed below.

4.2 Mechanisms of Neuroplasticity in Learning and After Lesions

4.2.1 Gene Expression

Learning of a motor skill requires gene expression in the motor cortex [7, 8]. If this expression is pharmacologically blocked, learning is reduced. Gene and subsequent protein expression is a common requirement of various learning processes [9, 10] as well as for cellular equivalents of learning, i.e., the changes in neuronal structure [11] and synaptic strength in the form of long-term potentiation (LTP) and depression (LTD) [12]. For motor skill learning, proteins are not only expressed during training but also thereafter while the subject is resting [7]. This delayed synthesis can be regarded as reflecting intersession consolidation processes [13].

Gene expression is induced by ischemia, especially in the peri-infarct cortex [14]. Some of these genes could also promote cellular plasticity offering the potential for stroke-induced plasticity as self-healing mechanisms of the brain. These mechanisms still remain to be elucidated.

4.2.2 Cellular Plasticity

Long-term potentiation (LTP) and depression (LTD) are commonly seen as cellular equivalents of the brain's learning abilities [15]. Either by repetitive stimulation, seen as the equivalent to

repetitive training – or by synchronizing two signals that converge at one neuron, potentially reflecting associative learning phenomena – an increase in synaptic strength is induced that lasts from hours to days, termed LTP [16]. LTD is induced by low-frequency stimulation and leads to a lasting reduction in synaptic strength [15]. Both LTP and LTD have been described in various brain regions including primary motor cortex (M1) [17]. The observation that the ability of M1 neurons to undergo LTP and LTD is reduced in trained animals provides indirect evidence for the hypothesis that primary motor cortex LTP/LTD is involved in motor skill learning [18]. In other words, the cellular mechanism that may lead to the formation of a movement memory trace has been used up by the learning process and needs time to recover before new learning can be accomplished. Two months after a skill has been learned in a 2-week training period and is well remembered, the synaptic strengthening that is observed in M1 shortly after training persists. But, the ability to undergo has recovered and is now expressed on a higher level of synaptic strength [17].

In the context of recovery after brain or spinal cord injury, the role of LTP and LTD is unclear. LTP is facilitated in the peri-infarct cortex [19]. This result may be incompatible with the hypothesis that LTP is used up during recovery as it is after healthy skill learning; hence, LTP would be reduced in the peri-infarct cortex not facilitated. But, the study lacks information about recovery of function or lesion size, so a valid comparison to healthy learning is impossible, and the issue of LTP utilization during recovery is left unanswered. In hippocampus, short-term ischemia leads to a disruption of LTP formation [20]. In humans, preliminary evidence indicates that LTP-like phenomena elicited in M1 of the lesioned hemisphere (cortical or subcortical lesions) by repetitive transcranial magnetic stimulation (TMS) predict good recovery at 6 months [21]. Paired associative stimulation (peripheral muscle and TMS stimulation of M1) – a potential human equivalent of associative LTP – can be elicited in the affected hemisphere M1, especially in those patients with limited deficits [22]. Hence, the ability of the lesioned cortex to undergo LTP may be a requisite for recovery.

4.2.3 Systems Plasticity in the Brain

Plasticity phenomena not only exist on the level of single neurons or networks but also in distinct functional systems of the brain. The input-output organization and the somatotopy of M1 undergo persistent changes during motor skill learning. Skill learning leads to an expansion of the cortical representation of the trained limb [23, 24]. Longitudinal motor cortex mapping experiments in rats show that this expansion is transient and is reversed after training ends although the skill is maintained [25]. In humans who continuously train new motor skills, e.g., professional pianists, task-related activation is smaller in area and more focused [26, 27]. Musicians also have enlarged gray matter volumes in various areas of cortex including the motor cortices [28]. The M1 of musicians contains memory traces of practiced skills that can be probed by TMS [29].

Representations in primary motor cortex are also modified while recovering from a stroke. Initially, large areas of motor and adjacent cortices are recruited in the attempt to accomplish a movement as detected by functional magnetic resonance imaging (fMRI) [30, 31]. If M1 itself is lesioned, expanded activation is found in peri-infarct cortex [32] or in premotor cortex [33]. As subjects recover, this overactivation is reduced, and movement-related activity focuses in the ipsilesional hemisphere contralateral to the moving limb [34–36]. If recovery is unsuccessful, more cortices remain overactivated in the lesioned as well as the nonlesioned hemisphere which has been interpreted as a sign of a frustrating attempt to recover meaningful movement [37]. But, recovery is not only accompanied by cortical activation changes. Larger activation in the cerebellum ipsilateral to the moving limb [34] and smaller activation in the contralateral cerebellum are associated with better recovery [35].

While movement-related activation observed with functional imaging methods demonstrates the brain areas that are involved in the control of

this specific movement, TMS can directly assess the output efficacy and the viability of descending pathways in the lesioned hemisphere. Larger motor evoked potentials in response to TMS and absence of ipsilateral responses to stimulation of the intact hemisphere are correlated with good functional recovery [38, 39].

4.2.4 Plasticity in Spinal Cord

There is convincing evidence in animals with a transected spinal cord that a use-dependent plasticity of neuronal circuits within the spinal cord exists [40, 41]. When stepping is practiced in spinal cat, this task can be performed more successfully than when it is not practiced [42, 43]. The training effects of any motor task critically depend on the provision of sufficient and appropriate stimuli to initiate a reorganization of neural networks within the spinal cord. This is usually achieved by a functional training. In contrast, the loss of motor capacity following neural injury becomes enhanced when locomotor networks are no longer used, for example, following an SCI or stroke [40].

4.2.4.1 Spinal Reflex Plasticity

The isolated spinal cord can exhibit some neuronal plasticity. Evidence for such plasticity at a spinal level has been obtained for the relatively simple monosynaptic reflex arc [44]. Monkeys could either be trained to voluntarily increase or decrease the amplitude of the monosynaptic stretch reflex in response to an imposed muscle lengthening [44], as well as of its analogue, the H-reflex [45]. The fact that the training effects persist after spinal cord transection [46] indicates that some kind of learning by neuronal circuits within the spinal cord is possible. Similarly, humans can be trained to change the gain of the monosynaptic stretch reflex ([47]; for review, see [48]).

The idea that the spinal cord can learn is also supported by studies of spinal reflex conditioning. Simple hind limb motor responses to cutaneous or electrical stimulation are enhanced in animals with transected spinal cords via classical reflex conditioning (i.e., pairing the stimulus with another stimulus that evokes a stronger motor response) [49]. These reflex responses are enhanced within minutes of conditioning indicating that synaptic efficacy along the reflex arc has changed, perhaps through long-term potentiation [49].

4.2.4.2 Task-Specific Plasticity

Today, it is obvious that there is also a considerable task-specific plasticity of the sensorimotor networks of the adult mammalian lumbosacral spinal cord (for review, see [40, 41, 50]). The detailed assessment of the modifiability of neuronal network function was the focus of research on central pattern generators (CPGs) underlying stepping movements [51–54]. The lumbosacral spinal cord obviously can execute stepping or standing more successfully if that specific task is practiced. Observations in spinal cats indicate that if the training of a motor task is discontinued and no other task is subsequently trained, then the performance of the task previously trained is degraded [40]. Consequently, plasticity can be exploited by rehabilitative purposes using specific training approaches following a neural injury.

In the cat, recovery of locomotor function following spinal cord transection can be improved using regular training, even in adult animals [55, 56]. The provision of an adequate sensory input during training is of great importance to achieve an optimal output of the spinal neuronal circuitry. Correspondingly, in association with hind limb exercise, reflex activity becomes normalized in adult rats following spinal cord transection [57]. Exercise obviously helps to normalize the excitability of spinal reflexes.

Several neurotransmitter systems within the spinal cord (glycinergic and GABA-ergic systems) are suggested to be involved in the adaptation to repetitive task performance [40]. In animals with a spinal cord transection, stepping can be induced by the administration of the noradrenergic agonist clonidine, which enhances the activity in spinal neuronal circuits that generate locomotor

activity [58–60]. Furthermore, serotonin seems to be involved in the production of locomotor rhythms [61].

Training paradigms of stepping and standing can modify the efficacy of the inhibitory neurotransmitter, glycine [40]. For example, when glycine is administered to a chronic spinal cat that has acquired the ability to step successfully, there is little change in its locomotor capability. If it is administered to a stand-trained cat, it becomes able to successfully step with body support [40, 50]. These findings suggest that the effect of strychnine is in so far specific in its action as it enables spinal networks to integrate sensory input by reducing inhibition [59, 60].

4.2.5 Subcortical Contributions to Movement Learning

The cerebellum is thought to use adaptive learning mechanisms to calibrate internal models for predictive control of movement. Such models are needed because sensory feedback is too slow for movements that need to be both fast and accurate – corrections would be issued too late. Instead, the brain generates motor commands based on internal predictions of how the command would move the body [62]. This feedforward control requires stored knowledge (i.e., "models") of the body's dynamics, the environment, and any object to be manipulated to be constantly calibrated though adaptation.

Many studies have shown that the cerebellum is essential for adapting a motor behavior through repeated practice – it uses error information from one trial to improve performance on subsequent trials. It is important to note that cerebellum-dependent motor learning is driven by errors directly occurring during the movement, rather than other types of feedback, such as knowledge of results after the fact (e.g., hit or miss). Studies have suggested that the type of error that drives cerebellum-dependent learning is not the target error (i.e., "How far am I from the desired target?"), but instead what has been referred to as a sensory prediction error (i.e., "How far am I from where I predicted I would be?") [2]. Damage to the cerebellum impairs the ability to adapt many types of movements, including: reaching [63], walking [64], balance [65], and eye movements [66].

The microcircuit involved in cerebellar adaptation was first proposed by Marr [67], Albus [68], and Ito [69]. These works continue to provide the basis for many of the current theories of cerebellar function. Central to the idea of cerebellar involvement in learning was the discovery that Purkinje cell output can be radically altered by climbing fiber induction of long-term depression (LTD) of the parallel fiber-Purkinje cell synapse [70]. Hence, climbing fiber inputs onto Purkinje cells can be viewed as providing a unique type of teaching or error signal to the cerebellum. More recently LTD, LTP, and non-synaptic plasticity have all been shown to exist at numerous sites within the cerebellum, both in the cortex as well as the deep cerebellar nuclei [for review, see 71]. Thus, there are multiple avenues for activity-dependent plasticity to occur within the cerebellum over relatively short time scales. It is presumed that the plastic changes in cerebellar output are responsible for changing motor behavior during the process of adaptation.

Another subcortical brain region involved in motor learning is the ventral tegmental area (VTA). This site is more involved in motor skill learning rather than motor adaptation. Ipsilateral dopaminergic projections from VTA to M1 [72] are specifically necessary for acquiring but not for performing a skill once acquired. Elimination of dopaminergic terminals in M1 [73] or destruction of dopaminergic neurons in VTA impairs the acquisition of a reaching skill in rat [74]. Dopamine modulates the excitability of M1 [75] and S1 [76] and, more importantly, is necessary for the formation of LTP in layer II/III synapses [73] that link different cortical regions (such as M1 and S1) via horizontal connections. The same synapses are the ones at which LTP can no longer be elicited after skill learning – LTP is used up as described above [18]. It is likely that the VTA-to-M1 projection relays signals of the same nature

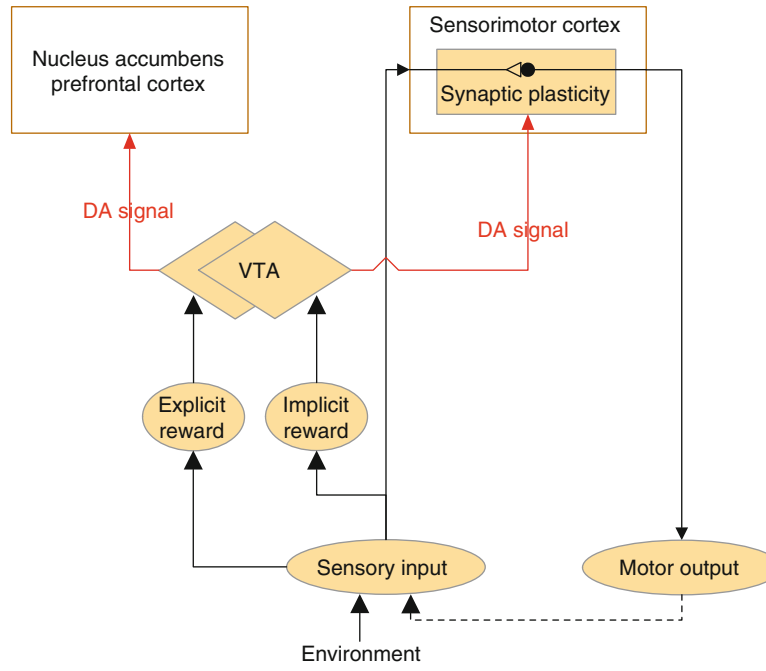

Fig. 4.1 Schematic representation of the integration of a postulated "implicit reward" into the simplified circuit that is required for motor learning. Via the dopamine (DA) signal, the reward could directly modulate synaptic plasticity in sensorimotor cortex synapses to store a new motor program

as compared to those that activate dopaminergic neurons from VTA to nucleus accumbens and prefrontal cortex. The latter encode rewarding feedback to behavior [77] (Fig. 4.1).

4.3 Learning and Plasticity During Rehabilitation Therapy

4.3.1 Lesions of Cortex and Descending Pathways

Rehabilitative training is associated with neurophysiological adaptations that are related to the improvement in motor function observed in individual stroke survivors [78]. Although correlation is no prove for causation, these studies provide an argument for neuroplasticity being a mechanism by which rehabilitative training can operate. It is likely not the only one. While bilateral arm training was associated with an increase in premotor cortex activation in both hemispheres that correlated with functional improvement in the Fugl-Meyer [79] and Wolf tests [80], conventional physical therapy (based on Bobath exercises) did not show altered brain activation despite being equally effective [80]. Conventional physical exercise may have utilized a mechanism other than those detectable by fMRI, e.g., by inducing changes in muscle, peripheral nerves, or spinal cord.

Lower extremity repetitive exercises in the form of aerobic treadmill training likely utilize yet another form of brain reorganization to improve gait. As compared with stretching exercises, improvements by treadmill training were related to increased activation of cerebellum and brainstem as detected with fMRI of paretic knee movement [81]. Interestingly, the areas recruited in cerebellum and brainstem corresponded to regions that control spinal pattern generators (cerebellar and midbrain locomotor region). These regions may have compensated for the loss of corticospinal projections that were injured by the stroke. It has also been shown that individuals with cerebral stroke can improve walking symmetry using adaptive mechanisms of learning on a split-belt treadmill [82, 83]. Here again, the hypothesis is that intact cerebellar mechanisms are responsible for this form of motor learning. Hence, subcortical reorganization may be the mechanism to target in lower extremity, and particularly walking, rehabilitation.

The availability of treatments that operate through distinct mechanisms may provide the rehabilitationist with an instrumentarium to individualize therapy for the particular patient. It seems likely that different patients with different brain injury and lesion profiles will require different therapeutic approaches.

4.3.2 Cerebellar Lesions

Recovery from a first ischemic cerebellar stroke is often very good, with minimal to no residual deficits in up to 83% of patients [84–86]. On the other hand, individuals with degenerative cerebellar disorders tend to have persistent or progressively worsening clinical signs and symptoms [87]. One study has shown that people with damage to the deep nuclei do not recover as well as those with damage to only the cerebellar cortex and white matter [88]. Thus, the etiology of the lesion and extent of damage are major indicators in recovery.

There is limited information on the effectiveness of rehabilitation interventions for individuals with primary cerebellar damage; there have been no randomized controlled trials published. Of the few studies on the effects of rehabilitation interventions in this patient population, all have been nonrandomized, noncontrolled small group [e.g., 89] or case study designs [e.g., 90]. Most work has been done on walking rehabilitation with common interventions including combinations of exercises targeting gaze, static stance, dynamic stance, gait, and complex gait activities [89, 90]. Dynamic balance activities in sitting, kneeling, and quadruped have also been advocated [89]. Ilg found that 4 weeks of an intensive coordination training followed by 8 weeks of home exercise could improve walking coordination and static and dynamic balance scores. It is not known whether such changes actually translate to improved real world function.

Locomotor training over ground and on treadmills, and with and without body weight support, has also been used with some success in single case examples [91, 92]. It is not clear how imbalance is corrected in the body weight support environment, however. With all gait and balance activities, it seems critical that the exercise be sufficiently and increasingly challenging, so as to facilitate plasticity in other intact areas of the nervous system [93, 94].

4.3.3 Spinal Lesions

4.3.3.1 Plasticity of Spinal Neuronal Circuits: Rehabilitation Issue

On the basis of the knowledge gained from animal experiments, the aim of rehabilitation after stroke or SCI should be concentrated on the improvement of function by taking advantage of the plasticity of neuronal centers and should less be directed to the correction of isolated clinical signs, such as the reflex excitability. For the monitoring of outcome and for the assessment of the effectiveness of any interventional therapy, standardized functional tests should be applied.

4.3.3.2 Functional Training in Persons with a Spinal Cord Injury

The coordination of human gait seems to be controlled in much the same way as in other mammals [95]. Therefore, it is not surprising that in persons with a complete or incomplete paraplegia, due to a spinal cord injury, locomotor EMG activity and movements can be both elicited and trained similar as in the cat. This is achieved by partially unloading (up to 60%) the patients who are standing on a moving treadmill ([96, 97]; for review, see [98]). In severely affected patients, the leg movements usually have to be assisted externally, especially during the transmission from stance to swing. In addition, leg flexor activation can be enhanced by flexor reflex stimulation of the peroneal nerve during the swing phase [99]. The timing of the pattern of leg muscle EMG activity recorded in such a condition is similar to that seen in healthy subjects. However, the amplitude of leg muscle EMG is considerably reduced and is less well modulated. This makes the body unloading necessary for the locomotor training. There are several reports about the beneficial effect of locomotor training in incomplete paraplegic patients (for review, see [56, 100, 101]),

and patients who undergo locomotor training have a greater mobility compared to a control group without training [102]. The neuronal networks below the level of an SCI can be activated to generate locomotor activity even in the absence of supraspinal input [59, 60, 103]. The analysis of the locomotor pattern induced in complete paraplegic patients indicates that it is unlikely to be due to rhythmic stretches of the leg muscle because leg muscle EMG activity is, as in healthy subjects, equally distributed during muscle lengthening and shortening [104]. In addition, recent observations indicate that locomotor movements induced in patients who are completely unloaded do not lead to leg muscle activation [105]. This implies that the generation of the leg muscle EMG pattern in these patients is programmed at a spinal level and requires afferent input from load signaling receptors.

During the course of daily locomotor training, the amplitude of the EMG in the leg extensor muscles increases during the stance phase and inappropriate leg flexor activity decreases. Such training effects are seen both in complete and incomplete paraplegic patients [96]. These training effects lead to a greater weight-bearing function of the leg extensors, i.e., body unloading during treadmill locomotion can be reduced during the course of training. This indicates that even the isolated human spinal cord has the capacity not only to generate a locomotor pattern but also to show some neuroplasticity which can be exploited by a functional training [106–109]. However, only persons with incomplete paraplegia benefit from the training program in so far as they can learn to perform unsupported stepping movements on solid ground [96]. In complete paraplegic patients, the training effects on leg muscle activation become lost after the training has been stopped [103].

4.3.3.3 Prerequisites for a Successful Training

The spinal pattern generator has to be activated by the provision of an appropriate afferent input and proprioceptive feedback to induce plastic neuronal changes [105].

Afferent input from receptors signaling contact forces during the stance phase of gait is essential for the activation of spinal locomotor centers [105, 109–112] and is important to achieve training effects in paraplegic patients [96] (Fig. 4.2). Furthermore, hip joint–related afferent input seems to be essential to generate a locomotor pattern [105]. For a successful training program for stroke and SCI subjects, spastic muscle tone has to be present as a partial compensation for paresis [113].

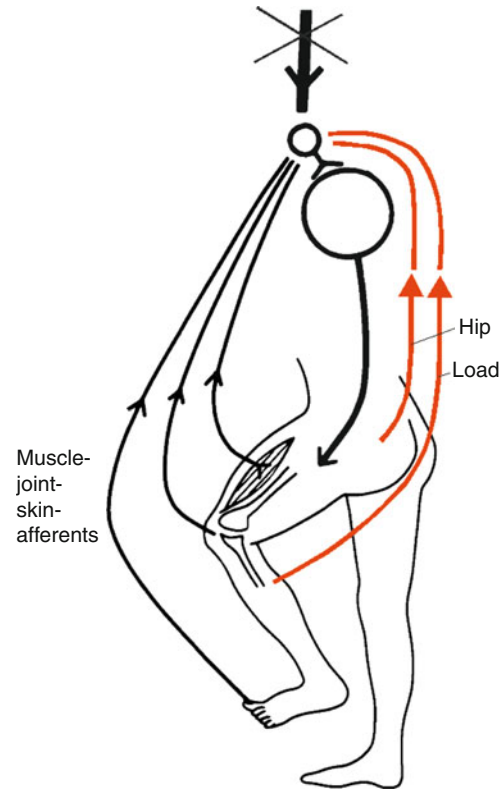

Fig. 4.2 Schematic demonstration of proprioceptive input during locomotor training in SCI subjects. The input from load and hip joint afferents was shown to be essential to achieve training effects

Only in patients with moderately impaired motor function a close relationship between motor scores (clinical assessment of voluntary muscle contraction) and locomotor ability exists. More severely affected SCI subjects with a low motor score undergoing a locomotor training can achieve an improved locomotor function without or with little change in motor scores [108, 114, 115]. In these cases, a relatively low voluntary force level in the leg muscles (reflected in the ASIA score) is required to achieve the ability to walk.

A considerable degree of locomotor recovery can be attributed to a reorganization of spared neural pathways ([116]; for review, see [117]). It has been estimated that if as little as 10–15% of the descending spinal tracts are spared, some locomotor function can recover [118, 119].

The improvement of locomotor activity could be due to a spontaneous recovery of spinal cord function that can occur over several months following a spinal cord injury [117, 120]. However, several observations indicate that the increase of leg extensor EMG activity also occurs independently from the spontaneous recovery of spinal cord function, as assessed by clinical and electrophysiological means [97, 107, 115, 117, 121]. Thus, functional training effects on spinal locomotor centers most likely contribute to an improvement of locomotor function in incomplete SCI subjects [97, 121]. However, part of the recovery in locomotion might also be attributed to changes that occur in the muscles during the training period, similar as observed in the rat [40].

4.3.3.4 Outlook

Unfortunately, patients with complete or almost complete paraplegia do not, as yet, profit from locomotor training for their mobility. In the future, these patients may profit from a combination of regeneration and exploitation of neuronal plasticity, as the research in spinal cord regeneration appears to be quite encouraging (for review, see [122]).

Furthermore, robotic rehabilitation devices become increasingly important and popular in clinical and rehabilitation settings for functional training and standardized assessments. Such devices allow a prolonged training duration, increased number of repetitions of movements, improved patient's safety, and less physical demands for the therapists. Novel sensor-, display-, control-, and feedback-information technologies have led to an improvement of training effects. By increasing patient's challenge and participation and by improving the assessments of clinical measures and performance, robots successively become an essential part of neurorehabilitation. In the future, rehabilitation robots offer a platform for the implementation of advanced technologies, which will provide new forms of training for patients with movement disorders. With the use of cooperative control strategies, e.g., by virtual reality technologies, not only the patient's engagement (especially of children) might become enhanced during training sessions but also the motivation to participate in the training can be improved.

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Part II

How Do We Apply Technology (Robots) for Treatment Challenges and Limitations: A Theoretical Framework

Error Augmentation and the Role of Sensory Feedback

5

James L. Patton and Felix C. Huang

Abstract

Brain injury often results a partial loss of the neural resources communicating to the periphery that controls movements. Consequently, the prior signals may no longer be appropriate for getting the muscles to do what is needed – a new pattern needs to be learned that appropriately uses the residual resources. Such learning may not be too different from the learning of skills in sports, music performance, surgery, teleoperation, piloting, and child development. Our lab has leveraged what we know about neural adaptation and engineering control theory to develop and test new interactive environments that enhance learning (or relearning). One successful application is the use of robotics and video feedback technology to augment error signals, which tests standing hypotheses about error-mediated neuroplasticity and illustrates an exciting prospect for rehabilitation environments of tomorrow.

Keywords

Learning • Motor control • Movement • Human • Rehabilitation • Adaptation • Training • Feedforward control

As research continues to support prolonged practice of functionally relevant activities for restoration of function, interactions with technology have revealed new prospects in the areas of motor teaching. The compelling question many researchers are currently pursuing is whether such new applications of technology can go further than simply giving a higher intensity or more prolonged care. This chapter will focus on how robotic devices combined with computer displays can augment error in order to speed up, enhance, or trigger motor relearning. Below, we outline the sources of this rationale, as well as present some early examples.

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5.1 Experience Enables Prediction of Consequences

While neurorehabilitation science is still in early stages with numerous debates, nearly all agree that a key mode of recovery is the nervous system's natural capacity to change in response to experience – neuroplasticity of neural control. Although for brain injuries such as stroke, there are many deficits that may not be related (contractures, weakness, cognitive deficits, attentional deficits, etc.), neuroplasticity is believed to be one of the most powerful and can be leveraged to foster functional recovery through the proper conditions of training, feedback, encouragement, motivation, and time.

Early exploration of training-induced neuroplasticity is hinged on studies of sensorimotor adaptation in healthy individuals. Tasks such as reaching for a cup are thought to be trivial but extremely difficult and frustrating to patients. We often take for granted the challenges of coupled nonlinear arm dynamics [1], long feedback delays [2], and slow activation times for muscle [3], must rely on sophisticated control by the nervous system. Consequently, rapid movements must be preplanned using a prediction or "neural representation" of the outcomes. These representations, also called internal models, are typically acquired via experience [4]. Research has shown that distorting sensory-motor relationships in a variety of ways can alter these representations. For example, mechanical distortions such as holding a heavy weight in one's hand causes errors in reaching accuracy, but people adapt and recover their ability to move normally within a single motion [5]. More complex loads can take hundreds of movements [6–8]. People often stiffen (i.e., co-contract their muscles) as a first strategy [9, 10], but stiffness quickly fades as they learn to counteract the forces, leading to *aftereffects* when forces are unexpectedly removed (Fig. 5.1) [11, 12]. It is important to note that both the adaptation and aftereffects can occur implicitly with minimal conscious attention to any goal. We have shown that this type of training can be used constructively to teach new movements [13, 14].

Motor learning is strongly driven to reduce performance errors [15, 16] and, in particular, deviations from a straight-line hand path in targeted reaching [17, 18]. Experiments have demonstrated that it is possible to train subjects to produce new arm movements [19, 20] or legs [21] by accentuating trajectory errors using robotic forces. Subjects in those studies were exposed to custom-designed force fields that promoted the learning of specific movements by exploiting short-term adaptive processes [22].

5.1.1 The Nervous System Responds Dramatically to Visual and Mechanical Distortions

Similar adaptation can occur when exposed to a visuomotor distortion. The robotic approaches above can be grouped with an older body of research on visuomotor adaptations, such as those induced by prisms (see [23] for a review), rotations, stretches, and other distortions of the conventional hand-to-screen mapping [17, 24, 25]. All of these distortions appear to induce learning and can reduce sensory dysfunction such as hemispatial neglect [26].

5.1.2 Neuroplasticity, Learning, Adaptation, and Recovery

Such adaptation described above, however, might not necessarily reflect long-term learning. There is strong evidence that when a person experiences more than one training experience, the latter experience tends to disrupt or interfere with the former [27–29]. One key premise of robot-mediated training is that adaptation will be retained if the resulting behaviors have functional utility. Our studies and the work of others have demonstrated permanent effects after training in the presence of visuomotor distortions [27, 30, 31]. Hence, individuals de-adapt if conditions require it, but also some motor memory is preserved well beyond the training phase. Here, we use the term "learning," since our ultimate goal is permanence. Further work is needed to understand what neural processes mediate the successful evolution between adaptation and long-term retention, and it may be that the two share many common neural resources, with a continuum between short and long-term neuroplasticity.

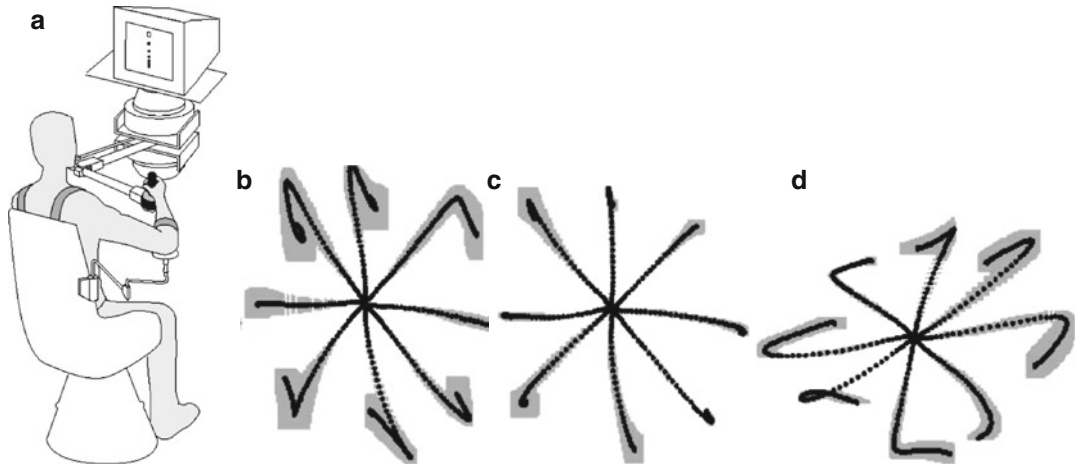


Fig. 5.1 A classic adaptation experiment in which a robot exerts a mechanical distortion. The subject attempted reaching movements to targets in eight different directions. (**a**) Subject seated at the robot, (**b**) initial exposure to the force field, (**c**) at the end of training, movements appear normal. (**d**) Removing the force field unexpectedly results in aftereffects (Adapted from Shadmehr and Mussa-Ivaldi [8])

Quite importantly, these adaptive responses can also be observed in stroke patients. Evidence is found in the oculomotor [32] and limb motor systems [20, 33, 34]. In fact, errors seen in individuals who have suffered a stroke are similar to simulation models that try to imitate the pathology with poor compensation for interaction torques [35] and resemble the problems seen in healthy subjects when they are exposed to force fields. At least part of the impairment has been attributed to "learned nonuse" that can be reversed by encouraging individuals to practice and relearn how to move their arm [36].

5.2 Multiple Forms of Neuroplasticity

Plasticity comes in many forms across many time scales making it difficult to fully identify all underlying mechanisms. Changes can range from very temporary shifts in neurotransmitter concentrations, facilitation or inhibition from collateral neurons, neural growth to establish synapses, or to actual neurogenesis where entire neurons are established. Making this more complicated, neuroplasticity can be seen as residing within a much larger spectrum of mechanisms with overlapping time scales that span short-term adaptation in milliseconds, long-term potentiation over minutes, permanent leaning, muscle hypertrophy, healing, or degeneration of whole tissue structures through development and aging. Finally, there are also aspects of the nervous system's control apparatus that can be seen as hierarchical agents, where people learn to learn, and learn to make decisions to learn. There are many ways in which the nervous system alters its behavior in response to new experiences, and many of these mechanisms are driven by error (Fig. 5.2).

There has been recent debate over whether the neural resources used are the same for adaptation to kinetic and kinematic distortions. Krakauer et al. [28] suggested that learning of kinematic distortions (a 30° rotation of visual display) and kinetic distortions (distortions of added mass) were independent processes because learning one did not interfere with the other. It would appear that these are separate processes (different red lines of Fig. 5.2). Flanagan and colleagues also showed similar results with a visuomotor rotation and a viscous force field [37]. However, Tong and colleagues argued that these studies should not show interference because the kinetic and kinematic distortions involved different variables, and the kinematic rotation depended on position while the kinetic mass depended on acceleration [29]. They demonstrated that when both the force field and the visuomotor rotation depended on

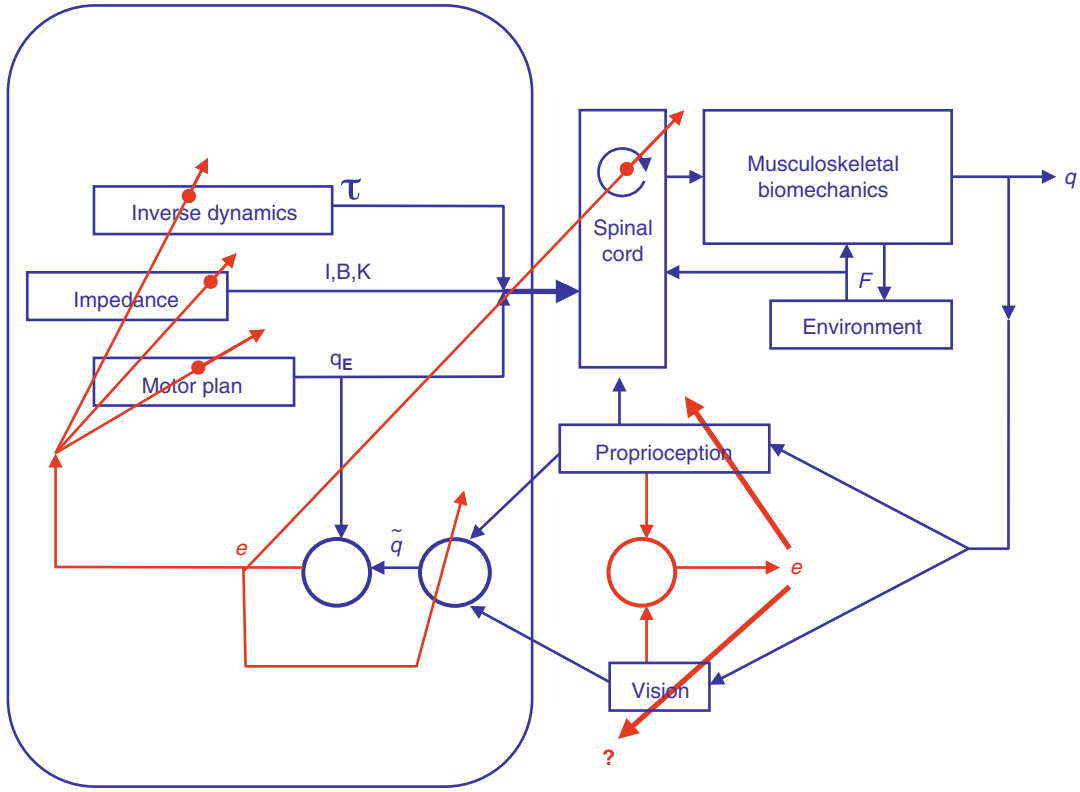


Fig. 5.2 A schematic flowchart that illustrates the believed error-mediated adaptation for the control of movement. News of outcome movements is fed back to the central nervous system to calculate errors, *e*, that is used for adjusting (adapting). Several known mechanisms exist that use error (*red lines*) to make alterations, such as recalibration of the proprioceptive system, alterations in preplanned inverse dynamics, impedance, and the intended trajectory

position (or on acceleration), interference was observed. These results strongly suggest that kinetic and kinematic adaptation occupy common neural resources in motor-working memory. One can take this one step further to test and facilitate rather than interfere, whereby experiencing a mix of force and visual feedback distortions can enhance learning even further [38].

5.3 The Crutch Effect

What is clear is that human–machine interactions have the extremely powerful ability to foster learning, but it is not clear precisely how to program them for therapeutic benefit. One possibility would be to have a system that *guides* one's actions to help one learn. This enables the patient to visit the positions and velocities of a task, being "shown the way" as a template. This template may offer the added benefits of keeping the joint mobile through the range of motion and preventing secondary effects such as contractures from immobility. While this may be an answer for people entirely paralyzed, this provides the correct kinematics without the correct kinetics. While there have been a few studies that have shown a benefit for haptic guidance in learning motions [39–41], it may be that such interaction forces do not ensure that the limb makes the correct motion. In one study on healthy people, simply watching the robot make a template motion caused subjects to learn about as well as the people that practiced with robotic guidance [42].

One problem may be that such guidance algorithms generate unnatural forces unless individuals actively make the desired motion, which renders the guiding robot unnecessary. Guidance interactions are not only unnatural; they may

encourage unwanted resistance, promote laziness, or reduce the subject to inattention. This can remove any desire to learn and lead the individual to simply rely on guidance like one might rely on a crutch. People could literally fall asleep practicing.

5.4 Guidance Versus Anti-guidance

The opposite line of attack – systematically altering the movement to enhance error – may be one possible answer. In an early study of error augmentation, our group focused on the chronic stroke population and compared error-magnifying forces to error-reducing forces in a short therapy session. We exposed hemiparetic stroke survivors and healthy age-matched controls to a pattern of disturbing forces that has been found by previous studies to induce dramatic aftereffects in healthy individuals. Eighteen stroke survivors made 834 movements on a manipulandum robot in the presence of a robot-generated force field. The force field pushed proportional to hand speed, perpendicular to movement direction – either clockwise or counterclockwise (Fig. 5.3a–c). We found significant aftereffects from the stroke-surviving participants, indicating the presence of a reserve capacity for neuroplasticity in these patients that has very little or nothing to do with stroke severity [20]. Significant improvements occurred only when the training forces magnified the original errors and not when the training forces reduced the errors, or when the there were no forces (Fig. 5.3d). Such adaptive capacity in stroke survivors is also supported by evidence that the nervous system is able to reorganize with practice [43]. These results point to a unifying concept: errors induce motor learning, and judicious manipulation of error can lead to lasting desired changes.

5.5 Error Augmentation for Leveraging Neuroplasticity

The great enlightenment philosopher George Berkeley pioneered the idea "Esse est percipi" (to be is to be perceived). Rather than using immersive environments for mere entertainment, technology has recently allowed us to constructively alter behavior through new perceptual distortions, essentially creating a "lie" to the interacting subject in a variety of ways. This is a bright prospect, not only in the world of engineering for rehabilitation but also in many areas in which people must learn to make new actions. One aspect is *error augmentation*, where we isolate and selectively enhance the perceived error.

There are several lines of support for error augmentation approaches for enhancing learning. Simulation models and artificial learning systems can show that learning can be enhanced when feedback error is larger [22, 44–46]. Subjects learning how to counteract a force disturbance in a walking study increased their rate of learning by approximately 26% when a disturbance was transiently amplified [21]. In another study, artificially giving smaller feedback on force production has caused subjects to apply larger forces to compensate [47]. Several studies have shown how the nervous system can be "tricked" by giving altered sensory feedback [17, 48–53]. Conversely, suppression of visual feedback has slowed the unlearning process [14]. It is clear that feedback that provides an error signal can influence learning and that the truth can be stretched for greater effect.

Nevertheless, not all kinds of augmented feedback on practice conditions have proven to be therapeutically beneficial in stroke [54]. It may be that there are limits to the amount of error augmentation that is useful [55, 56]. More error might mean more learning, but it would not seem logical for error augmentation to work in a limitless fashion.

5.6 Choices: Does More Error Mean More Learning?

The optimal method for error augmentation is not yet known and may depend on a number of contexts. We conducted a simple evaluation of the rate change of hand-path error while subjects made point-to-point reaching movements of the unseen arm [57]. Error deviations from a straight-line trajectory were visually augmented with either a

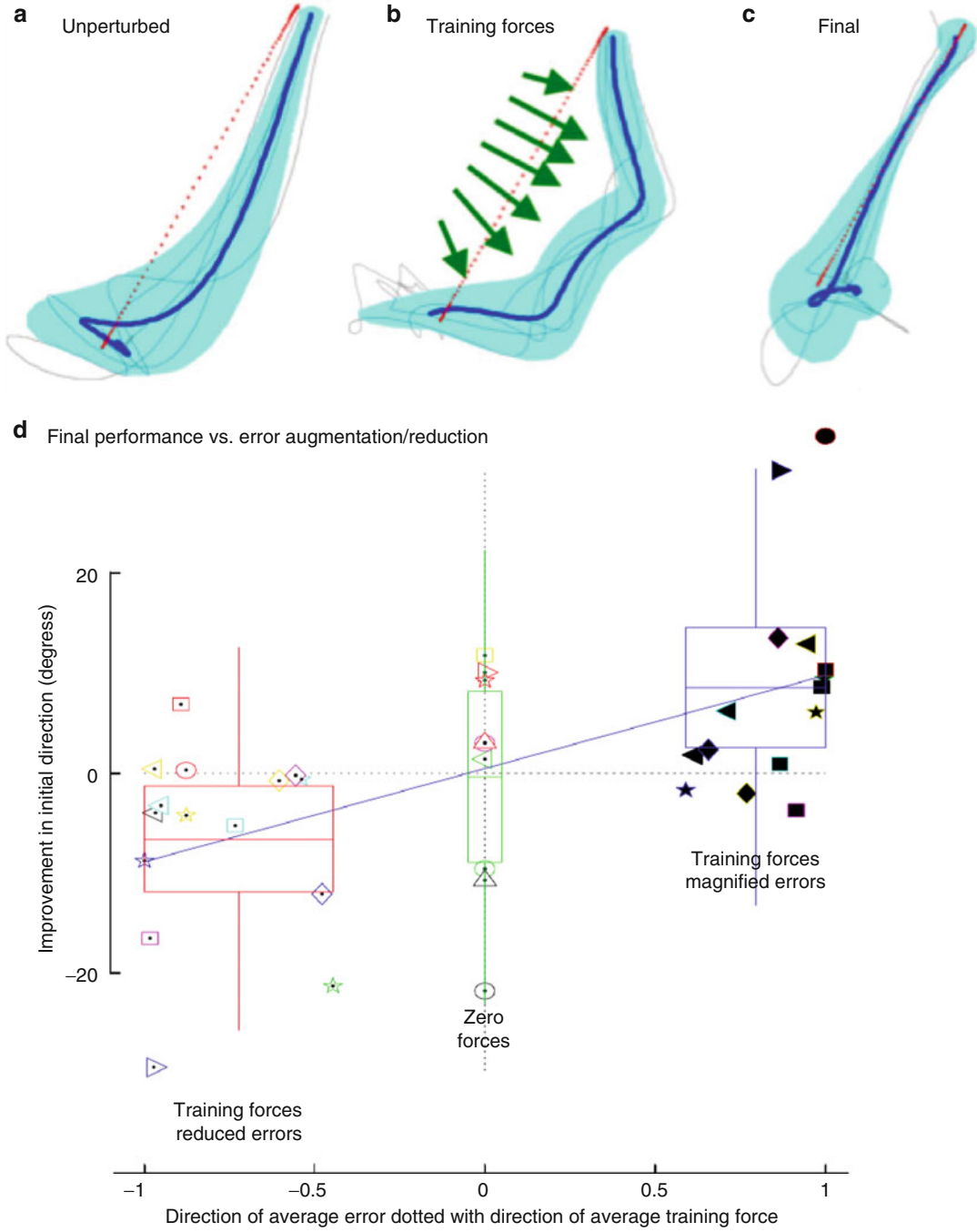


Fig. 5.3 (**a**) One stroke survivor's response to training forces that amplify the original counterclockwise movement error. The force field during training (*arrows* in **b**) resulted in a reduction of error following training that was sustained until the end of the experiment (**c**). (**d**) Cross plot of all subjects' final performance improvements vs the amount of error magnification/reduction in training. Error magnification was determined by calculating the dot product between the average training force direction and the average movement error direction. Performance improvement was calculated by measuring the reduction of initial direction error from the baseline phase to the final phase of the experiment. *Boxes* represent mean and 95% confidence intervals, and *whiskers* indicate two standard deviations (Adapted From Patton et al. [20]; used with permission)

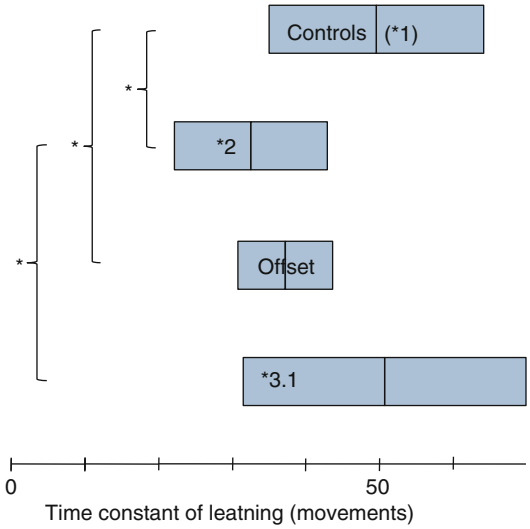


Fig. 5.4 Time constant of error decay during a visual error augmentation trial on healthy subjects, revealing a breakdown in higher gain of error augmentation 3.1. *Error bars* indicate 95% confidence intervals. *Horizontal lines* indicate significant differences (post hoc) between groups

magnification of 2, a magnification of 3.1, or by an offset angular deviation. The smaller time constants (fitting performance changes to an exponential curve) for the *2 and offset groups demonstrated that error augmentation could increase the rate of learning (Fig. 5.4). However the *3.1 group showed no benefit. This result was observed in a similar study where there was diminishing effectiveness from larger errors, causing smaller changes from one movement to the next [58].

The offset group above represents another type of error augmentation via the addition of constant error offset. This is in contrast to error magnification, where learning could become unstable if it causes the subject to overcompensate. Because of motor variability, sensor inaccuracies, and other uncertainties that influence learning [49, 56, 59], error magnification may be practicably limited to small gains. On the other hand, adding a constant bias to augment error may be equally or more effective because noise and other confounding factors would not also be magnified. A constant offset presents persistent errors throughout training, even as the learner improves. This technique may motivate learning longer during practice and hence cause the amount of learning to increase. However, each approach (biasing or magnifying) has their benefits and potential pitfalls: gain augmentation is vulnerable to feedback instability, whereas the biasing approach risks learning beyond the goal.

There are a variety of compelling aspects of error augmentation that arise from the fact that we often evaluate and adjust our control based on the error of previous movements rather than the current one – we learn to walk by repeatedly falling down and trying again. Such *postmovement evaluations* imply that we often are able to gain insights into the nature of the learning process from one attempt to the next. We can also more easily use what is known about how someone responds to prior environmental changes to customize a training environment for the subject. Such co-learning is a compelling new prospect in many areas that include rehabilitation, where the machine encouraging the patient to adapt is itself adapting as learning progresses.

5.7 Free Exploration and Destabilizing Forces

Beyond manipulation of force and trajectory signals, the concept of error augmentation can be further extended to training environments that amplify motor actions. Instead of error with respect to a specified movement, robot-guided training can exaggerate movements in real time, effectively augmenting the dynamic behavior of the arm. Robot assistance can certainly expand human capabilities through assistance as a function of applied forces or speed [60, 61]. Such approaches use *active impedance* such as negative damping. Beyond altering online performance, such augmentations can increase awareness of deviations from expected behavior – information critical for driving adaptation. Furthermore, a major advantage to this form of augmentation is allowing access to coordination training even when weakness limits voluntary motion. Most importantly, however, such augmented environments must both facilitate training and still allow easy transition to unassisted conditions.

To test this form of environment augmentation, we investigated the efficacy of manual skill training

with destabilizing forces, presented by a robotic interface. One key feature of our approach was to allow self-directed movement during training. While goal-directed movement focuses on kinematic performance, we expected that allowing training via exploratory movements would emphasize relevant force and motion relationships. Training on a variety of actions provides better improvement in overall function than repetitions of the same task [62, 63]. The free training paradigm also served as an excellent measure of learning generalization, since the structured evaluations after training (making circles) differed from the practice.

We found that improvements in performance persisted even when destabilizing forces were removed, and that training with combined negative viscosity and inertia resulted in superior learning when tested in the isolated inertial conditions [64]. In a follow-up study with stroke survivors (Fig. 5.5), similar training with negative viscosity resulted in improved coordination skill within a training session, while no improvement was observed in the control group where no forces were administered. It is important to emphasize that each group was evaluated in the absence of applied forces, which demonstrates that patients' training with negative viscosity does transfer to positive skills in the real world.

5.8 Making Error Augmentation Therapy Functionally Relevant

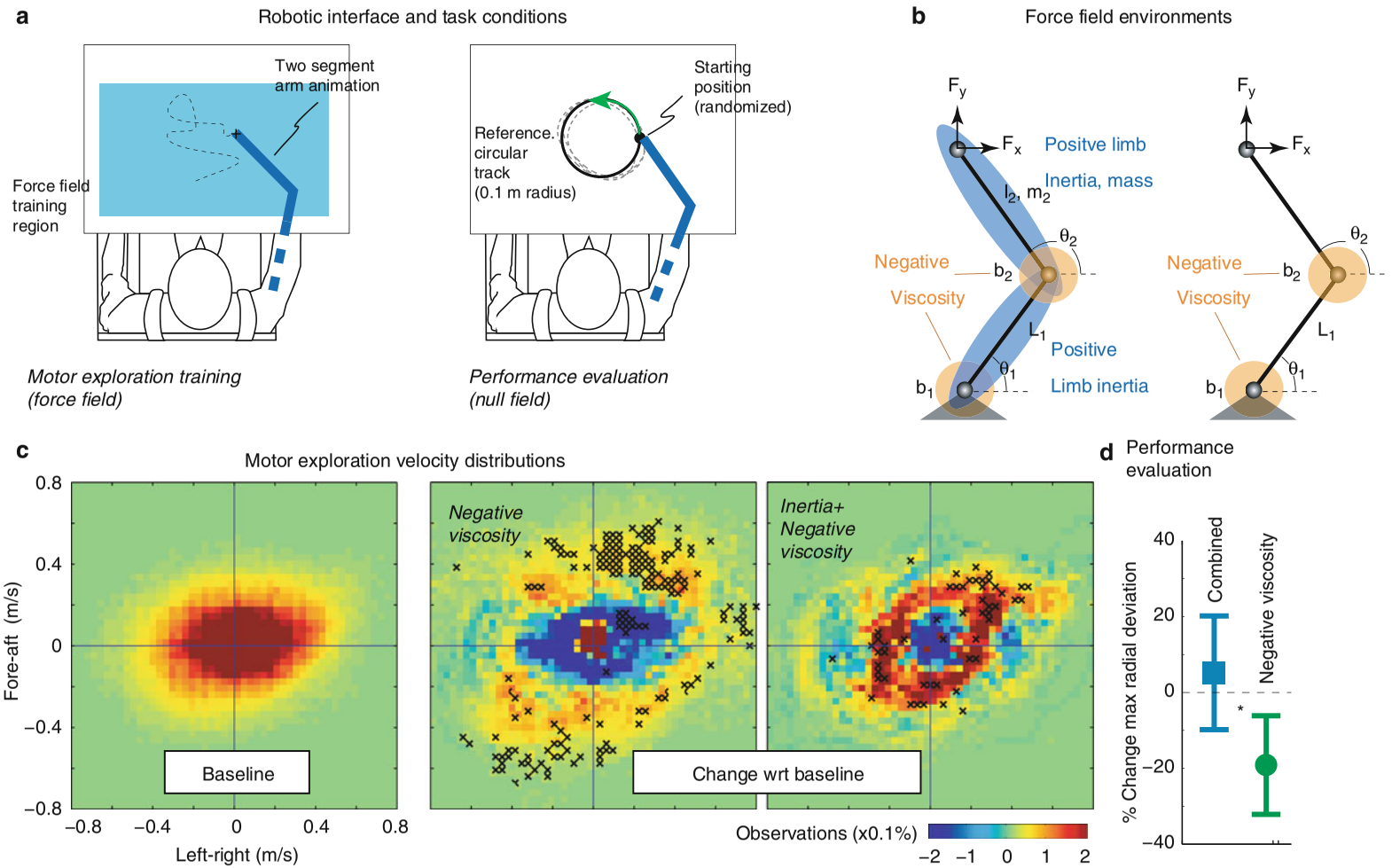
When a robotic device is coupled with a three-dimensional graphic display, the sensorimotor system is able to engage all the types of visual and motor learning described above [65, 66]. The haptic actuator is typically a specially designed robot to allow the user to easily move (back-drive) and may also exert forces that render the sense of touch. The augmented reality graphic display presents images in stereo, in first person, and using head tracking to appropriately correspond to the current eye location (Fig. 5.6). Images can be superimposed on the real world.

These haptic and graphic virtual environments offer several advantages. First, properties of objects can be changed in an instant with no setup and breakdown time. This element of surprise is critical for studying how the sensorimotor system reacts and learns to move in new situations. For rehabilitation, friction or mass can be suppressed, or mass can be reduced during the early stages of recovery.

A few studies have explored such virtual reality for rehabilitation [67–75] although many other studies on virtual reality applications for rehabilitation fail to effectively test how this technology can offer added benefit in clinically facilitating motor recovery. One concern is whether any training benefits are retained. Evidence from studies of healthy individuals shows little retention beyond the time that adaptation typically "washes out." Such findings, taken in isolation, would suggest reasons not to treat with error augmentation. Recent work, however, reflects a more careful approach to understanding retention and, more importantly, the accumulation of benefit from repeated visits [76].

In this recent study, stroke survivors with chronic hemiparesis simultaneously employed the trio of patient, the therapist, and machine. Error augmentation treatment, where haptic (robotic forces) and graphic (visual display) distortions are used to enhance the feedback of error, was compared to comparable practice without such a treatment. The 6-week randomized crossover design involved approximately 60 min of daily treatment three times per week for 2 weeks, followed by 1 week of rest, then another 2 weeks of the other

Fig. 5.5 Patients benefit from free exploration training with robot-applied negative viscosity to augment error. (**a**) The robot interfaced to the arm about a free pivot at the wrist. Subjects were allowed to freely interact with each load in a "motor exploration" stage. Following exploration, subjects made counterclockwise circular movements during task performance trials at random starting locations of a 0.1-m radius circular track. (**b**) The virtual arm augmented the existing dynamics of the human arm with negative viscosity in the elbow and shoulder and/or positive inertia to the upper and forearm. (**c**) Stroke survivors ($n = 10$) perform motor exploration with no load, revealing average baseline distribution with evident asymmetry in range. Negative viscosity training prompted significant increases (indicated as x's) especially in elbow flexion-extension. (**d**) Tests of learning show error decreased ($-19.1 \pm 0.1\%$, $p = 1.3e-2$) from negative viscosity training, while no change was found from inertia + negative viscosity training ($+5.1 \pm 16.2\%$, $p = 4.3e-1$)


a
Robotic interface and task conditions
Two segment
arm animation
Force field
training
region
Reference
circular
track
(0.1 m radius)
Starting
position
(randomized)
Motor exploration training
(force field)
Performance evaluation
(null field)
b
Force field environments
Fy
Fx
Positve limb
Inertia, mass
l2, m2
θ2
Negative
b2
Viscosity
L1
Positive
θ1
b1
Limb inertia
c
Motor exploration velocity distributions
Fore-aft (m/s)
Left-right (m/s)
0.8
0.4
0
−0.4
−0.8
Baseline
Negative
viscosity
Inertia+
Negative
viscosity
Change wrt baseline
Observations (x0.1%)
−2 −1 0 1 2
d
Performance
evaluation
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40
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Combined
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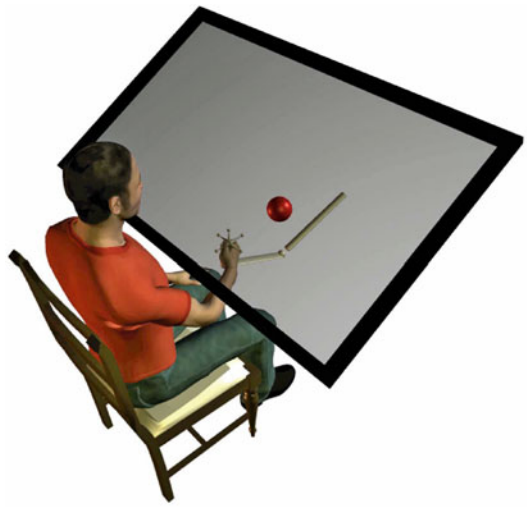

Fig. 5.6 A subject seated at a large workspace haptic/graphic display

treatment. A therapist teleoperated the patient using a tracking device that moved a cursor in front of the patient, who was instructed to match it with their hand's cursor (Fig. 5.7a). Error augmentation, using both haptic ($\boldsymbol{F} = 100[N/m] \bullet \boldsymbol{e}$) and visual ($\boldsymbol{x} = 1.5 \bullet \boldsymbol{e}$) exaggeration of instantaneous error, was employed for one of the 2-week periods without being disclosed explicitly to anyone (thus blinding the patient, therapist, technician-operator, and rater). Several clinical measures gauged outcome at the beginning and end of each 2-week epoch and 1 week post training. Results showed incremental benefit across most but not all days, abrupt gains in performance (Fig. 5.7b), and most importantly, a significant increase in benefit to error augmentation training in final evaluations. This application of interactive technology may be a compelling new method for enhancing a therapist's productivity in stroke functional restoration.

5.9 Why Might Error Augmentation Work?

While there are several mechanisms for how error augmentation might work, a full understanding of the sources is not known. One possible mechanism is that elevating error simply motivates subjects to persistently try to reduce error until they see an acceptably small (perhaps zero) error. A number of modeling and experimental systems have demonstrated better and faster learning if error is larger [15, 44, 77, 78]. Error bias, such as in the offset condition mentioned above, can lead a subject to "overlearn" beyond the desired goal, but this technique may be otherwise beneficial in situations where subjects do not fully learn. Based on our findings, we speculate that mixtures of force and visual distortions, combined with offset-based and gain-based error augmentation, might be optimal. However, optimal parameters governing such a mixture are not yet known and are likely to differ from patient to patient.

Another possible reason why error augmentation may lead to benefits is that the impaired nervous system is not as sensitive to error and hence does not react to small errors. Error augmentation might make errors noticeable by raising signal-to-noise ratios in sensory feedback. It may heighten motivation, attention, or anxiety, which has been suggested to correlate with learning [79]. Errors that are more noticeable may trigger responses that would otherwise remain dormant.

Error perception appears to be on a continuum that is not yet understood. Error *reduction* appears to stifle learning [80], and suppression of visual feedback has been shown to slow down the de-adaptive process [14]. This suggests that less perceived error could reduce learning. Considering the other extreme, too much error augmentation appears to dampen results, thus suggesting that there is a sweet spot of error augmentation intensities. The nervous system may react to excessively large error signals by decreasing learning so that there is little change in response to subsequent performance errors. Large errors thus may be regarded as outliers by a nonlinear "loss function" that governs motor adaptation [56]. These and other studies that induce sensorimotor conflict suggest that the nervous system can quickly "adapt its adaptation" by reweighing the interpretation of sensory information if it no longer is perceived reliable [49, 81].

Regardless of the mechanism, the bioengineering community is now observing successes with error augmentation, and the clinical research world

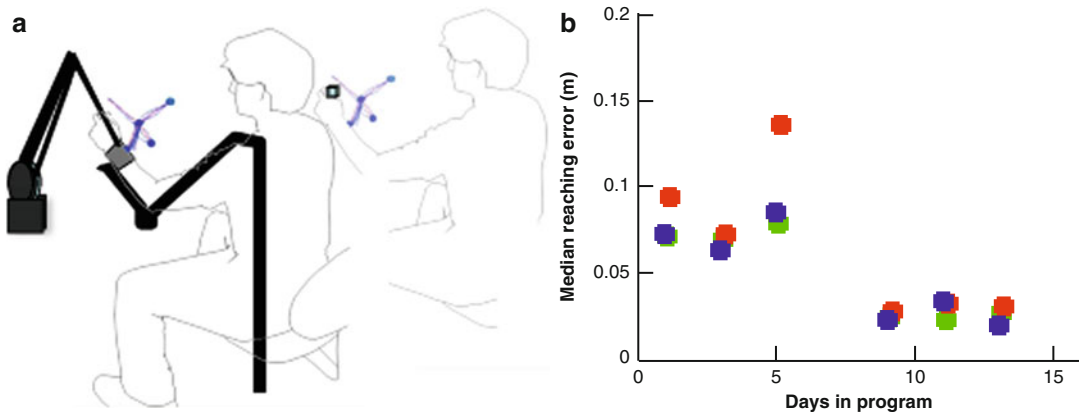

Fig. 5.7 (**a**) An error augmentation application for stroke rehabilitation where a subject and therapist work together, seated and using the large workspace haptic/graphic display to practice movement. The therapist provides a cue for the subject, and can tailor conditioning to the needs of the patient. The robot provides forces that push the limb away from the target, and the visual feedback system enhances the error of the cursor. (**b**) Typical chronic stroke patient improvement from day to day, each dot representing the median error measured for a 2-min block of stereotypical functional movements. While the patient shows progress across the 2-week period and final benefit, this person did not always improve each day

calls for more studies on its optimal application. These new studies should also reveal new insights on how the nervous system learns and recovers after injury. There is a clear advantage to such *distorted reality* feedback, where judicious manipulations of visual information can lead to practical improvements in the extent and rate of learning. Research also suggests that these training approaches may be broadly effective in facilitating motor learning in sports, piloting, performing arts, teleoperation, or in any other training situation requiring repetitive practice and feedback.

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Applying Principles of Motor Control to Rehabilitation Technologies

6

Robert L. Sainburg and Pratik K. Mutha

Abstract

Research into the neural control of movement has elucidated important principles that can provide guidelines to rehabilitation professionals for enhancing recovery of motor function in stroke patients. In this chapter, we elaborate four major principles of motor control that have been derived from this research: optimal control, impedance control, neural representations of movement, and motor lateralization. Research on optimal control has indicated that two major categories of cost contribute to motor planning: explicit task-level costs, such as movement accuracy and speed, and implicit costs, such as energy and movement variability. Impedance control refers to neural mechanisms that modulate rapid sensorimotor circuits, such as reflexes, in order to impede perturbations that cannot be anticipated prior to movement. Research on neural representations has indicated that movements are represented in at least two different types of coordinate systems: an extrinsic coordinate frame describing the space outside the body and an intrinsic reference frame describing the relative positions and movements of the body segments relative to one another. Finally, research on motor lateralization has indicated that different aspects of motor control have been specialized to the two cerebral hemispheres. In this chapter, we discuss the neurobiological basis of these four principles

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and elaborate the implications for designing and implementing occupational and physical therapy treatment for movement deficits in stroke patients.

Keywords
Motor control • Optimal control • Impedance control • Motor lateralization • Neural representation

6.1 Introduction

Deficits that result from strokes in sensory and motor regions of the brain represent a major impediment to recovery of function in activities of daily living for stroke survivors. Such deficits most commonly include hemiparesis, a syndrome encompassing unilateral motor dysfunction on the side of the body opposite to the brain lesion, and spasticity, characterized by abnormally high muscle tone and atypical expression of reflexes. Not surprisingly, occupational and physical therapy interventions have focused on alleviating motor disabilities following stroke, and have done so by exposing patients to a range of movement activities, with a major focus on repetitive experience or practice. In general, the intensity and amount of practice correspond to improvements in motor function, as measured by a variety of scales [1]. Unfortunately, gains made during therapy often show limited translation to activities of daily living (ADLs) and minimal carryover to the home environment.

Over the past decade, rehabilitation approaches have incorporated a new class of advanced technology intervention tools that can provide more cost-effective means of achieving higher intensity practice over longer periods of time. These computer-based and robotic technologies have been shown to at least match the efficacy of traditional therapy in promoting improvements in motor performance [2]. However, these interventions hold greater promise than simply replicating traditional therapy, by providing therapists with an unprecedented ability to specify and measure movement features such as movement speed, direction, amplitude, as well as joint coordination patterns. As these technologies become more readily available in the clinic, the most pressing question is how therapists can utilize these powerful tools to accelerate recovery in functional performance following stroke. In this chapter, using upper extremity reaching movements as a behavioral model, we will review principles that have been developed from research in motor control and learning that can be used to guide specific training strategies using computer-based movement interventions.

6.2 Principle 1: Optimal Control

While most therapists recognize that practice and repetition of motor activities leads to improvements in motor performance, a systematic identification of which movements should be practiced is often lacking. This is partly because the question of what defines a desirable movement has yielded no clear answer. Traditionally, a common guiding principle employed in occupational and physical therapy has been to make movements more "normal." Thus, the goal is to develop movement patterns that are similar to those exhibited by nonimpaired individuals. This idea emerged from the observation that certain characteristics of movements made by healthy individuals are fairly similar within a given task and even across tasks. For example, when reaching for an object in space, movement trajectories across healthy individuals appear fairly straight and smooth [3]. Such reliability of motor behavior is particularly interesting because of the abundance of possible solutions to most movement tasks and the variety of environments we move in. For example, when reaching for a cup of coffee in front of us, we have the choice of using one arm or both arms, standing up or remaining seated, leaning the trunk forward or reaching

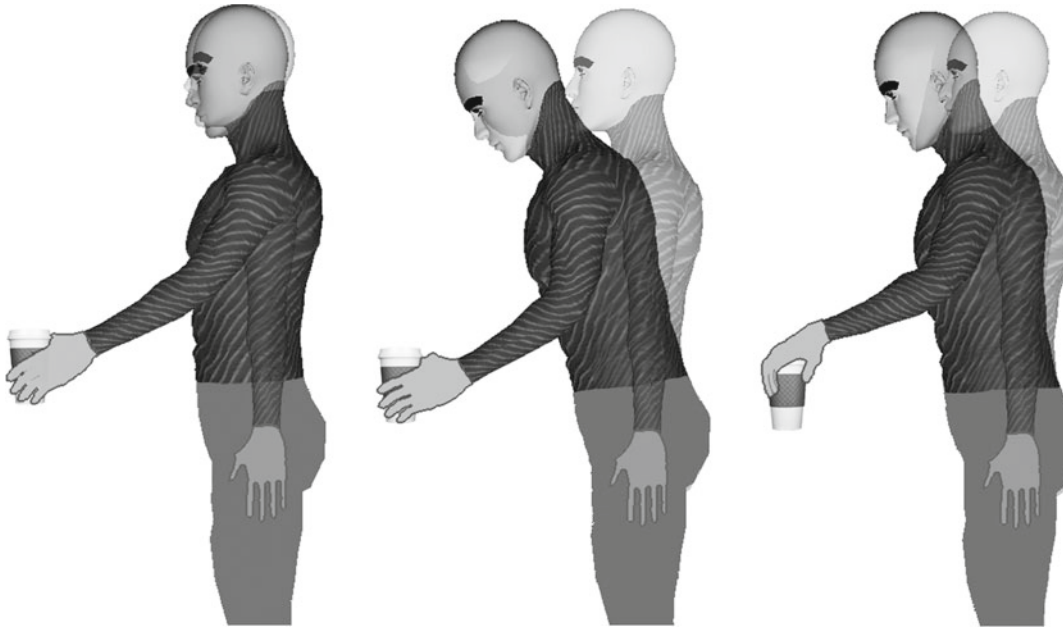

Fig. 6.1 Different ways of picking up a coffee cup starting from the same initial posture. The left pose involves shoulder flexion and elbow extension. The middle pose involves flexion of the trunk, slightly less shoulder flexion, and more elbow extension. The right pose shows some trunk flexion, shoulder abduction, elbow flexion, and forearm pronation

further with the selected arm(s), twisting our trunk to require shoulder abduction, or keeping it straight to require shoulder flexion, among other options (see Fig. 6.1). In addition, the relative motions between our body segments can produce a wide variety of curved trajectories of the hand in order to procure the cup. Each possible motion can also be achieved at a variety of speeds, as well as a variety of possible muscle activation patterns. There are literally infinite solutions to this simple task.

Regardless of these vast possibilities, people tend to display movement patterns that are consistent across different instances of the same movement or even across different movements, whether made by the same or different individuals. These similarities are often referred to as "invariant characteristics" of movement. Many studies have shown that when different people make reaching movements, invariant characteristics include approximate straightness of the hand trajectory and smooth bell-shaped velocity profiles (see Fig. 6.2) [3–7]. How do different people arrive at similar solutions within and across tasks despite the extensive redundancy in the musculoskeletal system and the diversity and uncertainty of the environments we move in? One way to arrive at the "best" solution when confronted with many different options is to employ optimization strategies when planning the movement. Optimization procedures have been developed for use in engineering applications and seek the minimum or maximum value for a given "cost function," subject to a set of constraints. For example, we can find the minimum price of a pound of coffee (function) for all the stores within a 10-mile radius of our house (constraint). Whereas this particular problem may be quite trivial, optimization routines are typically employed to find values for more complex problems, such as might be applied to human movement. Researchers have tested various cost functions that make sense heuristically and have shown that optimization of these costs reproduces many invariant characteristics observed in human motion. For example, Flash and Hogan [5] tested the idea that the smoothness of hand trajectories might reflect an important cost in the planning of

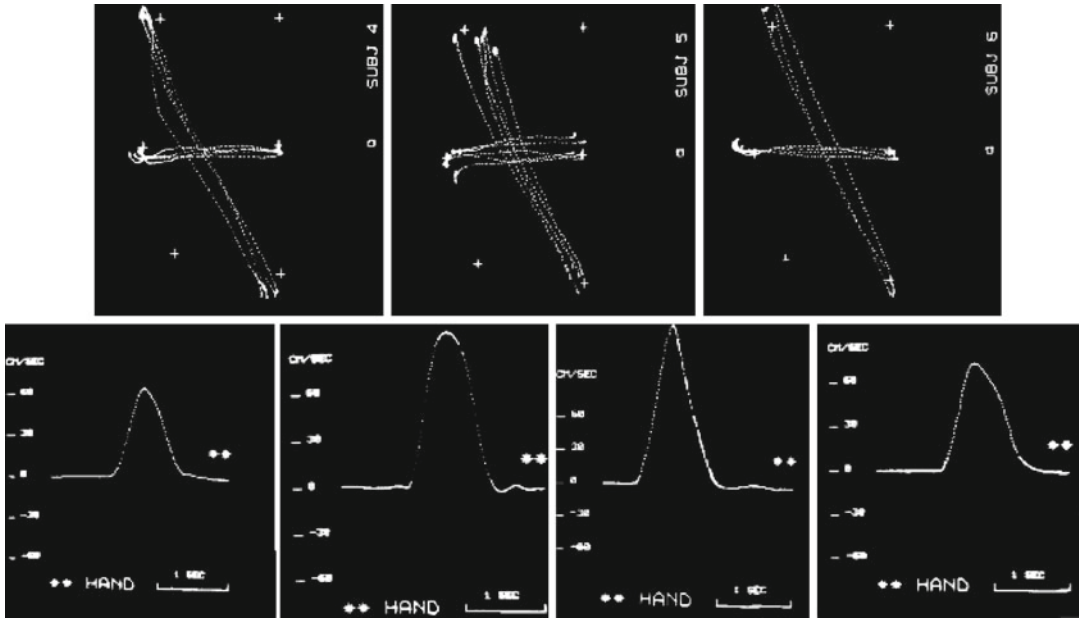

Fig. 6.2 Some "invariant characteristics" of point-to-point movements. The *top panel* shows fairly straight trajectories for multiple movements starting from and ending at varying locations for three different subjects. The *bottom panel* shows fairly similar bell-shaped velocity profiles for four different movements (Adapted from Morasso [3], with kind permission from Springer Science + Business Media; © 1981)

reaching movements and proposed a model that minimized the jerkiness of the hand trajectory (mathematically defined as derivative of acceleration with respect to time). Their simulation predicted straight movements with symmetrical, single-peaked, bell-shaped velocity profiles.

However, under several experimental conditions, minimum jerk trajectories and experimentally observed hand paths diverged, which led researchers to examine other plausible cost functions. For example, some researchers speculated that mechanical aspects of movements might reflect important costs for planning movements. Such cost functions have included mean squared torque change [6], peak work [8], or muscle energy [9] among others. These models accounted for some experimental observations that could not be accounted for by optimizations based on kinematic parameters [7]. While minimization of cost functions such as smoothness or torque change accurately predicted average behavior, Wolpert and colleagues [4] also accounted for the small, yet important, trial-to-trial variability seen during repetitions of the same task. They proposed that motor commands are corrupted with variability inducing noise, and in the presence of such noise, the CNS seeks to minimize the variance of the final arm position. This model also predicted many observed invariant characteristics of movements such as trajectory smoothness and the trade-off between movement accuracy and speed.

Two important inferences can be drawn from studies that have attempted to explain movement patterns based on optimization principles: (1) the nature of the costs associated with different tasks is often different, and (2) costs such as neural noise and mechanical energy do not reflect variables that we tend to have conscious awareness of, yet they appear to be accounted for during the process of motor planning. In other words, the planning of movements entails explicit performance criteria that are associated with successful task performance, such as getting hold of a cup of coffee, but also entails implicit criteria that we do not consciously consider, such as making energetically efficient and reliable movements.

An important aspect of the models discussed above is that optimization of a single cost function

yields a desired trajectory that is then simply executed in an open-loop manner, once it is planned. The role of sensory feedback mechanisms in these models is simply to correct deviations from the planned or desired trajectory, regardless of whether these deviations resist or assist in task completion. Thus, the output of feedback circuits is not incorporated in the optimization phase. More recently, the idea that determination of an optimal "control policy" incorporates knowledge about the "state" of the body and the environment, as relayed by feedback circuits, has gained prominence. According to this idea, the optimal solution is the best possible transformation from the current state to the motor commands that aid in achieving the task goal [10]. Not too surprisingly then, this *optimal feedback control* scheme yields task-specific cost functions that often represent a hybrid mix of explicit task-level variables that relate to performance goals, such as movement precision, as well as implicit mechanically related costs that correspond to muscle force or effort. For example, in a task that examined corrections to target displacements that occurred late in the movement, Liu and Todorov [11] recently showed that subject performance could be best described using a composite cost function that optimized for movement duration, accuracy, endpoint stability, and energy consumption. More importantly, subjects implicitly changed the relative contribution of these costs as the accuracy and stability requirements of the task were changed. Thus, rather than adopt a fixed policy across task conditions, subjects were able to flexibly adapt their control strategy in order to ensure maximum task success. These ideas of flexible control strategies and hybrid cost functions that include task-related and intrinsic biomechanical variables have important implications for designing therapy regimes.

6.2.1 Implications for Rehabilitation

It is important to recognize that damage to the CNS from stroke and the associated secondary changes in the musculoskeletal system could induce changes in the set of possible solutions as well as the costs associated with any given task. Therefore, patients may arrive at solutions to a motor task that may not look "normal," but may be "optimal" given their unique physiological and biomechanical pathologies. Thus, rather than simply attempting to make movements look more "normal," it is important to understand the biomechanical costs associated with different tasks. Most importantly, if movements of the hemiparetic arm elicit energetic costs that are substantially higher than those of the ipsilesional arm, it is very unlikely that the hemiparetic arm use will be spontaneously integrated into activities of daily living. As the technologies discussed in this volume become available in the clinic, assessment of biomechanical variables, such as joint power, will also become available. While most clinical assessments of function include either the ability to perform certain ADL tasks (Functional Independence Measure, FIM [12]) or the ability to perform simulated ADL tasks in particular times (Jebson–Taylor Hand Function Test, JHFT [13]), we suggest that direct analysis of biomechanical costs may provide an important supplement to these tests, as an indicator of energetic efficiency. This should provide a valuable addition to therapeutic assessment because even when ADLs are completed independently, if they are not performed within reasonable energetic costs, one might expect minimal carryover into the patient's spontaneous behavior.

It should be stressed that the role of task-level costs is also important for determining optimal control strategies for a given task. Such costs might include the accuracy and duration of movements. Computer-based technologies allow therapists to modify feedback to stress particular performance criteria, so as to emphasize certain costs. For example, in a targeted reaching task, one could provide reward based on duration, when focusing on improving movement time. However, if movement direction and straightness need to be stressed, visual feedback can be modified to amplify errors perpendicular to the desired trajectory while reducing errors in the direction of the desired movement. Such changes would penalize deviations from the desired movement

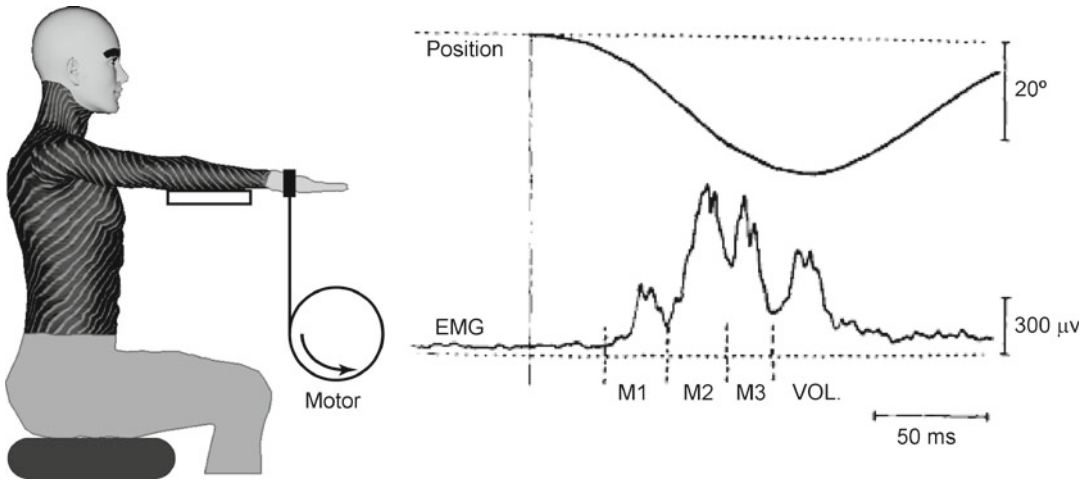

Fig. 6.3 Typical reflex response to muscle stretch. An example of the wrist extensor being stretched using a motor is shown on the *left*. The *right panel* shows the typical components of the electromyographic response to muscle stretch: the short-latency component M1 and the longer-latency components M2 and M3 (Adapted from Matthews [15], with permission from Elsevier)

path while allowing errors in the direction of movement. This approach would assign different costs to errors that contribute to task success versus those that do not. These types of capabilities are now becoming possible in the clinic, due to the increasing availability of computer-based robotic and virtual reality technologies.

6.3 Principle 2: Impedance Control

Optimal feedback control theory emphasizes that the derivation of the optimal control signal incorporates knowledge about the state of the body and the environment, as relayed by feedback circuits. If the state changes unexpectedly due to an external perturbation, or random noise, what should its influence be on the control strategy? For example, when a passenger in a vehicle drinks a cup of coffee, what should the control system do when the movement of the cup is unexpectedly perturbed by a bump in the road? Ideally, the components of the perturbing forces that assist in bringing the cup to the mouth smoothly should not be impeded. However, the components of the forces that resist in achievement of the task goal, such as accelerating the cup too rapidly, or in the outward or downward directions, should be compensated. According to the principle of minimal intervention proposed by optimal feedback control, the central nervous system "intervenes" only when errors are detrimental to goal achievement. Such a selective compensation of errors might explain why people allow slight variability in their performance as long as the overall goals of the task are satisfied. This compensation can reflect both short-latency, automatic responses, such as reflexes, as well as longer-latency reactions, which include voluntary corrections to movement errors. In this discussion, we will focus primarily on short-latency, involuntary responses since these responses typically have not been considered in previous rehabilitation protocols.

This type of selective modulation of feedback gains is consistent with evidence that even the simplest feedback circuits, reflexes, can be modulated based on task demands. The stretch reflex represents the simplest and most ubiquitous feedback circuit in the mammalian system. The typical response to a stretch of a muscle includes a characteristic three-phase response [14, 15], measured in the electromyogram (EMG) as shown in Fig. 6.3: The shortest-latency response, often referred to as M1, occurs within some 20–50 ms following perturbation onset and reflects circuitry

contained within the spinal cord. Following this, a medium-latency response, M2, is observed some 60–80 ms following the perturbation onset and is thought to reflect longer-latency spinal as well as transcortical circuits. This is followed by M3, a longer-latency reaction that is thought to reflect a voluntary corrective process. Studies examining how these responses are modulated have shown differential effects of different task conditions on the early and later phases of the reflex.

Early studies in which subjects were instructed to *resist* or to *not resist* a perturbation showed that M1 was not modified by such commands, while M2 could be greatly attenuated by the instruction to not resist, and M3 could actually be completely eliminated by this instruction [16]. More recent studies have shown that M2 can be modulated by spatial conditions in a task, such as when subjects are told to allow their hand to displace toward a particular target: When the arm is pushed toward the target, the later phases (M2, M3) of the stretch reflex that resist the perturbation are reduced. However, when the arm is pushed away from the target, the gains of these responses are increased. More importantly, this modulation varies with both the direction and the distance of the target [17]. This demonstrates that feedback circuits such as reflexes can be modulated in accord with task goals through implicit mechanisms. In fact, modulation of reflexes appears to be a fundamental mechanism that our nervous system employs to control limb impedance and thus resist perturbations. An elegant example of such reflex modulation was provided by Lacquaniti and colleagues for a ball-catching task [18]. This study demonstrated not only modulation but also reversal of the stretch reflex, in response to ball impact. Both the amplitude and expression of the stretch reflex were modulated in a systematic way as the ball dropped toward the hand. The result of this reflex modulation was to generate mechanical impedance to the forces imposed by ball impact, thereby generating a smooth and effective catching response.

Why is active impedance control through reflex modulation important for motor performance? During everyday tasks, environmental perturbations can rarely be predicted prior to movement. In the example of a passenger drinking coffee in a moving vehicle, changes in vehicle acceleration due to bumps and braking can rarely be anticipated. One can increase overall arm stiffness by coactivating muscles, but this uses a great deal of metabolic energy and interferes with the ability to bring the cup to the mouth. Franklin and colleagues directly tested how subjects might selectively modify impedance without interfering with coordination of the intended movement [19]. In this study, subjects performed reaching movements with the arm attached to a robotic manipulandum that imposed unstable force fields that had components directed perpendicular to the required movement (see Fig. 6.4a). With practice, the participants were able to adapt to the novel dynamics and produce straight trajectories. They achieved this adaptation by selectively increasing stiffness in the direction of the instability, but not along the movement direction (see Fig. 6.4b). Remarkably, at the joint level, this impedance modification was achieved without changing baseline force and torque profiles (see Fig. 6.4c): The coordination strategy remained kinetically efficient, even though subjects were also able to effectively impede the imposed perturbations. These authors concluded that the nervous system is able to simultaneously maintain stability through impedance control and coordinate movements in a manner consistent with optimized energy expenditure.

We recently showed that such selective modification of limb impedance occurs through continuous modulation of short- and long-latency reflexes [20]. In our study, participants reached to a visual target that occasionally jumped to a new location during movement initiation, thus changing the task goal during the course of motion. Unpredictable mechanical perturbations were occasionally applied, 100 ms after the target jump. Our results showed that reflex responses were tuned to the direction of the target jump: Response amplitudes were increased or decreased depending on whether the perturbation opposed or assisted achievement of the new task goal, respectively. We also showed that this reflex modulation resulted in changes in limb impedance to the perturbations. However, under conditions

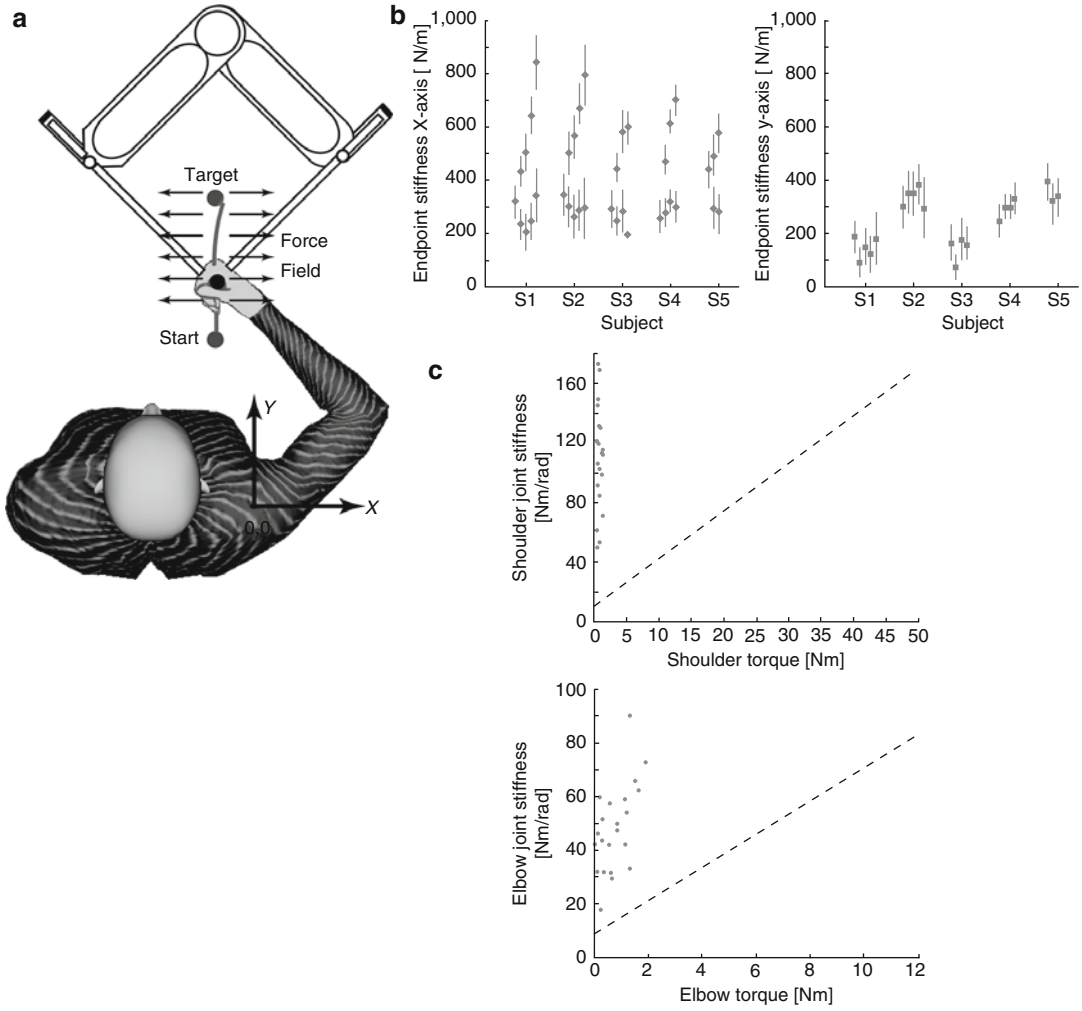

Fig. 6.4 Modulation of limb impedance. (**a**) The typical setup and the perturbing force field. The field acts to push the arm perpendicular (along *X*-axis) to the direction of motion (*Y*-axis). (**b**) An increase in limb stiffness along the *X*- but not *Y*-axis for all subjects. (**c**) Shoulder and elbow joint stiffnesses were independent of the respective joint torques (Adapted from Franklin et al. [19])

in which the movements were not mechanically perturbed, no changes in EMG or joint torque occurred at reflex latency relative to movements made with mechanical perturbations. These findings supported those of Franklin and colleagues by confirming that limb impedance is controlled without interfering with optimal coordination, by selectively modulating the expression of short- and long-latency reflex responses.

The studies discussed above point to the remarkable ability of the nervous system to determine optimal responses to unpredictable situations. Such control policies appear to mediate the modulation of limb impedance through regulation of feedback circuits such as reflexes to ensure that unexpected perturbations are countered in a task-specific manner. Reflexive resistance to a perturbation is increased when it is inconsistent with the task goal, but decreased when the perturbation is congruent with the goal of the task. These findings agree with the "minimum intervention principle" within the optimal feedback control framework. Thus,

controlling limb impedance in a task-specific manner appears to be an integral component of the motor control process.

6.3.1 Implications for Rehabilitation

The research summarized above indicates that the central nervous system invokes at least two aspects of control to achieve coordinated movements. First, the commands are specified that result in optimal coordination patterns that satisfy both costs associated with task performance and energetic costs. In addition, the nervous system appears to set control policies that modulate sensorimotor circuits, such as reflexes, to account for perturbations from unexpected changes in environmental or internal conditions. The importance of recognizing both of these features of control in clinical environments is fundamentally important because brain damage due to stroke can have differential effects on these two aspects of coordination. For example, Beer et al. [21] showed that hemiparesis disrupts optimal intersegmental coordination, resulting in inefficient coordination that fails to account for the dynamic interactions between the segments. This deficit does not appear to depend on extent of hemiparesis.

Traditional therapeutic strategies, as well as more recent robot-aided rehabilitation strategies, tend to target the optimal control process by practicing fairly consistent patterns of coordination and reinforcing task success. While this type of practice is critical for improving coordination and voluntary control, focusing on repetitive movements under consistent environmental conditions should only be a first step in rehabilitation training. In itself, this training may improve voluntary control of optimal coordination patterns, but is unlikely to train impedance control mechanisms. Because of this, patients may become adept at the training protocols, but show limited transfer to ADLs. We suggest that as patients improve their movement patterns under predictable conditions, training protocols should progressively incorporate unpredictable conditions. Such conditions might include random changes in target positions and varying force perturbations, thereby training patients to impede variations in environmental conditions that interfere with task performance.

6.4 Principle 3: Neural Representations of Movement

The literature reviewed above suggests that the nervous system takes into account costs related to task-level variables such as accuracy and precision as well as variables associated with biomechanics and energetics when determining optimal motor performance. Decades of neurophysiological research has supported the idea that neural representations of movement are best described in coordinates that reflect both of these categories of variables. Two general types of coordinate frames that have been used to describe neural representations of movement are extrinsic and intrinsic coordinates. An extrinsic coordinate frame is described relative to a space independent of the body, such as room coordinates, and is independent of body movement. For example, whether you are standing on your hands or your feet, the upward direction relative to the room (extrinsic coordinates) is always toward the ceiling. In contrast, an intrinsic coordinate frame describes the movements of specific body segments, relative to one another, or the activations of muscles. For example, elbow joint angle is a coordinate describing the angle between the upper arm and forearm, regardless of one's orientation in space. Both of these types of coordinates afford the nervous system with different types of information about a movement, for example, how the movement conforms to task requirements, as well as how energetically efficient the movement might be performed.

The seminal research by Georgopolous and colleagues showed that activity of neurons in primary motor cortex (M1) is broadly tuned, with maximum activity in a "preferred direction," defined in an extrinsic coordinate frame [22]. They trained monkeys to reach to targets presented in a range of directions from a central start location. The recorded neural activity could be

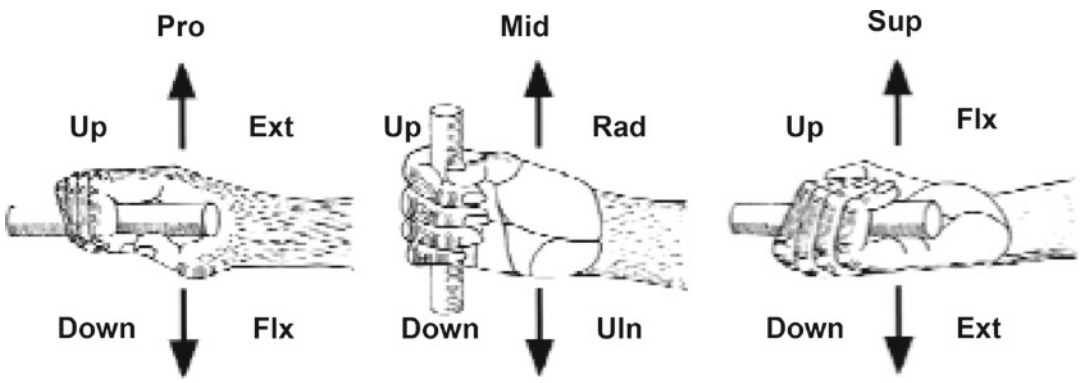

Fig. 6.5 Extrinsic and intrinsic coordinate frames defined by variations in hand orientation. Extrinsic directions (up and down) remain the same for all three orientations (pronation, mid, supination). Intrinsic coordinates (flexion and extension) are defined based on wrist angle and change based on changes in hand orientation (Adapted from Kakei et al. [34], with permission from Elsevier)

represented as a "population vector," computed as the vector sum of the activities of individual neurons. This vector corresponded with the direction of the hand movement, represented extrinsically. These findings showed that extrinsic, task-level variables, such as the direction of the hand motion in space, appear to be represented in primary motor cortex. Research examining other task-related variables, such as movement speed and distance, showed that these variables are also encoded in the activity of motor cortex neurons [23, 24]. Moreover, neural correlates of hand motion, represented in extrinsic space, have also been found in several other brain regions associated with motor planning and control, including premotor cortices [23, 25, 26], primary somatosensory cortex [27], and cerebellum [28]. Thus, it is clear that motor-related brain areas can represent movement in extrinsic coordinates that reflect performance at the task level. Other studies have shown that intrinsic variables, related to joint motion and biomechanical factors, also appear to be represented in the activity of neurons in primary motor cortex. Neural activity has been shown to correlate with muscle activity [29], as well as limb configuration [30], mechanical load [31], and force output [32]. For example, Kalaska and colleagues [30, 33] showed that neurons in motor cortex that correlate with the direction of hand motion are also modulated by limb configurations that reflect different biomechanical states. Further, neurons whose activities change based on variations in both task-level as well as intrinsic variables have also been identified. For instance, Kakei et al. [34] used a particularly clever method of dissociating task-level parameters, from intrinsic parameters when recording neural activity from motor cortex. The forearm orientation was used to dissociate intrinsic from extrinsic coordinates. As seen in Fig. 6.5, in all wrist orientations, the extrinsic coordinates for movement of the grasped bar are the same, up and down. However, in pronation (Pro) and supination (Sup), wrist flexion is associated with oppositely directed hand movements, down and up, respectively. When neuronal activities were recorded in primary motor cortex and ventral premotor cortex, three different types of neurons were identified: The first type responded best to the direction of hand movement in extrinsic space, regardless of forearm orientation. The second type encoded both extrinsic parameters (direction), but was also modulated by intrinsic parameters (forearm orientation). Finally, a third type of neuron seemed to encode muscle activity, a purely intrinsic parameter. The authors concluded that these areas of cortex are probably associated with transformations between these different intrinsic and extrinsic representations of movement.

Recently, Scott [35] has interpreted such findings, indicating multiple types of encodings for

motor cortical neurons, in the context of optimal feedback control. Scott proposes that motor cortex might provide an optimal feedback controller, which generates motor control signals that optimally integrate incoming sensory information about the intrinsic state of the body with higher-level task goals, often represented in an extrinsic coordinate framework.

Research on motor learning has also indicated that some aspects of learning are represented in intrinsic coordinates, while others seem to be represented in extrinsic coordinates. The primary paradigm used in recent motor learning research has been focused on fairly short-term motor adaptation, where researchers have explored adjustments in movement patterns to various kinds of altered environments. Typically, subjects are exposed to novel extrinsic task-level conditions such as when a cursor, representing the location of the hand, deviates from the actual hand location, or when perturbing forces require the learning of new dynamics. Under such conditions, subjects tend to readily adapt to the new environment, a process that appears to occur, at least in part, through changes in predictive control [36, 37]. This predictive nature of such adaptation is reflected by the occurrence of "aftereffects," following removal of the imposed environmental perturbation. Such aftereffects tend to mirror image the imposed perturbation and are based on the subject's expectation that they will continue to experience the novel environment. Thus, it appears that healthy subjects are able to adapt their motor behavior in response to environmental changes that are represented in both extrinsic space and intrinsic space. Such adaptive behavior is clearly dependent on the ability of the brain to represent both aspects of movement, as described at the beginning of this section.

In order to examine how motor learning might be represented in the nervous system, many studies have examined the coordinates over which the adapted conditions generalize best. For example, Krakauer et al. [38] examined how subjects adapt to visuomotor rotations by imposing an angular misalignment between the actual and visually represented direction of hand motion. Following adaptation, subjects generalized to movements that were made in the same direction, but from a different starting configuration of the arm. We have also shown that such adaptation can transfer between the limbs and that this transfer occurs according to extrinsic coordinates [39]. These results are consistent with other studies that have suggested that adaptation to errors introduced at the extrinsic task-level transfers along the same coordinates [40, 41]. Generalization of adaptation to dynamic conditions such as novel force fields in contrast has been shown to occur along intrinsic coordinates [42, 43]. Malfait et al. [44] in fact showed that learning of novel force fields transferred to movements made in different regions of the workspace, but that required similar joint excursions, but poorly to movements in which joint excursions changed. Thus, representation of the applied force field appeared to be linked to joint motions, or intrinsic coordinates. Mussa-Ivaldi and colleagues [45] have proposed that generalization of learning novel mechanical conditions is tightly linked to the dynamic state of the arm, indicated by the velocity and positions of the arm experienced during learning. In support of this idea, when novel dynamics are learned with the dominant arm, they appear to transfer to the non-dominant arm along intrinsic coordinates [42, 43]. Thus, while learning of novel visual-motor conditions appears to generalize in extrinsic coordinates, learning of novel dynamic conditions appears to transfer along intrinsic coordinates.

Taken together, findings from studies examining how movements are represented in neural activities and studies examining generalization of motor learning have converged, demonstrating that movements are represented in two types of coordinate systems: extrinsic and intrinsic. While the extrinsic coordinate frame is described relative to a space independent of the body, it often represents conformation to task-level variables, such as whether the knife is cutting in a plane perpendicular to the loaf of bread. Intrinsic coordinate frames describe movements of specific body parts, such as joints or muscles, and can reflect information important for assessing dynamic concerns, such as making energy efficient movements. Both of these dimensions of task performance can determine

how particular tasks generalize. If the salient feature of the task is related to dynamics, such as adapting to a novel force field, learning appears to be represented within and is generalized along intrinsic coordinates. If the salient feature of the task is related to extrinsic task-level constraints, such as adapting to altered visual feedback about hand position, learning appears to be represented within and is generalized best along extrinsic coordinates. One can speculate that learning new tasks, such as sports and ADLs, requires adaptation to both features of task performance. Thus, generalization will be determined by the extent to which the transfer condition is similar in both coordinate systems. For example, while tennis and table tennis share many features in task space, the dynamics of the two tasks (for example, peak joint torques and postural requirements) are so extremely different that one would expect little transfer from one task to the other.

6.4.1 Implications for Rehabilitation

There are two major implications of research on neural representations of movement and on motor generalization for the rehabilitation clinic. First, it is critical to recognize that motor tasks are represented in multiple coordinate systems that allow the nervous system to solve different problems related to motor performance. While extrinsic coordinate representations allow adaptation to task constraints, such as improving the accuracy and precision, dynamic coordinates allow the central nervous system to optimize intrinsic coordination and mechanical energy. Second, the fact that learning is expected to transfer across the coordinates that are most novel, given a particular task, it is important for therapists to consider both intrinsic and extrinsic aspects of task performance. It is typical to consider the similarities between two tasks in terms of extrinsic, task-related coordinates because one can readily determine whether the task is in the same region of space, is oriented similarly, and is performed at similar speeds as the task or tasks that are targeted for transfer. For example, one can practice stacking cones on a surface and expect that this might transfer to the task of procuring a glass from the cupboard (target ADL skill). However, one must also consider the dynamic requirements of the two tasks, in terms of both postural and limb movement requirements. Whether the two tasks are similar in terms of joint torques, or joint power, might depend on subtle differences in body configurations, and relative segment motions. This would be difficult to determine for any given target task, let alone a large range of ADL activities. It is, therefore, important to provide a great deal of variation in dynamic experience when practicing a given task. Robot and technology–aided rehabilitation provides tremendous potential in this regard. Rather than practicing stereotyped patterns with similar dynamic requirements, it is important to vary the dynamic context by changing the forces associated with the practiced movements, as patients become proficient at a given set of movement patterns.

6.5 Principle 4: Motor Lateralization

As discussed throughout this chapter, both optimal trajectory control as well as impedance control are integral mechanisms of movement control. Our recent work has suggested that these two mechanisms are lateralized to the left and right brain hemispheres, respectively. The seminal research of Sperry and Gazzaniga [46] on disconnection syndrome in split-brain patients first established neural lateralization as a fundamental principle of the cerebral organization. Gazzaniga proposed that distributing different neural processes across the hemispheres provided the basis for more complex functions to emerge in the course of human evolution: By reducing redundancy, more neurons could be allocated to each lateralized process. His research provided elegant support for this view of cerebral lateralization as a neural optimization process.

Interestingly, early research on hemispheric lateralization was largely limited to cognitive and perceptual processes and little focus was paid to lateralization of motor systems. We have recently proposed the dynamic-dominance hypothesis of

motor lateralization [47], based on left- and right-arm advantages in reaching performance in healthy adults. We suggest that optimal trajectory control and impedance control are lateralized to the left and right brain hemispheres, respectively. Both of these processes are employed during unilateral movements, indicating roles for both hemispheres in unilateral coordination. Consistent with this idea, neural imaging studies have shown that both hemispheres are indeed active during the movement of a single arm, even when those movements involve only finger motion [48]. If each hemisphere contributes specialized processes to control of each arm, then unilateral brain damage should produce movement deficits in the ipsilesional arm. Remarkably, this is the arm that is usually considered unaffected by unilateral brain damage. Studies in stroke patients, as well as in animal models of stroke, have confirmed this prediction: Deficits in coordination have been documented in the ipsilesional limbs, following damage to unilateral sensorimotor cortices [49–51].

Our recent studies have examined the specific nature of the ipsilesional movement deficits that result from left or right brain damage, in order to better understand motor lateralization. These studies have confirmed that right and left sensorimotor strokes produce predictable deficits in impedance control or optimal trajectory control, respectively [51, 52]. For example, Schaefer et al. [51] compared reaching movements in the ipsilesional arm of hemisphere damaged patients with those of healthy control subjects matched for age and other demographic factors. Subjects performed targeted reaching movements in different directions within a workspace to the same side of midline as their reaching arm. The left hemisphere damaged group showed deficits in controlling the arm's trajectory due to impaired interjoint coordination, but showed no deficits in achieving accurate final positions. In contrast, the right hemisphere damaged group showed deficits in final position accuracy, but not in interjoint coordination. These findings are exemplified in the hand paths shown in Fig. 6.6a. While control subjects made relatively straight and accurate movements, patients with left hemisphere damage (LHD) made movements that were very curved but, nevertheless, were accurate in final position. In contrast, patients with right hemisphere damage (RHD) made straight movements with poor final position accuracies. This double dissociation between the type of error (trajectory or final position) and the side of hemisphere damage (right or left) is emphasized in Fig. 6.6b, which shows the variance in hand positions during the initial trajectory phase (cross) or the final position phase (circle) of the movement. The ratio of errors at these two points in movement (peak velocity, movement termination) are quantified across subjects in the bar graphs, revealing that RHD patients had the greatest variance in final position, while LHD patients had the greatest variance in trajectory. Thus, these results indicate the distinct lateralization of optimal trajectory control and impedance-mediated final position control to the left and right hemispheres, respectively. It should also be emphasized that these errors were associated with functional impairments in the ipsilesional arm, as measured by the Jebsen Hand Function Test (JHFT). Thus, motor lateralization leads to deficits that depend on the side of the stroke, and can lead to functional deficits, as tested by clinical assessments, such as the JHFT.

6.5.1 Implications for Rehabilitation

While most robotic rehabilitation devices have been focused on developing movements in the contralesional arm, the research discussed above provides compelling evidence that ipsilesional practice should also be encouraged. In fact, for many patients, the ipsilesional arm will become the primary manipulator, thus efficient coordination of this arm and hand should be critical for effective performance of ADLs [53]. We therefore recommend bilateral training as a critical component to therapeutic intervention in unilateral stroke. In fact, most ADLs are performed with both hands contributing to different aspects of the activity. For example, when buttoning a shirt, the nondominant arm tends to stabilize the buttonhole, while the dominant arm manipulates

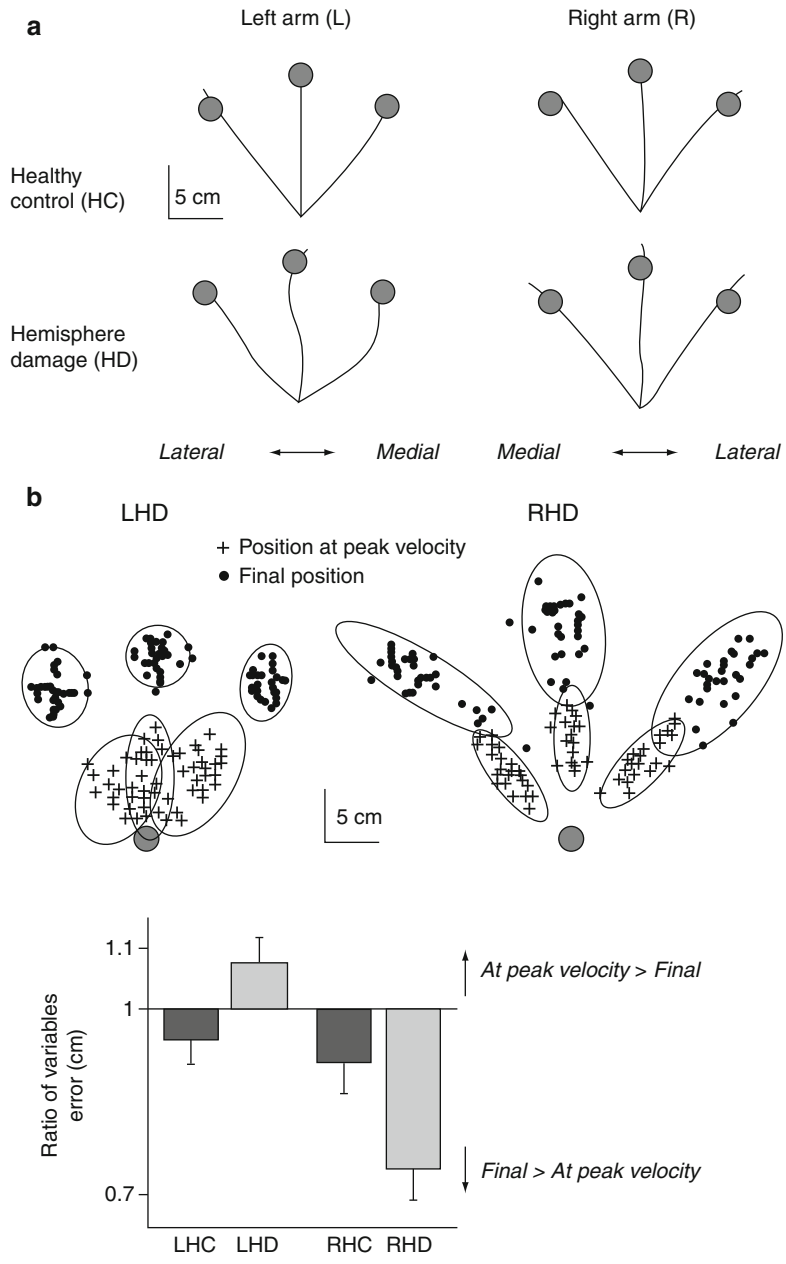

Fig. 6.6 Lateralization of motor deficits after stroke. (**a**) Typical hand paths for healthy control subjects performing with their right or left arm (*top panel*) and left and right hemisphere damaged stroke patients performing with their ipsilesional arm (*bottom panel*). (**b**) Hand locations at peak velocity (*crosses*) and movement end (*circles*) for a typical left and right hemisphere damaged stroke patient (*top panel*). Ellipses represent 95% confidence intervals. The bottom panel shows mean ratio of variables error at peak velocity to variable error at movement end across all subjects for the control and stroke groups (Adapted from Schaefer et al. [51])

the button through the hole. Bilateral training is not only important to facilitate remediation in the ipsilesional arm but also because unilateral training may not automatically carry over to spontaneous bilateral performance. In fact, recent research has indicated that learning novel kinetic and visuomotor environments with a single arm transfers only partially to bilateral movements, in which the same arm experiences the imposed environments [54, 55]. It is, therefore, critical that rehabilitation focus not only on unilateral performance, but that training be extended to bilateral movements. While some robotic devices are designed for bilateral movements [56], unilateral robotic training can be followed by bilateral training, even in the absence of bilateral robotic systems. In fact, bilateral training has a long history in occupational therapy treatment, where

manipulation of dowels and rolling pins has often been used to encourage bilateral arm use.

6.6 Summary and Conclusions

As the technology-based intervention tools discussed in this volume enter the clinic, they will provide rehabilitation professionals with the ability to prescribe and monitor movement experiences with unprecedented precision. This introduces the question of what specific aspects of movement should be practiced and monitored with these tools. In this chapter, we presented four principles of motor control that have an impact on this question and that have been derived from literature on the neural control of movement. These principles are: optimal control theory, impedance control, movement representations, and motor lateralization. We will review these principles and the implications for rehabilitation below.

Optimal control theory has examined plausible costs that might be considered by the nervous during motor planning and that might account for the reliable or "invariant" features of movements that occur across tasks and individuals. This line of research has indicated two major categories of cost that contribute to motor planning: explicit task-level costs, such as movement accuracy and speed, and implicit costs, such as energy and movement variability. When designing movement practice for patients, it is important to consider both types of costs when grading the difficulty of the task. We also suggest that it is critical to consider biomechanical variables related to energetic efficiency when evaluating patients' progress. While many clinical tests assess the ability to perform ADLs, as well as the time of such performance, a critical factor that should determine carryover into spontaneous daily activities is whether the movement can be performed at a reasonable energy cost. As the technologies discussed in this volume become available in the clinic, many of the devices will allow measures of mechanically related variables, such as work, power, and torque. Such variables can be exploited to monitor progress in making not only accurate and rapid but also energetically efficient movements.

Impedance control refers to neural mechanisms that modulate rapid sensorimotor circuits, such as stretch reflexes, in order to impede perturbations that cannot be anticipated during motor planning. These include forces that arise from the environment, such as inertial forces that result from braking and acceleration of a vehicle, or even inaccurate movements of one's own body, such as the effect on the upper body and arms of stepping on an uneven surface while carrying holding a cup. Robot-aided and virtual reality technologies allow the introduction of perturbations into patients' movement training experience. While it is currently most common to practice repetitive patterns under stereotyped conditions, introducing unpredictable perturbations should consolidate this learning and prepare patients for movement under natural environmental conditions.

Research on the neural representation of movement has indicated that movements are represented in at least two different types of coordinate systems. An extrinsic coordinate frame is described relative to a space independent of the body, while an intrinsic coordinate frame describes the movements of body segments relative to one another. Substantial research has indicated neurons in motor cortices appear to code for movements in both types of coordinate systems. Consistent with these findings, research on motor learning and generalization has indicated that motor learning can generalize along either intrinsic or extrinsic coordinates, depending on the salient features of the learned task. If the task entails substantial adaptation to novel dynamic conditions, learning tends to generalize along intrinsic coordinates. If the task entails adaptation to novel visual feedback conditions, then generalization tends to occur best along extrinsic coordinates. These findings suggest that both types of coordinates have to be considered when designing movement training in order to optimize transfer to natural movement conditions. It is, therefore, critical to provide a range of movement experiences that not only cover a large extrinsic workspace but that also include a large range of joint configurations and dynamic variations.

Finally, motor lateralization research has indicated that different aspects of motor control

have been specialized to the different cerebral hemispheres. The hypothesis that both hemispheres are normally recruited for each respective control mechanism, optimal trajectory control and impedance control, predicts that damage to a single hemisphere should produce deficits in the ipsilesional arm, often considered the unaffected arm in stroke patients. Recent research has verified this prediction, demonstrating deficits in trajectory control following left hemisphere damage and deficits in achieving accurate steady state positions following right hemisphere damage. The implications for rehabilitation are substantial: Patients with persistent hemiparesis will need to use the ipsilesional arm as the lead, and often sole, manipulator for ADLs. Thus, efficient performance of ADLs will require well-coordinated movements of this arm. Because most ADL tasks require some degree of bilateral coordination, we recommend that following unilateral training with one arm, both arms be trained simultaneously using bilateral tasks. Virtual reality environments provide an excellent paradigm to manipulate task conditions during bilateral arm training, such as requiring both arms to coordinate with each other for goal achievement and manipulating virtual objects.

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Functional Electrical Stimulation Therapy: Recovery of Function Following Spinal Cord Injury and Stroke

7

Milos R. Popovic, Kei Masani, and Silvestro Micera

Abstract

Functional electrical stimulation (FES) is a technology one can use to artificially generate body movements in individuals who have paralyzed muscles due to injury to the central nervous system. More specifically, FES can be used to generate functions such as grasping and walking in individuals with spinal cord injury (SCI), stroke, traumatic brain injury and other neurological disorders that do not affect lower motor neurons. This technology was originally used to develop neuroprostheses that were implemented to permanently substitute impaired functions such as bladder voiding, grasping, and walking. In other words, a consumer would use the device each time he/she wanted to generate a desired function. In recent years, FES technology has been used to deliver, therapies to retrain voluntary motor functions such as grasping, reaching and walking. In this application, FES is used as a short-term therapy, the objective of which is restoration of voluntary function and not lifelong dependence on the FES device, hence the name FES therapy or FET. The FET is used as a short-term intervention to help the central nervous system of the consumer to relearn how to execute impaired functions. In this chapter, we introduce recent findings and advances in the field of FET.

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The findings to date clearly show that FET for reaching and grasping is a therapeutic modality that should be implemented in every rehabilitation institution that is treating patients with stroke and SCI. The results obtained in a number of randomized control trials to date clearly demonstrate that FET for upper limb should not be ignored any longer. There is also considerable evidence to support the use of FET as a therapeutic modality to treat drop foot problem in both stroke and incomplete SCI populations. Several commercial FES systems are available that can be used to deliver FET for drop foot and grasping, and physiotherapists and occupational therapists should take advantage of this technology.

Presently, few teams in the world are investigating the use of more complex FES systems (6–16 channels FES systems that stimulate muscles in one or both legs in a physiologically appropriate manner) for retraining voluntary walking function in stroke and incomplete SCI populations. Although comprehensive randomized control trials have not been completed yet with either patient population, preliminary findings are very encouraging.

As surface FES technology is continuously improving and delivery methods for FET are evolving due to system miniaturization, better stimulation electrodes, and better stimulation protocols, it is foreseeable that, in the next 10–15 years, FET will become one of the dominant interventions for upper and lower limb rehabilitation. Many neuroprostheses are already commercialized and many more are near in the process of being developed and/or commercialized. Thus, we feel very confident that FET field is only beginning to evolve, and that, in the future, it may become one of the key therapeutic interventions not only for patients with stroke and SCI but also for patients with other neuromuscular disorders.

Keywords

Functional electrical stimulation (FES) • FES therapy • Spinal cord injury • Stroke • Neuroprosthesis

7.1 Introduction

Individuals with neurological disorders such as spinal cord injury (SCI), traumatic brain injury, and stroke are frequently unable to voluntarily move different body parts and perform functional movements. However, as long as the nerves innervating the muscles and the joints are intact, the electrical stimulation can be used to generate joint movements by contracting muscles that actuate the joints. If the muscle contractions produced using electrical stimulation are coordinated and generate functional movements such as standing, walking, or grasping this form of electrical stimulation is called functional electrical stimulation (FES). This technology was originally develop with an idea to create neuroprostheses. The neuroporstheses are devices that artificially generate functional movements discussed above in the limbs and body parts of paralyzed individuals, by artificially contracting muscles of that individual. In other words, for a consumer to perform a grasping task he/she would need to use the neuroprosthesis for grasping each and every time he/she wants to grasp an object. In the last decade it has been demonstrated by few research groups

that if the FES is applied as a short-term therapeutic intervention in stroke and incomplete SCI individuals, these individuals are able to partially or completely restore voluntary function that has been trained, namely reaching, grasping and walking. Therefore, FET can be used as a short-term intervention to help the central nervous system of the consumer re-learn how to voluntarily execute impaired functions, instead of making the consumer dependent on a neuroprosthesis for the rest of his/her life. In this chapter, we introduce recent findings and advances in the field of FET.

7.2 Functional Electrical Stimulation (FES)

7.2.1 Definitions

Individuals with SCI and stroke have injuries that prevent the central nervous system from generating a desired motor command and/or transmitting the desired motor command to the parts of the peripheral nervous system that innervate muscles. As a result, these individuals are frequently unable to voluntarily move different body parts and perform functions such as sitting, standing, reaching, grasping, and bladder voiding. However, as long as the nerves innervating the muscles, the muscles themselves, and the joints and soft tissues supporting the muscle-joint structures are intact, the electrical stimulation can be used to generate joint movements by contracting the muscles that actuate them. The electrical stimulation used for this purpose is called neuromuscular electrical stimulation (NMES). An organized and patterned NMES that aims to generate coordinated limb or body movements, instead of isolated muscle contractions, is called functional electrical stimulation (FES). One of the possible applications of FES technology is to artificially generate body movements such as grasping, standing, and walking. In such a context, the FES technology is used as a prosthetic device; in literature, this use of FES technology is referred to as *neuroprosthesis* or *neuroprosthetics*.

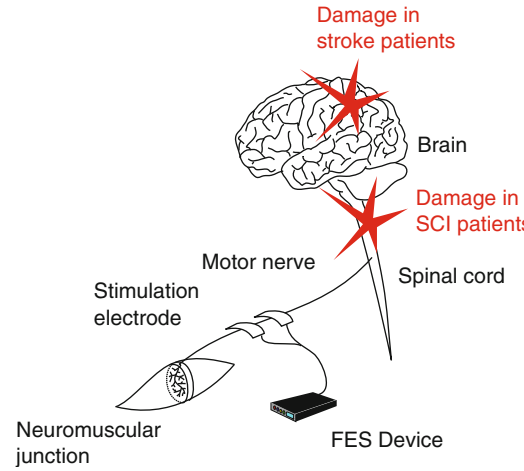

Fig. 7.1 A schematic representation of the surface FES system. The FES system causes a muscle contraction by electrically stimulating the motor axons that are connected to the muscles. The electrical stimulation generates action potentials in the motor neurons, which propagate along the motor neurons toward the muscle. When the action potentials reach the muscle, they cause the muscle to contract

7.2.2 Physiology

In nerve cells, information is coded and transmitted as a series of electrical impulses called action potentials, which represent a brief change in cell electric potential of approximately 80–90 mV. Nerve signals are frequency modulated; that is, the number of action potentials that occur in a unit of time is proportional to the intensity of the transmitted signal. Typical action potential frequency is between 4 and 12 Hz. An electrical stimulation can artificially elicit this action potential by changing the electric potential across a nerve cell membrane (this also includes the nerve axon) by inducing electrical charge in the immediate vicinity of the outer membrane of the cell (Fig. 7.1).

The stimulated nerve bundle includes motor nerves (efferent nerves – descending nerves from the central nervous system to muscles) and sensory nerves (afferent nerves – ascending nerves from sensory organs to the central nervous system). In some applications, FES can be used to directly stimulate muscles, if their peripheral

nerves have been severed or damaged (i.e., denervated muscles) [1]. However, the majority of the FES systems used today stimulate the nerves or the points where the junction occurs between the nerve and the muscle. The main reason is the fact that direct muscle stimulation requires considerably more energy to generate contractions (at least three orders of magnitude more [2]), which makes these systems more challenging to implement at home and in clinical settings.

The electrical charge can stimulate both motor and sensory nerves. In some applications, the nerves are stimulated to generate localized muscle activity, i.e., the stimulation is aimed at generating direct muscle contraction. In other applications, stimulation is used to activate simple or complex reflexes. In other words, the afferent nerves are stimulated to evoke a reflex, which is typically expressed as a coordinated contraction of one or more muscles in response to the sensory nerve stimulation.

When a nerve is stimulated, i.e., when sufficient electrical charge is provided to a nerve cell, a localized depolarization of the cell wall occurs resulting in an action potential that propagates toward both ends of the axon. Typically, one "wave" of action potentials will propagate along the axon toward the muscle (orthodromic propagation), and concurrently, the other "wave" of action potentials will propagate toward the cell body in the central nervous system (antidromic propagation). While the direction of propagation in case of the antidromic stimulation and the sensory nerve stimulation is the same, i.e., toward the central nervous system, their end effects are very different. The antidromic stimulus has been considered an irrelevant side effect of FES. However, in recent years, a hypothesis has been presented suggesting the potential role of the antidromic stimulation in neurorehabilitation [3]. Typically, FES is concerned with orthodromic stimulation and uses it to generate coordinated muscle contractions.

In the case where sensory nerves are stimulated, the reflex arcs are triggered by the stimulation of sensory nerve axons at specific peripheral sites. One example of such a reflex is the flexor withdrawal reflex. The flexor withdrawal reflex occurs naturally when a sudden, painful sensation is applied to the sole of the foot. It results in flexion of the hip, knee, and ankle of the affected leg, and extension of the contralateral leg in order to get the foot away from the painful stimulus as quickly as possible. The sensory nerve stimulation can be used to generate desired motor tasks, such as evoking flexor withdrawal reflex to facilitate walking in individuals following stroke, or they can be used to alter reflexes or the function of the central nervous system. In the later case, the electrical stimulation is commonly described by the term *neuromodulation*.

7.2.3 Technology

Nerves can be stimulated using either surface (transcutaneous) or subcutaneous (percutaneous or implanted) electrodes. Surface electrodes are placed on the skin surface above the nerve or muscle that needs to be "activated." They are non-invasive, easy to apply, and generally inexpensive. Due to the electrode-skin contact impedance, skin and tissue impedance, and current dispersion during stimulation, much higher-intensity pulses are required to stimulate nerves using surface stimulation electrodes as compared to the subcutaneous electrodes. A major limitation of the transcutaneous electrical stimulation is that some nerves, for example those innervating the hip flexors, are too profound to be stimulated using surface electrodes. This limitation can be partly addressed by using arrays of electrodes which can use several electrical contacts to increase selectivity [4–6].

Subcutaneous electrodes can be divided into percutaneous and implanted electrodes. The percutaneous electrodes consist of thin wires inserted through the skin and into muscular tissue close to the targeted nerve. These electrodes remain in place for a short period of time and are only considered for short-term FES interventions. One of the drawbacks of using the percutaneous electrodes is they are prone to infection and special care has to be taken to prevent such events. The other class of subcutaneous electrodes is implanted electrodes. These are permanently implanted in the consumer's body and remain in the body for the remainder of the consumer's life. Compared to surface stimulation electrodes,

implanted and percutaneous electrodes potentially have higher stimulation selectivity with much less electrical charge applied, both of which are desired characteristics of FES systems. To achieve higher selectivity while applying lower stimulation amplitudes, it is recommended that both cathode and anode are in the vicinity of the nerve that is stimulated. The drawbacks of the implanted electrodes are they require an invasive surgical procedure to install, and, as is the case with every surgical intervention, there exists a possibility of infection following implantation.

7.3 FES Therapy (FET)

7.3.1 Definition

FES can be used for neuroprosthetic and therapeutic purposes. If FES is used as a neuroprosthesis, the purpose of this device is to generate a body function that the consumer is unable to perform alone, such as walking, biking, bladder voiding, grasping, etc. In this application, the FES system needs to be worn or used each and every time the consumer needs to perform the desired function. In essence, the consumer uses the FES device as a permanent orthotic system.

The use of neuroprostheses as a means of providing short-term therapeutic intervention for improving and restoring voluntary function has been termed FES therapy or FET [7]. When the FES technology is used to deliver FET, the purpose of that intervention is to restore voluntary function. In other words, FET is used only temporarily as a short-term intervention with the objective of helping the neuromuscular system relearn to execute a function impaired due to neurological injury or disorder. In this application, the ultimate goal of the FES intervention is for the consumer to recover voluntary function, as much as possible, so the consumer does not need to use the FES system for the rest of his/her life. In this application, the central nervous system essentially relearns how to control the impaired muscles and how to contract them in a temporarily appropriate manner to generate the desired body function.

Some neuroprosthetic systems are also used for cardiovascular conditioning and muscle strengthening. Although the ultimate goal of this type of application is therapeutic, this is not FET. Good examples of these FES systems are neuroprostheses for rowing and biking. Each time the consumer wants to row or bike, he/she needs to use the neuroprosthetic system, without which he/she would not be able to perform this task at all.

The implanted FES systems are primarily used as permanent neuroprostheses, and some attempts have been made to use the BION implantable FES system for FET. On the other hand, the surface FES systems have been used equally well as neuroprostheses and platforms to deliver FET. In the past, the main focus of the FES field was on developing neuroprosthetic systems, in particular those that consumers had to use daily. In recent years, the advances made in the field of FET and the use of neuroprostheses for muscle strengthening and cardiovascular exercises have shifted the focus of the FES field, at least partially, toward the use of surface FES systems. As a result, a number of commercially available surface FES systems have been developed in the last decade.

7.3.2 Carryover Effect

Since the 1970s, some researchers and practitioners in the field of FES have observed that many consumers who use FES on a regular basis experience significant carryover in function that persists even when the device is not in use. This "enigma" of "carryover effect" has interested researchers [8], even though most of these reports were anecdotal in nature at the beginning.

One of the first papers that specifically discussed this phenomenon was an article authored by Merletti et al. in 1975 [9]. They investigated the carryover effect of FES on hand opening and elbow extension functions for stroke patients. Three of five patients showed the carryover effect after a 2 months training period, i.e., after the FES intervention session, functional tasks such as the shifting of an object between two specified areas on a desk were improved even without wearing the FES device. The observed carryover effect supported the potential role of neuroprostheses as therapeutic interventions in clinical practice. Despite the fact that FES-related carryover results

Fig. 7.2 NESS L300 foot drop system (Photo courtesy Bioness Inc., Valencia, CA, USA)

were observed as early as the 1970s, a rigorous investigation of FES carryover effect started only recently.

7.4 Current Evidences of FET

It took almost two decades before the carryover effect started being examined seriously. First, it was examined with the drop foot FES systems, where scientists explored the ability of the system to restore voluntary walking function in individuals with stroke. These studies were then followed by studies examining the use of a neuroprosthesis for grasping, and later, neuroprostheses for reaching and grasping for restoring voluntary arm and hand functions in individuals with stroke and SCI. Finally, the neuroprosthesis for walking was used to investigate restoration of voluntary walking function in individuals with incomplete SCI.

7.4.1 FET for Restoration of Lower Limb Function Following Stroke

Among stroke patients, the drop foot is a common symptom characterized by a lack of dorsiflexion during the swing phase of gait, resulting in short, shuffling strides. It has been shown that the drop foot stimulator effectively compensates for the drop foot during the swing phase of the gait. At the moment just before a heel-off phase of the gait occurs, the drop foot stimulator induces a stimulus at the common peroneal nerve which results in contraction of the muscles responsible for dorsiflexion (Fig. 7.2). There are number of drop foot stimulators, which use surface FES technology and have been FDA (US Food and Drug Administration) approved, that have been developed to date: the Odstock dropped foot stimulator [10], the WalkAide [11], and the NESS L300 (formally known as NESS drop foot system) [12]. The ActiGait [13] and the STIMuSTEP [14] are implantable drop foot stimulators that are also commercially available and have the CE mark in Europe. Drop foot stimulators are one of the most successful neuroprostheses to date. Overall, consumer perception of the drop foot stimulators is they are superior to the ankle-foot orthosis [15].

There has been a great deal of evidence showing the benefits of FES for the lower limbs of stroke patients. In most of the studies, the effect of the drop foot stimulator has been studied (only few studies have studied FET in gait with stroke patients, e.g., [16]). In the early phase, some studies showed a negative result with respect to the carryover effect [17, 18], while other studies showed positive effect on the carryover effect [10]. For example, Granat et al. [18] investigated the effect of a drop foot stimulator on hemiplegic patients ($n = 19$) in a two-period crossover study design (4 weeks control period followed by

4 weeks FES treatment period). The results demonstrated that there was a significant orthotic effect (positive effect when the subject was using the FES system) in inversion of ankle, while the same study did not show a therapeutic effect (positive effect when the subjects were not using the FES system, i.e., carryover effect). In a randomized controlled trial, Burridge et al. [17] investigated the effect of a drop foot stimulator on individuals with stroke. The test group ($n=16$) received conventional physiotherapy and FES treatment, while the control group ($n=16$) received conventional physiotherapy alone. They demonstrated that the mean increase in walking speed was 20.5% in the treatment group when the subjects in that group used the drop foot stimulator as an orthosis. The control group showed only a 5.2% increase in mean walking speed. The physiological cost index (PCI) was reduced 24.9% in the treatment group when they were using the drop foot stimulator as an orthosis, and was reduced 1% in the control group. However, the same study did not show any improvements in the treatment group when the drop foot stimulator was removed. In other words, they were not able to demonstrate the drop foot stimulator's carryover effect. Taylor et al. [10] investigated the effect of a drop foot stimulator in stroke ($n=9$) and multiple sclerosis (MS) ($n=2$) patients. Stroke patients showed a mean increase in walking speed of 27% and a reduction in PCI of 31% when the system was used as an orthosis. However, the same study showed a 14% increase in walking speed and a 19% reduction in PCI when the stimulator was removed from the patients, i.e., carryover effect. The MS patients showed similar benefits when they used the drop foot stimulator as an orthosis, with no noticeable carryover effects.

Recently, in a relatively larger population study, Stein et al. [11] investigated the effect of a drop foot stimulator in stroke ($n=41$) and MS ($n=32$) patients. They demonstrated that both stroke and MS patients showed increased walking speed when the system is used as therapeutic and orthotic devices. After 3 months of drop foot stimulator training, both groups had a similar and significant orthotic (increments of 5.0% and 5.7% for stroke and MS patients, respectively) and therapeutic (17.8% and 9.1% for stroke and MS patients, respectively) effects on walking speed during on ground figure-8 walking. After 11 months of following the baseline, the therapeutic effect on figure-8 speed diverged between the two groups to 28.0% and 7.9% for stroke and MS patients, respectively. Overall, PCI showed a decreasing trend. They concluded that both subject groups had an orthotic benefit from FES up to 11 months. The therapeutic effect increased up to 11 months in stroke patients, which is a nonprogressive neurologic disorder, while in the MS patients, as expected, the therapeutic effect increased only in the first 3 months following the baseline.

In summary, there is considerable evidence that the drop foot stimulators, if they are used to deliver FET, produce lasting positive changes in gait in individuals with hemiplegic stroke.

7.4.2 FET for Restoration of Lower Limb Function Following SCI

Impairment in lower limb function is a common symptom following SCI. Various FES systems have been developed to help individuals with SCI to improve walking function. In individuals with SCI, the scope of impairment is not limited to the ankle joint, as is the case with many stroke individuals, but rather affects many muscles in the legs, pelvis, and trunk. Thus, the FES technology for walking for individuals with SCI is more diverse and targets the muscles of the entire lower limb. However, it is not uncommon that in some individuals with SCI, the above-discussed drop foot stimulators have been also used as a means to assist with gait.

As early as the 1960s, Kantrowitz demonstrated paraplegic standing by applying continuous electrical stimulation to the quadriceps and gluteus maximus muscles of a patient with complete SCI, using surface FES technology [19]. This earliest neuroprosthesis for paraplegic "gait" provided continuous stimulation to the quadriceps to produce a mode of gait similar to long leg-brace walking, by inducing stiffened legs.

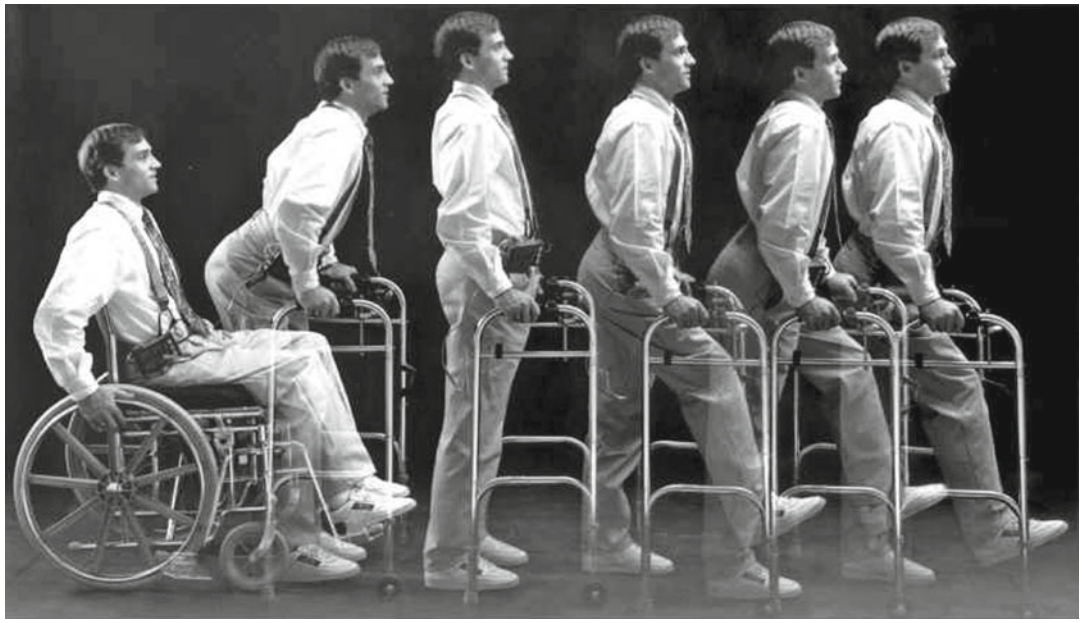

Fig. 7.3 Parastep electrical stimulation system (Photo courtesy Sigmedics, Inc., Fairborn, OH, USA)

Later systems used alternating bilateral quad/glut stimulation (during stance phase) out of phase with peroneal nerve stimulation to induce the flexor withdrawal reflex (during swing phase) [20]. Following that, Kralj et al. described a technique for paraplegic gait using surface electrical stimulation, which remains the most popular method in use today [21]. Electrodes are placed over the quadriceps muscles and peroneal nerves bilaterally. The user controls the neuroprosthesis with two pushbuttons attached to the left and right handles of a walking frame, or on canes, or crutches. When the neuroprosthesis is turned on, both quadriceps muscles are stimulated to provide a standing posture. The left button initiates the swing phase in the left leg by briefly stopping stimulation of the left quadriceps and stimulating the peroneal nerve. This stimulation is applied suddenly, so as to trigger the flexor withdrawal reflex, resulting in simultaneous hip and knee flexion, as well as dorsiflexion. After a fixed period of time, peroneal nerve stimulation is stopped, and quadriceps stimulation is initiated while the reflex is still active to complete the stride. Similarly, the right button initiates swing phase in the right leg. Many current FES systems for walking have employed this technique as the basic concept. As microprocessor technology developed, neuroprostheses for walking became more portable and flexible. Examples of this type of neuroprosthesis are Parastep [22, 23], HAS [24], and RGO [25], and the Case Western Reserve University (CWRU)/VA neuroprosthesis [26–29]. The Parastep system is one of most popular products and uses Kralj's technique [22, 23] (Fig. 7.3). The HAS and the RGO walking neuroprostheses are devices that, in addition to FES, also apply active and passive braces, respectively. The braces were introduced to provide additional stability during standing and walking and to conserve the user's energy. CWRU/VA neuroprosthesis is an implant system [26–29]. Parastep, HAS, and RGO systems were designed for orthotic use; however, they could be potentially implemented as FET devices as well.

The above neuroprostheses for walking apply the flexor withdrawal reflex to generate sapping movement during the walking cycle. There is a disadvantage in using this approach as the flexor withdrawal reflex is highly variable and is subject to rapid habituation. However, there are systems that do not use the flexor withdrawal reflex; instead they stimulate muscles in a manner that is as close as possible to the physiologically correct

muscle activation pattern that generates the bipedal walking cycle. Good examples of such systems are the Case Western Reserve University (CWRU)/VA neuroprosthesis [26–29], Praxis [30], and Compex Motion neuroprosthesis for walking [31, 32]. The Praxis and CWRU/VA neuroprosthesis are implantable FES device that have 22 and 8–16 stimulation channels, respectively. They are able to generate sit-to-stand, walking, and stand-to-sit functions, and are suitable for orthotic applications. However, recently the Cleveland team tested the therapeutic effects of their implantable system in a single-subject study [26]. Compex Motion neuroprosthesis for walking is an eight to sixteen channel surface FES system used to restore walking in stroke and SCI individuals [31]. The system uses a push button control strategy, similar to the one used in the Parastep system, and a gate phase detection sensor [33] to trigger the FES sequences. What is unique about this FES system is that it was specifically developed for FET applications. The benefits of FES for lower limbs of individuals with incomplete SCI were discussed in a review by Bajd et al. [34]. The review concluded that there are various benefits including therapeutic effect of FES for individuals with SCI, of strength training, drop foot stimulator, and plantar flexor stimulation during gait phase.

In addition to those studies, Wieler et al. [35] investigated, in a multicenter study, the effect of a drop foot stimulator and a withdrawal reflex stimulator on individuals with SCI ($n=31$) and with cerebral impairment ($n=9$). The results showed that the walking speed increased by approximately 40% when the drop foot stimulator was used as an orthotic device and 20% as when it was used as FET device.

Thrasher et al. [32] hypothesized that direct muscle stimulation would have greater rehabilitative potential than the stimulation of flexor withdrawal reflexes. They investigated the effect of a gait-patterned multichannel FES in five individuals with chronic, incomplete SCI. These subjects were trained for 12–18 weeks using Compex Motion multichannel neuroprosthesis for walking. All subjects demonstrated considerable improvements in walking function over the training period. Four of the subjects achieved significantly increased walking speeds, which were due to increases in both stride length and step frequency. The fifth subject experienced a significant reduction in preferred assistive devices. The results suggest that the proposed FES-based gait training regimen was effective for improving voluntary walking function in a population for whom significant functional changes are not expected, and that this application of FET is viable for restoration of voluntary gait in incomplete SCI.

In summary, there is mounting evidence that, in individuals with incomplete SCI, neuroprostheses for walking can be used as FET devices to improve voluntarily walking function. Most of the work has been done using drop foot stimulators. However, more complex FES systems have been recently tested as FET systems and have shown encouraging results with respect to improving voluntary walking function in more severely disable individuals with SCI.

7.4.3 FET for Restoration of Upper Limb Function Following Stroke

Impaired reaching and grasping functions are common symptoms among individuals with stroke. Numerous neuroprostheses have been designed to compensate for lost grasping [36–47], and grasping and reaching [7, 31, 48–50] functions in stroke patients.

Some notable grasping and/or reaching neuroprostheses (not necessarily developed for individuals with stroke) are the Freehand system [51], the NESS H200 (formally known as NESS Handmaster) [40] (Fig. 7.4), the Bionic Glove [41, 44, 52], the ETHZ-ParaCare neuroprosthesis for grasping [31, 53], the systems developed by Rebersek and Vodovnik [45], the Belgrade Grasping-Reaching System [49], Compex Motion neuroprosthesis for reaching and grasping [31], and the percutaneous systems by Chae et al. [36, 37]. These neuroprostheses for grasping were shown to restore the power grasp and the precision grip. The power grasp is used to hold larger and heavier objects between the palm of the hand and the four fingers. During a power grasp, the object is held in a clamp formed by partly flexed fingers and the palm counter pressure being

Fig. 7.4 NESS H200 hand rehabilitation system (Photo courtesy Bioness Inc., Valencia, CA, USA)

applied by the thumb lying more or less in the plane of the palm. Precision grip is used to hold smaller and thinner objects, such as keys and paper, between the thumb and forefinger. The precision grip is generated by flexing the fingers followed by opposition of the thumb. The Freehand system is an implantable FES system designed for individuals with SCI, while the remaining devices are surface FES systems that can be used to deliver FET to both stroke and SCI individuals.

Use of FES as means of improving hand function following stroke has been intensively studied for a long time. A meta-analysis in 1996 already proved that FES is effective in recovery of muscle strength after stroke in terms of muscle strength [54]. Recent studies that have specifically examined FET have suggested positive outcomes in acute [7, 41, 42, 48] and chronic [37, 46, 47, 52] stroke individuals. These were then followed by randomized control trials that confirmed the positive outcomes of FET in acute [38, 50, 55] and chronic [36, 50] stroke individuals. In most of discussed studies, surface FES technology has been used to deliver FET, while a percutaneous FES system has been used in studies published by Chae et al. [36, 37]. In most studies, the upper limb FET has been delivered in a clinical setting with the assistance of therapists. However, a self-administered FET intervention, i.e., those that were conducted at home, has been recently explored using the NESS system [53] and a new version of the Bionic Glove [41, 52, 56].

It is important to mention that, to date, most of the clinical trials conducted using FET for grasping in the stroke population targeted individuals who had partially preserved reaching and/or grasping functions. Namely, the targeted patients typically had Chedoke McMaster Stages of Motor Recovery scores 4 and 5, which means that they were able to place the hand voluntarily within at least 20–30% of the hand/arm workspace and were able to initiate some or many wrist, hand, and finger movements. However, recently in randomized controlled trials, Popovic and colleagues [48, 50] investigated the use of FET for reaching and grasping in severe stroke patients, i.e., stroke patients who had Chedoke McMaster Stages of Motor Recovery scores 1 and 2. These individuals were unable to initiate or execute voluntarily any component of reaching or grasping function. Popovic et al. have shown that the FET is able to improve both reaching and grasping functions in severe stroke patients (Fig. 7.5). What these studies have shown is that in severe stroke patients, the FET is able to improve gross motor function, but was unable to improve fine motor tasks of the hand.

7.4.4 FET for Restoration of Upper Limb Function Following SCI

An SCI at T1 level or above frequently results in a partial or complete loss of grasping and reaching functions. Various therapies, surgical interventions, and/or devices have been proposed to

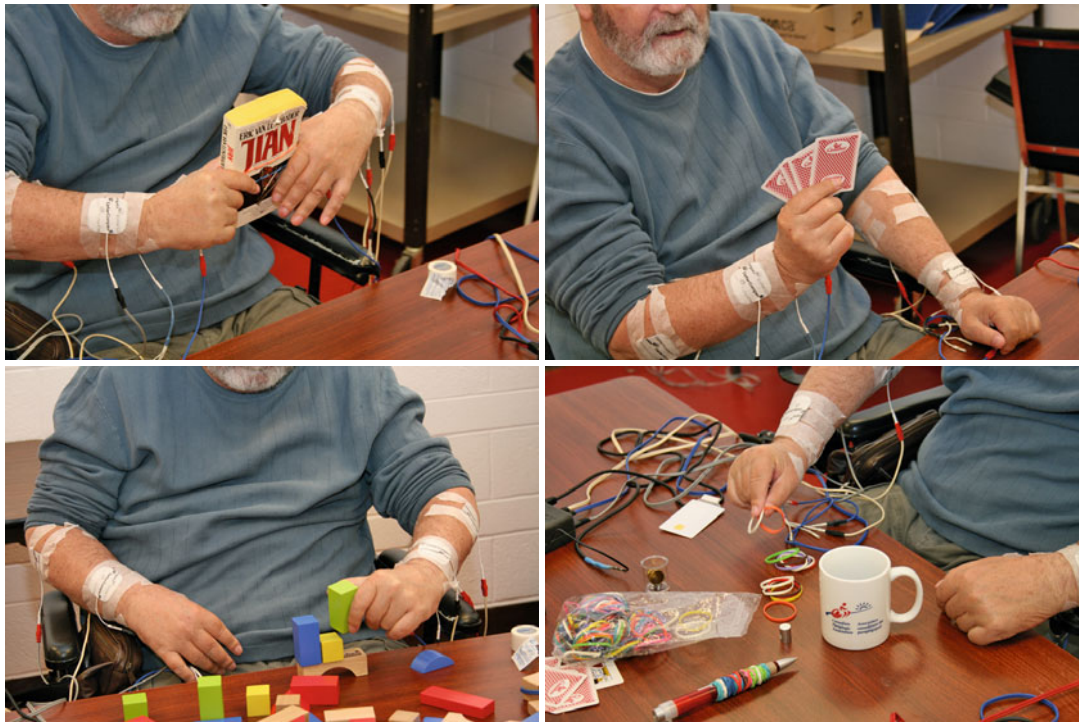

Fig. 7.5 Use of two Compex Motion systems for grasping for restoring bilateral voluntary hand function

help improve those functions in individuals with SCI. Among these interventions, FES devices have shown the most promise [57]. The same neuroprostheses for grasping and reaching as discussed above have been used with the SCI population. However, almost all these devices, except for Bionic Glove, ETHZ-ParaCare neuroprosthesis, and Compex Motion system, have been used with SCI subjects as orthotic systems and were all efficacious as orthoses.

While the benefit of FET has been intensively investigated with stroke patients, it has not been investigated with individuals who have SCI. From the above-listed FES systems that were used to deliver FET in individuals with SCI, ETHZ-ParaCare and Compex Motion systems were able to deliver both palmar and lateral grasps using the same electrode configuration. The ETHZ-ParaCare grasping neuroprosthesis was primarily used as an orthotic system. However, Mangold et al. [58] provided some evidence that a few of the SCI patients who used the device experienced a weak carryover effect. A clinical trial using Bionic Glove showed that the Bionic Glove can considerably improve upper limb function in individuals with C5–C7 SCI. This study was conducted by Popovic et al. (not the author of this article) and presents the first concrete evidence that FET for grasping could be effective in SCI population [36].

In 2006, the first randomized controlled trial was carried out carefully examining the impact of FET on grasping function in individuals with traumatic C4–C7 SCI [59]. In this study, the individuals received 40 one-hour FET treatments (treatment group) or 40 one-hour conventional occupational therapy treatments. The therapy was tested on individuals with complete and incomplete SCI. Although this particular study was underpowered, it provided clear evidence that both individuals with complete and incomplete SCI greatly benefited from the FET for grasping. This study was then followed by another randomized controlled trial; FET for grasping was evaluated in individuals with incomplete, traumatic C3–C7 SCI [60]. What is

relevant to mention is that this was a very conservative study with respect to FET. In this study, both control and treatment groups received 1 h of conventional occupational therapy daily, as described in [59]. Then both groups were given at least a 2 h break followed by another dose of therapy where the control group got 1 h of conventional occupational therapy and treatment group received 1 h of FET for grasping. Both groups received therapy 5 days a week (working days) for 8 weeks (40 session days in total). At the end of the study, there were 9 subjects in the treatment group and 12 in the control group. The results obtained were statistically significant and have revealed that FET dramatically improves hand function in this patient population. Also, the long-term follow-up in this study has shown that 6 months after the baseline assessment, both control and treatment groups maintained or further improved their hand function as compared to the assessments performed at discharge from the study [61]. In other words, this study suggests that the changes in the hand function produced by FET are dramatic and they persist over time.

7.4.5 Hybrid FET with Orthoses or Robotic Devices

In the past, it has been shown that FES-assisted walking has several limitations such as muscle fatigue, reduced joint torques generated using FES alone as compared to volitionally activated torques in healthy subjects, modified reflex activities, and spasticity [62]. To overcome these limitations, a combined use of FES and a mechanical brace or an orthosis has been suggested. These systems are better known as hybrid assistive systems (HAS) or hybrid orthotic systems (HOS) [24, 63, 64]. Such mechanical supports have been used mainly for safety and prevention of adverse events during standing and gait [62].

In recent years, the rehabilitation robotics field has experienced rapid growth. Instead of being passive orthotic systems or braces, rehabilitation robots now have active joints and are used to help move upper and lower limbs in a physiologically correct manner, mimicking proper walking and reaching functions, respectively. Similarly, FET has been used to allow patients to execute various repetitive upper and lower limb tasks. Since both technologies have advantages and disadvantages, it was only natural to consider merging these technologies as means to overcome the disadvantages and benefit from the advantages that these two technologies offer. For example, FES systems are currently unable to generate very accurate limb movements but are able to engage muscles in task execution and generate much more significant proprioceptive and sensory feedback, which is critical for retraining the neuromuscular system. On the other hand, robotic systems are very good in executing accurate limb movements, but, in general, these systems do not have to generate muscle activations and significant proprioceptive and sensory feedback. Hence, it is expected that the combination of FES with robotic devices will enhance the therapeutic effects of both interventions. A recent study by Freeman et al. [65] has proposed a robotic device for reaching movement with upper limbs that can be combined with FES. The study tested and confirmed the accuracy of the trajectory that the robotic system executed with 18 healthy subjects using FES applied to the triceps muscle. The results confirmed the efficacy of a combined robotic device and FES system and showed the feasibility of the proposed device. The same authors started to test the system with 5 stroke patients in treatment sessions comprised of up to 25 one-hour visits. For walking, Stauffer et al. [66] developed a hybrid robotic and FES system (WalkTrainer). The robotic device consisted of leg and pelvic orthoses, active bodyweight support, and a mobile frame that allowed the user to perform walking therapy during overground walking. The system also had a closed loop–controlled FES system. This system was tested with six paraplegic patients, and its feasibility as a rehabilitation tool was confirmed.

Hybrid rehabilitation systems, consisting of a robotic device and an FES system, are not a new idea. However, this idea has become a more attractive and realistic solution in recent years. It is very likely that in the near future we will see

more devices that are combining FES and robotic technologies to develop advanced neurorehabilitation tools and interventions.

7.5 Potential Mechanisms of FET

At the present time, the exact mechanisms responsible for the observed FET carryover effect are not known. However, a few hypotheses have been proposed that may provide at least a partial explanation of the FETs carryover effect.

Three possible "peripheral" mechanisms might be considered. At first, FET may improve the muscle functions in the remaining motor units through simple muscle training and strengthening. However, this does not necessarily happen only during FET; other training mechanisms can be used to improve muscle strength and endurance. Second, FET may improve the flexibility and range of motion of the affected limbs/joints, and as a consequence, the voluntary function may be improved. However, stretching during physiotherapy should be able to generate similar results. Third, FES might reduce the amount of spasticity in the affected limb, and by doing so, it may improve the motor function. Although it has been shown in the past that FES does improve the spasticity [67], the FET carryover effect has been observed even in the affected limbs that did not have spasticity. Thus, although all three above carryover mechanisms may be possible, they alone could not account for the observed carryover effect.

It has been reported that cortical reorganization can occur following stroke recovery [68]. As FES activates both motor and sensory nerve fibers, high-frequency sensory stimulation may be capable of modifying cortical connectivity [69]. Thus, through forced repetitive movements, FET may promote the neuroplasticity in the central nervous system through sensory nerve stimulation [70].

In addition to the cortical reorganization mechanism, Rushton [3] suggested a hypothesis that accounts for the carryover effect as uniquely due to FES. Electrical stimulation of a motor nerve fiber generates both an orthodromic (centrifugal) and an antidromic (centripetal) impulse. When the voluntary, descending command comes down from the brain to the spinal motor neuron, it can meet the antidromic impulse at the motor neuron during FES. This coincidence of two impulses at the spinal motor neuron can strengthen the synaptic connection via Hebb's rule. This enhancement of the synaptic connection would increase the efficacy of the voluntary, descending command to activate impaired muscle in individuals with stroke and SCI. Recent results that showed a facilitation of motor evoked potential using TMS after FES support this hypothesis [71, 72].

The last hypothesis that could also explain the mechanisms behind FET is the one proposed by Popovic et al. [31, 32, 48, 50, 59–61]. If a subject, who attempts to execute a motor task, is assisted with the FET to carry out that task, he/she is effectively voluntarily generating the motor command (desire to move the arm, leg, etc., i.e., command input). In this situation, FET is providing afferent feedback (system's output), indicating that the command was executed successfully. By providing both the command input and system's output to the central nervous system (CNS) repetitively for prolonged periods of time, this type of treatment facilitates functional reorganization and retraining of intact parts of the CNS and allows them to take over the function of the damaged part of the CNS. It is important to add that during the FET, the subjects perform motor tasks repetitively. The combination of performing diverse and meaningful tasks with high repetition and with a subject's persistent active engagement (i.e., the subject has to devote 100% of his/her attention to the tasks performed) may play a critical role in retraining voluntary motor function. This hypothesis and use of FET is fully in tune with recent findings in the field of neuroplasticity and suggests that FET is potentially another effective method that can be used to retrain the neuromuscular system.

In any event, the carryover effect is probably multifactorial and needs to be fully examined. However, what is certain is that the FET is an effective method for restoring voluntary upper and lower limb functions in individuals following

stroke and SCI. It is our impression that the FET is a very promising intervention that is only now being seriously examined and has the potential to revolutionize the way we rehabilitate individuals with diverse neuromuscular disorders.

7.6 Conclusions, Limitations, and Perspectives

This chapter summarizes the research findings regarding the effects of FET in individuals with stroke and SCI. The findings to date clearly show that FET for reaching and grasping is a therapeutic modality that should be implemented in every rehabilitation institution that is treating patients with stroke and SCI. The results obtained in a number of randomized control trials to date clearly point out that FET for upper limb should not be ignored any longer. There is also considerable evidence to support the use of FET as a therapeutic modality to treat drop foot problem in both stroke and incomplete SCI populations. There are a couple of FES systems on the market that can be used to deliver FET for drop foot and grasping, and physiotherapists and occupational therapists should take advantage of this technology. Presently, few teams in the world are investigating use of more complex FES systems (6–16 channels FES systems that stimulate muscles in one of both legs in a physiologically appropriate manner) for retraining voluntary walking function in stroke and incomplete SCI populations. Although comprehensive randomized control trials have not been completed yet with either patient population, preliminary findings are very encouraging.

The results obtained to date suggest that FET can be used effectively with both chronic and subacute stroke and SCI patients. However, the results published to date suggest that FET produces better results if it is applied during early rehabilitation, i.e., during subacute phase following injury. Further, the effect of FET has shown good results in individuals with complete and incomplete SCI, and stroke subjects. However, to date, statistically significant results have only been obtained with stroke and incomplete SCI patients. It should be noted that FET therapy does not require any voluntary movement in the affected limb as an indication for the therapy. In other words, FET can be applied to individuals who are profoundly paralyzed (i.e., cannot move the limb at all), and one can expect to see partial or full recovery of the limb function at the end of the FET.

As the surface FES technology is continuously improving and delivery methods for FET are evolving due to system's miniaturization, better stimulation electrodes, and better stimulation protocols, it is foreseeable that in the next 10–15 years, FET will become one of the dominant interventions for upper and lower limb rehabilitation. Many neuroprostheses are already commercialized and many more are in the process of being developed and/or commercialized. Thus, we feel very confident that FET field is only beginning to evolve, and that, in the future, it may become one of the key therapeutic interventions not only for patients with stroke and SCI but also for patients with other neuromuscular disorders.

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Part III

Robots for Upper Extremity Recovery in Stroke/Spinal Cord Injury: Technological Aspects

Forging *Mens et Manus*: The MIT Experience in Upper Extremity Robotic Therapy

8

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Abstract

MIT's motto is *Mens et Manus,* which translates into "Mind and Hand." It could not be a more appropriate motto for our line of research: using robotics and information technology to forge new or reinforce existing pathways to reconnect the brain to the hand. These reconnections allow an adult who has experienced a stroke or a child with cerebral palsy to improve the quality of their life. This chapter describes our efforts toward this goal since the initial development of the MIT-Manus in 1989. Since then, over 800 stroke patients have enrolled in our multiple studies and we have developed a complete robotic gym for the upper extremity. With the most recent endorsement of the American Heart Association and the Veterans

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Affairs/Department of Defense for incorporating robot-assisted therapy into stroke rehabilitation for upper extremity, we have begun realizing our motto toward tailoring therapy to a particular need.

Keywords
Rehabilitation robotics • Robotic therapy • Upper extremity • Stroke • Cerebral palsy

8.1 Introduction

The use of robotic technology to assist recovery after neurological injury has proven to be safe, feasible, and effective, at least in some forms (e.g., upper extremity) and for some patient populations (e.g., stroke). Nevertheless, there is vast room for improvement. But what is the best way to pursue further improvement? Ultimately, we would like to prescribe customized therapy to optimize and augment a patient's recovery. In this chapter, we review our experience in developing upper extremity robotic therapy and applying it in clinical practice. Based on that experience, we propose the most productive way to refine and optimize this technology and its application. Needless to say, this personal viewpoint will almost certainly neglect or underemphasize important developments; however, that should not be construed as a dismissal of other work but more as a symptom of the explosive growth of research in this field. Despite its inevitable limitations, we trust our perspective may have value.

8.2 The State of the Art

The 2010 American Heart Association (AHA) guidelines for stroke care recommended that: "Robot-assisted therapy offers the amount of motor practice needed to relearn motor skills with less therapist assistance. Most robots for motor rehabilitation not only allow for robot assistance in movement initiation and guidance but also provide accurate feedback; some robots additionally provide movement resistance. Most trials of robot-assisted motor rehabilitation concern the upper extremity (UE), with robotics for the lower extremity (LE) still in its infancy… Robot-assisted UE therapy, however, can improve motor function during the inpatient period after stroke." AHA suggested that robot-assisted therapy for the UE has already achieved class I, Level of evidence a for stroke care in the outpatient setting and care in chronic care settings. It suggested that robot-assisted therapy for UE has achieved class IIa, level of evidence a for stroke care in the inpatient setting. Class I is defined as "Benefit >>>Risk. Procedure/Treatment SHOULD be performed/administered;" class IIa is defined as "Benefit >>Risk, IT IS REASONABLE to perform procedure/administer treatment;" level A is defined as "Multiple populations evaluated: Data derived from multiple randomized clinical trials or meta-analysis" [1].

This is not an isolated opinion. The 2010 Veterans Administration/Department of Defense (VA/DOD) guidelines for stroke care came to the same conclusion endorsing the use of rehabilitation robots for the upper extremity but went further to recommend against the use of robotics for the lower extremity. More specifically, the VA/DOD 2010 guidelines for stroke care "Recommend robot-assisted movement therapy as an adjunct to conventional therapy in patients with deficits in arm function to improve motor skill at the joints trained." For the lower extremity, the VA/DOD states that "There is no sufficient evidence supporting use of robotic devices during gait training in patients post stroke." The VA/DOD suggested that robot-assisted therapy for the UE has already achieved rating level B, "A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh

harm." Regarding the lower extremity, the VA/DOD suggested against robot-assisted therapy: "Recommendation is made against routinely providing the intervention to asymptomatic patients. At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits" [2].

These endorsements came on the 21st anniversary of our initial efforts begun in 1989 (with support from the United States National Science Foundation) that led to what became known as "MIT-Manus." It would be difficult to deny the impact of this work on neurorehabilitation, described by our clinical colleagues as "perhaps one of the most important developments in neurorecovery in the last 75 years" (personal communication, Dr. Bruce Volpe). Creating this level of trust required decades of perseverance. The enormity of the challenge cannot be understated. This type of research is the antithesis of the rapid-fire breakthroughs expected in, say, information technologies. It requires slow and painstaking experimental trials and the creation of a large body of experimental evidence to demonstrate progress, but that is essential. Neurorehabilitation depends on neural plasticity and its potential to augment recovery ("good plasticity") or to limit recovery ("bad plasticity"). The central challenge of rehabilitation robotics is to provide tools to manage plasticity, harnessing the "good" and limiting the "bad." It is not simply to automate conventional practices. Primarily due to a lack of tools for measurement and experimental control, many conventional practices lack the support of scientific evidence. As a result, there is no clear design target for the technology nor any reliable "gold standard" against which to gauge its effectiveness. In fact, the biggest hurdle we face in the development of rehabilitation robotics is determining what constitutes best practice.

Consider the example of the failed efforts to automate treadmill training for stroke rehabilitation. Though elegant engineering solutions can be (and have been) applied to automate this process, the essential first step should be to determine whether treadmill training is effective (with or without automation). Unfortunately, recently unveiled results of a National Institutes of Health (NIH)-sponsored large, randomized clinical trial on treadmill training post stroke failed to demonstrate outcomes superior to a simple home exercise program (LEAPS Study) [3]. Thus, at least for stroke, a gait rehabilitation program that is based on treadmill training delivered by therapists (as in the LEAPS study) or robotic devices (such as Lokomat) do not appear to be advantageous [3–5]. Note that this result flies in the face of the "obvious" non-neuro-based benefits of treadmill training, including cardiovascular and greater intensity of gait practice [6]. The message seems clear: we must study the process of neurorecovery as well as the technologies that might augment this process. Otherwise we run the risk of harnessing "bad" plasticity, perhaps to the detriment of patients' recovery.

8.3 An Upper Extremity Gym of Robots

To begin with, we had to invent the technology since the available technologies were inadequate. We developed interactive robots to work with the shoulder and elbow (with and without gravity compensation), the wrist and the hand, as well as combinations of these modules. We further developed exoskeletal robots for neuroscience research (see Fig. 8.1).

8.3.1 Modularity

We chose to pursue a modular approach for several reasons. The foremost was entirely pragmatic: as we intended to introduce new technology to a clinical environment, it needed to be minimally disruptive – i.e., not too big, complex, or intimidating. A secondary reason was our recognition that engineers were unlikely to create optimal technology on the first pass. Though a design to address over 200 degrees of freedom (DOF) of the human skeleton was technically feasible, it would have been large, complex, and – most important – difficult to revise or modify. With a modular approach, individual modules could be refined and optimized without redesign of other modules.

Fig. 8.1 A gym of upper extremity robots. *Top row*: *left panel* shows a person with chronic stroke working with the antigravity shoulder-and-elbow robot, *middle panel* shows a person working with the planar shoulder-and-elbow robot, and *right panel* shows the wrist robot during therapy at the Burke Rehabilitation Hospital. *Middle row*: *left panel* shows the hand module for grasp and release, *middle panel* shows reconfigurable robots. The robotic therapy shoulder-and-elbow and wrist modules can operate in stand-alone mode or be integrated into a coordinated functional unit; *right panel* shows the shoulder-and-elbow and hand module integrated into a coordinated functional unit. *Bottom row* shows the exoskeletal robot for psychophysics. Each robot includes three active DOF affording psychophysical experiments with the shoulder, elbow, and wrist. For this exoskeletal robot, the links must be adjusted to the person's limb segments (using laser pointers). Once arm, forearm, and wrist are properly adjusted, we commence psychophysical experiments assisting or selectively applying perturbation force fields to shoulder, elbow, and wrist (either flexion/extension or abduction/adduction)

8.3.2 Gravity-Compensated Shoulder-and-Elbow Robot

The centerpiece of our effort for the upper extremity became known as MIT-Manus, from MIT's Motto *Mens et Manus* (Mind and Hand). Unlike most industrial robots, MIT-Manus was configured for safe, stable, and highly compliant operation in close physical contact with humans. This was achieved using impedance control, a key feature of the robot control system. Its computer control system modulated the way the robot

reacted to mechanical perturbation from a patient or clinician and ensured a gentle compliant behavior. The machine was designed to have a low intrinsic end-point impedance (i.e., be backdrivable) to allow weak patients to express movements without constraint and to offer minimal resistance at speeds up to 2 m/s (the approximate upper limit of unimpaired human performance, hence the target of therapy and the maximum speed observed in some pathologies, e.g., the shock-like movements of myoclonus). MIT-Manus had two active DOF and one passive DOF. It consisted of a semi-direct-drive, five-bar-linkage SCARA (Selective Compliance Assembly Robot Arm) mechanism driven by brushless motors [7–9]. Since then, several variants were deployed under the commercial name of InMotion2 robot (Interactive Motion Technologies, Watertown, MA, USA).

8.3.3 Gravity-Compensated Shoulder-Elbow-and-Wrist Exoskeletal Robot

From the human–machine, mechanical interface viewpoint, robots can be classified as end-effector or exoskeletal robots. End-effector robots interact with the human via a handshake, i.e., the interaction takes place through a single port. In other words, there is a power flow or exchange only at the tip of the robot. Exoskeletal robots are mounted on distinct human limb segments with more than one interaction port. End-effector robot designs like the MIT-Manus are simpler, afford significantly faster "don" and "doff" (setup time much smaller) than exoskeleton designs, but typically occupy a larger volume. We employ a "rule of thumb" to guide us in the selection of configuration based on the target range of motion. For limb segment movements requiring joint angles to change by 45° or less, fixed-based designs appear to offer better compromises. Conversely, exoskeletal designs appear to offer better choices for larger ranges of motion. That said, in some circumstances the application dictates the configuration. One such case occurs during psychophysical experiments in which we may want to carefully apply and control perturbations to one, but not another, joint and hence we designed a highly backdrivable, 3-active-DOF, gravity-compensated shoulder-elbow-and-wrist exoskeletal robot. Several variants were deployed under the commercial name of InMotion-Exos robot, which in addition to MIT-Manus shoulder-and-elbow capability, affords a selective capability of either wrist flexion/extension or wrist abduction/adduction, as shown in Fig. 8.1 (Interactive Motion Technologies, Watertown, MA, USA). The InMotion-Exos can be configured for uni- or bimanual use.

8.3.4 Gravity Noncompensated Shoulder-and-Elbow Robot

A 1-DOF module was conceived to extend the benefits of planar robotic therapy to spatial arm movements, including movements against gravity. Incorporated in the design are therapists' suggestions that functional reaching movements often occur in a range of motion close to shoulder scaption. That is, this robotic module was designed for therapy to focus on movements within the 45–65° range of shoulder abduction and from 30° to 90° of shoulder elevation or flexion [10]. The module can permit free motion of the patient's arm or can provide partial or full assistance or resistance as the patient moves against gravity. As with MIT-Manus, the system is highly backdrivable.

8.3.5 Wrist Robot

To extend treatment beyond the shoulder and elbow, we designed and built a wrist module for robotic therapy [11]. The device accommodates the range of motion of a normal wrist in everyday tasks, i.e., flexion/extension 60°/60°, abduction/adduction 30°/45°, pronation/supination 70°/70°. The torque output from the device is capable of lifting the patient's hand against gravity, accelerating the inertia, and overcoming most forms of hypertonicity. As with all of our exoskeletal designs, we purposely underactuated the wrist

robot with fewer DOF than are anatomically present. Not only does this simplify the mechanical design, it allows the device to be installed quickly without problems of misalignment with the patient's joint axes. In this case, the axes of the wrist's ulnar-radial and flexion-extension joints do not intersect, and the degree of nonintersection varies between individuals [12]. If robot and human had the same number of DOF but these were not co-aligned, motion might evoke excessive forces or torques. By allowing the human joint more DOF than the robot, excessive loads are avoided. Ease of use is another critical consideration in all our designs. We consider it a major determinant of success or failure in the clinical rehabilitation environment. The wrist robot must be attached to or removed from the patient (donned or doffed) within 2 min. Finally, the wrist-robot module can be operated in isolation or mounted at the tip of the shoulder-and-elbow, gravity-compensated robot. Hence, it enables a combination of translating the hand (with the shoulder-and-elbow robot) to a location in space and orienting the hand (with the wrist robot) to facilitate object manipulation.

8.3.6 Hand Robot

Moving a patient's hand is not a simple task since the human hand has 15 joints with a total of 22 DOF; therefore, it was prudent to determine how many DOF are necessary for a patient to perform the majority of everyday functional tasks. Here, our clinical experience with over 800 stroke patients was invaluable in that it allowed us to identify what was most likely to work in the clinic (and what probably would not). Though individual digit opposition (e.g., thumb to pinkie) may be important for the unimpaired human hand, it is clearly beyond the realistic expectations of most of our patients whose impairment level falls between severe and moderate; a device to manipulate 22 DOF is unnecessary (or at least premature). Our hand therapy module is a novel design that converts rotary into linear movement using a single brushless DC electrical motor as a free-base mechanism with what is traditionally called the stator being allowed to rotate freely [13]. The stator (strictly, the "second rotor") is connected to a set of arms, while the rotor is connected to another set of arms. When commanded to rotate, the rotor and stator work like a double crank and slider mechanism, in opposing configuration, where the crank is represented by a single arm and the slider is the shell or panel which interacts with the hand of the patient (see Fig. 8.1). The hand robot is used to simulate grasp and release with its impedance determined by the torque evoked by relative movement between stator and rotor. A torsional spring (connected in geometric parallel) is available to compensate for a patient's hypertonicity (inability to relax). The hand robot is capable of providing continuous passive motion, strength, sensory, and sensorimotor training for grasp and release; it can be employed in stand-alone operation or mounted at the tip of the planar robot.

8.4 Harnessing Good Plasticity to Augment Recovery

8.4.1 Clinical Evidence for Inpatient Care

Volpe et al. reported composite results of robotic therapy with 96 stroke inpatients admitted consecutively to Burke Rehabilitation Hospital in White Plains, NY [14]. All participants received conventional neurological rehabilitation during their participation in the study. The goal of the trial was to amass initial evidence to test whether movement therapy had a measurable impact on recovery. Consequently, we provided one group of patients with as much movement therapy as possible to address a fundamental question: does goal-oriented movement therapy have a positive effect on neuromotor recovery after stroke? Note in passing that, at the time of these studies, the answer to this question was far from clear.

Patients were randomly assigned to either an experimental (robot-trained) or control (robot-exposure) group. Individuals in the robot-trained group were seen for five 1-h sessions each week and participated in at least 25 sessions of

Table 8.1 Burke inpatient studies ($N = 96$) mean interval change in impairment and disability (significance $P < 0.05$)

Between-group comparisons: final evaluation minus initial evaluation	Robot trained ($N=55$)	Control ($N=41$)	P-value
Impairment measures (± sem)			
Fugl-Meyer shoulder/elbow (FM-se)	6.7 ± 1.0	4.5 ± 0.7	NS
Motor power (MP)	4.1 ± 0.4	2.2 ± 0.3	<0.01
Motor status shoulder/elbow (MS-se)	8.6 ± 0.8	3.8 ± 0.5	<0.01
Motor status wrist/hand (MS/wh)	4.1 ± 1.1	2.6 ± 0.8	NS
Disability evaluation			
Functional independence measure (FIM)	32.0 ± 5.0	25.5 ± 6.5	NS

sensorimotor robotic therapy for the paretic arm. Patients were asked to perform goal-directed, planar reaching tasks that emphasized shoulder-and-elbow movements with their paretic arm. MIT-Manus' low impedance guaranteed that the robot would not suppress attempts to move. When a patient could not move or deviated from the desired path or was unable to reach the target, the robot provided gentle guidance and assistance dictated by an impedance controller [15]. This robot action (which we dubbed "sensorimotor" therapy) was similar to the "hand-over-hand" assistance that a therapist often provides during conventional therapy. It is interesting to note that this form of "assistance as needed," which has been a central feature of our approach from the outset (and a challenge for our robot designs), has recently been adopted and promoted by other groups [16, 17].

Individuals assigned to the robot-exposure (control) group were asked to perform the same planar reaching tasks as the robot-therapy group. However, the robot did not actively assist the patient's movement attempts. When the subject was unable to reach toward a target, he or she could assist with the unimpaired arm, or the technician in attendance could help to complete the movement. The robot supported the weight of the limb while offering negligible impedance to motion. For this control group, the task, the visual display, the audio environment (e.g., noise from the motor amplifiers), and the therapy context (e.g., the novelty of a technology-based treatment) were all the same as for the experimental group, so this served as a form of "placebo" of robotic movement therapy. Patients in this group were seen for only 1 h per week during their inpatient hospitalization.

The study was "double blinded" in that patients were not informed of their group assignment and therapists who evaluated their motor status did not know to which group patients belonged. Standard clinical evaluations included the upper extremity subtest of the Fugl-Meyer Assessment (FM, maximum score = 66); the MRC Motor Power score for four shoulder-and-elbow movements (MP, maximum score = 20); and the Motor Status Score (MSS, maximum score = 82) [18–20]. The Fugl-Meyer test is a widely accepted measure of impairment in sensorimotor and functional grasp abilities. To complement the Fugl-Meyer scale, Burke Rehabilitation Hospital developed the Motor Status Scale to further quantify discrete and functional movements in the upper limb. The MSS scale expands the FM and has met standards for inter-rater reliability, significant intraclass correlation coefficients, and internal item consistency for inpatients [21].

Although the robot-exposure (control) and robot-treated (experimental) groups were comparable on admission, based on sensory and motor evaluation and on clinical and demographic scales, and both groups were inpatients in the same stroke recovery unit and received the same standard care and therapy for comparable lengths of stay, the robot-trained group demonstrated significantly greater motor improvement (higher mean interval change ± sem) than the control group on the MS-se and MP scores (see Table 8.1). In fact, the robot-trained group improved twice as much as the control group in these measures. Though this was a modest beginning, it provided unequivocal evidence that movement therapy of the kind that might be delivered by a robot had a significant positive impact on recovery.

8.4.2 Clinical Evidence for Chronic Care

The natural history of motor recovery of the paretic upper limb after stroke reveals a dynamic process that has traditionally been described by a period of flaccidity that is followed by changes in tone and reflex, as well as the frequent development of synkinesis or associated movement disorders. This synkinesis is characterized by involuntary, composite movement patterns that accompany an intended motor act [22]. Complete motor recovery, when it occurs, will unfold rapidly. However, the more commonly observed partial recovery, with broad variability in final motor outcomes, unfolds over longer periods [23, 24]. That said, the current state of knowledge regarding motor recovery post stroke indicates that the majority of gains in motor abilities occur within the first 3 months after stroke onset, and that over 90% of motor recovery is complete within the first 5 months [25]. We were able to recall one third of the 96 stroke inpatients mentioned earlier 3 years after discharge. We observed that both groups continued to improve after discharge from the hospital and after 5 months post stroke. Our data suggest that previous results limiting the potential of chronic patients' recovery were based on the effects of general rather than task-specific treatments during the recovery period post stroke. Recently, the Veterans Affairs completed the VA-ROBOTICS study (CSP-558), a landmark multisite, randomized clinical trial in chronic stroke of upper extremity rehabilitation robotics employing our gym of robots (planar shoulder-and-elbow, antigravity, wrist, and hand robots) [26].

The VA-ROBOTICS study vanquished for good the old conjecture that an adult brain was hardwired and static. It demonstrated that even for persons with multiple strokes, severe strokes, and many years post stroke, there is a real opportunity for meaningful improvement. At follow-up, 6 months after completing the intervention, the robot group demonstrated sustainable and significant improvement over the usual-care group on impairment, disability, and quality of life. The results are even more impressive if we consider the results of the complete program of robotic treatment rather than an analysis that focused on the first half of the study (see Fig. 8.2). In a nutshell, while the results at 12 weeks show that the difference between the first half of the robotic treatment group and usual care was slightly over 2 Fugl-Meyer points (as the therapists were learning how to use the robots), once the therapists were proficient in using the technology, the difference between the second half of the robotic treatment group and usual care was almost 8 points in the Fugl-Meyer assessment (the total robotic group versus the total usual care showed a 5-point change).

It is quite important to stress that VA-ROBOTICS enrolled moderately to severely impaired chronic stroke patients, and over 30% of these patients had multiple strokes. As such, the group represented a spectrum of disability burden that many studies have avoided and, in our research, represented the majority of the cases (65% of the volunteers were enrolled). Thus, even if the positive changes in the robotic therapy group might appear modest, the persistent statistically significant improvement at the 6-month follow-up evaluation suggests improved robustness and perhaps an incremental advantage that prompted further improvement even without intervention.

In this era of cost containment, cost-benefit analysis is essential, and in this case, it provided an important result. As expected, active interventions added cost beyond the usual care offered in the VA; for example, the extra cost of the robotic equipment plus an additional therapist cost the VA $10,000 per patient for 36 months. However, when we compared the total cost, which included the clinical care needed to take care of these veterans, there were no differences between active intervention and usual care. The usual-care group cost the VA roughly the same $15,000 per patient because that group used the rest of the VA health care system three times more often than the active intervention groups. In other words, for 36 weeks of care, the robotic group cost the VA $10,000 for robotic therapy and $5,000 for clinical care. For 36 weeks of care, the usual-care group cost the VA approximately $15,000. This suggests better care for the same total cost. These results were quite unexpected, and a full economical analysis is under way by the VA; we will have to wait for the detailed economical analysis to get further

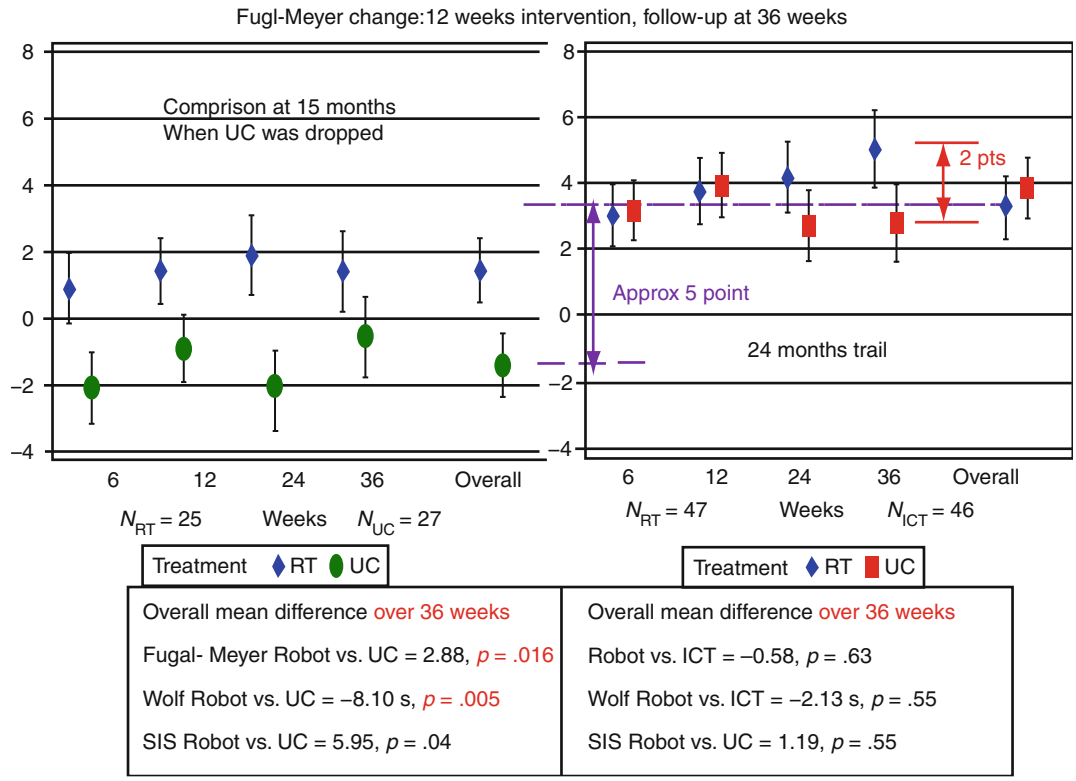

Fig. 8.2 Changes over time in the VA-ROBOTICS. Training lasted for 12 weeks with an additional 6-month follow-up after completion of the intervention. The *left panel* shows the comparison of the first half of the robot group with the usual care (first half as therapists learned how to employ the system). The *right panel* shows the comparison of the complete robot group with the Intensive Comparison Training (both groups executed 1,024 reaching movements with the paretic arm in an hour session). *Arrows* indicate the changes between usual care and robot group and between robot group and ICT at 36 weeks evaluation

information. Nevertheless, the preliminary results warrant guarded optimism.

Summarizing briefly, there is now objective evidence that in the "real" therapy world away from the clinical research environment, robotic therapy that involves an interactive high-intensity, intention-driven therapy based on "assist-as-needed" motor learning principles leads to better outcomes than usual care in chronic stroke (and probably even bigger impact for acute/subacute stroke).

8.4.3 Clinical Evidence Contrary to Common Clinical Perceptions

While appropriate robotic therapy has been demonstrated to augment recovery, we still don't know how to tailor therapy to meet a particular patient's needs. We do not know the optimal dosage. What is the minimum intensity to promote actual change? Is too much therapy detrimental? Should we deliver impairment-based or functionally based approaches? To whom: severe, moderate, mild stroke patients? Should therapy progress from proximal to distal or the other way around? Should we train subcomponents of a movement, such as reaching in a compensated environment and raising the arm against gravity, or train the complete spatial movement against gravity? Should we assist-as-needed, resist, or perturb and augment error? Who might be the responders who benefit most from these interventions? How should we integrate robotic gyms with therapy practice?

Our ignorance could not be more evident than when testing a common perception among

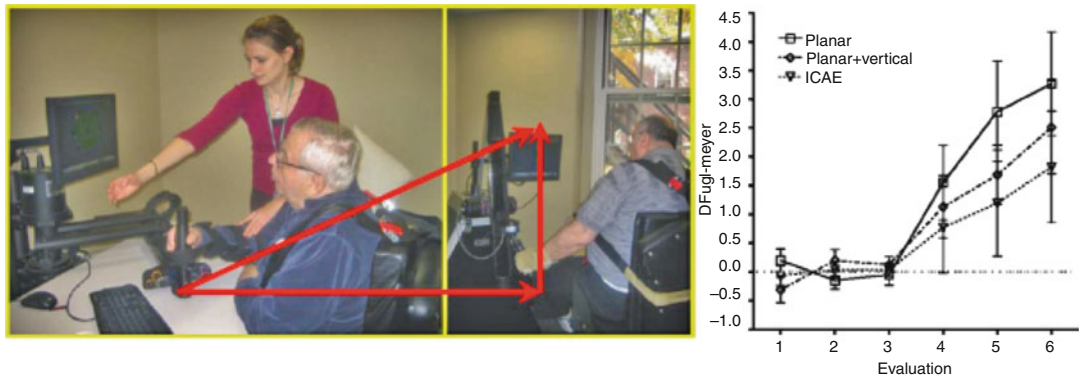

Fig. 8.3 Component training and spatial composition. The FMA changes at each point (mean, STD) with ICAE standing for intensive conventional arm exercise. Baseline demonstrates stability and no difference among groups. Changes from baseline to final and follow-up showed a significant benefit for both robotic groups

clinicians that training must involve spatial movement. While Lo and colleagues demonstrated that a combination of planar, vertical, wrist, and hand robot training improves both arm impairment and functional recovery, as well as quality of life, the added value of antigravity/spatial training was not addressed in that study. Though therapists long held the belief that training must be spatial, investigations comparing training in gravity-compensated and noncompensated environments had not been performed. To address this question, in a randomized clinical trial, we compared a combination of antigravity and planar robot training with planar training alone and compared its effectiveness to a control group who received intensive conventional arm exercise (ICAE) [27]. We hypothesized that planar robot training combined with robot-assisted reaching outside the constrained gravity-compensated horizontal plane would be superior to gravity-compensated planar robot therapy alone. We also hypothesized that a 6-week program of robot-assisted motor training would be more efficacious than ICAE across impairment, function and activity measures (half duration of the duration of VA-ROBOTICS).

All interventions were provided by the same therapist for 6 weeks: 1 h, three times a week for a total of 18 sessions. Robot therapy included the use of two different robots employed in the VA-ROBOTICS study. Robot-assisted planar reaching was performed with a 2-active-degrees-of-freedom (DOF) InMotion2 shoulder–elbow robot. The combined-robot group (planar + vertical) used the planar shoulder–elbow robot for gravity-compensated horizontal reaching followed by the 1-DOF InMotion-linear robot in its vertical position for reaching against gravity. The robots provided assistance with a performance-based algorithm, adapting forces as needed to challenge or assist movement. This algorithm, introduced in 2002, continuously challenges the patient by modifying (a) the time allotted for the patient to make the move and (b) the primary stiffness of the impedance controller that guides the movement. The better the patient performs, the more she or he is challenged to move quicker and receive less guidance; the controller updates its characteristics at each completion of multiples of five games [15]. In addition, the robots' compliant and backdrivable behavior allowed for expression of movement outside a rigid trajectory. The intensive conventional arm exercise (ICAE) sessions were time matched with the robotic sessions. The rate of movement repetition was not precisely matched to the robot, but overall intensity was much greater than with a conventional exercise program. (Fig. 8.3)

On the primary outcome, all three groups showed modest gains from baseline to final training without significant differences. The two robotic groups, however, showed significant within-group changes not seen in the ICAE control group, both at the end of treatment and after

a retention period. Remarkably, contrary to clinicians' expectations, the combined-training group was not superior to the gravity-compensated robot training group. In fact, the planar (gravity-compensated) robot training subjects showed the greatest change.

Independence in everyday living activities includes the ability to execute reaching motions at any given moment despite the opposition of gravity. In this investigation, the robot interventions were primarily differentiated by the presentation of two different types of reaching in a horizontal and in a vertical plane (gravity-compensated and noncompensated) versus reaching in a single (gravity-compensated) horizontal plane. It was hypothesized that a combined robotic training program would enhance recovery by increasing task challenge and generalization of reaching to more than one context. However, the successive presentation of arm activities with different environmental and motor demands did not lead to better overall group outcomes.

One interpretation of these results is that the motor system may use two distinct internal models for whole arm antigravity reaching and gravity-compensated planar reaching, and our blocked training in close succession interfered with motor consolidation [28, 29]. This interpretation is supported by a prior robotic study that found gravity, noncompensated vertical reaching promoted further recovery in chronic stroke beyond that resulting from gravity-compensated planar reaching if it followed, rather than abutted, gravity-compensated planar reaching, i.e., 6 weeks of planar reaching training followed by 6 weeks of antigravity training [10]. Whether motor memories require an interval to consolidate (Caithness G) or whether practicing the whole arm movement is necessary to promote optimal recovery [30] is a complex question that this study design cannot answer. However, given the findings, it is clear that further investigation of alternative sequencing of the two robot therapies is warranted. Perhaps combining these two robotic therapies on alternating days or weeks would provide a better recovery based on impairment and functional measures. Perhaps each domain may require a different schedule. Identifying the best sequence and presentation of therapies that make different demands on the patient is clearly an important empirical question, a necessary step toward using robotic therapy to optimize stroke recovery. However, it is equally clear that basing therapy programs on intuitively reasonable, preconceived but untested ideas will not suffice.

8.4.3.1 Which Processes Underlie Neuro-recovery?

A common assumption is that sensory-motor therapy works by helping patients to "relearn" motor control [31]. Though intuitively sensible, this notion may need to be refined. In the first place, normal motor learning does not have to contend with the neuromuscular abnormalities that are common sequelae of neurological injury, including spasticity, abnormal tone, disrupted or unbalanced sensory pathways, and muscular weakness. Thus recovery is likely to be a more complex process than learning. Secondly, normal motor learning is far from fully understood. Topics of ongoing, vigorous debate include questions such as: what variables or parameters of action does the brain command and control? How are these encoded and represented in the brain? How are these encodings or representations acquired and retained? These deep questions have practical relevance for therapy. For example, if the brain represents action as a sequence of muscle activations, it would seem profitable to focus sensory-motor therapy on muscles. However, a large and growing body of evidence indicates that under many circumstances the brain does not directly control muscles; instead it controls the upper extremity primarily to meet kinematic specifications (such as simple motion of the hand in a visually relevant coordinate frame), adjusting muscle activity to compensate for movement-by-movement variation of mechanical loads. That would suggest it may be more profitable to focus sensory-motor therapy on motions rather than muscles and on motor learning rather than muscle strengthening. In our research on robotic stroke rehabilitation, we have attempted to assess some of these possibilities and have developed adaptive treatment algorithms to incorporate such ideas.

Our performance-based adaptive algorithm uses nonlinear impedance control to implement a "virtual slot" extending between the start and goal positions during reaching movements [15]. Lateral deviation from the desired trajectory was discouraged by the stiffness and damping of the slot sidewalls. Desired motion was assisted by moving the back wall of the slot along a minimum-jerk virtual trajectory so that the slot progressively "collapsed" to a "virtual spring" centered on the reaching movement goal position. However, motion along the "virtual slot" (well aimed and faster than the nominal desired trajectory) was unimpeded.

A request to move was signaled by a target in the visual display changing color. If the patient failed to trigger the robot within two seconds, the robot began to act (i.e., the back wall of the "virtual slot" closed on the goal position). To trigger the robot, the patient had to move the handle (in any direction) at a speed above a modest threshold value. Even severely impaired patients with a paretic arm could trigger the robot – although trunk motion was discouraged by restraining seatbelts, in practice, sufficient trunk motion was possible to move the handle and trigger the robot; no particular instruction was given but to try to reach the target. Though ultimately inappropriate trunk motion is to be discouraged, this mode of triggering the robot encouraged severely impaired patients to participate actively rather than passively allow the robot to drive the arm.

Secondly, the revised algorithm continuously monitored the patient's performance. By combining records of the kinematics of actual patient motion and the kinetics of mechanical interaction between robot and patient, five performance measures were computed: we graded (a) patients' ability to initiate movement, (b) patients' movement range or extension toward the reaching movement target goal, (c) amount of mechanical power that the robot exerted to assist the hand toward the target, (d) the smoothness of the movement, and (e) the aiming/deviation from a straight line connecting the center to the reaching goal. These measures were used to adjust the parameters of the controller during a therapy session. For the first five cycles through the eight goal positions, the time allotted for a movement (the duration of the nominal minimum-jerk trajectory) and the stiffness (impedance) of the "virtual slot" sidewalls were adjusted to approximately track the patient's current performance and need for guidance. This was important as patient performance typically declined between the end of one therapy session and the beginning of the next as commonly seen in motor learning (acquisition of a skill and its retention). For every subsequent five cycles of the game, the controller parameters were adjusted based on the patient's performance and its variability during the previous batch of moves. The intent here was not just to track patients' performance but also to challenge them to improve. As patients aimed better, the stiffness of the "virtual slot" sidewalls was decreased, requiring better accuracy (and vice versa). As patients moved faster, the time allotted for movement was decreased, requiring faster movements (and vice versa). The speed threshold to trigger the robot was also adjusted to 10% of the peak speed of a minimum-jerk trajectory of that duration. Consequently, if nominal movement duration increased, the speed of motion required to trigger the robot decreased (and vice versa). Thus, the motor ability required to trigger the robot and move to the target was less demanding for more impaired patients and more demanding as performance improved. Again, this was intended to encourage active participation of even the most impaired patients and yet continuously challenge patients as they recovered.

Thirdly, to provide motivation, positive reinforcement, and knowledge of results, the revised algorithm provided specific, movement-related feedback in the form of a simple graphical display consisting of five displays reflecting patient's performance in the last batch of five repetitions [32]. Each readout was determined by the five performance measures discussed earlier. The therapist could elect to hide displays that were not meaningful for a patient to avoid discouraging patients who could not yet move well without boring patients who could.

This performance-based progressive therapy algorithm provided support for patients to progress from complete hemiplegia to normal arm

Table 8.2 Motor impairment outcomes of performance-based progressive robotic therapy

Severity	Impairment measure (mean ± sem)	FM SEC (max = 42)	% change	MP (max = 70)	% change
Moderate	Before treatment	17.0 ± 1.3		37.2 ± 2.5	
N = 12	After treatment	22.5 ± 1.3*	32%	45.4 ± 1.7*	22%
CNS > 4; NIHSS < 15	Follow-up (3 months)	24.5 ± 0.9*	44%	46.5 ± 1.9*	25%
Severe	Before treatment	8.2 ± 0.7		17.3 ± 1.8	
N = 16	After treatment	10.9 ± 0.9*	33%	23.7 ± 2.0*	52%
CNS < 4; NIHSS > 15	Follow-up (3 months)	12.5 ± 0.9*	37%	26.3 ± 2.2*	52%

FM SEC Fugl-Meyer, shoulder–elbow component, *MP* motor power, *CNS* Canadian Neurological Scale, *NIHSS* National Institutes of Health Stroke Scale
*Denotes significant change, $P < 0.001$

movement. The ability to initiate a movement was stressed for severely impaired patients, helping to ensure appropriate timing of afferent and efferent signals. Movement range is an important clinical measure of function but also rewards hypertonic patients for relaxing their arms, allowing the impedance controller to move their hands closer to the target. The amount of power that the robot exerted encourages a patient to attempt to do more of the movement. Finally, smoothness and aiming (deviation from a straight path) quantify the trade-off between speed and accuracy that is characteristic of unimpaired movement and probably most important for patients with moderate to mild impairment.

This adaptive algorithm was evaluated in multiple studies including VA-ROBOTICS. Here, we recount the typical changes observed in chronic stroke patients as reported elsewhere [33]. All patients were evaluated six times: three times in a 2-month period prior to the start of therapy to assess baseline stability (phase-in phase), then at the midpoint and at the discharge from robotic therapy (18 1-h sessions of robotic training, three times a week for 6 weeks), and finally at a follow-up evaluation session 3 months after training. Evaluators were blinded to the protocol used for treatment.

The first three evaluations showed no significant changes on any of the impairment scales, verifying that subjects were indeed at the chronic phase of their recovery in which no spontaneous improvement was observed. Subsequent evaluations showed that the adaptive protocol evoked a statistically significant improvement in motor performance which was maintained at the 3-month follow-up (see Table 8.2). More important for our understanding of recovery, the *magnitude* of the improvement achieved with this adaptive algorithm was many times greater than that achieved with our previous robotic therapy. The only change was the robot control scheme; the same robot assisted with the same set of reaching movements during the same number of sessions. A treatment protocol, which adapted to the patient in order to present a continuous challenge substantially, enhanced recovery.

An important and informative detail is that this enhancement of recovery was achieved with *fewer* repetitions. Because the adaptive protocol adjusted the time allotted for a movement and allowed long movement durations as needed, fewer repetitions could be accomplished in a 1-h therapy session. Under this adaptive protocol, patients typically made just over 12,000 movements over the course of treatment. Under the previous hand-over-hand sensory-motor protocol, patients made just over 18,000 movements in the same number of sessions.

This confirms that, although the process of recovery may share some features of motor learning (such as specificity), the relationship between learning and recovery may be subtle. Though movement is beneficial, movement alone is not sufficient; active involvement of the patient is essential. Though repetition may be beneficial, repetition alone is not sufficient; the benefits of robotic therapy do not exclusively derive from the high "dosage" of movement delivered but from the interactive nature of the therapy protocol.

8.4.3.2 Robot-Mediated Assay

First proposed over a decade and a half ago, devices for robot-aided neuro-rehabilitation are increasingly being incorporated into stroke patients' care programs. In addition to delivering high-intensity, reproducible sensorimotor therapy, these devices are precise and reliable "measuring" tools that can be expanded with multiple sensors to record simultaneously kinematic and force data. These measurements are objective and repeatable and can be used to provide patients and therapists with immediate measures of motor performance. Reducing the time to evaluate improvement or deterioration may offer new opportunities for designing therapeutic programs and ultimately for increasing the efficiency of patients' care. Across multiple regression models, we demonstrated that robot-based metrics can reliably estimate the clinical scales [34] with good correlations during training and validation ($R>0.7$). For example, we can estimate the Fugl-Meyer assessment (FMA) quite accurately for chronic stroke from the MIT-Manus kinematic metrics via:

$$\begin{aligned}\mathrm{FMA} = {} & 4.58 - 11.68 \times [\mathrm{AIM}] \\ & + 37.04 \times [\mathrm{Deviation}] \\ & - 29.30 \times [\mathrm{MeanSpeed}] \\ & + 62.55 \times [\mathrm{PeakSpeed}] \\ & + 83.96 \times [\mathrm{Smoothness}] \\ & + 1.72 \times [\mathrm{Duration}] \\ & + 2.98 \times [\mathrm{EllipseRatio}] \\ & - 17.28 \times [\mathrm{JoinIndependence}]\end{aligned}$$

where the metrics were extracted from unconstrained reaching movement toward targets presented in eight positions equally spaced around a 14-cm radius circle and back to the center, namely, the deviation from the straight line connecting the targets, aiming, movement mean and peak speed, movement smoothness (ratio of mean to peak speed), and movement duration; or the metrics were extracted from unconstrained circle drawing where the patient's hand was initially positioned at 3 o'clock and at 9 o'clock (right or left to the workspace center) and she or he was asked to draw clockwise and counterclockwise circles starting and ending at the same point, namely, the axes ratio (ratio of the minor to major axes of the best-fitting ellipse) and the joint angle correlation (degree of independence of the shoulder-and-elbow movements) [35].

Robot measurements can potentially outperform human-administered clinical scales and are limited only by the performance of the robot sensors. For example, MIT-Manus can measure positions with a resolution of 0.1 mm. The reliability of human-administered clinical scales has often been questioned; for example, Sanford reported an interrater variability of +/− 18 points on a 95% confidence interval for the total Fugl-Meyer scale, pointing out that small patient improvements will not be able to be identified by the score [36]. Krebs found up to a 15% discrepancy between therapists when evaluating the same patient for the upper extremity FMA scale [37]. Gregson estimated an interrater agreement of 59% for the MAS [38]. The MAS is considered a reliable clinical scale by some [38] but totally unreliable by others [39]. Besides having questionable reliability, human-administered clinical scales are also time-consuming. In contrast, robot measurements can potentially provide therapists and patients with immediate feedback. Real-time scoring cannot only greatly reduce the amount of time required for evaluations of patients' motor improvements but it is also becoming a key need for the new robot-aided neuro-rehabilitation scenarios. These include systems that continuously adapt the amount and type of delivered therapy based on patient's motor abilities [15, 40].

8.5 Discussion

We reiterate the observations (some of which we have made previously) to emphasize our perception of the state of the art. The available evidence demonstrates unequivocally that some forms of robotic therapy can be highly effective, even for patients many years post stroke. At the same time, other forms of robotic therapy have been singularly ineffective. The contrast is starkest when we contrast upper extremity and lower extremity therapy.

Of course, these differences might arise from the contrasting neuro-mechanical complexity of upper extremity reaching and grasping versus lower extremity locomotion, the former being "simpler" in some sense. However, that is a difficult case to make. While the mechanical complexity of locomotion is undeniable (it involves "hybrid" dynamics, a combination of discrete switching and continuous dynamics, one of the most challenging frontiers of robotics and control technology), locomotor behavior is very "old" in phylogenetic terms; it does not require a lot of "brain" to generate functional locomotion. In contrast, the prodigious versatility of "ordinary" human manipulation is very "new" in phylogenetic terms. It seems to require a highly ramified central nervous system and may even be a unique characteristic of human behavior.

We submit that the contrasting effectiveness of upper and lower extremity therapies arises from neural factors, not technological factors. Though, no doubt, it might be improved, the technology deployed to date for locomotor therapy is elegant and sophisticated. Unfortunately, it may be misguided, providing highly repeatable control of movement but ultimately doing the wrong thing. The technology we have deployed to date for upper extremity therapy is straightforward, though nontrivial, but it is firmly based on an understanding of how upper extremity behavior is neurally controlled and derived from decades of neuroscience research. The limitations of lower extremity robotic therapy lie not in the robotic technology but in its incompatibility with human motor neuroscience.

Of course, our knowledge of neural control of human movement is far from complete, and it is continually revised as new knowledge is gained. Thus, there remains ample opportunity to improve upper extremity robotic therapy. To draw an analogy, the state of robotic rehabilitation technology loosely resembles that of aviation in the late 1920s. Heavier-than-air flight had been reliably demonstrated and some applications (i.e., military) had been explored, but the lasting benefits of this technology were about to be realized. Contrasting the piston-engine biplanes of the 1920s with turbine-powered modern airliners may help to comprehend the magnitude and future potential of robotic therapy.

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Three-Dimensional Multi-Degree-of-Freedom Arm Therapy Robot (ARMin)

9

Tobias Nef and Robert Riener

Abstract

Rehabilitation robots have become an important tool in stroke rehabilitation. Compared to manual arm therapy, robot-supported arm therapy can be more intensive, of longer duration, and more repetitive. Therefore, robots have the potential to improve the rehabilitation process in stroke patients. In this chapter, the three-dimensional, multi-degree-of-freedom ARMin arm robot is presented. The device has an exoskeleton structure that enables the training of activities of daily living. Patient-responsive control strategies assist the patient only as much as needed and stimulate patient activity. This chapter covers the mechanical setup, the therapy modes, and the clinical evaluation of the ARMin robot. It concludes with an outlook on technical developments and about the technology transfer to industry.

Keywords

Exoskeleton • Rehabilitation • Stroke • Upper extremity • Virtual reality

9.1 State of the Art

9.1.1 Rationale for Application of Current Technology

Stroke remains the leading cause of permanent disability. Recent studies estimate that it affects more than one million people in the European Union [1, 2] and more than 0.7 million in the United States each year [3]. The major symptom of stroke is severe sensory and motor hemiparesis of the contralesional side of the body [4]. The degree of recovery depends on the location and the severity of the lesion [5]. However, only 18% of stroke survivors regain full motor function

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after 6 months [6]. Restoration of arm and hand function is essential to resuming daily-living tasks and regaining independence in life. Several studies show that sensorimotor arm therapy has positive effects on the rehabilitation progress of stroke patients [7–9].

The goal is to induce long-term brain plasticity and improve functional outcomes. Relevant factors for successful therapy include training intensity [10–12], duration [13, 14], and repetition [15].

With respect to these criteria, one-to-one manually assisted training has several limitations. It is labor-intensive, time-consuming, and expensive. The disadvantageous consequence is that the training sessions are often shorter than required for an optimal therapeutic outcome. Finally, manually assisted movement training lacks repeatability and objective measures of patient performance and progress.

Some shortcomings can be overcome by the use of robotics. With robot-assisted arm therapy, the number and duration of training sessions can be increased while reducing the number of therapists required per patient. Thus, it is expected that personnel costs can be reduced. Furthermore, robotic devices can provide quantitative measures and support the objective observation and evaluation of the rehabilitation progress.

Fig. 9.1 Typical setup for a robot-supported arm therapy system

9.1.2 Therapeutic Actions and Mechanism

Numerous groups have been working on arm-rehabilitation robots, and several different types of rehabilitation robots have been developed and tested with stroke patients. In this article, we discuss different types of robotic arm therapy by analyzing several arm robots. This is not an exhaustive analysis of arm therapy robots, and the interested reader is referred to appropriate review articles [16–18].

The typical setup for robot-supported arm therapy consists of the seated stroke patient with the most affected arm connected to the robotic device (Fig. 9.1). In most applications, the patient looks at a graphical display – either a large, immersive 3D projection or standard computer screen. The robotic device is characterized by its mechanical structure, the number and type of actuated joints, and the actuation principle. This section discusses these three key characteristics and their influence on the rehabilitation training.

9.1.2.1 Mechanical Structure: End-Effector-Based Robots and Exoskeleton Robots

End-effector-based robots are connected to the patient's hand or forearm at one point (Fig. 9.2). Depending on the number of links of the robot, the human arm can be positioned and/or oriented in space. The robot's axes generally do not correspond with the human-joint rotation axes. That is why, from a mechanical point of view, these robots are easier to build and to use.

Many researchers have developed and evaluated end-effector-based robots. The MIT Manus [19], the Mirror Image Motion Enabler [20], the Bi-Manu-Track [21], the GENTLE/s [22], and the Arm Coordination Training Robot [23] are examples of end-effector-based robotic devices. An important advantage of these robots is that

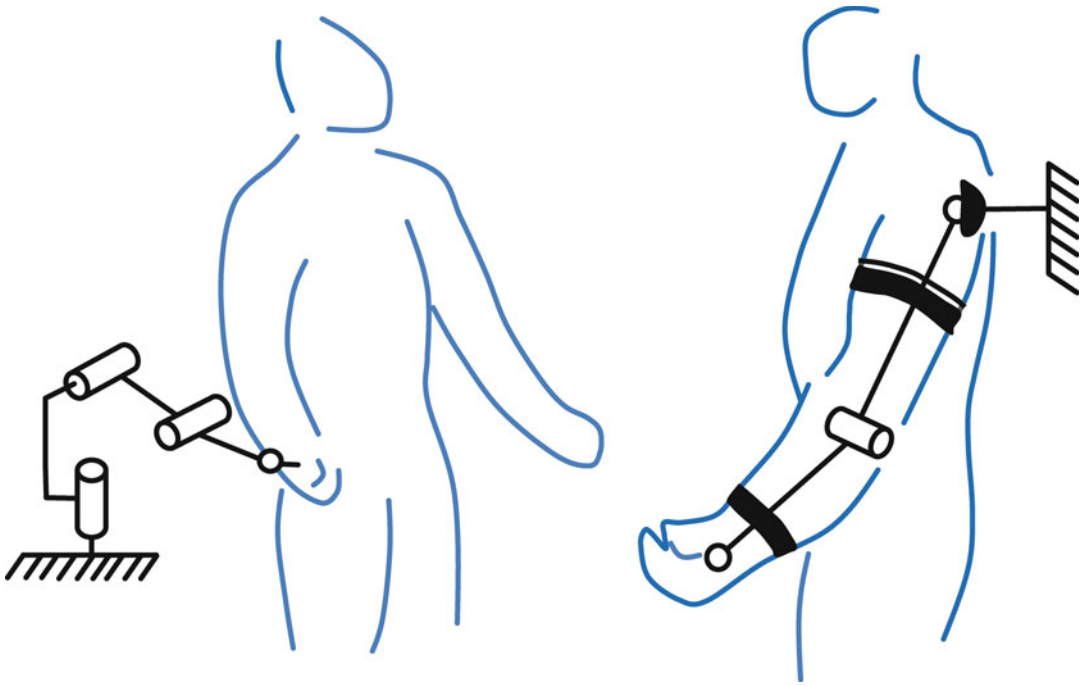

Fig. 9.2 Schematic view of end-effector-based (*left*) and exoskeleton (*right*) robots

they are easy to adjust to different arm lengths. A disadvantage is that, in general, the arm posture and/or the individual joint interaction torques are not fully determined by the robot because the patient and the robot interact just through one point – the robot's end effector.

The mechanical structure of the exoskeleton robot resembles the human arm anatomy, and the robot's links correspond with human joints. Consequently, the human arm can be attached to the exoskeleton at several points. Adaptation to different body sizes is, therefore, more difficult than in end-effector-based systems because the length of each robot segment must be adjusted to the patient's arm length. Since the human shoulder girdle is a complex joint, this is challenging and requires advanced mechanical solutions for the robot's shoulder actuation [24]. However, with an exoskeleton robot, the arm posture is fully determined, and the applied torques to each joint of the human arm can be controlled separately. The ability to separately control the interacting torques in each joint is essential, such as when the subject's elbow flexors are spastic. The mobilization of the elbow joint must not induce reaction torques and forces in the shoulder joint, which can be guaranteed by an exoskeleton robot, but not by an end-effector-based one. That is also why therapists use both hands to mobilize a spastic elbow joint. To avoid exercising forces to the shoulder, one hand holds the lower arm while the other hand holds the upper arm. This is comparable to an exoskeleton robot with a cuff affixed to the lower arm and another cuff affixed to the upper arm. Some examples of arm-rehabilitation exoskeletons include the Dampace [25], the Armeo (former T-Wrex) [26], the MGA-Exoskeleton [27], the L-Exos [28], the Caden-7 [29], the Intelligent Robotic Arm [30], and the ARMin I, II, and III devices [24, 31].

While it seems clear that end-effector-based robots have practical advantages (usability, simplicity, and cost-effectiveness) and exoskeleton robots have biomechanical advantages (better guidance), it remains an open research question whether and how this disparity influences therapeutic outcomes.

9.1.2.2 Number and Type of Actuated Joints

The number and type of actuated joints is another point of differentiation among robotic devices. Some groups focus on a functional training that includes the entire arm and hand (proximal and distal joints). This functional training can be based on activities of daily living (ADL) and requires sophisticated and complex robotic devices such as the GENTLE/s, the Dampace, the Armeo Spring, or the ARMin robot. The reason for ADL training is that there is evidence that functional and task-oriented training shows good results in stroke patients [9, 32]. This confirms previous observations made with the constraint-induced movement therapy. Intervention studies have shown that forcing the affected limb to perform ADLs yields functional gains, allowing the stroke patient to increase the use of the affected arm in the "real-world" environment [33–36].

Other groups have developed robots that focus on the training of distal parts of the human arm such as the hand [37], the wrist, and the lower arm [38, 39]. One may speculate that the distal approach results in a more powerful activation of the sensorimotor cortex, given their larger cortical representation [40]. The recently suggested competition between proximal and distal arm segments for plastic brain territory after stroke [41] would imply shifting treatment emphasis from the shoulder to the forearm, hand, and fingers. Other devices work more proximal on the elbow and shoulder [23, 42]. Namely, the Act3D robot implements an impairment-based, 3D robotic intervention that specifically targets abnormal joint torque coupling between the elbow and shoulder joint [43].

The research question is whether robotic training should focus on whole-arm/hand functional movements, only distal, or distal and proximal.

9.1.2.3 Actuation Principle: Nonmotorized Robots and Motorized Robots

Most motorized rehabilitation robots are powered by electric motors. Depending on the underlying control paradigm, the motors can either control the interaction force/torque between the patient and the robot or the position of the robot. This allows the robotic device to support the human arm against gravity, canceling gravitational forces and making it easier for the patient to move his arm. Also, motorized robots can support the patient in movement toward a target, such as an object within an ADL training scenario. If required, electric motors can also resist the patient in the movement, making the patient's arm heavier or making the patient feel that he is carrying an object with a given mass. Motorized robots can be used as an evaluation tool to objectively measure voluntary force, range of motion, and level of spasticity [44, 45]. Another important application is having the robot introduce force fields onto the endpoint of the human. The adaptation of the human to different force fields is expected to trigger plasticity changes in the brain and enhance rehabilitation.

Some recent rehabilitation devices have been developed to work without motors [25, 26]. The commercially available Armeo Spring device is based on the former T-Wrex device [46] and works without any motors. In this exoskeleton device, springs support the human arm against gravity. The mechanical design allows the therapist to adjust the spring length and to select the proper amount of support. Sensors measure the position and orientation of the human arm, which is transmitted to the graphical display where the patient can see his own movement on the computer screen. Compared to motorized robots, this approach has the great advantage of significantly lower costs and weight. Moreover, the device is easier to use and intrinsically safe. The disadvantage is that it is not possible to support the patient other than against gravity, so, for instance, the device cannot support the patient in directed reaching movements, nor can it challenge the patient by resisting movement. Some devices overcome this by adding brakes to the robot that dissipate energy and challenge the patient's movements [25]. Current evidence suggests that nonmotorized devices might be very well suited for the training of mildly impaired stroke patients who do not need as much support as heavily impaired subjects [46].

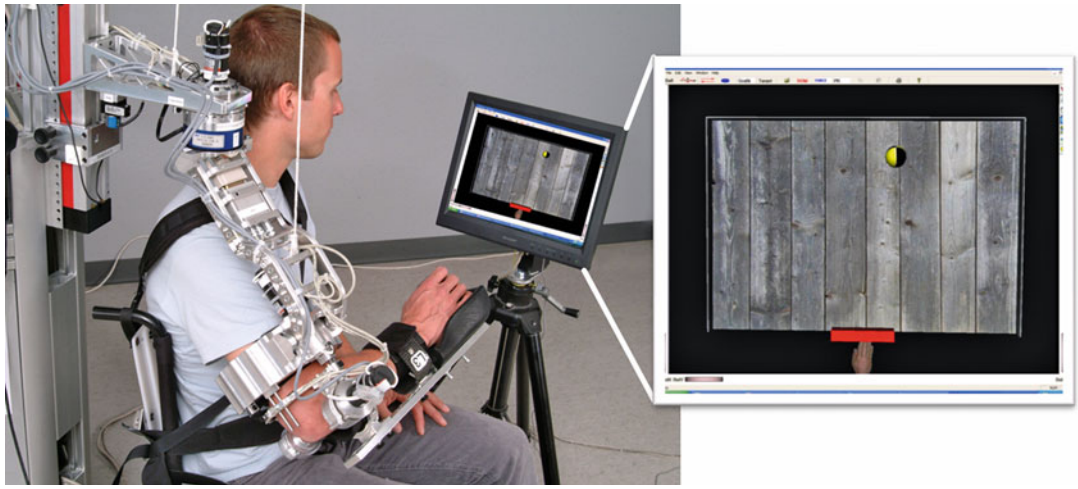

Fig. 9.3 ARMin I robot with a healthy test person (*left*). The person is looking at a computer monitor showing the movement task (*right*)

9.2 Review of Experience and Evidence for the Application of the ARMin Robot System

9.2.1 Technical Evaluation of the ARMin Robot System

The first version of the arm therapy robot, ARMin I, was designed and tested from 2003 to 2006 at the ETH Zurich in close collaboration with therapists and physicians from the University Hospital Balgrist, Zürich [31, 47]. This version is characterized by 4 degrees of freedom actuating the shoulder in 3D and flex/extend the elbow (Fig. 9.3). The upper arm is connected to the robot by an end-effector-based structure. Like later versions of the ARMin, the device could be operated in three modes: passive mobilization, active game-supported arm therapy, and active training of activities of daily living (ADL). The improved version, ARMin II, was characterized by a complete exoskeletal structure with two more degrees of freedom (six altogether) allowing also pronation/supination of the lower arm and wrist flexion/extension (Fig. 9.1). Particular efforts were undertaken to optimize shoulder actuation: a sophisticated coupling mechanism enables the center of rotation of the shoulder to move in a vertical direction when the arm is lifted [48, 49]. This function is required to provide an anatomically correct shoulder movement that avoids shoulder stress from misalignment of the robot and anatomical joint axes when lifting the upper arm above face level.

ARMin III (Fig. 9.4) was further improved with respect to mechanical robustness, complexity, user operation, and reliability [24]. Five ARMin III devices have been developed for a multicenter clinical trial. The next section describes the mechanics of the ARMin III robot in more detail.

9.2.2 Mechanical Setup of the ARMin III Robot

The ARMin III robot (Fig. 9.4) has an exoskeleton structure with six electric motors allowing it to move the human arm in all possible directions. Three motors actuate the shoulder joint for shoulder flexion/extension, horizontal abduction/adduction, and internal/external rotation. The elbow joint has two motors that actuate elbow flexion/extension and forearm pronation/supination. The last motor actuates wrist flexion/extension [24]. An optional module to support hand opening and closing can be attached to the ARMin III robot.

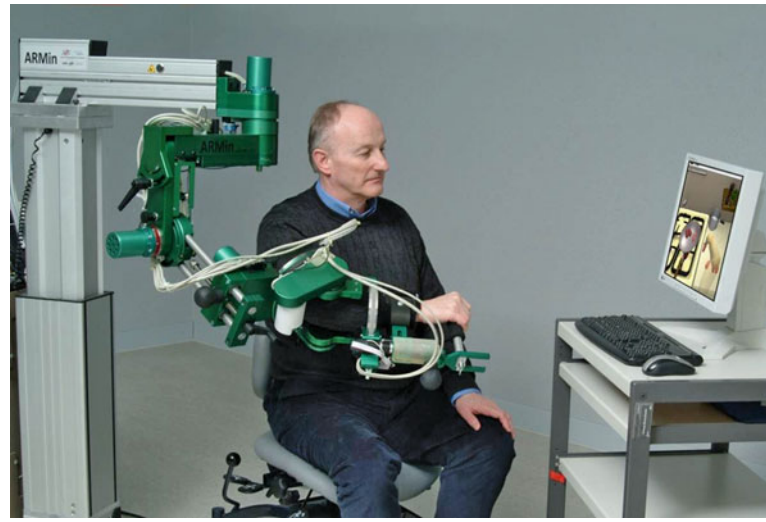

Fig. 9.4 ARMin III setup

All motors are equipped with two position sensors for redundant measurements. The motor and gears are carefully selected so that the friction is small and the backdrivability is good, an important requirement for sensorless force-control [49] and impedance-control strategies.

The patient's arm is affixed to the exoskeleton via two adjustable cuffs, one for the upper arm and one for the lower arm. To accommodate patients of different sizes, the shoulder height can be adjusted via an electric lifting column, and the lengths of the upper and lower arms are adjustable. Laser pointers indicating the center of the glenohumeral joint help the therapist position the patient in the ARMin III device. The ARMin III robot can be configured to accommodate either the left or the right arm. The transition between the two configurations does not require tools and takes less than 15 s.

A spring in the uppermost horizontal robotic link compensates for part of the weight of the exoskeleton. This lessens the load of the electric motor and has the desired effect of balancing the robotic arm when the power is off. Experience has shown that this is crucial for safety and for easy handling of the patient. The robotic shoulder actuation compensates for scapula motion during the arm-elevation movement, resulting in a comfortable and ergonomic shoulder motion [24].

9.2.3 Therapy Modes

The motorized ARMin robots work in three training modes: mobilization, game training, and ADL training. We found it was beneficial to start a typical 1-h training session with a slow and gentle mobilization exercise. Chronic stroke patients in particular seemed to profit from the passive mobilization that reduced spasm and "loosened" the arm and hand. After 10–15 min of passive mobilization, active training followed, including games, reaching exercises, and ADL training scenarios [50, 51].

9.2.3.1 Passive and Active Mobilization

In the mobilization-training mode, the robot moves the patient's arm on a predefined trajectory. The robot is position-controlled, and the feedback loops help the motors compensate for any resistance that the patient produces. This means that, regardless of what the patient is doing, the robot will follow the predefined trajectory. If the patient moves together with the robot in the desired direction (active mobilization), the motors have less work than if the patient remains passive (passive mobilization). However, in both cases, the resulting movement will look the same. Since it is often desirable for the patient to actively contribute to the movement, the motor torque can be measured and used as performance

measure to monitor how actively the patient contributes to the movement. In this case, the audio-visual display is used as feedback modality to let the patient and therapist know how actively the patient is contributing to the movement [45]. Note that, from a technical point of view, this position-controlled training is based on industry-standard position control and is straightforward to implement.

The mobilization requires predefined trajectories that fit the patient's needs in terms of velocity and range of motion. The therapist can either input the data via a computer graphical user interface (GUI) or – more conveniently – use a teach-and-repeat procedure that enables the robot to directly learn a desired trajectory from the therapist. To do this, the therapist moves the robotic arm together with the human arm in the desired way, and the robot records and stores the position data that enable the robot to repeat the movement as shown by the therapist.

9.2.3.2 Game Therapy

Computer games are a good way to motivate the patient to participate actively in the training and contribute as much as possible to a particular movement task. For example, in the ball game, a virtual ball is presented on a computer monitor. It rolls down on an inclined table (Fig. 9.5). The patient can catch the ball with a virtual handle that replicates the movement of the human hand. Thus, the patient "catches" the virtual ball by moving his hand to the appropriate position. An assist-as-much-as-needed control paradigm has been implemented to support the patient in this task: If the patient can catch the ball by himself, the robot does not deliver any support. If the patient cannot catch the ball, the robot supports the patient with an adjustable force that pushes or pulls the hand to the ball position and helps the patient to initiate and execute the appropriate movement.

Whenever the robotic device supports the patient, the color of the handle changes from green to red, and an unpleasant sound is produced to alert the patient and therapist that the robot has supported the movement. The goal for the patient is to perform the task with as little support as possible. The therapist selects the supporting force, typically scaled so that the patient can successfully catch 80% of the balls. Several options enable the therapist to select the therapy mode that best fits the patient's need. For instance, the incline angle of the virtual table can be modified, resulting in faster or slower rolling. The size of the handle and the ball can be changed, and the behavior of the ball (multiple reflections with the wall and the handle) can be changed to challenge the patient further. For some advanced patients, disturbing forces and force fields can be introduced by the robot to make the task harder and to challenge the patient even more. Also, the number and kind of joints, as well as range of motion of the involved joints, can be adjusted to the patient's need.

A prerequisite for this assist-as-needed control strategy is that the intended movement of the patient (i.e., where the patient wants to move his hand) is known. For the ball game, this is the position where the ball falls.

A similar supporting strategy has been implemented for a ping-pong game (Fig. 9.5). Here, the patient holds a virtual ping-pong racket and plays a ping-pong match against a virtual opponent. At the highest level of difficulty, the patient must control the position, orientation, and impulse of the virtual racket to hit the incoming ball so that it lands on the computer-opponent's side of the table. At easier levels, the robot takes care of the orientation and velocity of the racket, and the patient need only move the racket to a position where it will hit the incoming ball.

If required, the robot can also support the patient's arm and provide a force that pulls the hand to the desired spot. To increase the patient's motivation and engagement, a multiplayer application – where the patient plays virtual ping-pong against another patient instead of a virtual opponent – has been implemented and tested. This application allowed remote patients from different hospitals to meet virtually for a virtual ping-pong game.

Another therapeutic computer game is the labyrinth game, where the patient navigates his hand through a virtual labyrinth. A red dot on the screen indicates the actual position of the human hand. The patient must move the red dot through

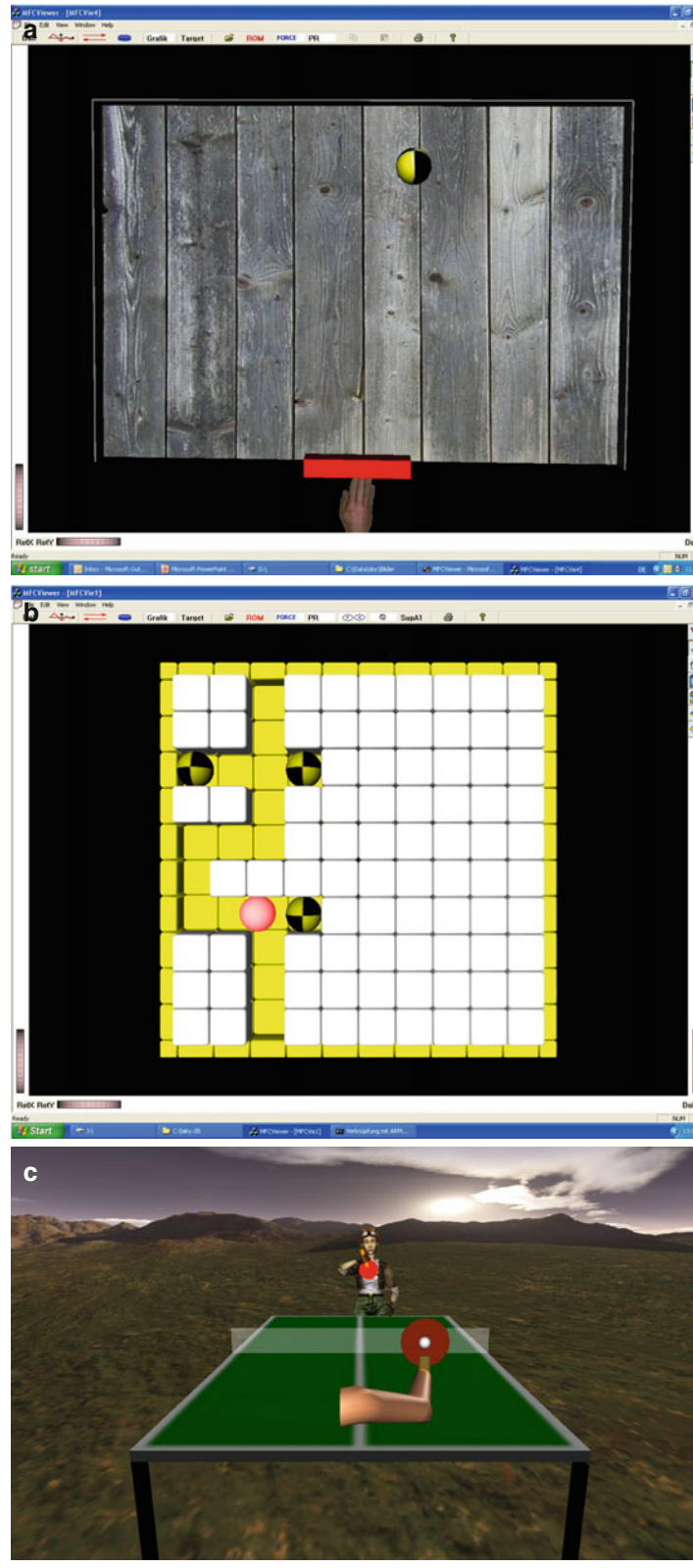

Fig. 9.5 Virtual reality scenarios for arm training. Ball game (**a**), labyrinth (**b**), and ping-pong game (**c**)

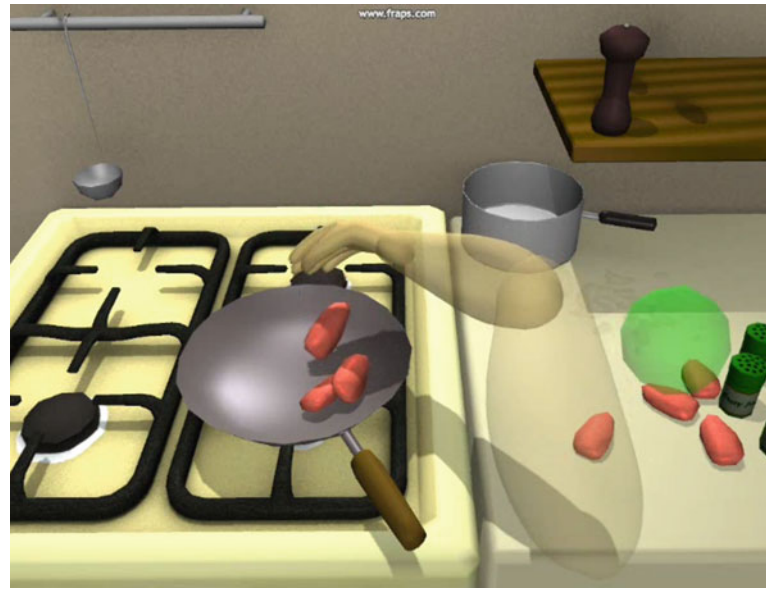

Fig. 9.6 Kitchen scenario

the labyrinth. Virtual walls block the red dot and robot motors produce resistance that prevents the hand from passing through the walls. Force-feedback technology delivers a realistic impression of the virtual wall to the patient.

We found the labyrinth game particularly useful for patient therapy since the patient can use the walls for guidance. By following the walls, his movements remain free in three movement directions and are restricted only in the direction of the wall. This seemed to help patients move their hands on straight lines [51]. If required, the patient can be supported by the robot in completing the labyrinth task. In these instances, the labyrinth task is selected in the way that the patient must elevate his arm in the course of the exercise. This means that the starting point is at the bottom of the labyrinth and the goal is on top of the labyrinth. The therapist can choose from two supporting strategies. One compensates for the weight of the human arm, thus supports the patient in lifting the arm. In case of 100% weight support, the patient's arm somewhat floats, and it is very easy for the patient to lift his arm. In the second supporting scheme, the robot allows upward arm movements but resists downward movements. With this strategy, the patient must lift his arm by himself, but whenever he gets tired, he can rest, and the arm will stay at the current position without any effort. Both strategies can also be combined [52]. To increase patient motivation, scoring is used based on the time, intensity, number, and time of collisions with the wall as well as the number of objects (positioned along the course of the labyrinth) that are collected by the patient.

9.2.3.3 Training of Activities of Daily Living

The purpose of ADL training is to support the patient in relearning ADL tasks, make the training a better simulation of real-life tasks, and further motivate the patient. An ADL task is presented on the computer screen, and the patient tries to complete the task. Like the game therapy, the robot supports the patient as much as needed and only interferes if necessary. Current research focuses on the implementation and evaluation of appropriate ADL tasks for robotic therapy. To date, implemented ADL tasks and used within ARMin therapy include:

- Setting a table
- Cooking potatoes
- Filling a cup
- Cleaning a table
- Washing hands
- Playing the piano
- Manipulating an automatic ticketing machine

For the kitchen scenario (Fig. 9.6), a virtual arm is presented on the computer screen. The

arm reflects the movement of the patient's arm, including shoulder, elbow, wrist, and hand opening and closing movements. A cooking stove, a kitchen table, and a shelf are fixed elements of the scenario. Cooking ingredients include several potatoes, black pepper, salt, and oregano. Available cooking tools include a pan and a dipper. Spoken instructions guide the patient through the cooking process. For instance, the patient must position the pan on the stove, turn on the heat, wait until the pan is hot, grasp the potatoes with his hand and put them into the pan, wait until he hears the sound of roasting, add pepper and salt, and stir the pan.

For this training scenario, the robot supports the patient only as much as needed, the patient has enough freedom to select his own movement trajectory, and the patient always sees feedback on how much he is currently supported by the robotic device. This is technically challenging because the cooking scenario involves several different movements [53, 54]. One possible solution that has been implemented with the ARMin system is to use virtual tunnels spanning from the start point to the goal point [55].

For instance, with the subtask of positioning potatoes in the pan, an invisible virtual tunnel starts at the initial location of the potatoes and ends above the pan. The robot lets the patient move freely within this tunnel. But once the patient hits the walls of the tunnels, the robot resists movement (similar to the labyrinth). Thus, the patient must follow the predefined path and not deviate from it. The diameter of the tunnel defines the amount of freedom the patient has. Furthermore, the patient is also free to select the timing and velocity of the movement. In addition, if required, the robot can also compensate for part of the arm weight and make the movement easier. Similar support strategies are implemented for the other ADL tasks [53].

9.2.4 Measurement Functionality of the ARMin Robot

The ability to objectively assess patient performance is one of the key benefits of robot-supported arm rehabilitation and allows the therapist to quantify therapy effects and patient progress. With the ARMin robot, the following parameters can be measured:

- Active range of motion
- Passive range of motion
- Muscle strength
- Abnormal joint synergies
- Spatial precision of hand positioning

The active and passive range of motion (ROM) are measured for each joint individually. When measuring, for example, the ROM of the elbow joint, all other joints are locked in a predefined position. The joint under investigation is controlled so that the patient can move it without resistance from the robot. The motor is only used to compensate for friction and gravity. The patient is instructed to extend the elbow as much as possible, and the robot measures the position of the elbow and stores the maximum values. When the passive range of motion is determined, the patient remains passive, and the joint is moved by the therapist while the robot records the maximum values of the joint position.

Muscle strength is measured with all joints locked in a predefined position. The motors are position-controlled with a fixed-reference position. Each joint is tested individually. For example, if the muscle strength of the abduction movement is tested, the patient is asked to abduct his arm as much as possible. Since the robot is position-controlled, and – in almost all cases – stronger than the human, the arm will not move. But the electric motor will need more current to work against the abduction torque. By measuring the motor current, the abduction torque can be determined using a model of the ARMin robot. The model describes the effects of gravity, friction, and the current-torque relationship in the electric motor.

Abnormal synergies result from abnormal muscle coactivation and loss of interjoint coordination. This means that, if a patient tries to abduct his arm, this goes together with an elbow flexion, forearm supination, and wrist and finger flexion [56]. To quantify abnormal synergies, all joints are locked in a predefined position. The patient abducts his arm as much as possible, and during the abduction torque, the joint torques produced by the patient in the shoulder, elbow, lower arm, and wrist are measured and recorded by the robotic device.

Currently under development is a procedure to assess the spasticity of the affected arm. Here, the robot moves the human limb at different velocities and measures the required force. This technique has been implemented and evaluated for the lower limb within the Lokomat gait training robot [57].

9.2.5 Evaluation of the ARMin Technology

Three different versions of the ARMin device (I–III) were used to evaluate the ARMin technology. Evaluation of the ARMin technology was carried out with different versions of the ARMin.

9.2.5.1 Technical Tests with Healthy Subjects

Before the robotic device can be used with test subjects, it must be tested without a person in it. The appropriate test procedure verifies device safety and tests all situations defined as critical in the risk-management document. After testing, the technical specifications of the robot were validated by measurement. Table 9.1 shows the measured technical data for the ARMin III robot [24].

The next step was to evaluate the robot with healthy subjects. After appropriate approval by an independent ethics committee (internal review board), a thorough technical evaluation was performed on healthy subjects before the robot was used with patients. After providing written informed consent, the test subjects were exposed to the robotic device. The purposes of this evaluation included:

- Testing the handling of the robotic device. This includes positioning the test subject, adapting the robotic device for different body sizes, changing from left-arm use to right-arm use, and comfort evaluation.
- Functionally testing the software. The questions were whether the test subject understood the instructions, whether he could successfully perform the exercises, and whether he liked the exercises. Special attention was also given to unwanted side effects, i.e., motion sickness and others.

Questionnaires validated the comfort and subjective feelings of the test subjects. One important side effect of this technical testing was that the therapist learned how to manipulate and use the robotic device before being exposed to patients.

Table 9.1 Measured technical data for the ARMin III robot [24]

Maximal endpoint load[a,b]	4.6 kg
Weight (excl. controller, hardware, frame)[b]	18.755 kg
Repeatability (endpoint)[b]	±0.5 mm
Stiffness (endpoint)[a,c]	0.364 mm/M
Force (endpoints)[a,b]	$F_{max} = (451\ N, 804\ N, 706\ N)^T$ with $G = (-g,0,0)^T$
Bandwidth for small endpoint movements (±1.5 cm)[d]	1.28 Hz

[a]Worst-case exoskeleton position
[b]Measured without subject (exoskeleton only)
[c]Stiffness measured at the endpoint by applying 20 N, while the motors are position-controlled
[d]Measured with healthy subject

9.2.5.2 Technical Tests with Stroke Patients

After the tests with healthy subjects concluded, technical tests with stroke patients were performed. After written informed consent was obtained, chronic stroke patients tested the device in one to five therapy sessions. The purpose of these tests was not to measure possible improvements in the patient's health status but to evaluate the technical ergonomic functionality of the ARMin robot. Specific goals included:

- Testing the handling of the ARMin device with stroke patients. Assessing the subjective feelings regarding comfort and ergonomics.
- Evaluating all training modes, including passive and active mobilization, game-supported therapy, and ADL training.
- Testing the level of difficulty of the tasks and the level of assistance that the robot provides to support the patients.
- Assessing patient motivation.

More than 20 stroke subjects participated in these preliminary tests [31].

9.2.5.3 Clinical Pilot Studies with Stroke Patients

A pilot study with three chronic stroke subjects (at least 14 months post-stroke) was performed with the ARMin I robot to investigate whether

arm training with the ARMin I improves motor function of the paretic upper extremity [51]. The study had an A–B design with 2 weeks of multiple baseline measurements (A) and 8 weeks of training (B) with repetitive measurement and follow-up measurement 8 weeks after training. The training included shoulder and elbow movements induced by ARMin I. Two subjects had three 1-h sessions per week, and one subject received five 1-h sessions per week. The main outcome measurement was the upper-limb portion of the Fugl-Meyer Assessment (FMA). It showed moderate, but significant, improvements in all three subjects ($p<0.05$). Most improvements were maintained 8 weeks after discharge. However, patients stated that the daily use of their paretic arm in the real world did not change. This finding was supported by constant ARAT and Barthel Index scores. This could be explained by the fact that, due to limitations of the ARMin I device, primarily non-ADL-related proximal joint movements were trained.

Therefore, another study was performed to investigate effects of intensive arm training on motor performance using the ARMin II robot, where distal joints and ADL tasks were also incorporated into the training [50]. The study was conducted with four chronic stroke subjects (at least 12 months post-stroke). The subjects received robot-assisted therapy over a period of 8 weeks, 3–4 days per week, 1 h per day. Two patients had four 1-h training sessions per week, and the other two patients had three 1-h training sessions per week.

The primary outcome measurement was the upper extremity portion of the FMA. The secondary outcome measures were the Wolf Motor Function Test (WMFT), maximum voluntary joint torques, and additional scores to assess transfer effects. Three out of four patients showed significant improvements ($p<0.05$) in the primary outcome. Improvements in FMA scores aligned with the torque measurements.

Most improvements were maintained, some even further increased, between discharge and a 6-month follow-up. The data clearly indicate that intensive arm therapy with the robot ARMin II can significantly improve motor function of the paretic arm in some stroke patients. Even those who are in a chronic state achieve sustainable improvements. Care must be taken in analyzing the results of this pilot study. Participants were selected outpatients, there was no control group, and there were only four participants. Thus, one cannot generalize these results. However, the result justified the start of a subsequent controlled, randomized, multicenter clinical trial.

9.3 Current Developments and Ongoing Testing

9.3.1 Randomized Clinical Trial

The limitations of the aforementioned studies indicate that a controlled, randomized clinical trial with a blinded assessment of functional outcome with a sufficient number of patients is required to investigate the effectiveness of the ARMin robotic arm treatment in a defined population of chronic stroke patients. A key aspect would be to investigate the effects of ADL training tasks based on reaching and grasping movements. ARMin III provides the required functions: large movement ranges, 3D movements, actuation of proximal and distal joints, patient-responsive control, audiovisual ADL tasks, and more.

Consequently, a prospective, controlled, randomized study was started in 2009. Its goal is to investigate whether task-oriented robot-aided therapy is more effective than conventional therapy in promoting functional recovery of the paralyzed arm. Robotic therapy is being performed with four ARMin III systems at four different hospitals. Within 2 years, 80 chronic stroke patients (more than 6 months post-stroke) will be randomly assigned to either an experimental or control group. The experimental group will perform task-related intensive therapy with ARMin III. Patients in the control group will receive standard motor-relearning therapy. Both groups will be trained for 8 weeks, three times per week, with 1 h for each training session. Outcome measures will be obtained prior to, during, and after the training phase by a blinded therapist. The primary

outcome measure will be the FMA. Further outcome measures will be used to evaluate task-oriented function and its use in the real word. Using the measurement functionality of ARMin, further information will be obtained, including data on abnormal joint synergies, active range of motion, muscle strength, and precision of hand positioning.

9.3.2 Technical Development and Ongoing Testing

Current work includes the development and evaluation of new assessment tools for spasticity measurement [57] and for quantification of abnormal joint synergies [56]. This work is important because the objective and sensitive quantification of therapy progress is crucial for proper clinical evaluations of therapeutic effects.

Another important line of work is to develop and evaluate new training scenarios. A training scenario has an underlying control strategy and a visible audiovisual display (virtual reality). With recent technical innovations, tools are available that allow implementation of sophisticated and realistic graphical scenarios. It remains an open question how an optimal virtual reality (VR) for stroke patients should look. Specific questions to answer are:

- What is the optimal media to present VR to patients (monitor, projection screens, etc.)?
- Is it better to use realistic or simplified graphical scenarios?
- Can 3D technology using stereoscopic vision improve the perception of objects in the 3D space?

The answers to these questions also depend on the patient population. Particularly in stroke patients with hemispheric neglect, the perception of complex graphical scenarios can be difficult and needs further investigation.

The underlying control strategy is a very interesting research question, and a lot of work has been dedicated to develop new patient-responsive control strategies [54, 58, 59]. Assisting a stroke patient in naturalistic ADL tasks (drinking, cooking, eating, dressing, and others) is quite a complex task and requires extensive technical development and clinical testing.

The ARMin III robot also serves as a model for the prototype of the commercial version of the ARMin device, which is being developed by Hocoma AG (Volketswil, Switzerland). The commercial version of the ARMin robot will be named Armeo Power, and it will be further optimized with respect to reliability, mechatronic robustness, user friendliness, ergonomic function, and design, as well as optimized manufacturing processes and costs. The Armeo therapy concept suggested by Hocoma consists of three Armeo products (Fig. 9.7) that are all driven from the same software platform. Each product is optimized for a specific phase of the rehabilitation process. Shortly after injury, a patient with no or very little voluntary activation of arm muscles trains with the motorized robotic device Armeo Power (former ARMin III). Once his motor function improves and some active movements are possible, the patient continues arm training with the nonmotorized, weight-supported exoskeleton Armeo Spring (former T-Wrex) [26]. After further improvements, the patient might continue training with the Armeo Boom, which consists of an overhead sling suspension system. This training seems suitable for patients who can actively move the arm but suffer from reduced workspace and poor motor control [60].

A successful commercialization would be beneficial for obtaining more clinical data of specific rehabilitation robots since a large number of rehabilitation facilities would use the same device for clinical practice and for research.

9.4 Perspectives and Conclusions

Upper-limb rehabilitation is one of the fastest growing areas in modern neurorehabilitation. Quality of life can be significantly improved when applying efficient arm therapy. The results of the pilot studies that have been presented within this chapter suggest that the new technology can be an important means to improve arm therapy. Thus, for the future, one might envision a combined training paradigm including both

Fig. 9.7 The Armeo Product line, with the commercial version of the ARMin device Armeo®Power (**a**), Armeo®Spring (**b**), and Armeo®Boom (**c**) (Copyright Hocoma AG, Switzerland, www.hocoma.com)

manual and additional robot-supported therapy. The technology for upper-limb rehabilitation with three-dimensional multi-degree-of-freedom arm robots is quite mature and will be commercially available very soon. However, the clinical data of the therapeutic effect currently are incomplete, and future work should focus on the evaluation of the clinical benefits. Further randomized clinical trials similar to the aforementioned ARMin study should be undertaken. Studies with focus on both the overall benefit of the combined technology (VR, robot, assist-as-needed control strategies, etc.) or studies comparing the influence of single elements (i.e., VR vs. robotics) are needed. These studies will require large numbers of participants, a multicenter setting, and several robotic devices of the same type. It is crucial that these robots will be reliable, easy to use, and supported and maintained by a professional organization. Therefore, it is expected that the numbers of clinical data and clinical studies will increase once the technology becomes commercially available.

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Passive Devices for Upper Limb Training

10

Arthur Prochazka

Abstract

About five million people in North America alone have weak or paralyzed upper limbs due to stroke or spinal cord injury. Motor rehabilitation can improve hand and arm function in many of these people, but in the current healthcare climate, the time and resources devoted to physical and occupational therapy after injury are inadequate. This represents an opportunity for technology to be introduced that can take over some of the supervisory functions of therapists, provide entertaining exercise therapy, and allow remote supervision of exercise training performed in the home. Over the last 10 years, many research groups have been developing robotic devices for exercise therapy, as well as other methods such as electrical stimulation of muscles. Robotic devices tend to be expensive, and recent studies have raised some doubt as to whether assistance to movements is even necessary, as motor gains evidently depend largely on the efforts made by the participant. This chapter reviews the evidence for spontaneous recovery, the means and mechanisms of conventional exercise therapy, the role of robotics and the advent of affordable passive devices, and voluntarily triggered functional electrical stimulation. It is argued that in the near future, in-home exercise therapy on instrumented passive devices, remotely supervised over the Internet, will become an affordable and important modality of physical therapy.

Keywords

Multiple sclerosis • Spinal cord injury • Stroke • Tele-rehabilitation • Upper extremity

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10.1 Introduction

There are about seven million stroke survivors in the United States [1]. Their motor deficits range from one-sided weakness (hemiparesis) to paralysis (hemiplegia). Up to 60% of all stroke survivors find it hard or impossible to perform activities of daily life (ADLs) because of poor hand function [2]. In addition, extrapolating from recent Canadian figures, up to 400,000 people in North America have bilateral paresis or paralysis of the upper extremity due to spinal cord injury (SCI) of either traumatic or nontraumatic origin [3]. Thus, about five million people in North America are in need of effective treatment for upper extremity paresis or paralysis.

In recent years, stroke survivors have been treated for only 3–4 weeks in acute care or rehabilitation hospitals. In the United States, inpatient rehabilitation stays decreased from 20 to 12 days between 1994 and 2001, with up to 61% of outpatients not receiving any follow-up therapy [4]. There is a general lack of reimbursement for therapy after patients have been sent home, so during the subacute period, therapists tend to focus on teaching compensatory strategies rather than improving hand function. When patients go home, they are provided with passive aids such as ankle and knee braces or splints, arm slings, and canes. Higher-functioning patients are taught "range-of-motion" (ROM) exercises of the arm and hand, passive stretching to reduce hypertonus, squeezing a ball, and other simple exercises. Some patients continue exercising after discharge, but after a few weeks, this is largely restricted to passive stretching, as this usually relieves hypertonus to some extent.

This unsatisfactory state of play has given rise to new methods of delivering upper extremity rehabilitation. These include constraint-induced movement therapy (CIMT) [5], exercise therapy (ET) with robotic devices [6], therapeutic and functional electrical stimulation (TES and FES) [7, 8], and in-home tele-therapy (IHT) supervised over the Internet [9–12].

10.2 Mechanisms of Functional Recovery: The Significance of Compensatory Strategies

In the weeks and months after a stroke or SCI, arm and hand function may improve, depending on the extent and level of the injury. Various means of early prediction of the extent of recovery have been identified [13–16]. For example, if there has been no emergence of arm synergies at 4 weeks poststroke, this is associated with a poor outcome at 6 months [13]. The affected arm then remains immobile and functionally virtually useless. Spastic hyperreflexia, shoulder subluxation, and pain may develop in the affected arm. On the other hand, after a minor stroke or incomplete SCI, manual dexterity recovers and reaches a plateau between 6 months and a year later [17–19]. Full recovery of upper extremity function has been estimated to occur in only about 12% of stroke survivors [13].

Spontaneous recovery is of course vital for those affected, but it also poses a problem for the evaluation of therapies, as it represents a shifting baseline that must be taken into account when comparing the efficacy of treatments in randomized controlled studies (RCTs). In RCTs of treatments undertaken during the acute or subacute period after SCI, the sample size required for an adequate statistical power can be prohibitive [20].

Some of the spontaneous recovery in motor function is evidently a result of the recovery of central nervous structures temporarily inactivated by the injury, or the adaptation of uninjured nervous networks to take over functions of neighboring injured networks, a process called plasticity [21–24].

10.3 Compensatory Strategies

In the more severe cases of stroke, the dominant component of recovery of functional movement is attributable to the acquisition of compensatory strategies such as the performance of tasks with

the less affected hand that would normally be done with both hands. Indeed, it is suggested that in severely disabled stroke survivors, therapy should be restricted to minimizing contractures and pain [25] and teaching compensatory methods [26]. These methods include learning new ways to perform tasks, for example, tying shoelaces with one hand, or using simple assistive devices, such as a universal cuff, to hold tools and utensils. The methods also include changing the person's physical environment and the objects they manipulate in daily life.

Compensatory strategies may, however, inhibit spontaneous functional recovery. For example, stroke survivors often tend to lean forward from the hip to position the more affected hand to grasp or stabilize objects. It has been argued that such compensatory movements of the trunk inhibit the relearning of movements at the shoulder and elbow, and so the trunk should be restrained during therapy and hand function tests [27, 28]. It has been argued that in the initial period after injury, the inability to use the paralyzed upper extremity leads to "learned nonuse," a form of motor neglect, which is sustained once compensatory methods have become habitual [29]. The use of compensatory strategies that are effective in coping with tasks of daily life, while useful and empowering, can also greatly reduce the motivation of interested parties, whether they be patients, therapists, or companies developing medical devices, to pursue new therapies, exercise regimes, or rehabilitative technologies.

10.4 Evaluation of Treatments: Deficiencies in the Design of Clinical Trials

To stand a chance of clinical adoption, any new approach or device must provide a clear advantage in improving the activities of daily life over well-established and simple compensatory methods. Furthermore, in the current economic climate, the new approach must be cost-effective, as measured by a reduction in the cost of homecare or improved societal productivity of the treated individual. Most studies of novel therapeutic methods do not address the cost/benefit issue, yet it is probably the single most important determinant of eventual adoption. Quality of life considerations, though recognized by patients and clinicians as being crucial, unfortunately tend to play a minor role in the adoption of novel methods.

The Physiotherapy Evidence Database (PEDro: pedro.fhs.usyd.edu.au/scale_item.html) rates the quality of clinical trials according to the following attributes: (1) subjects randomly allocated to groups, (2) allocation concealed, (3) groups similar at baseline on the primary outcome measures, (4) all subjects blinded, (5) all therapists administering the therapy blinded, (6) all assessors measuring at least one key outcome blinded, (7) adequacy of follow-up: all subjects originally randomized accounted for, (8) "intention to treat" analysis performed, (9) between-group statistical comparisons reported for at least one key outcome, and (10) measures of the size of the treatment effect and variability provided.

Regarding proper controls and blinding, studies that evaluate rehabilitation therapies face two very significant difficulties: (1) The placebo or expectation effect, whereby merely receiving a treatment additional to normal care can improve participants' morale and cause them to put more effort into motor recovery by becoming generally more active, exercising more, attempting more tasks, seeking additional therapies, and paying more attention to improvements as a result of expectation. (2) Blinding the control group as to their allocation. Many RCTs have been published where the control group received "standard therapy." Because ethics committees require participants to be informed of the details of the interventions, those in the control group quickly realize that they are not receiving the test treatment. In other words, they are not blinded, and so unlike the treatment group, they do not have a placebo effect. Another common approach is to use subjects as their own controls in a repeated

measures design; however, this has the drawback that not only placebo effects, but also practice, may contribute to the treatment effect. With the growing influence of the Cochrane Collaboration (www.cochrane.org), the issue of study design has become crucial [30].

All of this recently came to a head in an entertaining debate between the authors of a large multicenter trial of constraint-induced movement therapy (CIMT) (the extremity constraint-induced therapy evaluation "EXCITE" trial) [31] and Bruce Dobkin, editor of *Neurorehabilitation and Neural Repair*, who criticized several aspects of the design of the EXCITE trial, in particular the comparison of CIMT with "standard therapy." [32] According to Dobkin, "the attention, encouragement, family support, and motivation, among other incalculable interactions, rendered the CIMT group to become quite different than the control group." Instead, he proposed that the best control in future EXCITE-like trials ought to be an alternative upper extremity therapy if the intention was to demonstrate that the new strategy, rather than a plausible or existing alternative, can improve outcomes.

In their riposte, the EXCITE authors pointed out that the availability of resources for many post-hospitalization rehabilitation services is dwindling, so that "standard treatment" has in fact become "no treatment." [4] Policy makers and third-party payers might understandably be more interested in determining whether a proposed treatment provides a clinically important improvement over no treatment, rather than over an alternative treatment that may or may not be available and which itself may or may not be better than no treatment.

10.5 The Role of Exercise in Restoring Hand Function

It has long been accepted by the clinical rehabilitation community that manual exercises performed after stroke or spinal cord injury can improve functional recovery and possibly reduce spastic hypertonus and other unwanted sequelae. Surprisingly, there are few published meta-studies (studies of studies) that examine this basic assumption. One such study [33] concluded that there was insufficient evidence to draw definitive conclusions about the effectiveness of exercise therapy (ET) on arm function in stroke survivors, though differences between the studies included suggested that more ET may be beneficial than less. Another meta-study found "small to large effect sizes for task-oriented ET, in particular when applied intensively and early after stroke onset. In almost all high-quality RCTs, effects were mainly restricted to tasks directly trained in the exercise program." [34] The evidence-based review of stroke rehabilitation (EBRSR: www.ebrsr.com, [19]) concluded that in patients with less severe initial impairment, defined by a Chedoke McMaster score of stage four or greater, an aggressive restorative program geared toward regaining function in the affected upper extremity was recommended [25]. An associated meta-study concluded that sensorimotor training, motor learning training with the use of imagery, electrical stimulation, and the repetitive performance of novel tasks could all be effective in reducing motor impairment after stroke [35].

Two treatment regimes based on neurophysiological principles, the Bobath technique and proprioceptive neuromuscular facilitation, were widely adopted in the 1970s, with strong adherents in each camp. An RCT that compared these two methods with conventional ET concluded that there were no significant between-group differences in improvement of the patients' performance of activities of daily life [36].

CIMT, a particular form of intensive ET introduced over 20 years ago, was originally called forced-use training [37]. It was based on experiments in monkeys in which sensory input in one arm was abolished by deafferentiation. Binding of the other, normal arm led to forced use of the deafferented arm, which was associated with improvements in its motor function [38, 39]. This was accompanied by and attributed to cortical plasticity [40, 41]. In CIMT in stroke survivors, movements of the less affected arm are constrained with a mitt, ideally for 6–7 h for 2 weeks, while the more affected arm is intensively trained in functionally meaningful tasks [5]. In reality,

this goal is probably rarely if ever achieved: According to Wolf and colleagues, participants start at about 1.5 h of training time per day and work up to 4.5 h by the last training session [4]. Other features of CIMT are "shaping" (tasks increase in difficulty in the course of the program) and a "transfer package," consisting of a behavioral contract involving in-home exercises.

A CIMT course involves 6–7 h of training per day for 2 weeks and currently costs about $6,000, plus $450 for an initial medical evaluation, plus accommodation costs for 2 weeks for out-of-town participants. These costs are not reimbursed in the United States. Pressure for reimbursement has risen with the publication of the EXCITE trial [31] and recommendations such as that of the EBRSR: "CIMT is a beneficial treatment approach for those stroke patients with some active wrist and hand movement." [19, 42]

CIMT has stringent inclusion criteria: voluntary extension of at least 10° at metacarpophalangeal and interphalangeal joints and 20° at the wrist. This excludes 80–85% of people with hemiplegic upper extremities. In his critique of the EXCITE trial, Dobkin pointed out that of the 3,626 patients who were 3–9 months poststroke screened, only 222 (6%) were recruited for randomization. It is also worth noting that people who apply for inclusion in clinical studies tend to be more motivated, and therefore do not represent the whole population of stroke patients seen by clinicians.

Less intensive protocols have been suggested, e.g., modified CIMT (mCIMT) [43–45], comprising therapist-supervised CIMT for 30 min, three times a week and wearing a mitt on the less affected hand 5 h/day for 5 days/week [43]. The efficacy of mCIMT was supported in a recent RCT [46]. Interestingly, the clinical portion of mCIMT was reimbursed prior to this trial, under "Current Procedural Terminology (CPT)" codes [44].

Over the last 10 years, the idea that for ET to be effective, the less-affected extremity must be prevented from taking part, as in CIMT, has been strongly challenged [47–50]. In a recent RCT in chronic stroke survivors, bilateral training was more effective than unilateral training in improving the functional ability of the affected arm [51]. It was proposed that simultaneously moving both limbs during stroke rehabilitation training may activate balanced interhemispheric interactions [52]. An independent comparison of bilateral training and CIMT indicated that the former may uniquely improve proximal upper extremity *motor* impairment as assessed by the Fugl-Meyer test, whereas CIMT may produce greater *functional* gains in subjects with mild to moderate chronic hemiparesis [53].

Finally, task specificity of training is an important factor: It has been argued that "the best way to relearn a given task is to train specifically for that task. In animals, functional reorganization is greater for tasks that are meaningful to the animal. Repetition alone, without usefulness or meaning in terms of function, is not enough to produce increased motor cortical representations." [54]

10.6 Robotic Exercise Devices

Conventional ET focuses on the repetitive manipulation of simple objects such as blocks, stacking cones, therapy putty, skateboards, incline boards, climbing boards, ring trees, peg boards, and resistive prehension benches. None of these devices has sensors to quantify performance. ET sessions tend to be boring, and in the absence of supervision, compliance falls off quickly, particularly at home. The supervision of ET by therapists is costly, and in most cases it is restricted to clinics, which in turn limits access mainly to subacute patients. The objects used vary from one clinic to the next, and systematic rating of performance is rarely undertaken. The opportunity to address these factors with robotic devices was recognized at least 20 years ago [6, 9]. Robotic devices are able to provide standardized exercises, take over some supervisory functions, provide quantitative outcome measures, and, in conjunction with virtual reality software, add an element of entertainment that greatly reduces the tedium of conventional ET.

Robotic devices incorporate actuators and complex control systems, which make them costly. The simplest robotic rehabilitation devices are motors that impose cyclical motion on extremities.

They are commonly used in orthopedics [55] and occasionally in stroke and SCI [56]. BTE's PrimusRS (btetech.com) and Biometrics' E-Link (biometricsltd.com) have a modular design, allowing manipulanda to be attached to a rotary servo motor. The MIT-Manus (interactive-motion.com) is a robot that supports the arm and applies forces in the horizontal plane to assist or resist tracking [57, 58]. A large RCT just published in the *New England Journal of Medicine* concluded that upper extremity function in chronic stroke subjects did not improve more with MIT-Manus robotic ET than with usual care [59]. However, an editorial concluded: "In the bigger picture, the potential for robotic therapy after stroke remains enormous." [60] The KINARM, developed by Dr. Steven Scott at Queens University (bkintechnologies.com), is another example of a planar robotic device that supports the arm. The Motorika's ReoGo (motorika.com) is a telescopic device similar to a floor-shift gear-stick, which applies forces to the hand in 3-D space. The ReoGo was introduced into 25 of HealthSouth's chain of rehabilitation hospitals in the United States in 2007. The TheraDrive is a device incorporating commercial force feedback steering wheels that provide the user with driving and tracking games [61, 62].

It is important to note that the above robots do not exercise dexterous movements. The InMotion 3.0 wrist robot and the InMotion 5.0 hand robot were released recently to address this deficit, but the repertoire of dexterous movements they provide is still quite limited. Other experimental robots that address hand dexterity include a pneumatically activated glove [63], a manipulandum that applies forces about the wrist and elbow [64], a cantilevered device with attachments [65], and an arm support with jointed splints that allow grasp-release movements [66]. Some of these devices simulate real-life tasks by generating forces simulating contact with objects shown on screens (so-called haptic interfaces). A versatile haptic robot could potentially offer a wide range of simulated ADLs, but it remains to be seen whether this can be achieved at a reasonable cost.

The EBRSR concludes: "Sensorimotor training with robotic devices improves functional and motor outcomes of the shoulder and elbow, however, it does not improve functional and motor outcomes of the wrist and hand." [42] The above devices cost over $60,000 and so are unaffordable for in-home ET and for all but the largest rehabilitation centers. Arguably, the only affordable robotic device, at around $7,000, is the "Hand Mentor" (kineticmuscles.com), a powered wrist splint developed by CIMT pioneer Steven Wolf [67, 68]. Ironically, in light of the EBRSR's conclusion, this device *only* exercises wrist and finger flexion-extension movements and ignores ROM of the whole arm.

10.7 Virtual Reality and Passive Exercise Devices

A recent study entitled "Robot-assisted movement training for the stroke-impaired arm: Does it matter what the robot does?" [69] compared robotically assisted reaching with unassisted reaching in chronic stroke subjects. The two groups showed similar improvements, suggesting that the crucial factor in motor rehabilitation is not the assistance provided by a robot, but rather the participant's own voluntary efforts to move. This has turned the attention of therapists and researchers toward passive exercise devices and virtual reality, the most notable example being the rapid and widespread adoption of the Nintendo Wii gaming system [70–74]. The Wii allows users to play computer games with a handheld motion sensor. It was not designed for rehabilitation and lacks dexterous tasks requiring grasp/release, pronation/supination, pinch-grip/release, and picking up and transferring objects. The resistance to movement presented by real objects in tasks of daily life is also lacking. The motion signals are not available for display or outcome evaluation, though some groups are working on ways to intercept these signals. In spite of all these shortcomings, the Wii was embraced by rehabilitation clinics around the world before any studies had tested its efficacy, showing the need for affordable devices that make ET enjoyable. In 2010, the first such RCT appeared [75]. Participants within 6 months of a stroke were randomly allocated to two groups: one group playing virtual reality games with a Wii, and the control group receiving recreational therapy,

namely, card games, bingo, or "Jenga." Both groups had eight sessions, each lasting 60 min, over a 2-week period. Being for the most part in the subacute phase of recovery, both groups showed improved outcomes, the Wii group improving more on the Wolf Motor Function Test and the control group more on the Box and Block test. The study was insufficiently powered to test the significance of the differences. This study, while interesting, does not change the current lack of evidence that virtual reality ET is more effective than standard care [76].

A commercially available and affordable passive exercise device, the Tailwind (www.tailwindtherapy.com), provides bilateral arm training with rhythmic auditory cueing [47]. A recent RCT compared the efficacy of bilateral arm training with that of dose-matched therapeutic exercises in 111 stroke survivors [50]. Both methods improved upper extremity motor function by similar amounts. Bilateral training was associated with larger changes in brain activation in functional magnetic resonance images. Imaging methods may help not only in predicting the outcomes of rehabilitation [16] but also in matching individuals to the most suitable type of rehabilitation [32]. The Tailwind device does not incorporate computer gaming, which, as discussed above, is an important motivator in maintaining regular ET over weeks and months.

The Armeo, developed by the makers of the Lokomat (www.hocoma.ch), is a counterbalanced arm support with an instrumented gripper that allows functional movement against resistance in a virtual reality environment [77, 78]. A recently published RCT involving chronic stroke survivors compared semiautonomous ET on T-WREX, a gravity-support device similar to the Armeo, with semiautonomous conventional ET in which a tabletop was used to provide gravity support [79]. The size of the improved benefit with T-WREX was small, and the self-reported functional use of the upper extremity was not different between groups. The benefits of the T-WREX were therefore characterized as modest and functionally insignificant. However, it was noted that even a small benefit provides something to build on. It was argued that rehabilitation technology that incorporates functional causality, quantitative feedback, and entertaining aspects is likely to motivate patients to ET. The Armeo costs over $60,000 and is therefore only suitable for clinics.

A much simpler gravity support system, the Armeo Boom, was recently commercially released. A study with a precursor of this device, the "freebal," in ten patients with mild hemiparesis found that gravity compensation facilitated active arm movement excursions without impairing motor control. It was concluded that gravity compensation may be a valuable modality in conventional or robot-aided therapy to increase the intensity of training for mildly impaired patients; [80] however this remains to be proven in clinical trials.

Several other passive exercise devices have been designed and tested, for example, the AutoCITE workstation [81, 82], the APBT, a tabletop mechanism that couples the forces generated during contralateral wrist flexion and extension to the affected hand [83], and the SMARTArm, a linear low-friction slider that exercises movements about the shoulder and elbow [84]. In a single-blind RCT involving stroke survivors with severe and chronic paresis, 10 received training using the SMARTArm with EMG-triggered electrical stimulation, 13 received training using the SMARTArm alone, and 10 received no intervention (control). Both SMARTArm groups demonstrated similar, significant improvements in upper arm impairment and activity measures after training and at follow-up. There was no change in the control group. Improvements in ADLs were not tested.

The author and his collaborators have developed a passive exercise workstation called the Rehabilitation Joystick for Computerized Exercise (ReJoyce) (Fig. 10.1). It comprises a spring-loaded, segmented arm that presents the user with a variety of spring-loaded attachments representing ADLs, such as a doorknob, key, gripper, jar lid, and peg. Sensors in the arm and the attachments provide signals that are used by the system's software to evaluate motor function and to control video games that exercise specific types of hand movement. The system incorporates remote tele-supervision of exercises performed in users' homes. An RCT was completed involving 13

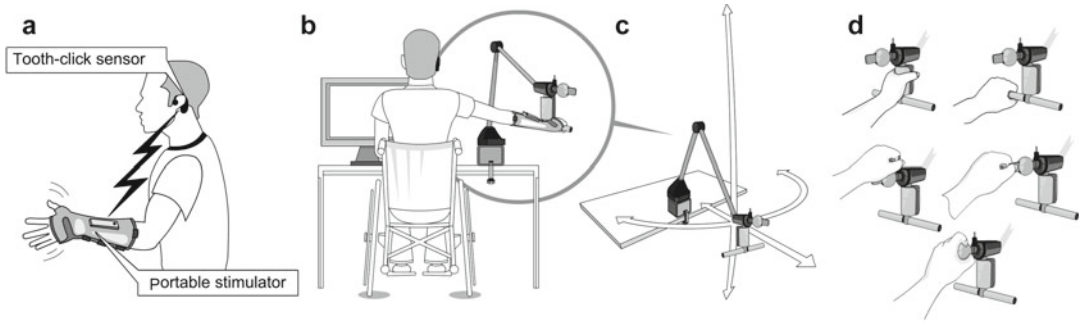

Fig. 10.1 (**a**) Tooth-click activated FES garment. (**b**) Participant using workstation to play computer game and interact with tele-supervisor. (**c**) Range of motion of manipulandum assembly. (**d**) Tasks performed on the manipulanda (Reproduced with permission from Kowalczewski et al. 2011)

tetraplegic participants who had sustained a spinal cord injury more than a year previously. Participants were block-randomized into two groups, both receiving test treatments 1 h/day, 5 days/week for 6 weeks in a crossover design. Treatment 1: conventional ET, computer games played with a trackball, therapeutic electrical stimulation. Treatment 2: computer games played on a ReJoyce workstation, hand grasp/release augmented with user-triggered electrical stimulation of forearm muscles. The study demonstrated the feasibility of delivering tele-supervised ET over the Internet. Statistically and clinically significant improvements were produced by treatment 2 (ReJoyce ET) and a trend for improvement by treatment 1 (conventional ET).

The ReJoyce system is produced by Rehabtronics Inc., a University of Alberta spin-off company. The system, including software, was designed to be affordable for clinics and, through short-term rental, by individual users who could receive tele-supervised treatment in their homes.

10.8 Therapeutic and Functional Electrical Stimulation

TES refers to cyclical stimulation to increase muscle strength. *FES* refers to voluntarily triggered stimulation to assist in functional tasks. Early studies showed that TES can significantly reduce hypertonus and improve motor function [85, 86]. The success rate in mild cases of stroke was lower than in severe cases. (This is important because only the mildly disabled group meet the inclusion criteria for CIMT.) These conclusions were supported in a retrospective audit of patients at the Salisbury stroke unit in the United Kingdom [87].

Surface FES stimulators for foot drop have been commercially available in Europe since the late 1970s [88] but only recently in the United States and Canada [89, 90]. The first commercial hand stimulator was the Automove, which detects weak voluntary electromyograms (EMGs) of the finger extensors and then briefly stimulates these same muscles to facilitate hand opening [91]. Therapeutic effects have been reported in controlled studies using EMG-triggered FES [92–96]. More recent studies have shown that FES-ET performed daily for several weeks can result in clinically significant improvements in hand function in subacute and chronic stroke participants [12, 97–100]. However, our SCI study, and preliminary results in stroke participants, indicates that even after an extended FES-ET program, most people still have better hand function while using their FES devices.

The only commercialized FES device for hand function is the Bioness H200 [101, 102]. It comprises a hinged splint containing pad electrodes and a stimulator triggered by push-button. It currently costs around $6,000. In the 1990s, the author developed the Bionic Glove, an FES garment triggered by wrist movements [103], and the Impact Cuff, triggered by tapping or bumping

the hand [104]. The Bionic Glove was shown to have both functional and therapeutic benefits in people with tetraplegia [105]. In the meantime, an improved version has been developed, the "HandStim," comprising a neoprene wristlet containing a small stimulator that is controlled by a wireless tooth-click sensor similar to a Bluetooth earpiece [106, 107].

10.9 Tele-Supervision

From all of the above, it is clear that the emerging technologies to deliver ET and FES have the potential greatly to improve upper limb function in daily life, but providing sufficient support after participants leave rehabilitation clinics is problematic, as revealed for example in a pilot study of the Impact Cuff (Prochazka, A. PCT Patent Application, WO99/19019, 1997). Although the users liked the devices and initially used them on a daily basis, they reported difficulties in tasks they had performed well under supervision. In the absence of advice and assistance, usage rapidly dropped off. This transition is a well-known hurdle in rehabilitation [108]. We reasoned that if participants could only perform regular supervised exercise after discharge, they would benefit much more. However, laboratories and clinics are not ideal locations for outpatients to perform regular training sessions. Travel is often problematic, expensive and stressful, limiting the frequency of attendance. This led us to add the capability of in-home tele-supervision to the ReJoyce system. In the study mentioned above, we deployed Internet-connected ReJoyce workstations in the homes of all 13 tetraplegic participants, who were located over a wide geographic region in Alberta and Saskatchewan (approximately the area of France and England combined). Participants were tele-supervised daily by a small team of therapists and students based in Edmonton. The practical and logistic challenges that had to be overcome are detailed in a recent book chapter [109].

An unresolved issue is whether tele-supervision will become an important component of in-home treatment in the future. In order for tele-supervision of motor rehabilitation to be widely adopted, the case for reimbursing the participants for the cost of renting devices, and the therapists or personal trainers who would provide the remote supervision, must be supported through properly designed clinical trials.

10.10 Perspectives and Conclusions

There is general agreement in the field that the time is ripe for physical and occupational therapy of the upper limb after stroke, spinal cord injury, and other disabling conditions to take advantage of the new technology. It is time that exercise therapy move from the boring equipment currently used in clinics worldwide to computerized devices that provide task-specific, entertaining games, preferably performed in the participant's home environment, supervised remotely over the Internet. The advantages of this approach are many: increased compliance, task-specific training on a variety of customized activities, quantification of performance, and perhaps most compelling, the ability to provide continuing in-home therapy after acute care in clinics, in a manner that avoids the need for participants to travel, yet retains the important component of one-on-one supervision by enabling therapists to treat participants at times that suit them all. A crucial factor is cost. This chapter has made the case for affordable passive exercise devices that provide entertaining exercises involving full range of motion and manual dexterity, with optional tele-supervision and in some cases functional electrical stimulation.

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Part IV

Robots for Upper Extremity Recovery in Stroke/Spinal Cord Injury: Clinical Applications

Restoration of Hand Function in Stroke or Spinal Cord Injury

11

Derek G. Kamper

Abstract

Neurological injury, such as that resulting from stroke or spinal cord injury, often leads to impairment of the hand. Due to the importance of the hand in so many activities of our lives, diminished motor control can adversely affect quality of life, sometimes substantially. In the past 20 years especially, robotic and mechatronic technology has been developed to alleviate some of the functional losses resulting from neurological injury. The devices generally fall into one of two categories based on intended use: assistive technology, programmed to perform specific tasks for the user, and therapeutic technology, designed to facilitate therapeutic practice. Assistive devices are intended for chronic use when neurological recovery has reached a plateau, while the goal of therapeutic devices is to enhance recovery to the point where the devices are no longer needed. In the past, assistive robots have largely been developed to serve the needs of individuals with spinal cord injury, while therapeutic devices have targeted stroke survivors. As technology continues to evolve, however, it may be appropriate to consider greater application of assistive devices for stroke survivors, especially those with severe, chronic hand impairment. Conversely, as the population with incomplete tetraplegia grows, development of therapeutic devices for retraining hand movement in these individuals may become more feasible.

Keywords

Hand function • Stroke • Spinal cord injury • Assistive technology • Therapeutic technology

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11.1 Hand Neuromechanics

The hand is a wonderfully versatile instrument. We use our hands to communicate; to express ourselves through art, music, and writing; and to manipulate objects. In fact, our hands are our primary means of interacting with our environment.

The utility of the hand arises from its neuromechanical complexity. The hand, distal to the wrist, is comprised of 19 bones. The bones are connected through joints which provide 21 degrees of freedom (DOF). The thumb contains five DOF, and each finger has another four. The rotational axes of some of these consecutive DOF run at oblique angles to each other and are offset. This arrangement facilitates certain movements, such as thumb opposition [1].

A total of 27 muscles control these DOF. Three of these muscles, flexor digitorum profundus (FDP), flexor digitorum superficialis (FDS), and extensor digitorum communis (EDC), are each comprised of multiple compartments, which give rise to tendons for each finger. Most of these musculotendon units cross multiple joints and, thus, can influence multiple DOF simultaneously (Fig. 11.1). Many interact with anatomical structures such as annular ligaments serving as pulleys or aponeuroses such as the extensor hood, which runs across the dorsal side of the phalanges of the fingers. Four to sometimes five tendons insert into the extensor hood of each digit.

The extrinsic muscles, such as FDP, FDS, and EDC, originate proximal to the hand. These are the long, relatively large (in terms of cross-sectional area) muscles of the hand which provide most of the power. Tendons convey forces from these muscles across the wrist to the digits. The intrinsic muscles, such as the lumbricals and interossei, have both their origins and insertions within the hand. These muscles are generally smaller and tend to direct the forces generated at the fingertips and thumb tip. Due to the largest hand muscles being located in the forearm, high forces can be created in the hand while maintaining dexterity. Voluntary forces at the index fingertip can exceed 60 N, and thumb tip forces can exceed 100 N. Joint rotational velocity can exceed 1,200°/s.

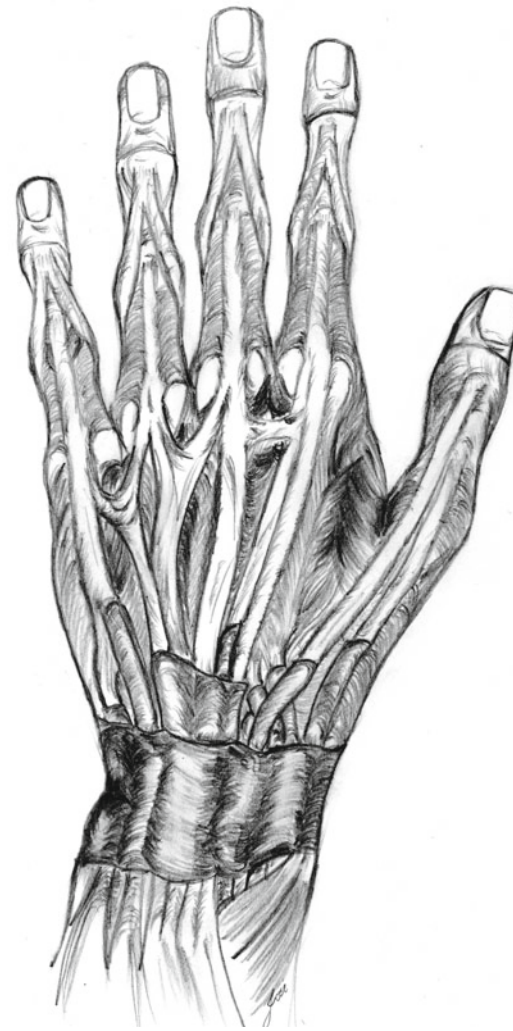

Fig. 11.1 Illustration of the tendinous network on the dorsal side of the hand (Drawn by Jose Ochoa Escobar)

With these substantial numbers of muscles and DOF, motor control of the hand is complex. For example, significant activation of all seven muscles which actuate the index finger is needed to create even an isometric flexion force at the fingertip [2]. While neurological coupling between the finger muscles does occur [3], individuated finger movement can be performed to a remarkable extent in humans, especially for the thumb and index fingers [4]. Indeed, seemingly similar muscles for the same digit, such as EDC and extensor indicis, may be selectivity excited for different movements [5],

and different compartments of even the same muscle may be activated independently [6].

This independence reflects the disproportionately large regions of the motor cortex and the corticospinal pathways devoted to the hand muscles [7]. Indeed, multiple representations of the hand [8] or of tasks involving the hand [9] have been located in the motor cortex. Specificity of cortical excitation is such that motoneurons for intrinsic hand muscles receive monosynaptic input from the cortex [10]. The major influence of cortical drive upon the hand motoneurons is further evidenced by the more limited role of brainstem pathways. While rubrospinal projections to cervical motoneurons may be prevalent in lower primates [11], these pathways are much sparser and of questionable physiological significance in humans [12].

Of course, coordinated motor control also depends heavily on sensory feedback information. Accordingly, the hand is richly innervated with sensory nerves. It has been estimated that 17,000 cutaneous mechanoreceptors are present in the glabrous skin alone of the hand [13]. Proprioceptive acuity, especially in the thumb, is superior to other body segments, such as the toes [14]. To support this sensory precision, a disproportionately large portion of somatosensory cortex is devoted to the hand [15].

11.2 Pathophysiology

With its heavy reliance on cortical innervation, control of the hand is especially affected by reduction of cortical input, such as after stroke or spinal cord injury. The resulting loss of motor control can have a profound impact on self-care, employment, and societal participation.

11.2.1 Stroke

Stroke is the leading cause of major long-term disability within the United States. Estimates number the current stroke population within the United States at greater than six million [16], a value that is only expected to grow as the population ages. Roughly 30–50% of these stroke survivors will have chronic hemiparesis, involving the hand in particular [17]. Deficits in voluntary digit extension are especially common [18].

A stroke is produced by either occlusion of blood vessels or hemorrhage in the brain. The extent and location of the resulting brain lesion or lesions can vary widely. Thus, it is often stated that no two strokes are alike. Yet, despite this diversity, stereotypical patterns of impairment emerge. In those stroke survivors with chronic hand impairment, the initial paresis and flaccidity are typically replaced by hyperexcitability of specific hand muscles. This hyperactivity may be manifest in several ways.

A signature presentation is a phenomenon termed spasticity. Externally imposed stretch of a spastic muscle results in a spinal reflex under conditions which would not produce a reflex response in nonspastic muscles. In the hand, spasticity is predominantly observed in the finger flexors, such as FDS and FDP. Interestingly, spasticity is largely absent in the long thumb flexor (flexor pollicus longus), even in individuals with spasticity in the finger flexor muscles [19], possibly due to the loss of the direct cortical input to the thumb muscles after stroke.

While a number of hypotheses have been proposed as to the origin of spasticity, one compelling theory is that the motoneuron pool of the spastic muscle sits at an elevated resting potential. Thus, excitation from the IA afferents during the stretch is sufficient to elevate some of the motor units above the firing threshold. In support of this supposition, one study found that 83% of the low-threshold motor units observed in the paretic biceps brachii exhibited spontaneous discharge [20]. In contrast, none of the units in the control subjects showed this spontaneous firing. Indeed, static stretch alone of certain muscles can be sufficient to generate neuromuscular excitation in some stroke survivors [21]. Absolute muscle length and change in muscle length both influence the magnitude of the spastic response. For example, flexion of the wrist, thereby shortening FDS and FDP, can dramatically reduce the magnitude of the stretch reflex triggered by imposed extension of the MCP joints [22]. The reflex response

can be triggered by heteronymous, as well as the aforementioned homonymous, reflex pathways following stroke [23].

This hyperactivity may also be present during voluntary contraction. Attempts to open the hand using long finger extensors may actually result in net finger flexion due to excessive coactivation of the finger flexors. Thus, the first phase of grasp, opening the hand to position it around the object, may be substantially impaired. Object release may also be affected as deactivation of the finger flexors may be abnormal. Stroke survivors have been shown to have prolonged relaxation time in FDS following a grasp, both for the impaired and less impaired sides [24]. Deactivation time does shorten following administration of cyproheptadine, an antiserotonergic agent, possibly suggesting a role for monoamines in increasing the probability of firing within the motoneuron pool.

Despite the hyperexcitability of the flexor muscles, weakness is profound in the hand. Even in moderately impaired subjects, grip strength in the impaired hand is only 50% of that of the ipsilesional hand. The relative weakness in the fingers is asymmetrical, especially in severe hand impairment. For this population, index finger extension force is only 9% of the normal force value, while flexion forces reach roughly 27% of normal levels [25]. As absolute flexion force is normally much greater than absolute extension force in the fingers, this greater relative impairment exacerbates motor deficits. Thus, limited extension of the digits is a primary impediment to function following stroke [26].

Weakness may result from a number of sources, such as muscle atrophy (although ultrasound analysis revealed relatively little atrophy in the hand muscles) and change in muscle fiber type and composition; the primary cause, however, is neurological. Stroke survivors with chronic hemiparesis are often unable to fully activate the existing muscle fibers [27]. Even the fibers which can be voluntarily excited may not be fully activated due to reduced peak firing rates in motor units [28]. Additionally, activation patterns are abnormal, with the aforementioned excessive coactivation of agonists/antagonists, along with a substantial reduction in EMG modulation. Hand muscle activation patterns change surprisingly little for intended force generation in different, even opposite, directions in stroke survivors.

11.2.2 Spinal Cord Injury

Spinal cord injury (SCI) is one of the leading causes of chronic disability in the young. Around 260,000 individuals in the United States have SCI, with 12,000 new cases added each year [29]. The mean age at incidence is 40.2 years, and life expectancy is an additional 34 years for an injury occurring at that age. Interestingly, the increasing prevalence of SCI due to falls has led to a bimodal distribution of SCI incidence disproportionally skewed toward the young and the old. Falls are now the second most common cause of SCI, after automobile accidents [29].

The resulting functional impairments are dependent upon the location and extent of damage to the spinal cord. Compression, blunt trauma, and shearing, in addition to severing, of the cord are all potential mechanisms of SCI. Injury within the cervical region of the cord leads to tetraplegia, involving impairment of all four limbs. An estimated 55% of new cases will result in tetraplegia, while the other 45% will experience paraplegia due to injury below the cervical level. As acute treatment has improved, the number of incomplete spinal cord injuries has risen. With an incomplete injury, some of the neural tracts traversing the level of injury remain viable, such that some sensation and/or motor function is preserved [30]. Fifty percent or more of new SCI cases involve incomplete injury [29, 31].

Motoneurons below the level of the injury site often remain viable. In the lower extremity, this can give rise to potentially disabling spasticity and spasms. This is much less common in the upper extremity, but abnormal interlimb reflexes, in which stimulation of lower limb nerves can produce excitation of hand muscles, may be present [32]. In low tetraplegia (C5–C8), some muscle tone may be prevalent, although extensor muscle tone seems to be as prevalent as flexor muscle tone, unlike the situation in stroke survivors. In high tetraplegia (C1–C4), flaccidity is common in the hand muscles.

Still, some motoneurons will be damaged, even multiple segments below the level of the injury. One study observed up to a 90% loss of motor units in the thenar muscles of the thumb in subjects at the C4–C5 level [33]. While axonal sprouting may help to increase the number of muscle fibers innervated, denervation atrophy often leads to disuse atrophy, further reducing strength. Even in cases of incomplete cervical SCI, atrophy of 70% of the triceps brachii muscle can be seen [34]. In contrast to stroke, substantial atrophy of the hand muscles is a common sequela of SCI.

Muscle imbalance can also lead to impairment. For example, C7 return can bring extension but with a lack of flexor activity to counteract the extensors. As noted previously, controlled force production or movement of the digits requires the coordinated activation of many muscles, including seeming agonist/antagonist pairs such as EDC and FDP. Without the activation of the digit flexors, quality of hand movement is poor. For individuals with C8 tetraplegia, control of the extrinsic muscles is spared, but the intrinsic muscles may be paralyzed. The resulting imbalance again impairs hand function.

Tract damage coupled with a reduced number of targets for cortical neurons may be accompanied by substantial brain plasticity. The loss of ascending sensory input also contributes to these changes in which areas of the brain formally associated with the hand become associated with other tasks or parts of the body. For example, one study reported expansion of cortical neurons responsive to touch of the face into regions normally responsive to the hand in adult monkeys following transaction of the cervical dorsal columns [35].

The loss of descending input also leads to changes in the basic firing pattern of motor units. Reduced nerve conduction velocities, diminished tetanic force production, and elongated twitch times were reported in the thenar thumb muscles for individuals with chronic tetraplegia [36]. Some researchers have attributed these changes not only to alterations in descending neural excitation but also to a reduction in the serotonin normally transported through descending axons [37].

The lack of muscle contraction can lead to hand edema, as venous return is limited, thereby restricting movement. If the paralyzed hand muscles are not stretched and range of motion is not performed at the corresponding joints, contractures may develop as the resting muscle length shortens to accommodate the new hand posture. Additionally, connective tissue may form around the tendon or joint capsules, further impeding joint rotation. While contracture of flexor hand muscles was often encouraged in the past to facilitate a tenodesis grasp, current practice focuses on trying to prevent these contractures while maintaining a functional tenodesis grasp for those with low tetraplegia.

11.3 Rehabilitation Technology

Technology has been developed in an effort to facilitate hand rehabilitation for both stroke and SCI survivors. The nature of the technology has been shaped by its intended use. In some cases, the primary goal was to create tools that could provide assistance for tasks which could no longer be performed by the user. Such assistive devices are intended for chronic use. Alternatively, therapeutic devices were built to facilitate rehabilitation over a finite set of training sessions, with the ultimate goal of promoting recovery so that the device is no longer needed.

Development of assistive technology has especially been spurred by the needs of individuals with tetraplegia, where both hands are often substantially impaired. The loss of control of both hands can be extremely disabling due to the importance of the hands to daily living. Thus, the relatively large mass and bulk of the added equipment needed to provide assistance may be better tolerated in this population, as the potential increase in function is so great. Additionally, a number of individuals with tetraplegia are extensive wheelchair users, particularly of power wheelchairs. These wheelchairs provide a platform for supporting external equipment to assist hand function.

In contrast, technology for stroke survivors has focused on therapeutic devices. While the ipsilesional hand may exhibit some deficits [38], these deficits are relatively mild in comparison

with the contralesional hand. Thus, the functional limitations of the upper extremities following stroke are generally not as great as in tetraplegia, and subsequently the drive to incorporate assistive devices is not as large. Additionally, the majority of stroke survivors are ambulatory, which makes the additional weight and bulk of assistive devices potential detriments to function.

11.3.1 Assistive Devices

As the dexterity of the hand is still difficult to replicate in mechatronic devices, assistive technology has traditionally focused on facilitating a specific subset of tasks. For example, a set of adaptive tools have been created which can insert into a splint worn on the wrist. These tools include modified utensils, brushes, and electric razors. In this manner, the hand is no longer required for grasping these tools; basic activities of daily living, such as feeding and grooming, can be performed with residual control of the arm. While this adaptive equipment can be very effective, it does require proper motor control of the arm as well as typically some assistance to change tools in order to perform a different task. Facilitation of grasp and manipulation of other objects is limited.

To provide a greater degree of assistance, such as might be required by those with a higher-level cervical injury, and to allow for greater task flexibility, robotic assistants have been produced. These robots could be located at a workstation, mounted directly to the user's wheelchair, or placed atop a mobile platform (and thus move autonomously). One of the first successful assistive robots was the Handy 1 [39], a robot workstation that could be used for eating, drinking, grooming, and even art projects (Fig. 11.2). The Handy 1 employed a Cyber 310 robotic arm, which had five DOF in addition to a gripper end effector. It was controlled through a PC 104, and the user could operate the device through a single switch. Newer robots have been incorporated into updated feeding assistants. My Spoon (SECOM Co., Ltd., Tokyo, Japan) and a feeding robot designed explicitly for Korean food [40] are currently being produced. These devices are more compact than their predecessors and offer control options for the user. Other robotic workstations have been designed to provide alternative services. For example, the Desktop Vocational Assistant Robot (DeVAR) was created to provide assistance within an office environment. It consisted of a commercial PUMA-260 robot coupled to a Griefer prosthetic hand from Otto Bock Healthcare (Duderstadt, Germany).

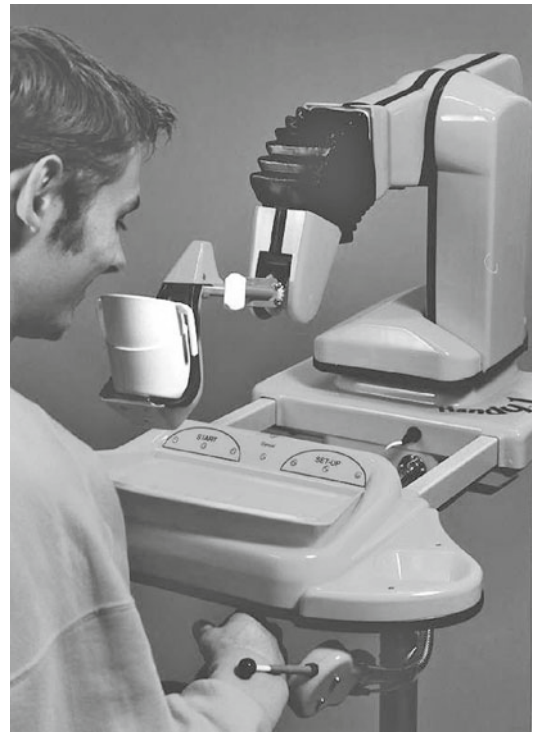

Fig. 11.2 The Handy 1 workstation, intended to help users with eating, drinking, and grooming. First developed by Mike Topping at Staffordshire University (Reprinted with permission from: Topping [92]. © Emerald Group Publishing Limited; all rights reserved)

To increase the range of tasks and situations in which they could be employed, robotic systems were developed which could be mounted directly to a wheelchair. The KARES system created at the Korea Advanced Institute of Science and Technology (KAIST) has six DOF in its robotic arm and a gripper at its end [41]. KARES could perform tasks such as grasping objects and turning off and on light switches under direction from the user. Its successor, KARES II, had a mobile

Fig. 11.3 The *i*ARM wheelchair-mounted assistive robot, seen here assisting a user to mail a letter (Photo courtesy of Exact Dynamics, Didam, the Netherlands)

platform, which could extend the workspace of the robot, and compliant control which facilitated interactions with the environment [42]. The Raptor Wheelchair Robot System was developed by the Rehabilitation Technologies Division of Applied Resources Corp. (RTD-ARC) expressly as an assistive device. It received US Food and Drug Administration (FDA) approval and was sold commercially beginning in 2000 [43]. The Raptor arm had four DOF with a gripper which permitted grasping of objects. The most commercially successful wheelchair-mounted device has been the MANUS, which has evolved into the *i*ARM (Exact Dynamics, Didam, the Netherlands). The *i*ARM provides six DOF and a gripper end effector and can be powered from a wheelchair battery [44]. It is designed for close interaction with the user (see Fig. 11.3). A wide variety of control options are available dependent upon the capabilities and preferences of the user.

Attempts have also been made to provide mobile robotic assistants which could move independently from the wheelchair. The MoVAR device, developed at Stanford University and the Rehabilitation Research and Development Center at the VA Palo Alto Health Care System, consisted of a PUMA robot arm affixed to a powered omnidirectional base [45]. Autonomous mobile robots, intended for a number of possible applications, could also provide valuable functions for individuals with tetraplegia. For example, the assistant Care-O-bot®3 (Fraunhofer IPA) or the courier Pyxis HelpMate (Pyxis Corporation) had the potential to benefit those with tetraplegia by retrieving and transporting objects.

Recently, some assistive devices have been developed expressly for the hand to facilitate grasp and release [46]. The Rehabilitation Glove, created at the Royal North Shore Hospital in Sydney, Australia, uses intelligent polymers to actuate a glove worn by the user. The Soft Extra Muscle Glove (Bioservo Technologies, Isafjordsgatan, Sweden) could help individuals with incomplete tetraplegia by amplifying their grasping force.

One of the key limitations preventing widespread employment of assistive devices is the control of these devices. Our hands are able to perform a wide variety of tasks with limited conscious input. With assistive technology, user intent must be conveyed to the device in a translatable manner. For example, to bring a cup of water to the mouth for drinking, the robot needs to not only know that this is the intended action but also the location and orientation of the cup, the grasping force to be used, the speed at which it should be moved, and the path to be taken to avoid collisions. While some of these decisions can be made by the device, to truly have the

desired flexibility, these parameters should be modifiable by the user. Providing this type of control for external devices remains challenging, especially for individuals with limited motor control. Thus, while joysticks and trackballs may be good input devices for some users, they may not be feasible for individuals with high tetraplegia. Instead, inputs like head trackers, eyelid switches [47], and a tongue-driven mouse [48] have been created to maximize the utility of residual motor control for indicating user intent.

One means of providing facile control of multiple DOF of an assistive device is to use neurological signals directly from the user. Implantable electrode arrays of up to 100 electrodes can be placed directly into the human motor or premotor cortex. These cortical signals are mapped into intended movements which can then be employed to drive external devices. For example, recordings from motor cortex have been successfully used in monkeys to drive a robot to move to specific locations in space [49]. Another group implanted cortical electrodes in individuals with tetraplegia to control a mouse on the computer screen [50]. A noninvasive alternative is to use electroencephalogram (EEG) signals to drive assistive technology. The EEG signals have been used to control an actuated hand orthosis by an individual with tetraplegia [51].

11.3.2 Therapeutic Devices

While assistive technology has continued to evolve to improve functionality, obviously, the best outcome would be for the user to regain sufficient motor control such that the assistive technology is no longer needed. Thus, in recent years, there has been a substantial shift in research focus from assistive robots to therapeutic devices which would facilitate rehabilitation of the impaired movement.

This thrust has been spurred by research showing that the central nervous system exhibits much greater plasticity than previously imagined. Even the mature nervous system is constantly changing and adapting to new circumstances. For example, repeated practice of hand movements, such as performed by musicians, can lead either to seemingly beneficial cortical changes in sensorimotor representation and processing [52, 53] or to harmful changes, such as in focal dystonia [54].

Experimental evidence suggests that intensive repetitive training of new motor tasks is required to induce long-term brain plasticity [55]. This finding seems to be applicable to motor relearning after brain injury, such as from stroke, as well. In animal models of brain injury, practice appears to be the primary factor leading to synaptogenesis and brain plasticity [56–58]. Thus, even long after injury, the central nervous system retains some degree of plasticity. Numerous studies employing the constraint-induced technique, in which focus is placed on intensive practice with the impaired arm while use of the ipsilesional arm is restricted, have shown improvement in hand capabilities [59–62]. Similarly, following stroke, repetitive practice has been shown to lead to functional improvement [62]. Imaging performed during constraint-induced training studies has shown evidence of cortical plasticity following the training [63, 64].

While the importance of practice to motor relearning after injury is widely accepted, the optimal type of practice remains a matter of debate. Some proponents have favored simpler movements, which can be repeated more frequently. For example, one study looked at repetitive wrist flexion/extension and forearm pronation/supination, supported by the Bi-Manu-Trak, a device with a single DOF which could be used to support either the wrist or forearm motion [65]. Subacute stroke survivors participated in trials in which they performed these movements over 6 weeks. The gains in upper extremity Fugl-Meyer scores [66] were substantial (mean 18 points) compared to the gains in another group receiving electrical stimulation therapy (3-point gain). In a later study, however, similar improvements were seen in both the group receiving therapy with the arm trainer and with the group receiving electrical stimulation [67]. Byblow and Stinear looked at the benefits of repeated practice of a simple wrist flexion/extension movement. In this paradigm, the less impaired wrist drove the impaired wrist through custom-developed mechanical coupling [68]. A follow-up study confirmed

some beneficial effects for this therapy when combined with other activities [69]. Furthermore, the results of another study showed no benefit to adding functional grasps to training of arm movements [70]. These studies, however, did not measure functional task performance.

Alternatively, a number of researchers and therapists have recommended task-specific training, in which participants focus on the tasks they wish to be able to perform in their daily lives. According to this view, just as one practices a tennis serve to improve one's serving, so should stroke survivors practice opening a jar or a task of similar importance to them. Indeed, retraining of walking after stroke consists of repeated walking. In the upper extremity, functionally based training has been shown to lead to some improvements over strength-based training, for example [60]. Reaching toward physical objects as part of a task was seen to lead to enhanced quality of movement as opposed to simply reaching to a location in space in stroke survivors [71]. Practice, however, is often limited by time or stamina. The possibly greater complexity of functional tasks may limit the number of repetitions that can be performed. Additionally, it may prove more difficult to generate functional tasks for which partial success, which helps maintain engagement of the client during a challenging exercise, is possible. The nonfunctional exercise, e.g., opening and closing the hand, may be achieved to varying degrees while the criteria for success for a functional task, e.g., opening a pill bottle, may appear more binary for a client.

Task performance of any type with the hand can prove challenging after stroke. The 21 DOF are difficult to control, even with a therapist guiding rehabilitation. Thus, a number of mechatronic devices have been developed within the last 10 years to facilitate hand rehabilitation following stroke. One approach has been to focus on a single, fundamental movement of the hand, namely opening and closing. To promote practice of this motion, mechatronic objects have been created which can expand or contract to open or close the hand, such as the hand module for the MIT-MANUS robot [72] and a haptic knob grasped by the user [73].

For devices that directly couple to the hand, one of two strategies has generally been adopted: either the structure of the device remains distal to the fingertip and is externally grounded or it resides on or proximal to the hand and is grounded to the hand or arm. The first category of devices connects to the hand only at the tips of the digits. The great advantages of this approach are that only one interface between the finger and device is needed per digit, minimal mass is added to the hand, and interference between adjacent digits or joints is minimized. For example, a small robot was created to provide either haptic feedback or rehabilitation for the index finger [74]. The robot is affixed to a tabletop and connects to the tip of the index finger. The two active DOF of the robot can control fingertip position throughout the sagittal plane workspace of the finger. Amadeo System (Tyromotion, GmbH, Graz, Austria) and HandCARE [75] also use variations of this approach for stroke rehabilitation (Fig. 11.4); the fingertips are attached to linear tracks or cables, respectively, which directly control fingertip location, thereby affecting, although not rigidly controlling, all of the joints in the digit. There are, however, some disadvantages to this approach. One drawback is that the hand position and orientation must be fixed as the devices are externally grounded. Thus, it is not possible with these devices to incorporate hand training into reach-to-grasp movements, for example, or to permit movement of the user. Training with real objects is largely precluded, and joint-level control is limited.

An alternative approach is to internally ground the device to the hand or arm. Typically, in this design, the actuation force is transmitted across the joint to be controlled, although the PERCRO L-EXOS system from the Scuola Superiore Sant'Anna uses a hybrid approach. The terminal portion of this exoskeleton controls the thumb and index fingers through contact solely with the distal segments of these digits, although the actuators are internally grounded to the forearm. More commonly, a glove or exoskeleton is utilized to connect to the hand and permit force transmission across the joints of interest. To limit complexity, a number of devices of this design

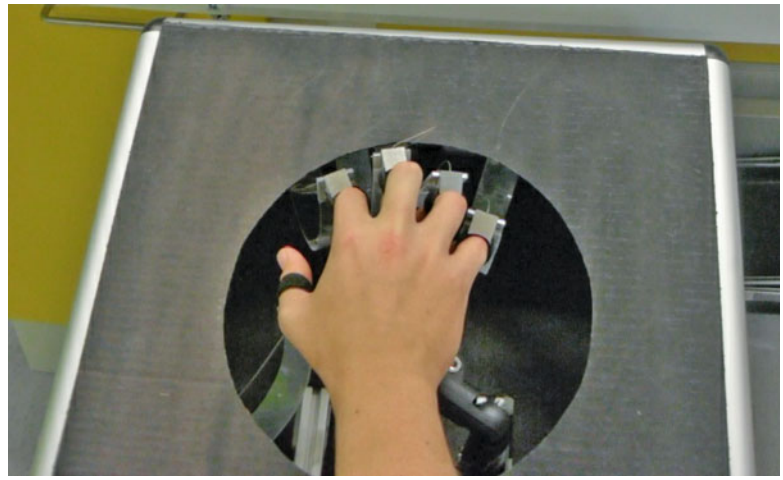

Fig. 11.4 HandCARE3 system. Cables attached to the fingertips can pull the digits open. The springs shown provide a restoring force to push the digits back into flexion when the pulling force is removed (Photo courtesy of Dr. Etienne Burdet of the Imperial College London)

move multiple digits simultaneously. HWARD [76], HEXORR [77], and the Hand Mentor (Kinetic Muscles Inc., Tempe, AZ) are exoskeletons that rotate all four MCP joints of the fingers (and additionally all four PIP joints for HEXORR) together. HWARD and HEXORR use fixed platforms but provide thumb actuation; the Hand Mentor does not actuate the thumb but can move with the arm.

To increase the extent of hand tasks allowed, some devices have provided independent control of each digit. The Rutgers Master II-ND [78] was one of the first devices developed for hand rehabilitation. It uses pneumatic cylinders on the palmar side of the digits to move the fingertips. The PneuGlove [79], in contrast, uses air bladders on the palmar side of a glove to assist digit extension and provide resistance to flexion for each digit. It takes advantage of the asymmetry in impairment of finger extension and flexion in stroke survivors, so that only extension is assisted. Similarly, the CyberGrasp haptic system (Immersion Corporation, San Jose, CA) has been incorporated into a rehabilitation virtual reality paradigm [80]. The CyberGrasp can provide extension forces only to each digit independently through a cable system traversing the back of the hand.

All three of these systems permit considerable movement of the arm. The PneuGlove and CyberGrasp can be used with either real or virtual objects. Another device, the X-Glove, built at the Rehabilitation Institute of Chicago, employs linear motors that pull on cables running along the dorsal side of the digits to offer independent extension assistance for each digit (Fig. 11.5).

To perform more complicated tasks, mechatronic devices may need to actively control more DOF within the hand. One exoskeleton which does allow independent control of finger joints has been designed for rehabilitation of occupational injuries [81] but may also be useful for stroke rehabilitation. DC motors actuate the exoskeleton, which controls the individual joints through Bowden cables. Thus, the mass of the motors can be located off the hand, although the Bowden cables do introduce considerable friction which may slow response time. An 18-DOF device has been developed at Gifu University in Japan for hand and wrist rehabilitation following stroke [82]. The motors actuating the joints are located directly at the joints (see Fig. 11.6). A single motor can thus rigidly control joint rotation in either the clockwise or counterclockwise direction, although the torques that can be provided are relatively small due to the limited motor size.

11.4 Current Status

While assistive robots may be very beneficial for a targeted population, they serve a relatively small market relative to the technological sophistication of the devices. Numbers of the Handy 1

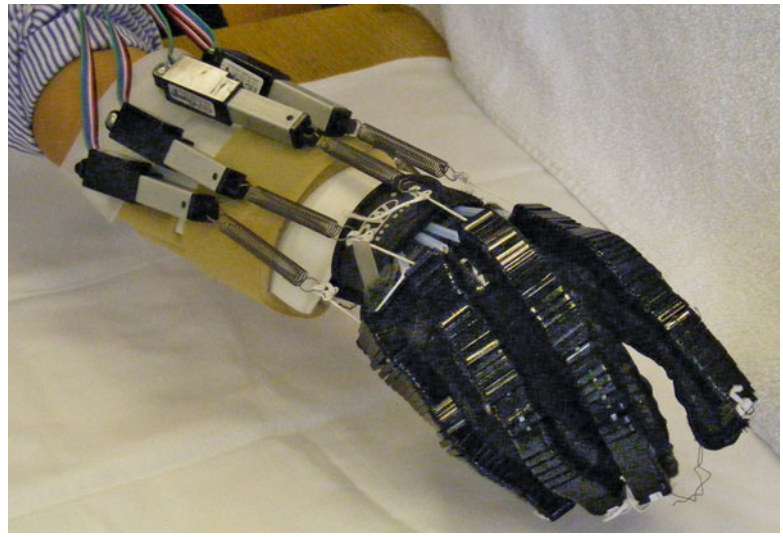

Fig. 11.5 The eXtension-Glove (Rehabilitation Institute of Chicago, Chicago, IL, USA), intended to assist digit extension following stroke. Cable runs through guides on the back of each digit to a linear motor driven by a microcontroller. The entire device is portable

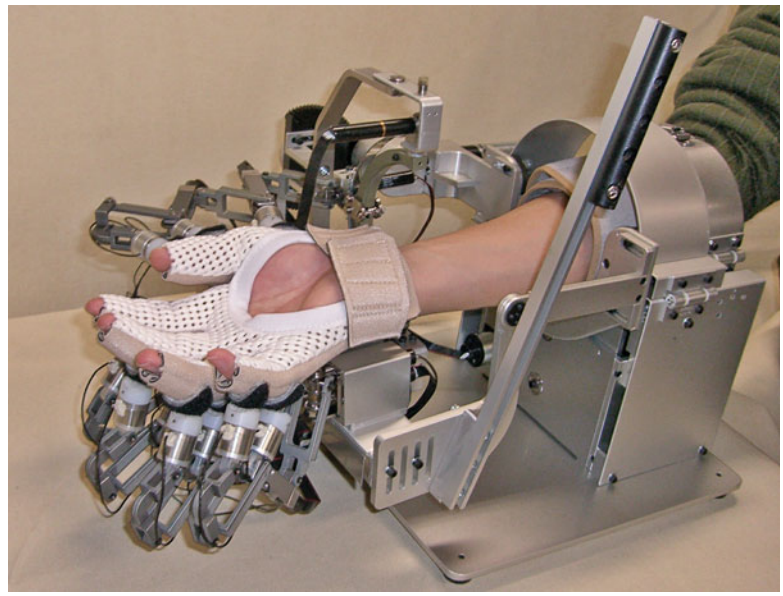

Fig. 11.6 Picture of a hand exoskeleton with 18 actuated DOF. Motors are located at the joints of interest. The exoskeleton can be controlled by the contralateral hand using a master–slave paradigm (Photo courtesy of Dr. Haruhisa Kawasaki of Gifu University)

and MANUS (*i*ARM) sold are in the hundreds rather than thousands or tens of thousands. Thus, research and manufacturing costs have to be spread across a limited number of units, and overall costs remain high, thereby limiting the potential for more widespread adoption from individuals who might benefit from use of the technology. Assistive technology targeting low tetraplegia, such as C7–C8, may be able to take advantage of residual function to reduce complexity and cost. Wearable devices which facilitate grasp and release, for example, would be helpful for this population.

Intriguingly, the emergence of aging populations in many developed countries has led to a new push in the area of assistive devices to meet the needs of the growing geriatric populace. Mobile assistants like EL-E [83], HERB (Intel Labs Pittsburgh, Pittsburgh, PA), and ASIMO (Honda Corporation) are being developed in the hopes of serving an older population with potentially restricted mobility and diminished

upper extremity function. These assistants could also prove beneficial for individuals with tetraplegia. Research in powered exoskeletons continues to grow as well to meet the expected needs of either the military or the elderly. Devices like the Stride Management Assist (Honda Corporation, Tokyo, Japan) and Sarcos XOS skeleton (Sarcos, Salt Lake City, UT) are designed to augment the capabilities of the wearer. Again, this technology may also be applicable to helping those with SCI.

Assistive technology which is wearable may also be a boon for stroke survivors. Current therapies have had limited success helping those with severe hand impairment. These individuals are generally excluded from trials such as constraint-induced therapy [62], as these therapies have not proven effective for them. Many stroke survivors with severe hand impairment, however, retain some ability to voluntarily close the hand. While grasp is weak, it is present. The problem lies in opening the hand sufficiently to position it for grasp and to reopen the hand to release the object. Seemingly, assistive devices could provide this hand opening. The impaired hand could then participate in simple but functionally important tasks, such as stabilizing objects as they are manipulated by the other hand (e.g., opening a jar) or carrying objects, such as a bag. For stroke survivors, hemiparesis involving both the upper and lower extremities is common. Thus, the inability to carry or hold an object with the contralesional hand can greatly affect activities of daily living or mobility as the ipsilesional hand may be needed to control a cane during walking. Actions like carrying a glass of water from the sink to the table may then not be possible. In fact, some stroke survivors become nonambulatory inside their homes due largely to the lack of useful hand function.

While a number of therapeutic devices continue to be developed for the stroke hand, studies examining efficacy of these devices remain sparse. The majority of these studies consist of single or multiple case studies, such as with the Rutgers Hand Master [78], the Hand Mentor [84], CyberGrasp [85], and HandCARE [86]. Encouraging results were seen in larger studies for HWARD [76] and the haptic index finger device [74], although these studies did not include a true control group. In those studies employing a control group receiving similar amounts of therapy to the group using the device, gains were generally not significantly different between the groups [79, 87, 88]; both groups showed improvement. Equivalent improvement, however, is not necessarily a negative outcome. One of the key benefits of the therapeutic devices is their facilitation of extended practice, either in the clinic or, ideally, in the home. Opportunities for therapy are often limited; for example, individualized outpatient therapy in the United States typically totals less than 3 h per week. The therapeutic devices may enable the repetitive practice necessary for rehabilitation and improve motivation to keep the user engaged.

It is anticipated that more efficacy studies will follow as these technologies become more mature. Key questions remain, however, regarding the best uses of the devices to facilitate rehabilitation: Should the device assist or resist movement? Should movement error actually be augmented? [89] How do we ensure maximum effort of the user without making the task so difficult that the user quits? How complex should the training tasks be?

These therapeutic devices, while developed largely for the stroke population, may be appropriate for individuals with incomplete tetraplegia as well. Indeed, preliminary studies using massed practice therapy in SCI have shown some improvement, both in animal models [90] and in individuals with tetraplegia [91]. Gait therapy for paraplegia increasingly relies on body-weight-supported treadmill training. This is often done in conjunction with therapeutic devices to facilitate leg movement, such as the Gait Trainer I (Reha-Stim, Berlin, Germany), the Lokomat (Hocoma Medical Engineering, Inc., Zurich, Switzerland), or the AutoAmbulator (HealthSouth, Birmingham, AL, USA). Surprisingly, similar practice with the upper extremity is much more limited. A number of the previously described devices that have been developed for stroke therapy could be applied to the SCI population as well.

Conclusions

The neuromechanical complexity of the hand makes it a challenging target for therapy after stroke or SCI. For those individuals in whom the prospect for functional return is limited, a number of assistive mechatronic devices have been developed to perform some of the tasks previously executed with the hands. As robotic grippers become more dexterous, the capabilities of these devices will expand. Additionally, growing research in the area of wearable exoskeletons to assist the geriatric population should benefit as well those with neuromuscular injury, including stroke survivors.

Therapeutic devices for the hand continue to evolve, with new actuators and materials promising even greater gains in the ratio of power to weight. The primary obstacle in terms of hardware, however, remains the interface between the device and the hand. The optimal means of exploiting these mechatronic devices remains to be determined as well. The efficacy of using this equipment in therapeutic hand training of individuals with incomplete tetraplegia warrants exploration.

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The Advanced Appreciation of Upper Limb Rehabilitation in Cervical Spinal Cord Injury

12

Ninja P. Oess and Armin Curt

Abstract

The nature of an upper limb function impairment following a cervical spinal cord injury (SCI) is bilateral and rather symmetric, which increases the impact of the injury on the independence and quality of life of the affected patient. Therefore, this disorder is very different from stroke and other damages within the peripheral nervous system. Physical training therapy is of high clinical importance in patients with a cervical SCI so as to increase neural plasticity, and thereby improve motor recovery. New rehabilitation therapies based on robots, passive workstations, and functional electrical stimulation (FES) systems have been developed. However, the overall clinical value of these new technology-based therapies in SCI patients needs to be evaluated. Different methods can be used to test or describe the condition of the upper limb function before and after a novel physical training therapy session. We present a detailed functional classification of the hand that can distinguish different levels of impairment with typical impacts on activities of daily living. In consequence, changes between these levels (improvement or deterioration) can be considered clinically meaningful. In addition, upper limb function following SCI can be assessed with measures of capacity and performance, as well as surrogates (electrophysiological and biomedical recordings). While performance tests target on clinically relevant changes by assessing activities related to daily life (i.e., hand function), measures of capacity and surrogates focus on detailed functions (motor and sensory scores, conduction velocity) that do not necessarily correlate with clinically meaningful changes. Nevertheless, capacity tests and surrogates can detect subtle changes induced by interventions that might be missed by clinical measures.

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Tetraplegia • Upper limb function • Rehabilitation • Assessment • Clinically meaningful improvement

12.1 Introduction

Patients with a cervical spinal cord injury (SCI) suffer to a variable extent from a complete or incomplete tetraplegia affecting upper and lower limbs. The density (completeness) and level of lesion is clinically appreciated by motor and sensory deficits (as scored by the ASIA scores) and autonomic dysfunction (i.e., bladder–bowel and cardiovascular dysfunction). The rehabilitation of hand and upper limb function has been identified as one of the primary desires in tetraplegic patients, even more important than ambulation [1, 2]. Indeed, the independence of persons with tetraplegia in the activities of daily living (ADL) depends extensively on the arm and hand function [3]. Therefore, the appropriate assessment and rehabilitation of upper limbs is a clinically highly relevant goal in cervical SCI. Substantial efforts for the rehabilitation of hand and arm function in persons with tetraplegia or other neurological disorders have been directed toward developing new robots [4–6], passive workstations [7, 8], and functional electrical stimulation (FES) [9, 10]. Nevertheless, the clinical value of these novel or advanced technologies and the most appropriate and effective introduction into rehabilitation practice is still lacking. Several clinical measures (measures of capacity, performance, and quantitative sensory testing) and surrogates (electrophysiological and biomechanical recordings) are applied to measure changes in the sensory and motor function. Yet, the clinical relevance of these measures and surrogates in the context to evaluate the outcome of upper limb rehabilitation and to estimate the value of novel rehabilitation technologies needs to be established.

This chapter is organized as follows: An overview of existing clinical assessments and classifications of upper limb function after SCI is followed by a section introducing therapeutic perspectives based on new technological devices. Next, we present measures of upper limb and hand capacity. Finally, we address surrogates for the description of functional impairment.

12.2 Clinical Assessments and Classification of Upper Limb Function After SCI

12.2.1 Upper Limb Function in Neurological Disorders

Upper limb function following a high level SCI is specific and differentiates from that following other neurological disorders, such as stroke, multiple sclerosis, and peripheral nerve damage. In order to appropriately address the very specific needs and confounders of hand–arm function, the underlying pathophysiology in upper limb impairment needs to be accounted for.

In ischemic stroke, the most common type of strokes, different areas of the brain (cortical and subcortical) can be affected causing a transient impairment or structural damage of the brain. Motor functions and limb movements depend on the ability to imagine, plan, organize, and accomplish a goal-directed movement or action. The impairment of upper limb motor function following stroke is due to the damage of descending central motor pathways (corticospinal fibers) and challenges of motor planning depending of the involvement of premotor areas. The typical hand and arm in stroke patients is characterized by a hemiparesis (partial or complete paralysis) and hemispasticity (increased muscle tone) in the contralateral limb. Characteristic postures can include any of the following: a tight fist, a bent forearm and elbow, and an arm pressed against the chest.

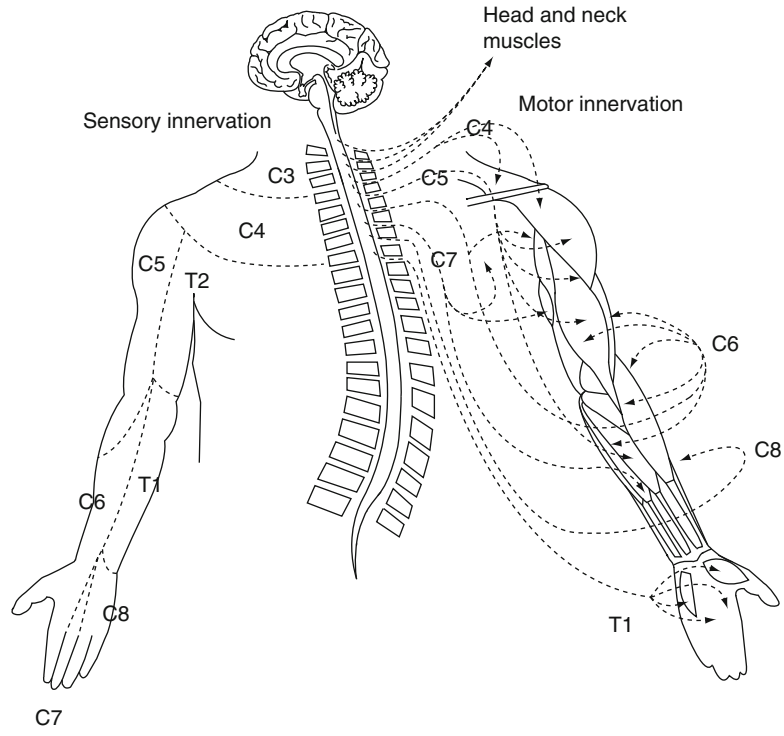

Fig. 12.1 Dermatomes (*left*) and myotomes (*right*) of the upper limbs are specifically innervated leaving typical maps of sensory and motor functions and deficits, respectively.

In multiple sclerosis, a musculoskeletal weakness and impairment of hand function is due to a demyelination of axons within the brain and spinal cord. The demyelination typically affects the white matter areas of the brain and the ascending–descending myelinated spinal tracts that lead to a broad spectrum of disabilities, such as fatigue, cognitive and limb sensory-motor impairment. Due to the high variability and extent of affected brain–spinal cord areas, the impairment of hand–arm function can be very inconsistent and does not follow a typical pattern.

In peripheral nerve injuries of hand–arm nerves (i.e., median and ulnar nerves), the sensory-motor deficit depends on the involved peripheral nerves, while the spinal cord and brain are not affected. Peripheral nerve damages present very specific deficits and the causes include traumatic injuries and nerve entrapment syndromes that can be disclosed by neurophysiological recordings.

12.2.2 Upper Limb Function in Cervical SCI

In cervical SCI, the loss of sensory-motor functions depends on the affected spinal segments while peripheral nerves and brain function are not involved. Therefore, motor planning and other functions related to movement initiation and control remain intact at the cortical level, while the deprivation of afferent inputs and the impairment of efferent outputs challenge the movement control. Based on the somatotopic organization within the spinal cord, impairment of upper limb function in SCI can be rather well predicted. The segmental sensory (left) and motor innervations (right) of the cervical cord predispose the development of a typical impairment pattern (Fig. 12.1). It is important to recognize that dermatomes and myotomes of the upper limbs are differently organized dependent on the specific segments and the peripheral nerve

distribution as arranged by the cervicobrachial plexus. In consequence, dermatomes and myotomes possibly damaged after SCI can be determined from the segmental level of lesion. Unlike in stroke, peripheral nerve damages and to a very variable extent in multiple sclerosis, cervical SCI patients suffer from a bilateral impairment of hand–arm function, which challenges also bimanual hand functions (manipulation of objects with two hands like opening a jar). In addition, upper limb impairment in SCI is rather symmetrical which deprives the ability to compensate upper limb function by the better or even non-affected hand–arm increasing their dependence on upper limb function.

12.2.3 Scoring of Upper Limb Function

In general, spinal cord injury can be described according to international standards for the neurological classification of spinal cord injury (ISNCSCI) as approved by the American Spinal Injury Association (ASIA) and the International Spinal Cord Injury Society (ISCoS) [11]. The injury is characterized by the neurological sensory and motor level, completeness or incompleteness, and ASIA impairment scale (AIS). Beyond the neurological classification, the patient's ability in accomplishing ADL tasks can be described with a spinal cord independence measure (SCIM). Three versions of this disability scale (SCIM I–III) have been consecutively developed, validated, and are clinically used [12–14]. The SCIM protocol scores the ability for self-care, respiration and sphincter management, and mobility. Independence when using the upper limbs is preferable measurable with the self-care items of the SCIM III test. Furthermore, the condition of the sensor-motor function of upper limbs in cervical SCI can be defined by classifications addressing specific purposes. The very first intention of these classifications was to allow for the comparison following functional upper limb surgery in tetraplegia and, in particular, following tendon transfers to improve grasp [15–17]. In 2004, Fattal distinguished two different types of classifications. The first one is based on a metameric structure describing residual or lost dermatomes and myotomes, while the second is based on remaining or lost functions [15]. Meanwhile, these classifications are used to define upper limb function in a wider setting. The most prominent upper limb classification in surgical restoration was developed by Moberg [18], later modified [19] and finally adopted at the Conference of Giens in 1984 [20]. This classification is based both on a metameric and functional description of the forearm and hand. It consists of 11 groups. The groups from 0 to 9 correspond to active muscles below the elbow, and the last group called X brings together all the atypical functions. Except for group X, each group is characterized at the (metameric) sensory and motor level, and at the functional level. The sensory level is described by measuring cutaneous sensibility. In addition, vision is tested since grip is controlled by both vision and sensibility in the hand [18]. The motor level, by contrast, is defined by the remaining active muscles with a minimum strength of 4 MRC (British Medical Research Council) [21]. The movements that can be carried out by the elbow, wrist, and fingers characterize the functional level.

12.2.4 Framework for the Classification of Upper Limb Function in SCI

In the interest to enable comparisons between different specific approaches in the treatment and rehabilitation of upper limb function in SCI, a common classification is recommended. The proposed framework includes an algorithm for an upper limb classification and a measure of upper limb performance. These measures do not require any specific instruments or measurement tools, they are applicable at bedside in acute and chronic SCI, and can complement more elaborated lab tests.

The classification of upper limb function describes the remaining motor functions of the hand, forearm, and shoulder related to spinal myotomes that differentiates pattern of motor function based on the level and completeness of

SCI. It is based to some extent on previous classifications, such as the modified classification of Moberg (functional part) [20] and the classifications of Freehafer [22] and Hentz [23], but it is not specifically directed toward the needs in functional surgery. The classification distinguishes five different levels of hand function that are considered to be of clinical relevance, and changes between these levels (improvement or deterioration) can be considered as clinically meaningful changes (Table 12.1; left section) which have been discussed in the frame of a Delphi study.

12.2.5 Classification of Upper Limb Function

Level 1 (*No hand function*): Patients have no voluntary control of the elbow, wrist, and hand muscles. Besides, they have no grasping function, and active placing or reaching of the arm is severely limited.

Level 2 (*Passive tenodesis hand*): Includes patients with neither voluntary control of extrinsic and intrinsic hand muscles nor ability to actively extend the wrist. Opening and closing of the hand is only possible by passive tenodesis effect. That is, by supination of the forearm to induce passive dorsiflexion of the wrist and in turn generate extension of the fingers or inversely by pronation of the forearm to produce passive palmar flexion of the wrist and in turn generate flexion of the fingers. Bimanual grasping by stabilizing objects between two hands or passive tenodesis grasp is effective only in a limited workspace.

Level 3 (*Active tenodesis hand*): Patients have no voluntary control of extrinsic and intrinsic hand muscles but can actively extend the wrist. Thus, an active tenodesis effect can be performed, namely, by active dorsiflexion or palmar flexion of the wrist to generate passive finger movements. Single-handed grasping function is limited to a reduced workspace.

Level 4 (*Active extrinsic – tenodesis hand*): Includes patients with voluntary control of the wrist and some extrinsic hand muscles. Thus, grasping with or without tenodesis effect and opening and closing of the hand can be carried out. However, dexterity of the hand and workspace are reduced.

Level 5 (*Active extrinsic – intrinsic hand*): Patients have voluntary control of extrinsic and intrinsic hand muscles within an entire workspace. Furthermore, they have the ability to perform different grasp forms such as the pulp pinch; nevertheless, muscle strength and dexterity can be limited.

12.2.6 Upper Limb Performance

For each level of the upper limb function classification, the SCIM III (self-care items) scores have been estimated and are given in Table 12.1. The SCIM III is a performance test and reveals clinically relevant changes in the upper limb function. Several iterations have been performed for improvement and validation, and the SCIM III represents a solid disability scale routinely used in clinical practice and as a reference for the upper limb function in SCI.

The SCIM III score estimated for level 1 is 0 point, while the score calculated for level 2 ranges between 0 and 4 points. Level 3 matches with a score between 4 and 13 points, whereas level 4 is linked to a score between 4 and 16 points. Finally, the score estimated for level 5 is between 12 and 18 points. The maximum score of the SCIM III (self-care items) that a patient sitting in a wheelchair can reach is 18 points instead of 20 given that the items "bathing lower body" and "dressing lower body" cannot be performed without the wheelchair.

The combination of the classification and functional scoring allows for distinguishing different patterns of innervations (levels 1–5) and levels of independence as provided by upper limb function. The SCIM complementary to the specific levels also provides information on how well the subject within one of the levels performs, and therefore, the combination of the two measures is more sensitive to the overall affection of upper limb function. In advantage to the neurological classification by ASIA, changes in these measures translate imminently into clinically meaningful changes.

Table 12.1 Clinical and scientific framework of upper limb rehabilitation in SCI

Clinically meaningful thresholds			Body function/structure	Capacity measures/surrogates
Hand function classification	Independence measure		Neurological classification	Lab assessments
	SCIM III (self-care items)			
Level 1:				
No hand function	Feeding	0	*ISNCSCI* (*ASIA*)	*Measures of capacity*:
No voluntary control of elbow – wrist – hand muscles. No grasping function and severely limited active placing or reaching of the arm	Bathing upper body	0	– Neurological level	– GRASSP
	Bathing lower body	0	(i) Sensory level	– VLT-SV
	Dressing upper body	0	• PP	– MCS
	Dressing lower body	0	• LT	– Thorsen
	Grooming	*0*	(ii) Motor level	– CUE
	Sum of self-care	*0*	• ULMS	– Sollerman
			• LLMS	– GRT
			– Impairment scale	– Vanden Berghe
			AIS A–E	*Surrogates*:
			– Zone of partial pre-servation (ZPP)	Electrophysiology:
			– Spinal cord syndromes	– SSEP
			(i) Central cord	– CHEP
			(ii) Brown-Sequard	– MEP
			(iii) Anterior cord	– NCS
				– EMG
				Biomechanics (kinetics, kinematics):
				– Muscular activity (EMG)
				– Strength (dynamometry, manometry)
				– Angles, ROM (goniometry)
				– Trajectories (motion capture systems, instrumented gloves)

Level 2:		
Passive tenodesis hand	Feeding	0–1
Passive hand functions with neither voluntary control of extrinsic and intrinsic hand muscles nor ability to actively extend the wrist. Opening and closing of the hand is only possible by supination or pronation of the forearm (passive tenodesis effect) with no active grasping movements of the hand. Bimanual grasping by stabilizing objects between two hands or passive tenodesis grasp is effective only in a limited workspace	Bathing upper body	0–1
	Bathing lower body	0
	Dressing upper body	0–1
	Dressing lower body	0
	Grooming	*0–1*
	Sum of self-care	*0–4*
Level 3:		
Active tenodesis hand	Feeding	1–2
No voluntary control of extrinsic and intrinsic hand muscles but active wrist extension allowing for passive movements of fingers dependent on an active tenodesis effect. Limited single-handed grasping function in a restricted workspace	Bathing upper body	1–2
	Bathing lower body	0–2
	Dressing upper body	1–3
	Dressing lower body	0–2
	Grooming	*1–2*
	Sum of self-care	*4–13*
Level 4:		
Active extrinsic – tenodesis hand	Feeding	1–3
Voluntary control of wrist and some extrinsic hand muscles allowing for grasping with/without tenodesis enabling some active opening and closing of the hand but reduced dexterity and reduction of workspace	Bathing upper body	1–2
	Bathing lower body	0–2
	Dressing upper body	1–3
	Dressing lower body	0–3
	Grooming	*1–3*
	Sum of self-care	*4–16*

(continued)

Table 12.1 (continued)

Clinically meaningful thresholds			Body function/structure	Capacity measures/surrogates
Level 5:				
Active extrinsic – intrinsic hand	Feeding	3–3		
Voluntary control of extrinsic and intrinsic hand muscles with full workspace and the ability to perform different grasp forms (pulp pinch) but potential limitations of muscle strength and dexterity	Bathing upper body	2–3		
	Bathing lower body	1–2		
	Dressing upper body	3–4		
	Dressing lower body	1–3		
	Grooming	*2–3*		
	Sum of self-care	*12–18*[a]		

Abbreviations: *SCI* spinal cord injury, *SCIM III* spinal cord independence measure III, *ISNCSCI* International Standards for the Neurological Classification of Spinal Cord Injury, *ASIA* American Spinal Injury Association, *PP* pin prick, *LT* light touch, *ULMS* upper limb motor score, *LLMS* lower limb motor score, *ZPP* zone of partial preservation, *GRASSP* Graded and Redefined Assessment of Strength, Sensibility, and Prehension, *VLT-SV* Short Version of the Van Lieshout Test for arm/hand function, *MCS* Motor Capacities Scale, *THAQ* Tetraplegia Hand Activity Questionnaire, *CUE* Capabilities of Upper Extremity Instrument, *GRT* Grasp and Release Test, *RLAH* Ranchos Los Amigos Hospital functional activities test, *SSEP* somatosensory evoked potential, *MEP* motor evoked potential, *NCS* nerve conduction study, *EMG* electromyography, *ROM* range of motion

[a]Maximum score of 20 points cannot be reached when the patient is sitting in a wheelchair

12.3 Therapeutic Perspectives

12.3.1 New Technology-Based Therapies

Studies conducted on humans following an incomplete SCI showed adaptations in the interaction of multiple supraspinal centers with the more restricted descending systems in the spinal cord. Indeed, after an incomplete injury, a significant level of neural plasticity occurs that results in a reasonable recovery of locomotion [24]. In addition, a study carried out on rats with a partial SCI demonstrated that training increases neural plasticity, and thereby, improves motor recovery. Yet, recovery showed to be task specific [25]. In consequence, after an incomplete cervical SCI, diversified training therapy of the upper limb is required to both avoid muscular atrophy of the remaining (active) motor functions and recover, to variable extents, the lost neuromotor functions.

As for an athlete below saturation, the more a patient practices physical exercise, the more he or she will progress, whether the training is carried out with conventional therapy or robot-assisted therapy. There are, however, some advantages of technological-based therapies over conventional therapies. Robot-supported training can be more intensive, of longer duration and more repetitive compared to manual arm training [5]. Besides, the motivation of the patient to perform repeated training exercises can be enhanced if they are embedded in entertaining computer games. Indeed, in a study comparing technological-based therapy (using T-WREX) and conventional therapy, the subjects reported a preference for training with T-WREX [7]. In addition, if the device is designed to collect relevant data in a standardized way, the data can be studied by the therapist and used to enhance recovery [24].

Considerable efforts have been put into the development of new upper limb training devices, such as robots (MIT-Manus [4], ARMin [5], and MEMOS [6]), passive workstations (T-WREX [7] and ReJoyce [8]), and FES systems (Compex Motion-based neuroprosthesis [9], ETHZ-Paracare and Freehand Systems, Ness Handmaster, Bionic Glove, and NEC-FES system [10]).

12.3.2 Robotic Systems

MIT-Manus is a robot for physical therapy of the arm and wrist. It comprises two modules and 5° of freedom, two for elbow and forearm motion and three for wrist motion. The robot can move, guide, or perturb the movement of a patient's upper limb and record quantities, such as position, velocity, and force. The patient–robot interface consists of video games for elbow, shoulder, and wrist exercises [4]. A study comparing intensive robot-assisted therapy, using MIT-Manus, with intensive conventional therapy and usual care showed, at 12 weeks, that intensive robot-assisted therapy did not significantly improve motor function as compared with usual care or intensive conventional therapy. After 36 weeks, robot-assisted therapy improved motor function as compared with usual care but not with intensive conventional therapy [26].

ARMin III is an exoskeleton robot for arm-supported training therapy. ARMin III provides three actuated degrees of freedom for the shoulder and one for the elbow joint. An additional module provides actuated pro- and supination of the lower arm and wrist flexion and extension [5]. The robot offers three different therapy modes: the movement therapy, the game therapy, and the ADL training mode. A study on the effect of intensive arm training with ARMin II on four patients with stroke showed that intensive robot-assisted arm therapy can significantly improve motor function in some stroke patients [27].

MEMOS is a robot allowing physical exercise for improving upper limb motor recovery. It is a planar robot in a cartesian configuration, which is based on a simple mechatronic structure. A handle is fixed to a trolley that is moving in a horizontal (XY) plane. A force transducer estimates the force exerted by the patient in the X and Y directions. The elbow and shoulder exercises are incorporated in video games that provide visual feedback of the different positions of the handle [6]. A study on robot-aided therapy in stroke patients showed significant improvement in motor performance (kinematic and dynamic components) of the arm movement following training with MEMOS [28].

12.3.3 Passive Workstations

T-WREX has been developed to enable stroke patients with chronic hemiparesis to practice arm movement without continuous supervision from a therapist. It consists of an orthosis that assists in arm movement, a grip sensor that senses hand grip pressure, and software that simulates functional activities. The exoskeleton has 4° of freedom and passively counterbalances the weight of the arm against gravity by means of elastic bands [7]. A study comparing motor training with T-WREX and conventional training with a tabletop for gravity support in chronic stroke patients showed that all subjects significantly improved motor function. In addition, rehabilitation therapy with T-WREX was associated with modest maintenance of progress at 6-month follow-up as compared with conventional therapy [29].

ReJoyce can assess hand function and provide upper limb rehabilitation training for individuals with stroke and SCI. The apparatus consists of a four degrees-of-freedom spring-loaded arm (joystick) attached to a table or desk. The automated exercises comprise ADL tasks played in the frame of computer games by manipulating attachments on the device. The joystick has integrated sensors that provide quantitative information on displacement of the manipulated attachments and prehension force. A study comparing FES and ReJoyce-based therapy with FES and conventional exercises in SCI participants showed that FES together with ReJoyce-based therapy resulted in (statistically and clinically) greater improvements than those obtained with the more conventional protocol [8].

The robotic systems and passive workstations described above mainly generate movement and task-specific motor recovery of the upper limb. Apart from ReJoyce, the other devices have initially been developed for stroke patients with a chronic hemiparesis and assessed in similar patients. These devices can also be used for robot-assisted training in SCI patients but do not provide bimanual exercises. Furthermore, the overall clinical value of these technologies and a thorough evaluation of their specific advantages/disadvantages against conventional and competitive novel treatment approaches in SCI needs to be established.

12.3.4 FES Systems

FES uses electrical currents to stimulate nerves innervating paralyzed extremities. Neuroprostheses for grasping, such as the Compex Motion-based neuroprosthesis [9], the ETHZ-Paracare, the Freehand and the NEC-FES systems, the Ness Handmaster, and the Bionic Glove, are devices incorporating FES and which are designed to restore or improve grasping function [10]. Clinical trials have shown that a number of acute SCI patients could improve locomotion and grasping function with FES assistance to the point where they no longer need the FES system. Other acute SCI patients were not able to improve their function with aid from FES [10]. In order to determine which types of SCI patients benefit from FES-based therapies and why, a detailed assessment has to be implemented.

12.4 Measures of Upper Limb/Hand Capacity

12.4.1 Capacity and Performance Measures of Upper Limb Function

Multiple clinical measures (measures of capacity, performance, and quantitative sensory testing) and surrogates (electrophysiological and biomechanical recordings) are applied to determine and follow upper limb function. These measures (except for performance measures) assess very specific detail functions and aspects, and are mainly targeted to disclose rather specific effects of interventions (torques, angles, ROM). Clinical measures of capacity and performance typically consist of specific movements and/or ADL's tasks that the patient has to perform in standardized environments (controlled setups) and from which defined parameters are measured and scored according to a predefined scale.

Capacity tests (such as the GRASSP [30, 31], the VLT-SV [32], and the MCS [33]) are based on raw movements and/or ADL tasks that the patient carries out specifically for the evaluation in an artificial environment (e.g., in the laboratory, in the clinic), whereas performance tests (such as the THAQ [34], the RLAH [35], and the COPM [36]) assess ADL tasks that the patient executes in the usual course of his/her life in a normal environment (e.g., at home, at work). Thus, in capacity tests, specific parameters are measured precisely, whereas performance tests evaluate tasks accomplishments. The advantage of capacity tests is that they are more reliable, while they do not reflect reality necessarily well. Inversely, performance tests provide less precise measures but reflect reality better.

Many tests have been developed to assess upper limb function, while only a limited number have been constructed specifically for cervical SCI (Table 12.2; instruments listed from most recent downwards) [30–35, 37–43]. It is assumed that tests developed specifically for SCI patients are more sensitive and responsive than more general tests as applied in other neurological disorders.

Reliability and validity are important clinimetric properties of upper limb function evaluation tests. Among the ten instruments listed in Table 12.2, six (the GRASSP, the VLT-SV, the MCS, the CUE [39], the Sollerman test [40], and the GRT [41]) have been assessed for reliability and validity, from which one (the GRT) has only partly succeeded the validation test. Some instruments, which have initially been developed for patients with stroke and other diagnoses, are also frequently used in the clinic to evaluate SCI patients. From these tests, we have selected those which have been tested for reliability and validity. Table 12.3 summarizes the tests primarily developed for stroke patients [44–52] and Table 12.4, for patients with diagnosis other than SCI and stroke [36, 53–62].

12.4.2 Clinimetric Properties

The reliability and validity of upper limb function assessment tests have been studied to ensure that the instruments are precise and accurate. The reliability is defined as the reproducibility of results obtained when the instrument is administrated repeatedly [63]. The reproducibility evaluation can be performed by the same rater (intra-rater reliability), by different raters (inter-rater reliability), or on two different occasions to evaluate the stability of the instrument (test–retest). The most commonly used index of reliability to measure reproducibility is the intraclass correlation coefficient (ICC). It represents the proportion of the variability in the observations due to the subject effect, that is, the subject variance σ_s^2 divided by the total variance of the observations, and is given by [64]: $\rho_c = \sigma_s^2 / \left(\sigma_s^2 + \sigma_e^2\right)$, where σ_e^2 is the variance of the measurement error. The ICC is comprised between 0 (no agreement between repeated measurements) and 1 (perfect agreement between repeated measurements). For ordinal measures, the weighted Cohen's kappa (κ) coefficient is commonly used. In general, the criterion of acceptability for ICC and κ (kappa) is a value equal or superior to 0.70 [63].

The validity, by contrast, is defined as the degree to which an instrument actually measures what it is intended to measure. There are three basic types of validity: content validity, construct validity, and criterion validity [63]. Content validity is the extent to which the items of the instrument reflect the domain of interest. The items must represent fields that are important to patients. Construct validity is the degree to which scores obtained with the instrument relate consistently to other measures based on the same theoretical hypothesis. This implies that a theoretical rationale has been developed to underlie the tested instrument. The criterion validity is the extent to which the results of an instrument are related to results of another instrument – a criterion standard – which has previously shown to be accurate. In this study, criterion validity is considered. To measure criterion validity, the parametric Pearson r or nonparametric Spearman ρ (rho) correlation coefficients, between the tested instrument and the criterion standard, are used in general. According to Gowland et al. [46], the instrument is considered valid if the coefficient is greater than 0.60.

Table 12.2 Clinical assessment protocols of upper limb function in SCI patients

Instrument	Purpose	Proximal arm	Distal arm/hand	Time to complete	Method used	Parameter measured	Scoring	Reliability	Validity	Advantages	Disadvantages
GRASSP (Graded and Redefined Assessment of Strength, Sensibility, and Prehension), 2008 [30, 31]	Clinical and research tool, upper limb function in C0-T1 patients	Shoulder, elbow	Forearm, wrist, hand (grasp)	30–45 min (both sides)	10 manual muscle tests, SW-filaments test, 3 grasp movements, 6 single-handed basic ADL tasks	Muscle contraction/ ROM, pressure sensibility, grasp pattern, capacity to complete task	0–5 0–4 0–4 0–5	[37] $n=72$ Inter-rater ICC = 0.84–0.96 Test-retest ICC = 0.86–0.98 $p<0.0001$	[37] $n=72$ SCIM III $r=0.57$–0.68 SCIM III-SS $r=0.74$–0.79 CUE $r=0.77$–0.83 $p<0.0001$	Applicable in acute and chronic stages of SCI	Single hand specific, test kit has to be purchased
VLT-SV (Short Version of the Van Lieshout Test for Arm/ Hand Function), 2006 [32]	Clinical and research tool, upper limb function in C5–T1 patients	Shoulder, elbow	Forearm, wrist, hand grasp (pinch, grip)	25–35 min (both sides)	10 single-handed/ bimanual specific movements and basic ADL tasks	Capacity to perform task	0–5	$n=12$ Inter-rater ICC = 0.98 and 0.99	$n=55$ GRT $\rho=0.87$ and 0.90	Scoring based on principle that different tasks have different hierarchical levels	Cannot be used in acute phase
MCS (Motor Capacities Scale), 2004 [33]	Clinical tool, upper limb function in C4–C7 patients, surgery evaluation	Shoulder, elbow	Forearm, wrist, hand grasp	20–50 min	31 single-handed/ bimanual specific movements and basic ADL tasks	Independence degree, capacity to perform task, grasp pattern	1–5 1–2 1–4	$n=52$ Inter-rater ICC = 0.99	$n=52$ Sollerman $r=0.96$ ASIA-MS $r=0.74$	Measures different important parameters	Specific for surgery evaluation in C4–C7 patients, patient assumed in wheelchair

THAQ (Tetraplegia Hand Activity Questionnaire), 2004 [34]	Clinical tool, upper limb function, surgery and FES evaluation	Shoulder, elbow	Forearm, wrist, hand grasp	30–45 min	Questionnaire regarding 153 self-administrated single-handed and bimanual ADL tasks	Self-perceived capacity to perform task, independence degree, task importance	0–3 0–3 0–2	Not available	Not available	Telephone interview possible	Neither tested for validity nor reliability, test self-administrated at home (no control), possible bias to please interviewer, specific for surgery and FES evaluation
Thorsen's Functional Test, 1999 [38]	Research tool, hand function, FES evaluation	Not assessed	Forearm, wrist, hand grasp (pinch, grip)	<90 min (including preparation)	8 basic single-handed ADL tasks	Capacity to perform task	0–2	Not available	Not available	Easy administration	Neither tested for validity nor reliability, proximal arm not assessed, specific for FES evaluation, single hand specific
CUE (Capabilities of Upper Extremity Instrument), 1998 [39]	Research tool, upper limb function in C5–T1 patients	Shoulder, elbow	Forearm, wrist, hand grasp	~30 min (both sides)	Questionnaire regarding 32 single-handed/bimanual self-administrated specific movements and basic ADL tasks	Self-perceived capacity to perform task	1–7	$n=154$, Test-retest ICC = 0.94	$n=154$ FIM-SM $r=0.738$ $\rho=0.798$ UEMS $r=0.782$ $\rho=0.798$	Telephone interview possible	Test self-administrated at home (no control), possible bias to please interviewer

(continued)

Table 12.2 (continued)

Instrument	Purpose	Proximal arm	Distal arm/hand	Time to complete	Method used	Parameter measured	Scoring	Reliability	Validity	Advantages	Disadvantages
Sollerman Hand Function Test, 1995 [40]	Clinical tool, hand function before surgery	Not assessed	Forearm, wrist, hand grasp (pinch, grip)	20 min (both hands)	20 single-handed/ bimanual basic ADL tasks	Capacity to perform task, time to complete task, grip pattern	0–4	$n=6$ Inter-rater $r=0.98$ Test-retest $r=0.98$	$n=59$ ICSHT $r=0.76$	Rapid, measures different important parameters	Proximal arm not assessed, test kit has to be purchased
GRT (Grasp and Release Test), 1994 [41]	Research tool, hand function in C5–C6 patients, neuro-prosthesis evaluation	Not assessed	Forearm, wrist, hand grasp	90–150 min (both with/ without neuropros-thesis)	6 single-handed basic ADL tasks	Ability to pass or fail task within a given time	Number of passed/ failed tasks	[42] $n=19$ Test-retest ICC = 0.87–1 $p<0.01$	[42] $n=19$ Partly validated FIM (in general low ρ)	Objective	Only partly validated and in general low correlation, too long, proximal arm not assessed, specific for neuroprosthesis evaluation in C5–C6 patients, single hand specific, based only on time not on movement quality
Vanden Berghe Hand Function Test, 1991 [43]	Clinical tool, hand function, surgery evaluation	Not assessed	Forearm, wrist, hand grasp	30–195 min (operated hand)	9 single-handed basic ADL tasks, 6 single-handed/ bimanual ADL tasks	Time to complete task, independence degree	Time(s), 0–3	Not available	Not available	Easy administra-tion	Neither tested for validity nor reliability, proximal arm not assessed, specific for surgery evaluation

RLAH (Ranchos Los Amigos Hospital Functional Activities Test), 1980 [35]	Research tool, upper limb function in traumatic C4–C7 patients, use of learned skills and orthotic device after discharge evaluation	Shoulder, elbow	Forearm, wrist, hand grasp	–	Questionnaire regarding 45 single-handed/ bimanual self-care ADL tasks	Self-perceived independence degree	1–3	Not available	Not available	Telephone interview possible	Neither tested for validity nor reliability, specific for use of learned skills and orthotic device after discharge evaluation in C4–C7 traumatic patients, patient assumed in wheelchair

Table 12.3 Clinical assessment protocols of upper limb function in stroke patients

Instrument	Purpose	Proximal arm	Distal arm/hand	Time to complete	Method used	Parameter measured	Scoring	Reliability	Validity	Advantages	Disadvantages
WMFT (Wolf Motor Function Test), 2001 [44]	Research tool, upper limb function, forced non-use of non-affected arm therapy evaluation	Shoulder, elbow	Forearm, wrist, hand grasp	40 min (both sides)	21 single-handed specific movements and basic ADL tasks, 3 force measure tasks	Time, quality of movement and force	Time (s), weight (lb)	[45] $n=19$ Inter-rater ICC = 0.95–0.99 $p<0.0001$	[45] $n=19$ FMA $\rho=0.61$ $p<0.02$	Norm values	Low validation correlation, specific for forced non-use of non-affected arm therapy evaluation, single hand specific, movement quality scoring reported to be
Chedoke-McMaster Test, 1993 [46, 47]	Clinical and research tool, whole body function	Shoulder, elbow	Wrist, hand grasp	45–60 min (whole body)	Muscle scale, 10 specific movements and ADL tasks (5 walking tests)	Spasticity, reflex/voluntary activity, independence/assistance (walking distance)	1–7 1–7 (2 bonus)	$n=32$ Intra-rater Inter-rater Test-retest ICC = 0.97–0.99	$n=32$ Fugl-Meyer $r=0.95$ $p<0.001$ FIM $r=0.79$ $p<0.05$	Both impairment classification and disability evaluation	Whole body function test, no ADL tasks, test manual has to be purchased
ARAT (Action Research Arm Test), 1981 [48]	Occupational therapy practice, clinical and research tool, upper limb function	Shoulder, elbow	Forearm, wrist, hand grasp (pinch, grip)	~40 min (both sides)	16 single-handed basic ADL tasks, 4 single-handed specific movements	Capacity to perform task or movement	0–3	$n=20$ Inter-rater $r=0.99$ Test-retest $r=0.98$	$n=50$ UEFT $r=0.97$	Items arranged in hierarchical order of difficulty	Validation evaluation based on patient data from UEFT study, single hand specific

Fugl-Meyer Test, 1975 [49]	Clinical and research tool, whole body function	Shoulder, elbow	Forearm, wrist, hand grasp	~10 min (for upper limb, 30 min in total)	(Normal) reflex activity, single hand-arm specific movements, coordination/ speed, sensation, joint motion/joint pain	Presence/ absence of reflex (hyper) activity, pattern/ capacity to perform movement, tremor/ dysmetria/time, light touch/ position, ROM/ amount of pain	0–2 0–2 0–2 0–2 0–2 0–2 0–2 0–2 0–2	[50] $n=12$ Inter-rater ICC=0.97 [51] $n=19$ Intra-rater $r=0.995$ $p<0.001$ Inter-rater $r=0.990$ $p<0.001$	[52] $n=50$ DeSouza test $r=0.97$ $\rho=0.95$	Assesses different parameters, very rapid	Whole body function test, no ADL tasks, single hand-arm specific, ceiling effect observed [45]

Table 12.4 Clinical assessment protocols of upper limb function in non-SCI/stroke patients

Instrument	Purpose	Proximal arm	Distal arm/hand	Time to complete	Method used	Parameter measured	Scoring	Reliability	Validity	Advantages	Disadvantages
DASH (Disabilities of the Arm, Shoulder, and Hand), 1996 [53, 54]	Clinical and research tool, upper limb function in patients with musculoskeletal disorders	Shoulder, elbow	Forearm, wrist, hand grasp	~10–20 min	Country-specific questionnaire regarding ~30–40 single-handed/bimanual self-administrated ADL tasks	Self-perceived symptoms and capacity to perform task	0–4	Country specific	Country specific	Internationally validated (14 countries), very rapid, telephone interview possible	Test self-administrated at home (no control), possible bias to please interviewer
COPM (Canadian Occupational Performance Measure), 1991 [36]	Occupational therapy practice and clinical tool, occupational performance in patients with various disabilities	Shoulder, elbow	Forearm, wrist, hand grasp	20–40 min	Questionnaire regarding performance in self-care/productivity/leisure areas	Identification of problem areas and importance in daily functioning, self-perceived ability and self-satisfaction with performance	1–10 1–10 1–10	[55] $n=26$ Test-retest item pool 56% $\rho=0.88–0.89$ $p<0.001$	[55] $n=26$ Discriminant validation, BI, FAI, SASIP-30, EQ-5D, RS	International (35 countries), patient-centered, not diagnosis specific, crosses developmental stages	Not upper limb specific, scores between patients not comparable
Jebsen[a] Hand Function Test, 1969 [56]	Clinical and research tool, hand function in patients with various diagnosis	Not assessed	Forearm, wrist, hand grasp	~15 min in healthy subjects (both hands)	7 single-handed basic ADL tasks	Time to complete tasks	Time (s)	[56] $n=26$ Test-retest $r=0.60–0.99$	[57] $n=111$ MHQ AUC = 0.52–0.66 failed validation test	Objective, norm values, very rapid, easy administration	Failed validation test (AUC has to be >0.75), rates only time not movement quality, proximal arm not assessed, single hand specific, test kit has to be purchased
MRM (Minnesota Rate of Manipulation Test for Disability Evaluation), 1965 [58, 59]	Industrial tool, hand function, healthy workers with good manual skills selection	Not assessed	Forearm, wrist, hand grasp	~15 min (both sides)	5 single-handed and bimanual basic ADL tasks	Time to complete tasks	Time (s)	[59] $n=118$ Inter-rater $r=0.75$ (we assume Pearson's correlation coefficient)	[59] $n=118$ AMA rating scale $r=0.55$ $p<0.01$ (we assume Pearson's correlation coefficient)	Objective, very rapid, easy administration	Rates only time not movement quality, proximal arm not assessed, test kit has to be purchased, no information regarding type of validity and reliability correlation calculated, very low validation values

Box and Block test, 1960 [60]	Occupational therapy practice tool, upper limb function in patients with cerebral palsy	Not assessed	Forearm, wrist, hand grasp	–	1 single-handed basic ADL task	Ability to pass or fail task within a given time	Number of passed/ failed tasks	[61] $n=69$ Test-retest ICC = 0.89–0.97	[61] $n=69$ ARAT $r=0.80–0.82$ SMAF $r=0.42–0.54$	Objective, norm values [61, 62], rapid	Single hand specific, proximal arm not assessed, based only on time not on movement quality

Abbreviations: *SCI* spinal cord injury, *SW* Semmes-Weinstein, *ADL* activities of daily living, *ROM* range of motion, *ICC* intraclass correlation coefficient, *SCIM III* spinal cord independence measure version III, *SCIM III-SS* spinal cord independence measure version III – self-care subscore, A*SIA-MS* neurological classification of spinal cord injury approved by the American Spinal Cord Association and the International Spinal Cord Injury Society – motor score, *FES* functional electrical stimulation, *FIM-SM* functional independence measure – motor score, *UEMS* upper extremity motor score, *ICSHT* International classification for surgery of the hand in tetraplegia, *FIM* functional independence measure, *FMA* Fugl-Meyer motor assessment, *UEFT* Upper Extremity Function Test, *BI* Barthel Index, *FAI* Frenchay Activities Index, *SASIP-30* stroke adapted sickness impact profile-30, *EQ-5D* Euroqol 5D, *RS* Rankin scale, *MHQ* Michigan hand outcomes questionnaire, *AUC* area under the curve, *AMA* American Medical Association, *SMAF* Système de mesure de l'autonomie fonctionnelle

[a]Although this instrument does not fulfill the selection criterions (it failed a validation test [57]), we have included it in this table given that it is very frequently used in SCI patients

12.4.3 Prehension Patterns

The analysis of prehension patterns during the performance of ADL tasks plays an important role in upper limb function evaluation tests, particularly in capacity tests. Indeed, most capacity tests are based on raw movements and/or ADL tasks, which have been selected to test specific types of grasps. Numerous taxonomies of prehension have been established as described by McKenzie and Iberall [65, 66]. We have identified the most common types of grasps from the taxonomies of Sollerman et al. [40], Schlesinger [67], and Light et al. [68]. Fig. 12.2 illustrates the (a) pulp pinch, (b) tip pinch, (c) lateral pinch, (d) tripod pinch, (e) five-finger pinch, (f) diagonal volar grip, (g) transversal volar grip, (h) spherical volar grip, (i) extension grip, and (j) hook grip. In literature, the names are used rather inconsistently, e.g., the pulp pinch is also called the palmar pinch, or the transverse volar grip is named cylindrical grasp.

From both an anatomical and a functional point of view, Napier [69] distinguishes two basic patterns of hand movements called precision and power grip. Accordingly the precision grip is performed during activities that require high precision, while the power grip in activities that necessitates power. These grips can be performed either separately or in combination and embody the whole range of prehensile patterns. In precision grip, the object is pinched between the flexor side of the fingers and that of the opposing thumb. In power grip, by contrast, the object is held as in a clamp between the flexed fingers and the palm with the thumb applying more or less counter pressure. Thus, these two movements are distinct both in the anatomical and in the functional sense. The theory of Napier is the following: Although the size and shape of an object may influence the type of prehension employed, it is actually the nature of the intended activity that finally influences the type of grip. This theory is shared by Cutkosky [70], who has constructed taxonomy of manufacturing grasps. In his classification, grasp patterns are divided into two main branch lines, power and precision grips. Some grips belong either to one group or to the other one, whereas other grips, such as the spherical volar grip, may belong to both groups.

12.4.4 Types of Measurement

Capacity and performance measures of upper limb function are based on various items, such as timing, counting, ordinal rating, or weighing. Ordinal scales generally rate the grasp pattern or capacity to execute a task [41]. They are subjective and somewhat imprecise. Among the 19 tests summarized, in Tables 12.2–12.4, 10 use only ordinal rating and 7 use ordinal rating in combination with (an)other type(s) of measurement. Counting is utilized, in addition to ordinal rating, in the GRASSP when scoring the Semmes–Weinstein Monofilaments. The time to complete a task is also incorporated as a factor in the ordinal scales of the Sollerman, Vanden Berghe [43], and the Fugl-Meyer [49] tests. Moreover, in the WMFT test [44], in addition to timing and ordinal rating, weighing is used to measure force strength with a dynamometer. Tests based mainly on timing, such as the Jebsen test [56], the MRM [58, 59], the GRT [41], and the Box and Block test [60], are objective but do not rate quality of movement. As a result, they can neither differentiate normal from compensatory movements nor distinguish between a patient who cannot perform a grasp pattern and a patient who can execute a grasp pattern but cannot complete a given task. Eighty-nine percent of the instruments of Tables 12.2–12.4 are based on ordinal rating, 42% on timing, 16% on counting, and 5% on weighing. Thus, most of the upper limb function capacity and performance tests are based on ordinal rating and are, as a result, subjective and somewhat imprecise.

12.4.5 Purpose of the Instruments

The purpose section of Tables 12.2–12.4 indicates whether the tests were initially developed for use in the clinic, in occupational therapy practice, in research, or industry. Furthermore, some instruments have specifically been designed to evaluate surgical interventions (the MCS and the Vanden Berghe's test), FES-based therapy (the Thorsen's test [38]), forced non-use of non-affected arm therapy (the WMFT), and use of

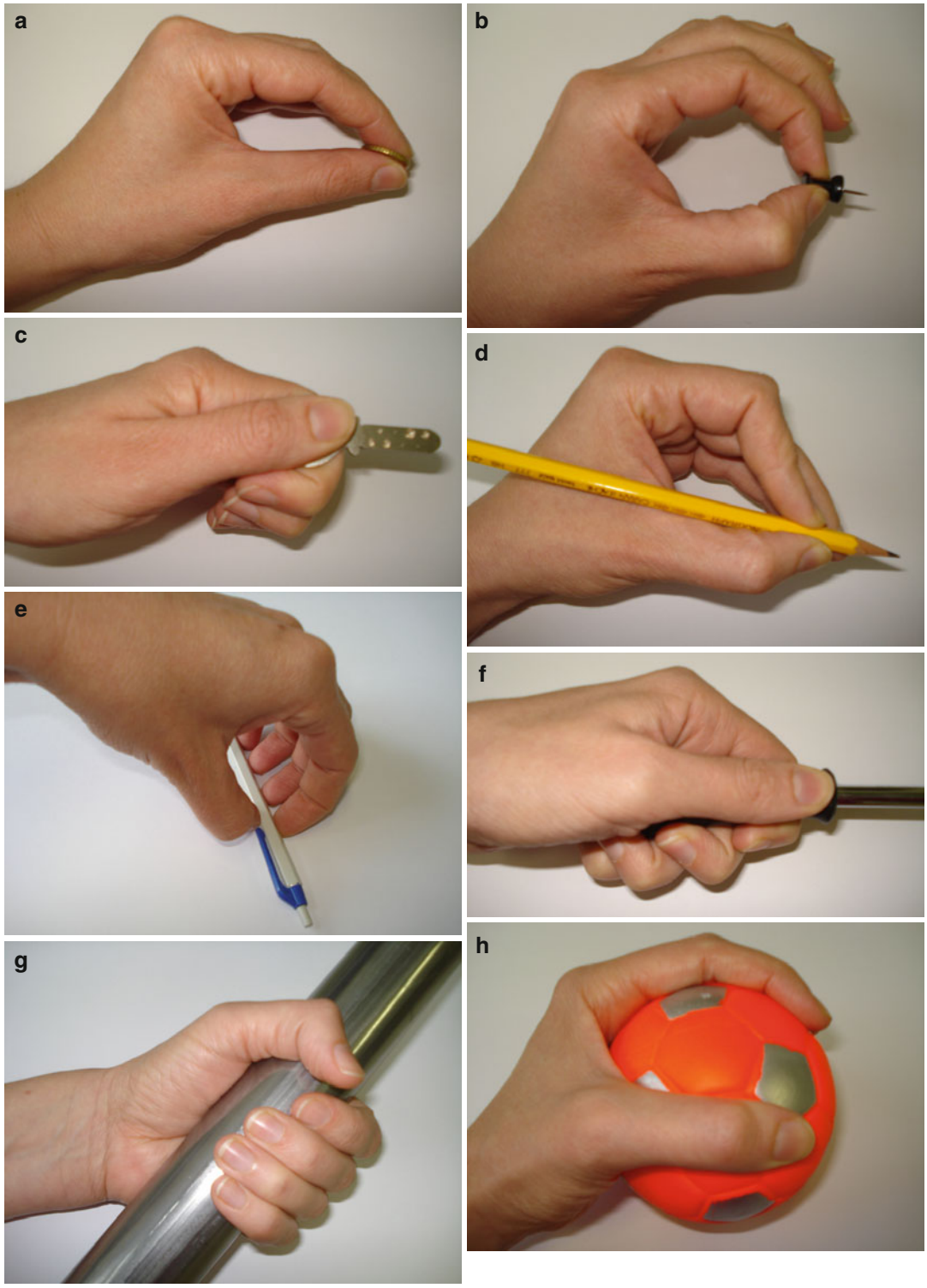

Fig. 12.2 (**a**) The pulp pinch, (**b**) the tip pinch, (**c**) the lateral pinch, (**d**) the tripod pinch, (**e**) the five-finger pinch, (**f**) the diagonal volar grip, (**g**) the transversal volar grip, (**h**) the spherical volar grip, (**i**) the extension grip, and (**j**) the hook grip.

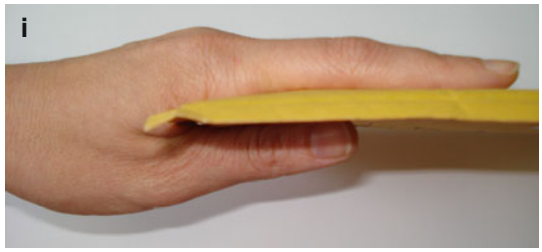

Fig. 12.2 (continued)

learned skills and orthotic device after discharge (the RLAH). The MRM test has even been developed in the industry to select workers with good manual skills. Tests developed to assess changes in upper limb function within a specific frame should be very good for that specific purpose. That is, an instrument designed to evaluate FES-based therapies should be most sensitive and responsive for FES interventions but is probably less efficient to assess upper limb function for general questions or other interventions.

12.4.6 Basic Characteristics

The majority of the studied tests evaluate the proximal arm and the distal arm/hand. Nevertheless, 35% of them (the Thorsen's, the Sollerman's, the GRT, the Vanden Berghe's, the Jebsen's, the MRM, and the Box and Blocks tests) concentrate on the distal arm/hand but do not assess the proximal upper limb. Although the Jebsen test does not fulfill the selection criterions (it failed in a validation test [57]), we have included it in our study given that it is very frequently used in SCI patients.

The time necessary to complete a test is not only a sensitive parameter but is also of relevance in clinical practice where tests below 30 min are considered rapid tests that can be applied during clinical sessions.

The methods used to rate the upper limb function are most often specific movements and/or ADL tasks carried out with a single hand or bimanually. The tasks can either be basic, such as grasping an object and transporting it from one place to another, or more complex, such as grooming. Forty percent of the tests developed specifically for SCI patients (Table 12.2) are only based on single-handed movements and/or ADL tasks. Instruments based on both single-handed and bimanual tasks are more suitable to assess the upper limb function of cervical SCI where typically both arms are affected.

12.4.7 Questionnaires

Some instruments, such as the THAQ, the CUE, the RLAH, the DASH [53, 54], and the COPM [36] are presented in the form of a questionnaire. They are based on questions regarding the patient's ability to carry out raw movements, specific ADL tasks, or activities in the usual course of his/her life. For most questionnaires, the patient self-rates his/her own capacity or performance. The COPM questionnaire is a particular instrument where the patient and therapist balance together the patient's abilities and disabilities within his/her environment and role of expectations. The patient identifies the problem areas in daily functioning and, together with the

therapist, establishes therapeutic goals, applies the treatment, and evaluates the outcome. In the outcome evaluation, the patient self-rates his/her ability and satisfaction with the present performances. Thus, the COPM emphasizes the importance of the patient's perception of need and self-satisfaction and the notion that he/she is a fundamental part of the therapeutic process. The advantages of questionnaires are that the answers can be collected by telephone interview and that the raw movements and/or ADL tasks can be self-administrated by the patient at home. Yet, for most questionnaires, there is no examiner to verify that the patient performs the ADL tasks correctly. Furthermore, a bias in the answers is possible if the patient wants to please the interviewer [15].

12.5 Discussion

Most of the traditional upper limb capacity and performance measures are based on ordinal scales and, as a result, are subjective and somewhat imprecise. For this reason, a new generation of upper limb function assessment tests for cervical SCI patients is required. These instruments should be objective and precise. They should evaluate both the distal and proximal arm/hand as well as single-handed and bimanual movements. Furthermore, this new generation of tests should be rapid and rate grasp pattern. At last, they should be evaluated for reliability and validity. Obviously, clinical measures of capacity evaluate very specific details, and observed changes might not correlate well with the clinical appreciation. The minimal clinically important difference (MCID) is defined as the smallest change in a measurement that signifies an important improvement according to the patient's and clinical perception [71]. The MCID is required for an appropriate appreciation of treatment effects. For example, the increase of muscle strength in a tetraplegic patient from 2.0 to 5.0 NM is most likely of greater clinical value than the recovery from 20 to 22 NM where the effects on ADLs are probably less important. Both changes might be significant in a group evaluation but likely have a different impact on the patient's condition.

12.6 Surrogates for the Description of Functional Impairment

Changes in sensory and motor function can be measured by different means such as clinical measures (measures of capacity and performance, described above, and quantitative sensory testing) as well as surrogates (electrophysiological and biomechanical recordings).

12.6.1 Electrophysiology

The electrophysiological measures consist of somatosensory evoked potential (SSEP), contact heat evoked potential (CHEP), motor evoked potential (MEP), nerve conduction study (NCS) response, and electromyogram (EMG) recordings, as outlined in Table 12.1.

Evoked potentials (EPs) and NCS recordings are electrical potentials retrieved from the nervous system following the stimulation of a sensory or motor nerve. EPs can represent conditions within the peripheral as well as central nervous system, while NCS specifically reflect the conditions of peripheral nerves where typical characteristics of electrical signal behavior (conduction velocity, latency, and amplitude) are used for diagnosis.

12.6.1.1 Somatosensory Evoked Potential (SSEP)

SSEPs are elicited by an electrical stimulus of a peripheral sensory or mixed nerve while the stimulus is applied on the skin and the evoked potentials are recorded from the patient's scalp. From the SSEP, the time that it takes for sensory nerve fibers to transmit a stimulus from the point of stimulation to sensory areas of the brain can be established. When the nerve pathway is damaged, the signals become slowed or abolished. During the course of rehabilitation, changes in latency or amplitudes can indicate changes of spinal cord and brain function.

12.6.1.2 Contact Heat Evoked Potential (CHEP)

Little is known about the differences between normal and pathogenic pain. The mechanism and genesis of pain in pathogenic conditions following a SCI can be studied using a CHEP stimulator. The stimulus is applied with a thermode on the skin to the thermal pain sensory receptors expressed by Aδ (delta) and C fibers. The heat pulses are delivered rapidly with adjustable peak temperatures to elicit the differentials warm/heat thresholds of the receptors. The resulting evoked potentials can be measured using scalp electrodes. CHEPs offer a useful tool in assessing the condition within spinothalamic pathways (thermal and nociceptive sensation) and their relation to pain.

12.6.1.3 Motor Evoked Potential (MEP)

MEPs are elicited by the direct stimulation of the exposed motor cortex (during surgery) or by the transcranial stimulation of the motor cortex. The stimulus generates a contraction of a contralateral muscle from which MEPs are recorded with surface electrodes. A transcranial electrical stimulation (TES) is applied through cutaneous electrodes, whereas a transcranial magnetic stimulation (TMS) is generated across a magnetic field. The main limitation of TES is the local discomfort of the electrical currents applied over the scalp. TMS offers a diagnostic and follow-up tool for neurological disorders where the impairment and eventual recovery of the corticospinal tracts is fundamental to the medical condition (for example spinal cord ischemia or trauma) and the evaluation of medical interventions.

12.6.1.4 Nerve Conduction Study (NCS)

In motor NCS, an electrical stimulus is elicited over a peripheral motor nerve and cup electrodes are used to record the electrical potential generated in the muscle supplied. In sensory NCS, the electrical stimulation is applied on a sensory peripheral nerve and electrical potentials are recorded from a sensory dermatome of the nerve, or vice versa. F-wave and H-reflex studies are part of NCSs and represent different reflex responses within peripheral nerves and spinal segments. Although NCSs are mainly used to diagnose peripheral nerve dysfunction (such as carpal tunnel and Guillain–Barré syndromes) and muscle disorders (such as muscle atrophy), they provide also useful information of spinal cord function, where specifically, the damage of alpha motor neurones (traumatic or nontraumatic) reveals an alteration of motor NCS (reduced or abolished CMAP) while sensory NCS remains normal.

12.6.1.5 Electromyography (EMG)

An EMG is a technique used to detect the electrical activity in muscles where changes in electrical potentials of muscle cells can be used for diagnostic purposes. In surface EMG, cup electrodes are used to record signals from superficial muscles, whereas in intramuscular EMG, needles are introduced into the muscle to receive the signals from deep muscles or localized muscle activity. Surface EMGs allow for a gross analysis of muscle activation, whereas needle EMGs enable to record from single muscle fiber. The goal of EMG is to diagnose neurological and muscular disorders.

12.6.2 Biomechanical (Kinetic, Kinematic) Measures

Changes in biomechanical parameters of the upper limb function, such as muscle activity, muscle strength, joint bending angles, range of motion, and movement trajectories can be measured with specific techniques, such as EMG, dynamometry, goniometry, optical, inertial, mechanical and magnetic 3D motion capture systems, and instrumented gloves, as outlined in Table 12.1.

12.6.2.1 Muscle Activity

The EMG techniques described above can also be used in biomechanics to measure muscular activity of the upper limb during movements, and thereby, evaluate the efficacy of new technology-based rehabilitation treatments.

12.6.2.2 Muscle Strength

Digital-palmar prehensile strength can be measured using a Jamar dynamometer, a vigorimeter (a manometer with tubing and rubber ball), or a classic manometer. The Jamar dynamometer displays a mass unit (kg or lb), whereas the manometers express a force unit (kp) or pressure unit (mmHg). As described by Fattal, Gansel finds that manometry provides a better sensibility and reproducibility, in comparison with the Jamar dynamometer, for muscle forces below 2.3 kg [15]. By contrast, thumb–index lateral prehensile strength can be measured using a Preston dynamometer (kgs or kg), a B and L pinch gauge dynamometer (N), or a pinch dynamometer (kg) [15]. The measured strength is not generated by a single muscle but rather by several muscles.

12.6.2.3 Angles, Range of Motion (ROM), and Trajectories

Upper limb static passive and active joint flexion as well as ROM can be measured using traditional goniometry. However, simultaneous recording of dynamic changes in joint bending angles and movement trajectories requires the use of motion capture systems or instrumented gloves. Upper limb movements can be tracked with optical (Vicon, CA, Qualisys AB, Sweden), inertial (Xsens, the Netherlands), electromechanical (Gypsy 7, Meta Motion, CA), and magnetic (Ascension Technology Corp., VT) 3D motion systems. Besides, instrumented gloves offer an easy-to-handle and low-cost solution for hand and finger motion tracking [72–75].

In the frame of instrumented gloves, a 3-axis accelerometer such as the one incorporated in the DG5 VHand 2.0 glove (DGTec Engineering Solutions, Italy) makes it possible to track movements in the x, y, z directions as well as pitch and roll, whereas a 3-axis gyroscope enables one to measure yaw, pitch, and roll. An optical tracking system like the one of the P5 Glove (Essential Reality LLC, NY) provides 6° of tracking (x, y, z, yaw, pitch, and roll) but presents the following disadvantage that the glove must always remain in the tracking field of the optical signal receiver device. Finger joint bending angles are monitored using sensors embedded in the gloves. A survey from Dipietro et al. [76] synthesizes the main gloves developed as far as now and the various sensing technologies that they integrate.

12.7 Discussion

Surrogate measurements are important to reveal changes in the neural and biomechanical conditions underlying the upper limb functional impairment. Thus, they make it possible to evaluate the efficacy of new technology-based therapies and surgical interventions. Furthermore, the motivation of the patient is an important factor during the rehabilitation process. Therefore, even small changes measured with surrogates can positively influence the patient's upper limb function. Nevertheless, it is important to keep in mind that surrogate measurements may correlate with clinically important changes in upper limb function that, however, needs to be confirmed by validation.

Conclusion

Therapy of the upper limb function in tetraplegics is of high clinical importance. For this reason, new technological training devices, such as robots, passive workstations, and FES systems are continuously being developed and improved. The clinical value of these devices can be evaluated and compared by determining whether patients manage to pass a clinically meaningful threshold using the hand function classification and SCIM III (Table 12.1; left section) while undergoing therapy. During the rehabilitation process, changes in the upper limb function and structure can be established with the ASIA classification (Table 12.1; middle section). The ASIA classification is an important tool that enables clinicians to make a precise neurological diagnosis of a spinal cord lesion. Nevertheless, changes measured with the ASIA scale will not necessarily be related to clinical relevant changes in the upper limb function. Traditional upper limb function capacity and performance tests are in general

subjective and somewhat imprecise given that they are mainly based on ordinal rating. A new generation of objective and precise tests that have been evaluated for reliability and validity is required. Clinical capacity measurements and surrogates (Table 12.1; right section) target very specific detailed functions and aspects of the upper limb. In a similar manner as for the ASIA classification, changes measured with capacity tests and surrogates do not necessarily correlate with clinically meaningful changes. Therefore, changes in level and function of upper limbs as detailed by the classification of hand function and SCIM III (Table 12.1; left section) describe clinically meaningful changes that may (or not) be related to changes in body function/structure and capacity measures/surrogates. By contrast, changes observed with the ASIA scale and in laboratory assessments need to be evaluated in combination with clinical measures to reveal clinically relevant changes.

The minimal clinically important difference (MCID) is defined as the smallest change in measurement that signifies an important improvement. Ideally, relevant levels of capacity measures and surrogates would be defined a priori (time to accomplish a task, muscle strength, finger joint ROM, muscular activity, NCS latency, and amplitude) that are considered to present changes in upper limb function either as beneficial or detrimental.

However, beyond clinical appreciation capacity measures and surrogates play additional important roles in the evaluation of upper limb function. In the absence of clinically meaningful changes, kinetics and kinematics (and other surrogates) can disclose even small changes that are still without obvious clinical effects but provide insight of activity-dependent changes and therefore can be important for the motivation of patients. They can be used to predict outcomes and in the condition where clinically relevant changes are not obvious still potential mechanisms might become disclosed that are missed by clinical means.

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Part V

Robotics for Lower Extremity (Locomotion): Technological Aspects

Technology of the Robotic Gait Orthosis Lokomat

13

Robert Riener

Abstract

Rehabilitation robots allow for a longer and more intensive locomotor training than that achieved by conventional therapies. Robot-assisted treadmill training also offers the ability to provide objective feedback within one training session and to monitor functional improvements over time. This article provides an overview of the technical approach for one of these systems known as "Lokomat" including new features such as hip ab/adduction actuation, cooperative control strategies, assessment tools, and augmented feedback. These special technical functions may be capable of further enhancing training quality, training intensity, and patient participation.

Keywords

Exoskeleton • Actuated gait orthosis • Gait rehabilitation • Cooperative control • Augmented feedback • Lokomat

13.1 Introduction

A major limitation of manual-assisted, body weight–supported treadmill therapy (BWSTT) is that a training session relies upon the ability and availability of physical therapists to appropriately assist the patient's leg movement through the gait cycle. Robotic devices can eliminate this problem through the use of a mechatronic system that automates the assistance of the leg movement [1, 2]. This article presents the technological steps in the evolution of the design and development of Lokomat, an internationally well-established robot for gait therapy.

Manually assisted BWSTT involves therapist assistance while the patient practices stepping movements on a motorized treadmill and with simultaneous unloading of a certain percentage of body weight. Manual assistance is provided as necessary (and as far as possible) to enable upright posture and to induce leg movements associated with adaptive physiological human gait. Over the last two decades, there has been growing evidence of support for the use of this technique in neurorehabilitation programs for stroke and SCI subjects.

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Whereas evidence demonstrates improvement in locomotor function following manually assisted treadmill training, its practical implementation in the clinical setting is limited by the labor-intensive nature of the method. Specifically, training sessions tend to be short because of the physical demands and time costs placed upon the therapists' resources. This resource constraint yields significant limitations upon access to the therapy and, ultimately, to the effectiveness of the therapeutic approach with patients. Particularly, in individuals with limb paralysis and/or a high degree of spasticity, appropriate manual assistance is difficult to provide; these patients require more than two therapists, which increases the already high cost and also limits training time [3]. The success and promise of BWSTT and the limitations and resource constraints in the therapeutic environment have inspired the design and development of robotic devices to assist the rehabilitation of ambulation in patients following stroke or SCI.

The research team of the Spinal Cord Injury Center of the University Hospital Balgrist in Zurich, Switzerland, an interdisciplinary group of physicians, therapists, and engineers, began to work on a driven gait orthosis in 1995 that would essentially replace the cumbersome and exhausting physical labor of therapists in the administration of locomotor training [1]. The "Lokomat" (commercially available from Hocoma AG, Volketswil, Switzerland) consists of a computer-controlled robotic exoskeleton that moves the legs of the patient in an adjustable conjunction with a body weight support system (Figs. 13.1 and 13.2). Later on, other exoskeletal systems were developed including the "Autoambulator" by Healthsouth Inc. (USA); the "Lopes" by the University of Twente, The Netherlands; [4] and the "ALEX" by the University of Delaware, USA [5].

An alternative to exoskeletal systems are end effector–based systems such as the commercially available Gait Trainer [2]. The Gait Trainer operates like a conventional elliptical trainer, where the subject's feet are strapped into two footplates, moving the feet along a trajectory that is similar to a gait trajectory. Another research group at the Los Amigos Research and Education Institute, Downey, California (USA), developed the "PAM" (pelvic assist manipulator), which is a device that assists the pelvic motion during human gait training on a treadmill, and "POGO" (pneumatically operated gait orthosis), which moves the patient's legs with linear actuators attached to a frame placed around the subject [6].

13.2 Orthosis Design

13.2.1 Mechanical Aspects

The Lokomat® is a bilaterally driven gait orthosis that is used in conjunction with a body weight support system [1]. The Lokomat moves the patient legs through the gait cycle in the sagittal plane (Fig. 13.1). The Lokomat's hip and knee joints are actuated by linear drives integrated into an exoskeletal structure. Passive foot lifters support ankle dorsiflexion during the swing phase. The leg motion can be controlled with highly repeatable predefined hip and knee joint trajectories on the basis of a conventional position control strategy. The orthosis is fixed to the rigid frame of the body weight support system via a parallelogram construction that allows passive vertical translations of the orthosis while keeping the orientation of the robotic pelvis segment constant. The patient is fixed to the orthosis with straps around the waist, thighs, and shanks.

The angular positions of each leg are measured by potentiometers attached to the lateral sides of the hip and knee joints of the orthosis. The hip and knee joint trajectories can be manually adjusted to the individual patient by changing amplitude and offsets. Knee and hip joint torques of the orthosis are measured by force sensors integrated into the orthosis in series with the linear drives. The signals may be used to determine the interaction torques between the patient and the device, which allows estimation of the voluntary muscle effort produced by the patient. This important information may be optimally used for various control strategies as well as for specific biofeedback and assessment functions.

The Lokomat geometry can be adjusted to the subject's individual anthropometry. The lengths of the thighs and shanks of the robot are adjustable via telescopic bars so that the orthosis may be used by subjects with different femur lengths ranging between 35 and 47 cm. A new Lokomat

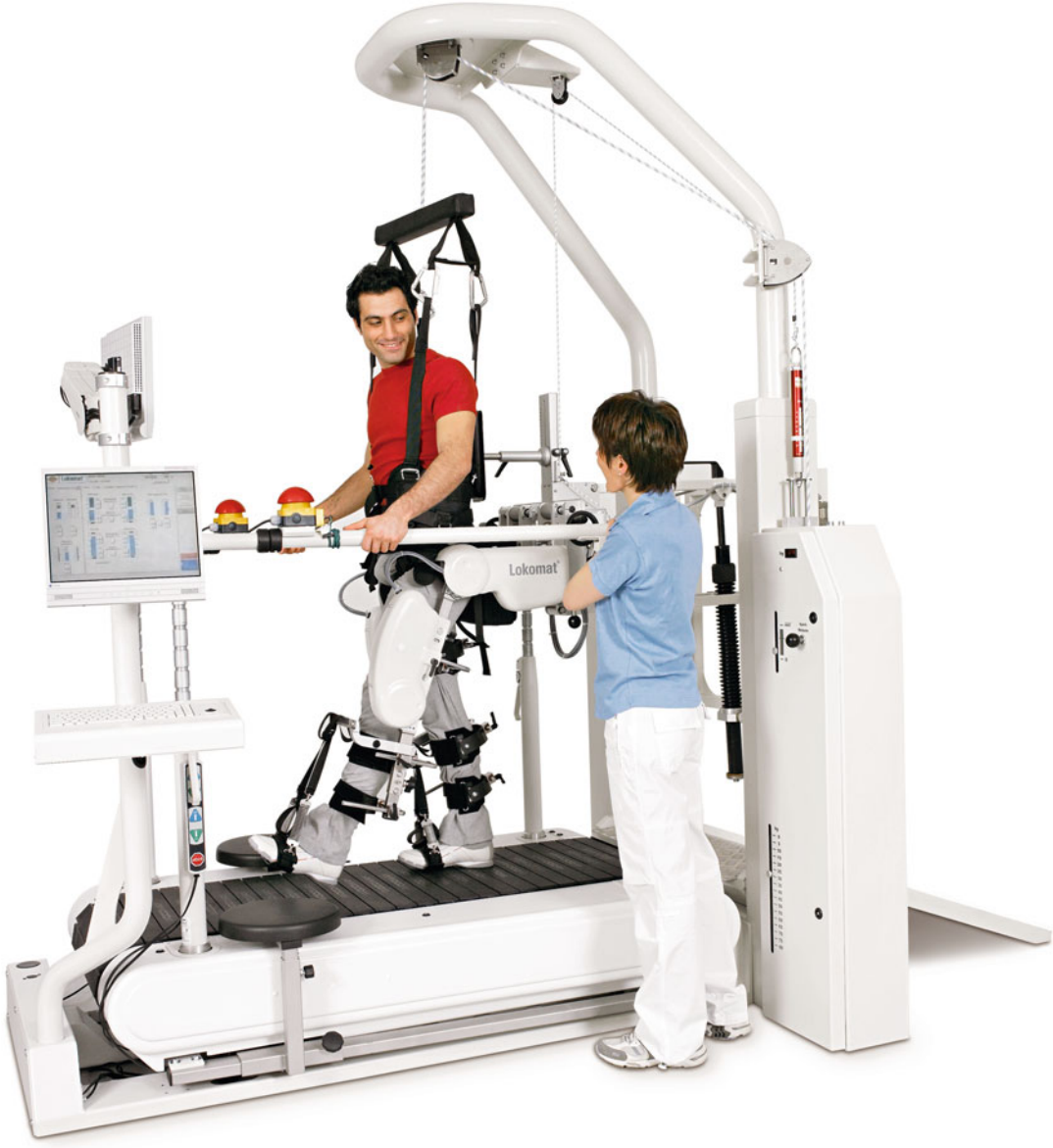

Fig. 13.1 Current (2007) version of the Lokomat system with a spinal cord–injured patient (Printed with permission of Hocoma AG, Volketswil)

was designed and developed in 2006 to accommodate pediatric patients with shorter femur lengths between 21 and 35 cm (equivalent to body heights between approximately 1.00 and 1.50 m). The width of the hip orthosis may also be adjusted by changing the distance between the two lower limbs. The fixation straps, available in different sizes, are used to safely and comfortably hold the patient's limb to the orthosis.

13.2.2 Drives

Ruthenberg and coworkers [7] reported the maximal hip torque during gait to be approximately 1 Nm per kilogram of body weight and an estimated average torque of approximately 35 Nm. In the Lokomat, hip and knee joints are actuated by custom-designed drives with a precision ball screw. The nut on the ball screw is driven by a

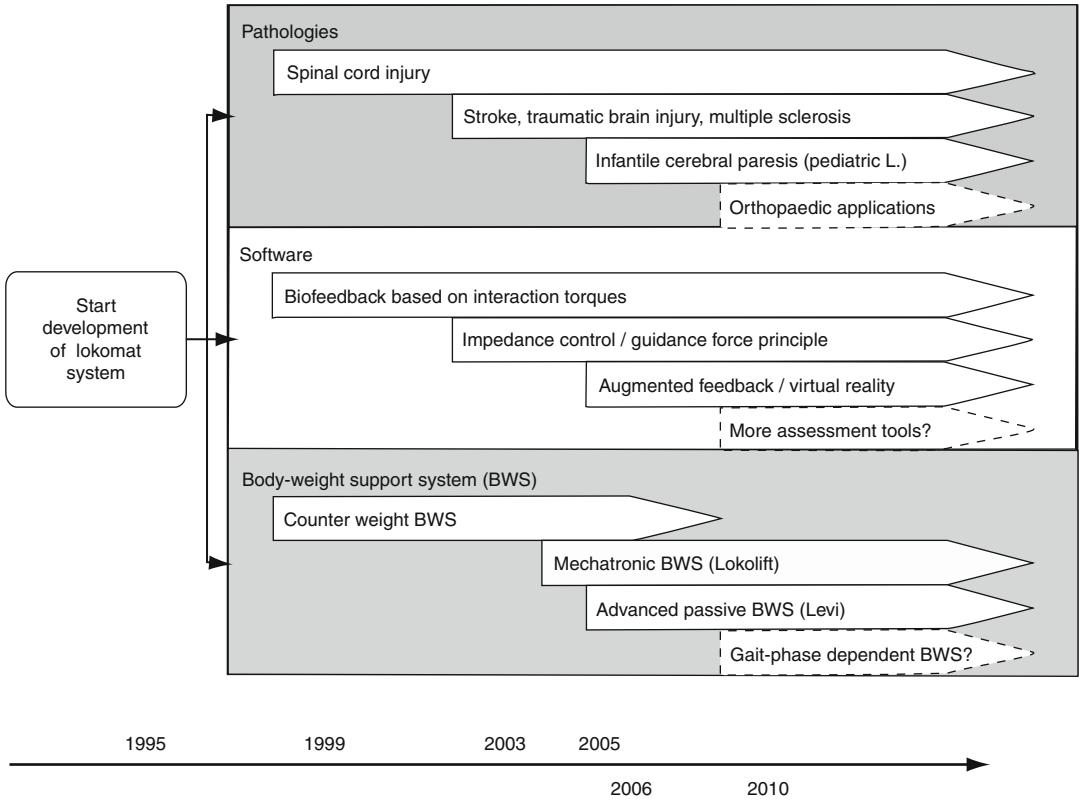

Fig. 13.2 Rough timeline and outlook of features of the Lokomat system (From: Riener et al. [31]. Used with permission)

toothed belt, which is in turn driven by a DC motor. The nominal mechanical power of the motors is 150 W. This yields an average torque of approximately 30 and 50 Nm at the knee and hip, respectively. Maximum peak torques are 120 and 200 Nm, respectively. This design has been demonstrated to be sufficient to move the legs against gravitational and inertial loads and, thus, to generate a functional gait pattern required in a clinical environment and suitable for most patients, even those with severe spasticity.

13.2.3 Safety

Whereas the mentioned peak torques are required in order to move the patient's joints in the presence of considerable interaction forces produced at the joints (e.g., due to spasticity) or between the patient's feet and treadmill (e.g., due to minor deviations of robot and treadmill speed), they can pose an inherent risk to the musculoskeletal system of the patient. In order to minimize this risk, various measures of safety were implemented into electronics, mechanics, and software. The electronic and mechanical safety measures follow principles of medical device safety regulations and standards (e.g., galvanic insulation). Additionally, passive back-drivability and mechanical endstops avoid incidents that human joints get overstressed or blocked in case of actuator malfunction. The software safety measures manage proper operation of the device through control of nominal ranges of force sensors and also through the use of redundant position sensors. Software also checks plausibility of movement and stops the device as soon as the movement deviates too much from the known desired gait trajectory. Another important safety feature is realized by the existence of the body weight support system, where the patient can

be brought to a safe situation, when all drives have to be deactivated, e.g., when stumbling, or if spasticity causes the interaction forces to exceed the given threshold values. A wireless sensor system tracks the therapist's presence and prompts input from the therapist in order to ensure therapist's attention and to improve patient safety. Furthermore, several manual emergency stops enable the therapist (or patient) to cause a sudden stop of the movement whenever desired.

13.3 Body Weight Support System

Body weight support systems enable patients with leg paresis to participate in functional gait therapy, both on the treadmill and in overground walking [8]. A simple system consists of a harness worn by the patient, ropes and pulleys, and a counterweight used to partially unload the patient. However, these simple systems do not ideally accommodate the wide range of conditions a patient with sensorimotor deficits will encounter in gait therapy. The supporting vertical force varies mainly because of the effect of inertia that is induced by the vertical movement components performed during gait [9]. A mechatronic body weight support system called "Lokolift" has been developed to allow a more precise unloading during treadmill walking. The Lokolift combines the key principles of both passive elastic and active dynamic systems [9]. In this system, at unloading levels of up to 60 kg and walking speeds of up to 3.2 km/h, the mean unloading error was less than 1 kg and the maximum unloading error was less than 3 kg. This new system can perform changes of up to 20 kg in desired unloading within less than 100 ms. With this innovative feature, not only constant body weight support but also gait cycle–dependent or time variant changes of the desired force can be realized with a high degree of accuracy. More recently, a spring-based (passive) system has been developed that allows similar results like the Lokolift system [10]. A chronological overview of the different developmental stages of the Lokomat system is given in Fig. 13.2.

13.4 Control Strategies

In early clinical applications, the Lokomat was only used in a position control mode, where the measured hip and knee joint angles are fed into a conventional PD controller. In the position control mode, the Lokomat does not systematically allow for deviation from the predefined gait pattern. However, rigid execution and repetition of the same pattern is not optimal for learning. In contrast, variability and the possibility to make errors are considered as essential components of practice for motor learning. Bernstein's demand that training should be "repetition without repetition" [11] is considered to be a crucial requirement and is also supported by recent advances in computational models describing motor learning [12]. More specifically, a recent study by Lewek et al. [13] demonstrated that intralimb coordination after stroke was improved by manual training, which enabled kinematic variability, but was not improved by position-controlled Lokomat training, which reduced kinematic variability to a minimum.

In response to this important finding, "patient-cooperative" control strategies were developed that "recognize" the patient's movement intention and motor abilities by monitoring muscular efforts and adapt the robotic assistance to the patient's contribution, thus giving the patient more movement freedom and variability than during position control [14, 15]. It is recommended that the control and feedback strategies should do the same as a qualified human therapist, i.e., they assist the patient's movement only as much as needed and inform the patient how to optimize voluntary muscle efforts and coordination in order to achieve and improve a particular movement.

The first step to allow a variable deviation from a predefined leg trajectory, thus giving the patient more freedom, can be achieved by an impedance control strategy. The deviation depends on the patient's effort and behavior. An adjustable torque is applied at each joint depending on the deviation of the current joint position from the trajectory. This torque is usually defined as a zero order (stiffness) or higher order (usually

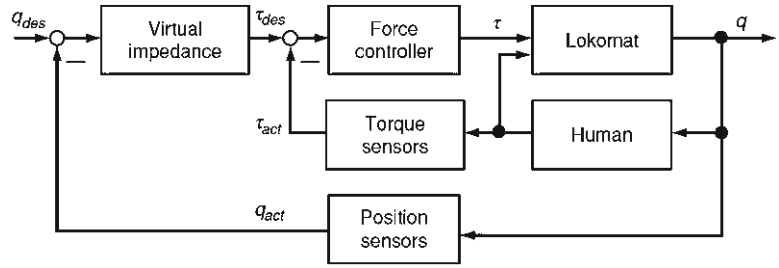

Fig. 13.3 Example of an impedance control architecture for the compliance of rehabilitation robot [14]. Symbols: q is the vector of generalized positions or joint angles; τ is the vector of generalized joint torques; index "*des*" refers to the desired reference signal; index "*act*" refers to the actual, measured signal (From: Riener et al. [31]. Used with permission)

first or second order) function of angular position and its derivatives. This torque is more generally called mechanical impedance [16]. Figure 13.3 [14] depicts a block diagram of an impedance controller.

The impedance controller was initially tested in several subjects without neurological disorders and several subjects with incomplete paraplegia [14]. In the impedance control mode, angular deviations increased with increasing robot compliance (decreasing impedance) as the robot applied a smaller amount of force to guide the human legs along a given trajectory. Inappropriate muscle activation produced by high muscle tone, spasms, or reflexes can affect the movement and may yield a physiologically incorrect gait pattern, depending on the magnitude of the impedance chosen. In contrast, subjects with minor to moderate motor deficits stated that the gentle behavior of the robot feels good and comfortable.

The disadvantage of a standard impedance controller is that the patient needs sufficient voluntary effort to move along a physiologically correct trajectory, which limits the range of application to patients with only mild lesions. Furthermore, the underlying gait trajectory allows no flexibility in time, i.e., leg position can deviate only orthogonally but not tangentially to the given trajectory. Therefore, the impedance controller has been extended to a so-called path controller [15], in which the time-dependent walking trajectories are converted to walking paths with free timing. Furthermore, the impedance along the path can vary in order to obtain satisfactory movement especially at critical phases of gait (e.g., before heel contact) [15]. This is comparable to fixing the patient's feet to soft rails, thus limiting the accessible domain of foot positions calculated as functions of hip and knee angles. Along these "virtual rails," the patients are free to move. Supplementary to these *corrective* actions of the Lokomat, a *supportive* force field of adjustable magnitude can be added. Depending on the actual position of the patient's legs, the supportive force act in the direction of the desired path. The support is derived from the desired angular velocities of the predefined trajectory at the current path location. Supportive forces make it possible to move along the path with reduced effort. Compared to the impedance controller, the path controller gives the patient more freedom in timing while he or she can still be guided through critical phases of the gait.

13.5 Additional Hip and Pelvis Actuation

The original Lokomat version restricts the gait pattern to a two-dimensional trajectory in the sagittal plane of the human body. This lack of lateral movement leads to a reduced weight shifting and, thus, to a lower load transfer between treadmill and supporting leg. It is assumed that this has a negative effect on the balance training and the excitation of the cutaneous, muscular, and joint receptors. Therefore, the Lokomat version installed at the Balgrist University Hospital has been extended by three additional actuated degrees of freedom. Two

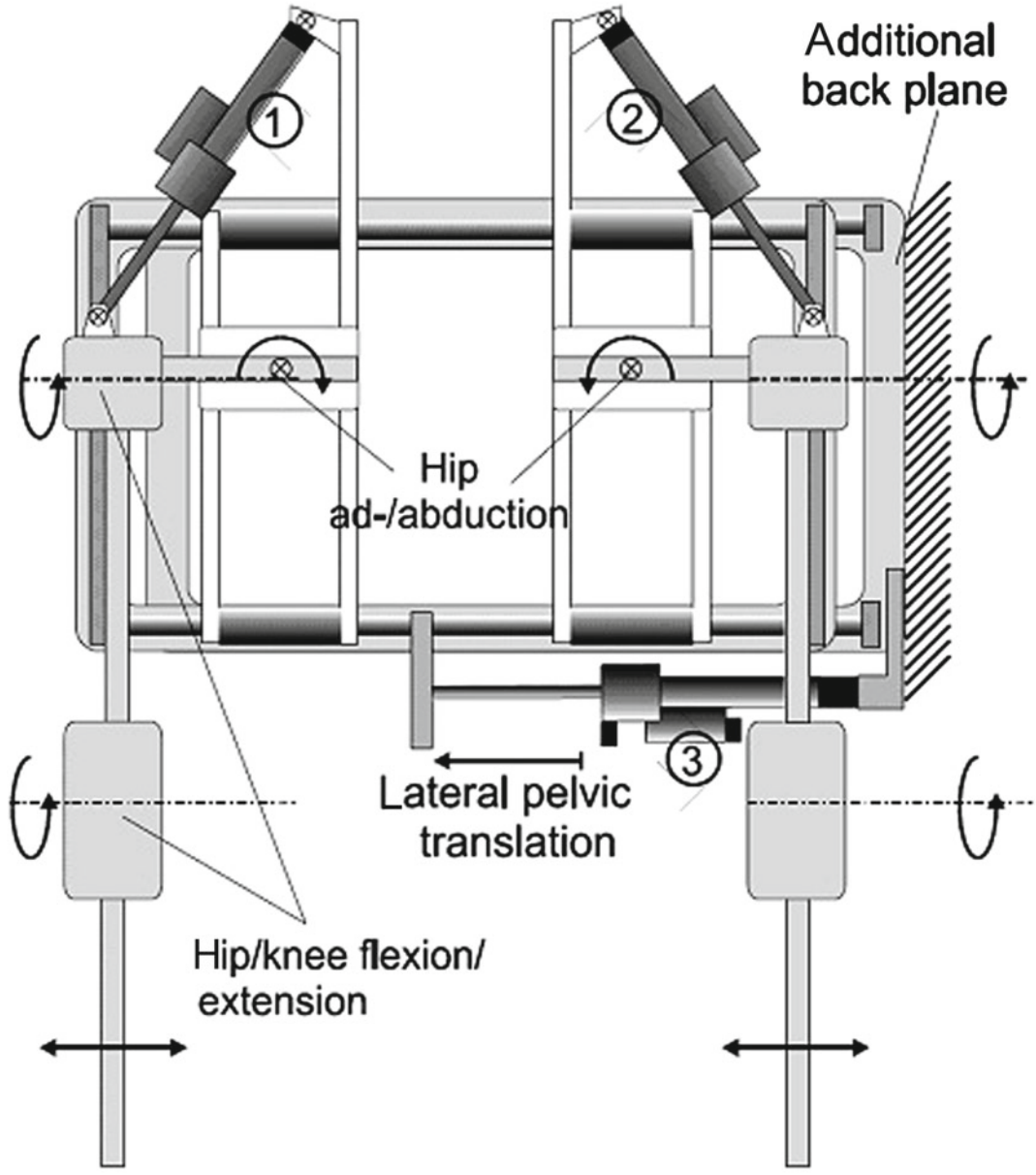

Fig. 13.4 Sketch of the front view of the extended Lokomat hardware

degrees of freedom perform hip ad/abduction, and 1° of freedom enables the Lokomat to accomplish a lateral pelvis displacement movement (Fig. 13.4). Three linear actuators have been added to drive the ad/abduction (No. 1 and 2 in Fig. 13.4) and the lateral pelvis displacement (No. 3). The linear drives are equipped with redundant position sensors as well as force sensors.

Several control strategies have been implemented and tested with the new hip–pelvis actuation. First, the new degrees of freedom have been position-controlled. For this purpose, gait trajectories of healthy subjects have been recorded, which then served as the desired trajectories for the PD position controllers. Later, a controller was developed that is able to emulate the viscoelastic

properties of passive spring–damper elements. The integrated force sensors allow measuring the interaction forces between the patient and the Lokomat so that an impedance controller could be implemented. The interaction force has been controlled by a proportional force controller with feed-forward of the desired force value in order to display the virtual spring–damper element to the patient. The desired value depends on the angular velocity of the joint and the deviation from the desired angular position. In the meantime, further controllers have been derived that are based on the path controller that is performing the knee and hip joint movements in the sagittal plane.

This extended Lokomat version has been tested with several healthy subjects. All subjects agreed that gait training with lateral pelvis displacement and ad/abduction feels more physiological and comfortable than without. The optimal amplitudes of lateral pelvis displacement and ad/abduction are not only dependent on the subjects' heights but also differ due to individual walking behaviors. Therefore, the amplitudes of the new degrees of freedom were chosen to be adjustable.

13.6 Assessment Tools

Using robotic devices in locomotor training can have more advantages than just supporting the movement and, thus, increasing the intensity of training. Data recorded by the position and force transducers can also be used to assess the clinical state of the patients throughout the therapy. The following clinical measures can be assessed by the Lokomat.

13.6.1 Mechanical Stiffness

Spasticity is an alteration in muscle activation with increased tone and reflexes. It is a common side effect of neurological disorders and injuries affecting the upper motor neuron, e.g., after brain or spinal cord injuries. Formally, spasticity is usually considered as "a motor disorder characterized by a velocity-dependent increase of tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexitability of stretch reflexes" [17]. It appears as an increased joint resistance during passive movements. Recently, Sanger et al. [18] introduced a more functional rather than physiological definition describing spasticity as "a velocity-dependent resistance of a muscle to stretch." Most commonly, spasticity is evaluated by the Ashworth Test [19] or Modified Ashworth Test [20]. In both tests, an examiner moves the limb of the patients while the patient tries to remain passive. The examiner rates the encountered mechanical resistance to passive movement on a scale between 0 and 4. However, such an evaluation is subject to variable factors, such as the speed of the movement applied during the examination and the experience of the examiner and interrater variability.

The mechanical resistance can also be measured with the Lokomat [21, 22], which is capable of simultaneously recording joint movement and torques. The actuation principle allows for assessment of the hip and knee flexion and extension movements in the sagittal plane. The stiffness measurement can be performed immediately before and following the usual robotic movement training without changing the setup. To measure the mechanical stiffness with the Lokomat, the subject is lifted from the treadmill by the attached body weight support system so that the feet can move freely without touching the ground. The Lokomat then performs controlled flexion and extension movements of each of the four actuated joints subsequently at different velocities. The joint angular trajectories are squared sinusoidal functions of time replicating the movements applied by an examiner performing a manual Ashworth Test. Measured joint torques and joint angles are used to calculate the elastic stiffness as slopes of the linear regression of the torque–position plots. As the recorded torques also include passive physical effects of the Lokomat and the human leg, the measured torque is offline-compensated for inertial, gravitational, Coriolis, and frictional effects obtained from an identified segmental model of the orthosis including the human leg. Patient data comparisons with manual assessments of spasticity based on the Modified Ashworth Scale demonstrated that higher stiffness

values measured by Lokomat corresponded with higher ratings of spasticity [21, 22]. Assessment of spasticity is still in an experimental status and needs further validation in future studies.

13.6.2 Voluntary Force

For some patients, maximum voluntary force is a measure of limiting factor for walking. In order to assess the maximum voluntary force in the Lokomat [21], the examiner instructs the patient to generate force in each joint, first in flexion and then in extension directions. The force is generated against the Lokomat, which is position-controlled to a predefined static posture, thus providing a quasi-isometric measurement condition. Simultaneously, the joint moments are measured by the built-in force transducers and displayed to the patient and the therapist. The maximum moments for flexion and extension are used as outcome variables. An improved version standardizes the computerized sequence and instructions and uses a time-windowed calculation for the output values [23]. It was shown that this measurement method has a high inter- and intratester reliability and can be used to assess the strength of the lower extremities [23].

13.6.3 Range of Motion

In a manner similar to conventional clinical range of motion assessments, the therapist moves the leg of the patient until the passive torque produced by the patient's joint reaches a certain threshold that is qualitatively predefined by the therapist based on his or her expertise. As the patient's legs are attached to the device with the anatomical and technical joint axes in alignment with each other, and the recorded joint angles correspond with the patient's joint angles, the passive range of motion is determined by the maximum and minimum joint angles measured. This parameter can be used for further assessments and training. The Lokomat measures the joint range of motion within values typical for human gait and may represent only a fraction of the patient's physiological range. This test provides important additional measures of the patient relevant to the gait and further conditions making contractures and other joint limitations (e.g., due to shortened tendons) quantifiable. These measures are directly relevant to activities of daily living.

13.7 Biofeedback

Compared to manual treadmill therapy, robotic gait retraining changes the nature of the physical interaction between the therapist and the patient. Therefore, it is important to incorporate the features into the Lokomat system to assess the patient's contribution and performance during training and to provide necessary real-time feedback and instructions derived from precise measurements taken by the system. The patient may have deficits in sensory perception and cognition interfering with his/her ability to objectively assess movement performance and making it difficult to engage the patient and to encourage active participation in the movement and training. With the new feature of Lokomat, the technology of biofeedback has a potential to challenge and engage the patient in order to increase the benefit on motor recovery and neurological rehabilitation [24, 25].

The built-in force transducers can estimate the muscular efforts contributed by the patient's knee and hip joints. Incorporating this information into an audiovisual display can simulate the "feedback" the therapist usually gives to the patient during manual training, where the therapist estimates the patient's activity based on the effort required to guide the patient's legs.

The goal of the biofeedback function is to derive and display performance values that quantify the patient's activity in relation to the target gait function such that the patient can improve muscle activity toward a more functional gait pattern. An early implementation of a force-biofeedback strategy for the Lokomat has been described [14, 26, 27].

In order to obtain relevant biofeedback values, the gait cycle is divided into stance phase and swing phase. For each phase, weighted averages

Fig. 13.5 Walking through a virtual environment. Lokomat in combination with a virtual reality back-projection display system (From: Riener et al. [31]. Used with permission)

of the forces are calculated at each joint independently, thus yielding two values per stride per joint. Eight biofeedback values are available for each gait cycle from all four joints of the two lower limbs. Because of the bilateral symmetry, four weighting functions are required for the averaging procedure (hip stance, hip swing, knee stance, knee swing). The weighting functions were selected heuristically to provide positive biofeedback values when the patient performs therapeutically reasonable activities (e.g., active weight bearing during stance, sufficient foot clearance during swing, active hip flexion during swing, active knee flexion during early swing, knee extension during late swing). The graphical display of these values has been positively rated by the patients and leads to an increased instantaneous activity by the patients [28, 29]. However, there is no direct clinical evidence showing that this training with computerized feedback leads to better rehabilitation outcomes or faster recovery compared to Lokomat training without feedback.

To further increase patient's engagement and motivation, virtual reality and computer game techniques may be used to provide virtual environments that encourage active participation during training (Fig. 13.5). A first feasibility study showed

that the majority of subjects could navigate through a virtual environment by appropriately controlling and increasing their activity of left and right legs while walking through a virtual underground scenario [30].

Conclusion

Robotic rehabilitation devices such as the Lokomat become increasingly important and popular in clinical and rehabilitation environments to facilitate prolonged duration of training, increased number of repetitions of movements, improved patient safety, and less strenuous operation by therapists. Novel sensor, display and control technologies improved the function, usability, and accessibility of the robots, thus, increasing patient participation and improving performance. Improved and standardized assessment tools provided by the robotic system can be an important prerequisite for the intra- and intersubject comparison that the researcher and the therapist require to evaluate the rehabilitation process of individual patients and entire patient groups. Furthermore, rehabilitation robots offer an open platform for the implementation of advanced technologies, which will provide new forms of training for patients with movement disorders. With the use of different cooperative control strategies and particular virtual reality technologies, patients can be encouraged not only to increase engagement during walking training but also to improve motivation to participate therapy sessions.

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Beyond Human or Robot Administered Treadmill Training

14

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Abstract

The demand for rehabilitation services is growing apace with the graying of the population. This situation creates both a need and an opportunity to deploy technologies such as rehabilitation robotics, and in the last decade and half, several research groups have deployed variations of this technology. Results so far are mixed with the available evidence demonstrating unequivocally that some forms of robotic therapy can be highly effective, even for patients many years post-stroke, while other forms of robotic therapy have been singularly ineffective. The contrast is starkest when we contrast upper-extremity and lower-extremity therapy. In fact, 2010 Stroke Care Guidelines of the American Heart Association and of the Veterans Administration/Department of Defense (VA/DoD) endorsed the use of the rehabilitation robotics for upper-extremity post-stroke care but concluded that lower-extremity robotic therapy is much less effective and declared

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"still in its infancy." We submit that the contrasting effectiveness of upper- and lower-extremity therapies arises from neural factors, not technological factors. Though, no doubt, it might be improved, the technology deployed to date for locomotor therapy is elegant and sophisticated. Unfortunately, it may be misguided, providing highly repeatable control of movement but ultimately doing the wrong thing. The technology we have deployed to date for upper-extremity therapy is firmly based on an understanding of how upper-extremity behavior is neurally controlled and derived from decades of neuroscience research. The limitations of lower-extremity robotic therapy lie not in the robotic technology but in its incompatibility with human motor neuroscience. In this chapter, we briefly review the evidence supporting such negative views, and based on our experience with upper-extremity robotic therapy, we describe what we are presently investigating to revert and work toward a future endorsement of the American Heart Association and VA/DoD for rehabilitation robotics for lower-extremity post-stroke care.

Keywords
Stroke • Lower extremity • Gait • Rehabilitation Robotics • Anklebot • MIT-Skywalker

14.1 Introduction

Rehabilitation of human motor function is an issue of the utmost significance, and the demand is increasing due to a growing elderly population and the incidence of age-related disorders. Robot-aided therapy has been developed as a promising method to meet the enormous demand for effective rehabilitation services; robots are able to support the labor-intensive tasks of therapists and provide more frequent therapy. In addition, direct interaction with a robotic device enables quantitative measurement of human performance, which is essential for systematic training. However, while upper-extremity robotic therapy has proven effective and is now recommended by the American Heart Association and by the Veterans Administration/Department of Defense (VA/DoD), lower-extremity robotic therapy is much less effective and was declared "still in its infancy" [1].

To be more specific, the American Heart Association (AHA) 2010 guidelines for stroke care recommended that: "Robot-assisted therapy offers the amount of motor practice needed to relearn motor skills with less therapist assistance. Most robots for motor rehabilitation not only allow for robot assistance in movement initiation and guidance but also provide accurate feedback; some robots additionally provide movement resistance. Most trials of robot-assisted motor rehabilitation concern the upper extremity (UE), with robotics for the lower extremity (LE) still in its infancy . . . Robot-assisted UE therapy, however, can improve motor function during the inpatient period after stroke." AHA suggested that robot-assisted therapy for the UE has already achieved Class I, Level of Evidence A for Stroke Care in the Outpatient Setting and Care in Chronic Care Settings. For stroke care in the inpatient setting, it suggested that robot-assisted therapy for UE has achieved Class IIa, Level of Evidence A. Class I is defined as "Benefit >>> Risk. Procedure/Treatment SHOULD be performed/administered;" Class IIa is defined as "Benefit >> Risk, IT IS REASONABLE to perform procedure/administer treatment;" Level A is defined as "Multiple populations evaluated: Data derived from multiple randomized clinical trials or meta-analysis" [1].

The 2010 Veterans Administration/Department of Defense guidelines for stroke care came to the same conclusion endorsing the use of rehabilitation robots for the upper extremity, but going further and recommending against the use of robotics for the lower extremity. More specifically, the VA/DoD 2010 guidelines for stroke care "recommend robot-assisted movement therapy as an adjunct to conventional therapy in patients with deficits in arm function to improve motor skill at the joints trained." For the lower extremity, the VA/DoD states that "There is no sufficient evidence supporting use of robotic devices during gait training in patients post-stroke." The VA/DoD suggested that robot-assisted therapy for the UE has already achieved rating level B: "A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm." For the lower extremity, the VA/DoD suggested against robot-assisted therapy for the LE: "Recommendation is made against routinely providing the intervention to asymptomatic patients. At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits" [1].

This negative perception of LE robotic rehabilitation is not without merit. For example, large studies employing the Lokomat (Hocoma, Zurich, Switzerland) showed statistically significantly inferior results when compared to those produced by usual care for both chronic as well as for subacute stroke patients [2, 3]. Figure 14.1 shows the results of two studies comparing LE rehabilitation robotics with usual care.

The middle row shows results with chronic stroke patients (stroke onset >6 months), who trained three times per week for 30 min for 4 weeks, demonstrating improvements for the Lokomat-trained (white bars) and the usual-care group (black bars). The usual-care group improved significantly more than the Lokomat-trained group and retained that advantage at 6 months follow-up. This was true for both severely as well as moderately impaired patients [2]. For subacute stroke patients (stroke onset<6 months) who trained for 8 weeks, a qualitatively similar result was observed. Both groups improved from admission to midpoint, to completion, and to 3 months follow-up, but patients in the usual-care group improved more, and the difference between groups was statistically significant.

There are many plausible reasons for these results and the apparent immaturity of lower-extremity robotic therapy. First, the technologists assumed that body-weight-supported treadmill training delivered by two or three therapists was an effective form of therapy. Their devices are elegant engineering solutions aiming to automate this labor intensive and demanding form of therapy, which is based on the conjecture that by "strengthening" spinal cord central pattern generators, gait in stroke patients might be enhanced [4]. However, a recent NIH-sponsored randomized controlled study (RCT) demonstrated that contrary to the hypothesis of its clinical proponents, body-weight-supported treadmill training administered by two or three therapists for 20–30 min followed by 20–30 min of overground carry-over training did not lead to superior results when compared to a home program of strength training and balance (LEAPS Study [5]). This is a landmark result that must be seriously acknowledged by roboticists: The goal of rehabilitation robotics is to optimize care and augment the potential of individual recovery. It is not to automatize current rehabilitation practices, which for the most part lack scientific evidential basis, primarily due to the lack of tools to properly assess the practices themselves.

To move LE robotics beyond its infancy, we must determine what constitutes best practice. Alternatives must be carefully examined. We have been exploring two alternatives, namely:

(a) Whether therapeutic LE robots should aim at reproducing kinematic features of walking. Lower-limb devices like the Lokomat (Hocoma) or Autoambulator (Healthsouth/Motorika) constrain natural motion and impose nominal kinematics of healthy subject's gait. Merely tracking the kinematic patterns of leg motion may compromise the role of interaction between the neuromuscular periphery and gravito-inertial mechanics. Numerous studies in neuroscience and robotics suggest that human locomotion may emerge from nonlinear

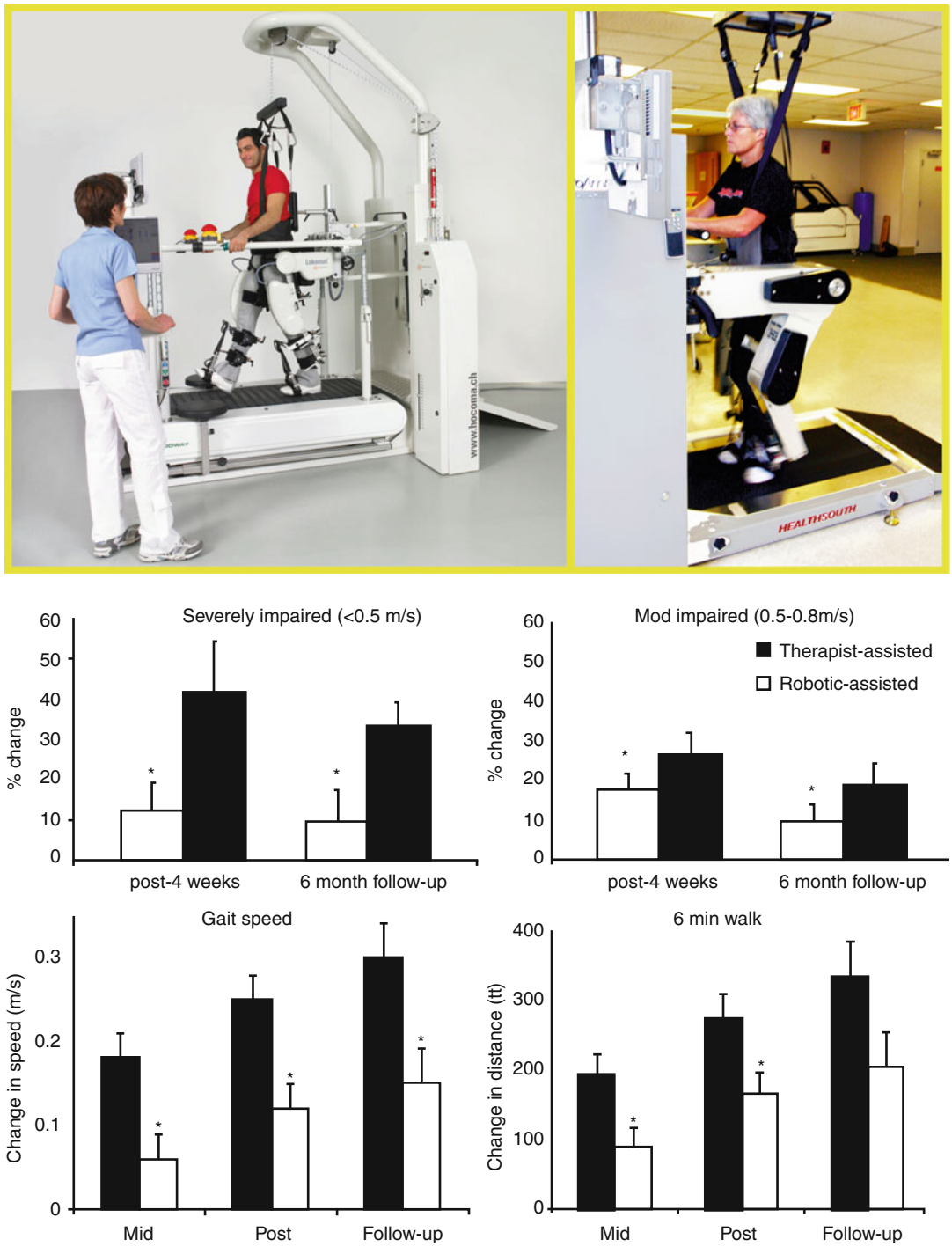

Fig. 14.1 Replicating healthy subject's kinematics: Lokomat (Courtesy Hocoma), Autoambulator (Courtesy Braintree Rehabilitation Hospital), and clinical results of robotic therapy in stroke using Lokomat (Courtesy T.G. Hornby). *Top row* shows on the *left* the Lokomat and on the *right* the Autoambulator. *Middle row* shows the results with chronic stroke (enrollment >6 months post-stroke) and the *bottom row* shows results of subacute stroke trials (enrollment between 3 and 6 months post-stroke)

dynamic interactions between neural circuits and limb mechanics. If so, current therapeutic robots disrupt the natural rhythmic dynamics of the neuromechanical system by imposing "pre-planned" kinematics and may inadvertently interfere with the natural neural control of walking.

(b) Whether therapeutic LE robots should aim at engaging neural circuitry at the spinal level. Animal studies (especially those demonstrating "fictive locomotion") indicate that neural circuits in the lower central nervous system and spinal cord generate rhythmic patterns appropriate for locomotion, the so-called central pattern generators (CPGs). However, it remains unclear whether CPGs play an essential role in human locomotion. Hence, it is unclear whether engaging these central pattern generators is sufficient for effective therapy, or if we should instead explicitly engage the supraspinal network, much like we do for upper-extremity robotic therapy and usual-care gait training approaches.

This chapter will review two of our robotic devices, Anklebot and MIT-Skywalker, both specifically designed to depart from existing LE robotic therapy, and some of the initial results obtained from investigating what may constitute best practice.

14.2 Anklebot

We focused our initial LE development efforts on the ankle because it is critical for propulsion and balance during walking. Following stroke, "drop foot" is a common impairment. It is caused by a weakness in the dorsiflexor muscles that lift the foot. Two major complications of drop foot are "slapping" of the foot after heel strike in the early stance (foot slap) and dragging of the toe during swing, making it difficult to clear the ground (toe swing). In addition to inadequate dorsiflexion ("toe up"), the paretic ankle also suffers from excessive inversion (sole toward midline). Both begin in the swing phase and result in toe contact (as opposed to heel contact) and lateral instability during stance. Lack of proper control during these phases increases the likelihood of trips and falls. In fact, deficits of propulsion and balance contribute to more than 70% of stroke survivors sustaining a fall within 6 months [6], leading to higher risks for hip and wrist fractures in the first year [7–9]. The ankle is also the largest source of mechanical power during terminal stance [10]. The plantarflexors contribute as much as 50% of positive mechanical work in a single stride to enable forward propulsion [11–14]. In preswing, plantarflexors also act to advance the leg into swing phase while promoting knee flexion at toe-off [15]. Additionally, the ankle helps maintain body-weight support during gait [16–18] and balance. In summary, given its importance in over-ground propulsion and balance, we elected to focus first on the ankle. The Anklebot has the potential to address both propulsion and balance problems since it is actuated in both the sagittal and frontal planes [19].

14.3 Background

Conventional assistive technology for drop foot includes a mechanical "rigid" brace called an ankle–foot orthosis (AFO) [20]. Recently, there has been considerable work developing "smart" AFOs with mechanical stiffness tailored to the particular patient's size, weight, and needs. This passive solution is capable of storing some energy and restoring it when appropriate [16]. Although these AFOs offer biomechanical benefits, they have disadvantages that can be improved on [19]. Improvements in assistive technology include computerized functional electrical stimulation (e.g., WalkAide, Innovative Neutronics, Inc., Austin, TX; L300™, Bioness, Inc., Valencia, CA) and implantable microstimulators (BIONs) to stimulate the deep peroneal nerve and tibialis anterior muscle in order to flex the ankle during swing.

Recent advances in therapeutic robotics have led to several devices specific to the lower extremity (LE), including those for ankle rehabilitation [21–23]. These include the active ankle–foot orthosis (AAFO), a novel actuated ankle system placed in parallel with a human ankle that allows dorsi-plantarflexion. The AAFO consists of a

series elastic actuator attached posterior to a conventional AFO and a motor system that modulates the orthotic joint impedance based on position and force sensory information [21]. Anderson and Sinkjaer [24] developed an ankle joint perturbation device that imposes ankle joint rotation to stretch ankle extensors. It provides dorsiflexion but not plantarflexion during gait, and its backdriveability is limited. Another perturbation device has been developed by Zhang [25]. It stretches the ankle throughout its range of motion (ROM) to evaluate joint stiffness. The "Rutgers Ankle" Orthopedic Rehabilitation Interface is another ankle rehabilitation device [23]. It is a Stewart platform haptic interface and consists of a computer-controlled robotic platform that measures foot position and orientation. The system uses double-acting pneumatic cylinders, linear potentiometers, and a six-degrees-of-freedom force sensor. It provides resistive forces and torques on the patient's foot in response to virtual reality-based exercises. Ferris and colleagues have similarly developed an AFO for the human ankle joint that is powered by artificial pneumatic muscles. That device is able to provide 50% of the peak plantarflexor net muscle moment and about 400% of the peak dorsiflexor net muscle moment during unassisted walking [11]. Finally, Bharadwaj and colleagues developed a robotic gait trainer (RGT) [26]. It employs rubber "muscle" actuators and has a tripod layout similar to MIT's Anklebot [19]. However, contrary to MIT's Anklebot, the RGT has a limited range of motion in both the sagittal and frontal planes (23° in dorsi-plantarflexion and 5° in inversion–eversion). It is also severely limited by its low maximum operating frequency of 0.5 Hz. The average dorsi-plantarflexion and inversion–eversion of the ankle during toe-off is around 26° (max 41°) and 15° (max 25°) [15]. The frequency content of human foot–floor interaction forces can reach 15 Hz or more [27]. Furthermore, accurate control of impedance appears to be a clinically important feature, particularly during gait. While the RGT can produce different impedances, it cannot achieve controllable impedance since any stiffness variation must be always accompanied by a change of force and/or equilibrium, which is not a limitation of the Anklebot. The RGT has no provision to control other important aspects of impedance. For example, there is no way to control the amount of energy that is *dissipated* during a specified motion. This might be especially important during gait, for example, to prevent the foot from slapping following heel strike.

The design, characterization, donning procedure, and safety features of the adult version of the Anklebot have been previously described [19]. We briefly summarize its salient design features and measurement capabilities. It is a portable wearable exoskeletal ankle robot that allows normal range of motion in all three degrees of freedom of the ankle and shank during walking overground, on a treadmill, or while sitting (25° of dorsiflexion, 45° of plantarflexion, 25° of inversion, 20° of eversion, and 15° of internal or external rotation – Fig. 14.1a), but provides independent assistance or resistance in two of those degrees of freedom (dorsi-plantarflexion and eversion–inversion) via two linear actuators mounted in parallel. Anatomically, internal–external rotation is limited at the ankle, the orientation of the foot in the transverse plane being controlled primarily by rotation of the leg at the hip [15]. Underactuation, i.e., actuating fewer degrees of freedom than are anatomically present, affords on key advantage: It allows the device to be installed without requiring precise alignment with the patient's joint axes (ankle and subtalar joints). This is actually an important characteristic of all our robotic devices. In this configuration, if both actuators push or pull in the same direction, a dorsi-plantarflexion torque is produced. Similarly, if the two links push or pull in opposite directions, inversion–eversion torque results.

The Anklebot is a backdriveable robot with low intrinsic mechanical impedance, weighs less than 3.6 kg, and can deliver a continuous net torque of approximately 23 Nm in dorsi-plantarflexion and 15 Nm in eversion–inversion. The robot can estimate ankle angles with an error less than 1° in both planes of movement (maximum 1.5°) over a wide range of movement (60° in dorsi-plantarflexion and 40° in eversion–inversion) and can measure ankle torques with an error less than 1 Nm. It has low friction (0.74 Nm) and inertia (0.8 kg per actuator for a total of 1.6 kg at the foot) to

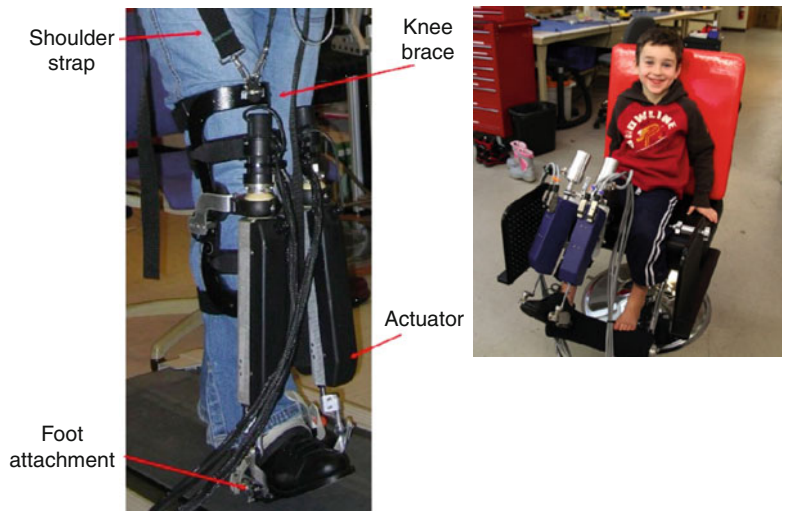

Fig. 14.2 Adult and pediatric Anklebots. *Left photo* shows the adult Anklebot and on the right the pediatric version (ages 5–8 years old). The devices have 3 degrees of freedom (*DOF*) with active dorsi-plantaflexion and inversion–eversion. They can be employed in seated position or while standing overground or over a treadmill (From: Krebs et al. [72]; used with permission, Courtesy IEEE)

maximize backdriveability. Of course, the Anklebot torque capability does not allow lifting the weight of a patient. At best, we can cue the subject to use their voluntary plantarflexor function by providing supplemental support to the paretic ankle plantarflexors during the stance phase. Our design is aimed at supporting foot clearance during swing phase assisting a controlled landing at foot contact. The torque generated by the Anklebot can compensate for drop foot during early and final stance phases of gait and insufficient muscle action during push-off. We can also generate torque during the midswing phase to evoke concentric activity in the dorsiflexor muscles. In this respect, the Anklebot can provide continuous torques up to ~23 Nm in the sagittal plane, which is higher than required to position the foot in dorsiflexion during midswing.

More recently, we developed a pediatric version of this device for children with cerebral palsy (CP) between ages 5 and 8 (Fig. 14.2). Impairment at the ankle joint is of particular importance in CP. In some youngsters, it manifests as "equinus foot," which is a simple name for a complex problem. It manifests itself as equinus gait (true or apparent) that, if allowed to mature as the child matures, can only be corrected through invasive orthopedic surgery. At present, equinus foot is typically addressed in the clinic via an AFO that restricts the ankle's range of motion.

We will conclude this description of the salient features of the Anklebot by noting that we showed that unilaterally loading the impaired leg with an unpowered adult Anklebot's additional mass had no detrimental effect on the gait pattern of subjects with chronic hemiparesis [28]. Similarly, loading the most impaired leg with the pediatric Anklebot had no detrimental effect on the gait pattern of children with cerebral palsy (Fig. 14.3).

14.4 Clinical Results

Initial clinical results with stroke survivors with chronic hemiparetic gait who underwent a 6-week interactive seated Anklebot training program were quite promising [29]. This initial study's purpose was to assess the potential benefits of paretic ankle training on impairment and whether reducing impairment would translate into functional improvement in overground walking speed. We hypothesized that subjects with mild-to-moderate hemiparesis would successfully complete regular training sessions of up to 60-min duration and that the training would reduce impairments and improve motor control at the paretic ankle, potentially enhancing independent gait function through increased walking velocity and changes in spatiotemporal gait parameters. We used a visually guided, visually evoked training paradigm in

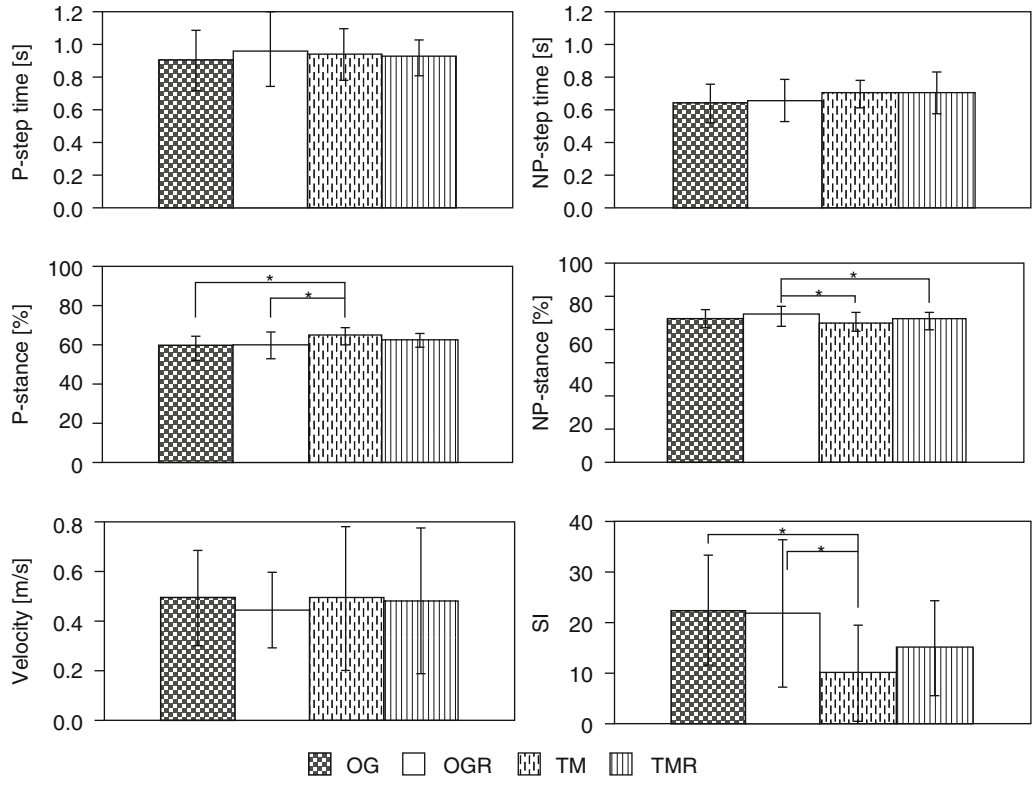

Fig. 14.3 Influence of loading with the Anklebot. The *top left panel* shows gait differences with and without the adult Anklebot in nine (9) persons with chronic stroke both overground and on a treadmill (*OG* overground, *TM* treadmill, *OGR* overground with the robot, *TMR* treadmill with the robot, *P* paretic, *NP* nonparetic, *SI* symmetry index, * indicates significant differences between conditions at $P = 0.05$). The *right panel* shows gait kinematics (mean ± SD) collected from a single representative subject for the hip, knee, and ankle joints during the four conditions (*OG* no robot, *OG* with robot, *TM* no robot, and *TM* with robot). For each condition, a total of six (6) gait cycles were averaged. The *dashed lines* indicate neutral stance measured before the trials (Khanna et al. [28]; used with permission). The *bottom left panel* shows the changes in ten (10) healthy and ten (10) CP children walking with added weight on their nondominant knee. Data suggests that both healthy and CP children ages 5–8 years old can play and walk with asymmetrical loading of up to 2.5 kg (From: Krebs et al. [72]; used with permission, Courtesy IEEE)

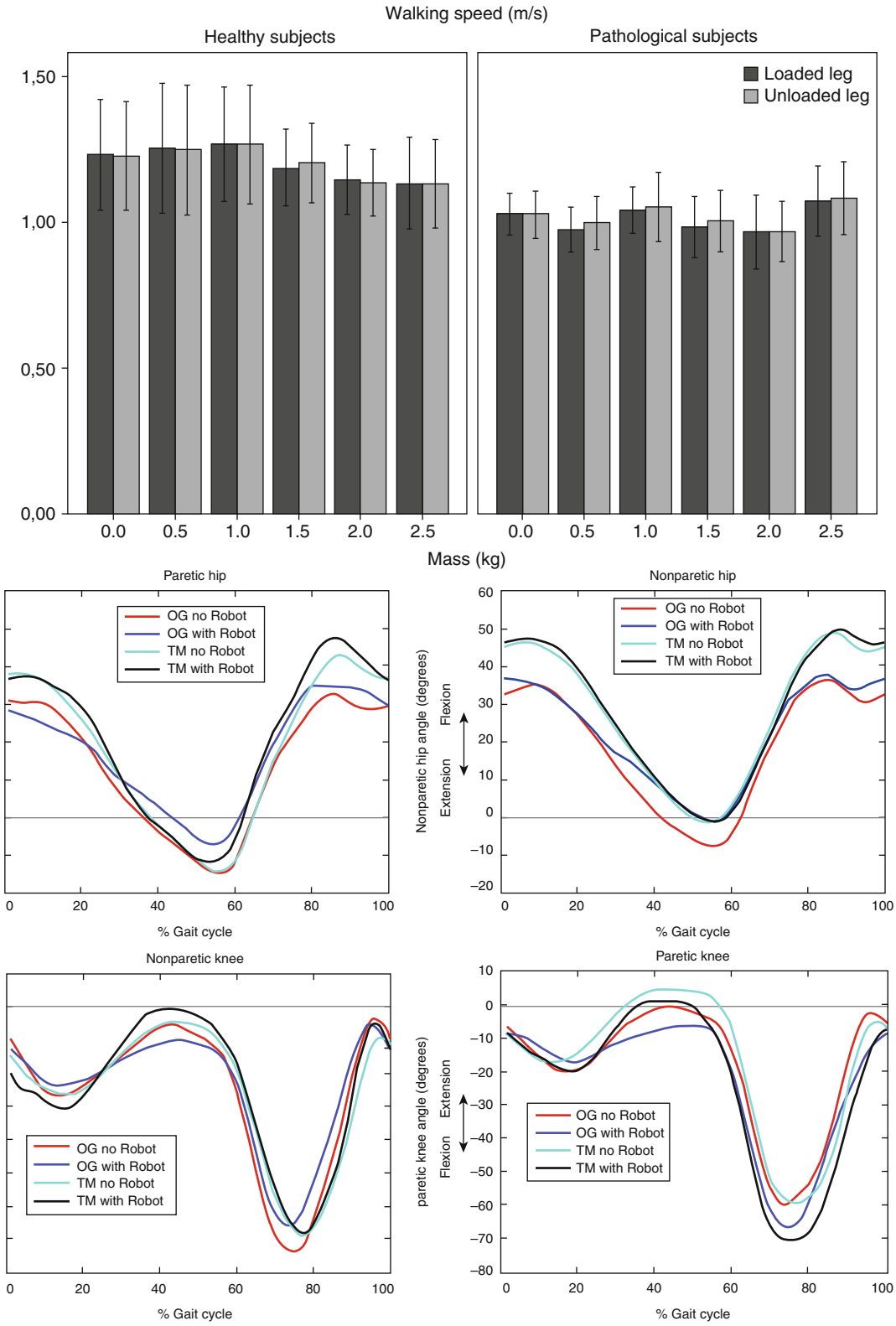

Fig. 14.3 (continued)

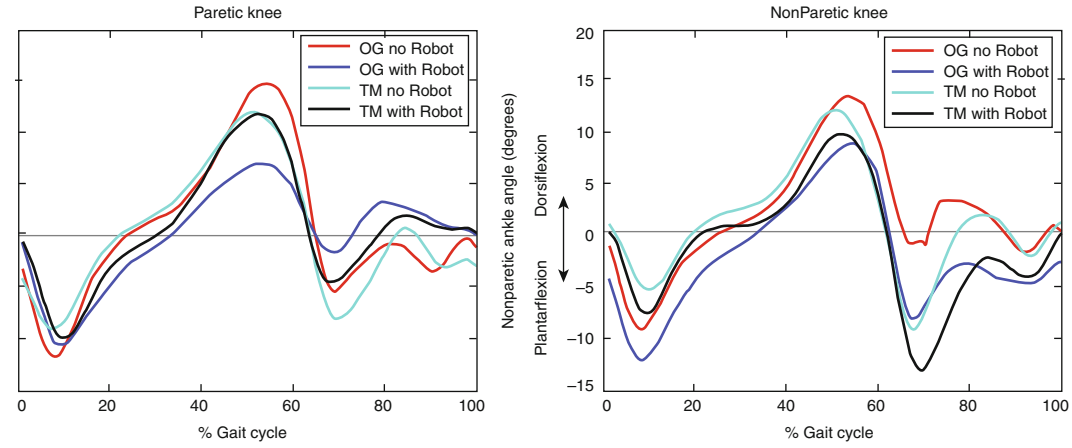

Fig. 14.3 (continued)

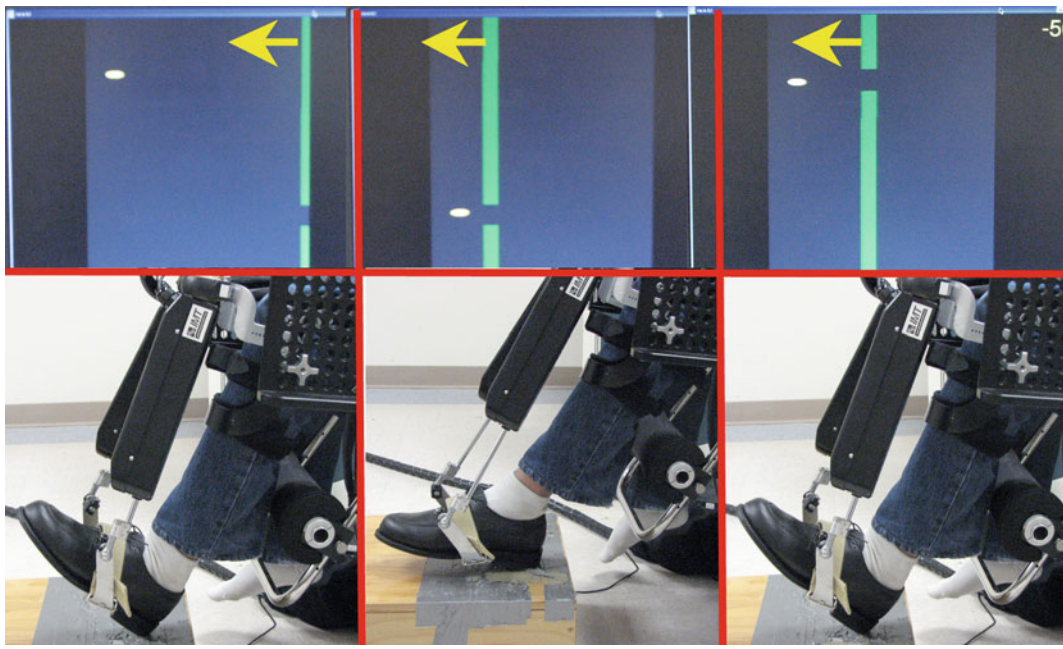

Fig. 14.4 The *upper panels* depict a target moving from right to left across the screen as shown by the *arrows* (which are not part of the actual video display). The *oval-shaped cursor* is moved vertically by corresponding changes in dorsiflexion and plantarflexion movements, as depicted in *lower panels*. The subject's heel pivots on a sturdy platform, and the knee brace that supports the robot proximally is anchored to a mounting plate that is attached to the chair. The objective is to move the ankle and align the cursor with the openings as they approach. The ankle motion required to reach targets in each direction is scaled to a maximum of 80% per individuals' active ankle ranges of motion in plantarflexion and dorsiflexion. The level of difficulty can be programmed by altering the speed of target progression across the screen, changing the aperture width of the targets, and by altering the level of robotic assistance/resistance. There is also an option to present a performance score (*upper right corner*) reflecting the net of successful versus unsuccessful gate passages

which the amount of assistance changed and challenged participants to improve performance. In this initial trial, we trained subjects in a seated position ("open chain") and not in task-specific gait training. Figure 14.4 shows the training, and Table 14.1 shows subject's changes with training.

Table 14.1 Selected spatiotemporal gait parameters before and after 6 weeks of seated ankle robot training

Variable (units)	Baseline	6 weeks	% change	*P*-value
Walking speed (cm/s)	51.4 ± 11.1	61.7 ± 10.9	20	0.032
Stride length (cm)	78.2 ± 10.5	86.3 ± 9.3	10	0.048
Cadence (steps/min)	75.3 ± 7.5	83.4 ± 8.1	11	0.045
P single support (%)	21.1 ± 2.4	24.2 ± 2.4	15	0.033
P double support (%)	46.6 ± 4.6	40.3 ± 4.0	−14	0.010

Mean ± SE, *P* paretic

Results suggest the potential for seated visuomotor ankle robot training to improve chronic hemiparetic gait velocity with concomitant gains in multiple indices of paretic ankle motor control, including speed, accuracy, and smoothness. Time profile analysis revealed that control of targeting accuracy increased during the first 3 weeks while maximum improvements in mean and peak velocities and normalized jerk were made in the last 3 weeks. The 20% increase in overground walking velocity suggests that seated robotics training to reduce ankle impairments may translate into improved functional mobility.

The effects of seated ankle robot training on gait function compare favorably with those from a number of task-oriented locomotor interventions. For example, Hornby's results with the robotic partial body-weight-supported treadmill training (BWSTT; e.g., Lokomat) and therapist-assisted BWSTT therapy showed similar gains to those reported here (0.07 and 0.13 m/s, respectively), although those were achieved with 12 sessions versus the 18 used here [2]. Notably in that study, subjects receiving robotics-assisted training did not improve their paretic single-support duration while subjects receiving therapist-assisted training improved from 20% to 22% of the gait cycle, similar to results reported in this study (21–24%). For subacute stroke, a 9-week pilot crossover design employing Lokomat and conventional therapy showed an overall improvement in 10-m walk speeds from 0.13 to 0.27 m/s, a range comparable to the current findings [30]. Of interest, the same group failed to replicate and observe any differences between robotics and conventional training in a subsequent larger randomized clinical trial [31]. Macko and colleagues showed that 6 months of treadmill exercise improved 10-m walking speed in subjects with chronic stroke by 17% [32], compared to the 20% increase after only 6 weeks with the ankle robot. Taken together, distinct locomotor training approaches have produced about the same degree of overground speed improvement demonstrated in the current pilot study. Yet, not all of those studies have shown significant improvements in spatiotemporal gait metrics such as paretic single support. Of course, we must take all these results with the appropriate caveats as the number of subjects is small, the intensities and duration of the interventions are different, the patient populations are distinct, and so forth.

14.5 Exploratory Study: Anklebot Treadmill and Overground Training

We are exploring the feasibility of using dynamic entrainment as an approach to support human walking while exploiting the natural oscillatory dynamics of the lower limbs. Much like a mechanically assistive version of music therapy, the concept is to use periodic ankle mechanical perturbations to entrain patients' gait and encourage them to walk faster. In this novel robotic therapy, a robot may be programmed to entrain the patient's walking frequency and gradually "drag" it toward the normal walking frequency. We tested the method's feasibility in healthy subjects and in persons with chronic stroke or multiple sclerosis (MS) walking on a treadmill. Entrainment with a finite basin and phase locking were reliably observed, supporting the role of a neuromechanical oscillator in human walking [33, 34]. Stroke and MS patients, as well as healthy subjects, showed entrainment to the periodic mechanical perturbation demonstrating the feasibility of the proposed strategy. Entrainment with phase locking was observed

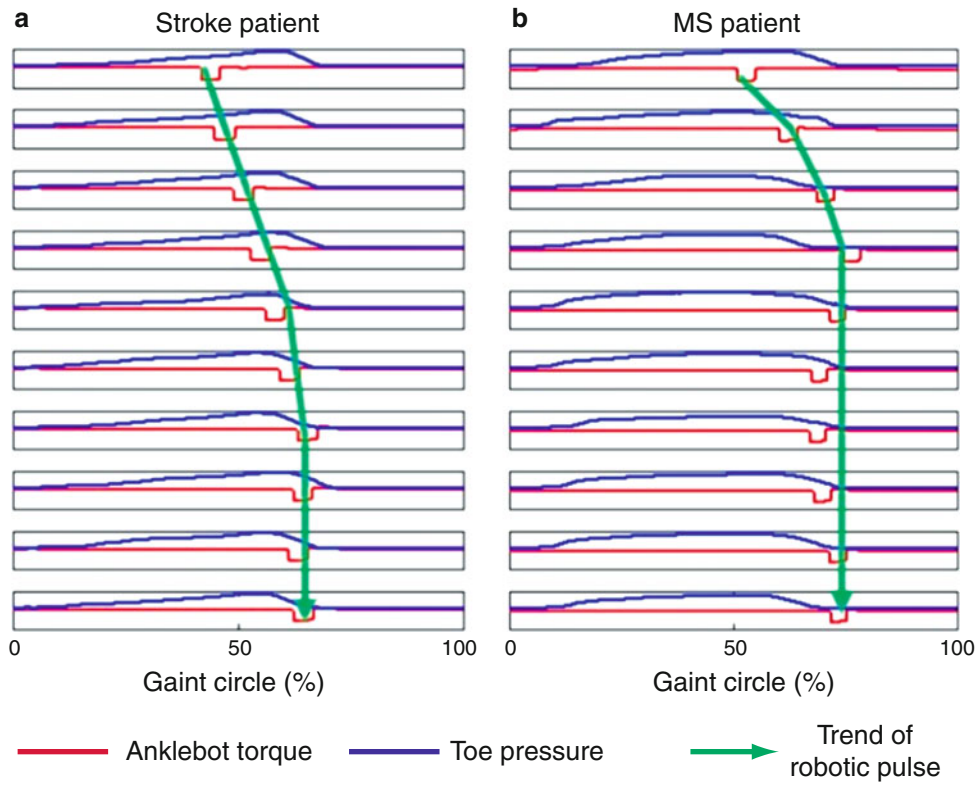

Fig. 14.5 Transient behavior and subsequent entrainment to an accelerating perturbation: (**a**) and (**b**) show the Anklebot torque profile (*red*) and toe pressure (*blue*) for each gait cycle of a stroke patient and an MS patient, respectively. Stride number increases from top to bottom, and perturbation cadence gradually increased; the perturbation cadence is faster in the lower gait cycles. The onset of the torque pulse drifted initially but converged to a specific phase of the gait cycle as visualized by the *green arrow*. Phase locking indicates that the subjects gradually increased stride frequency to synchronize with the gradually increased perturbation frequency. The toe pressure shows that the robotic torque pulse locked within the push-off phase (From: Ahn et al. [34]; used with permission, Courtesy IEEE)

when the perturbations had a constant period as well as when the perturbation cadence gradually increased. Typical gaits entraining to a gradually accelerating perturbation for stroke and MS patients are shown in Fig. 14.5.

As with unimpaired subjects [33], entrainment was always accompanied by a specific relation between the gait cycle and the robotic perturbation; in entrained gaits, the terminal stance phase consistently coincided with the square torque pulses exerted by the Anklebot. The observation of *phase locking* was reliable; Fig. 14.5 shows that subjects synchronized their cadence to the perturbation to maintain the phase relation even when the perturbation cadence changed. Because of this phase locking, the torque from the Anklebot occurred at ankle push-off, where it assisted in propulsion.

Entrainment to an external periodic perturbation is a distinctive characteristic of nonlinear limit-cycle oscillators. The entrainment to periodic mechanical perturbation that we demonstrated indicates that a nonlinear dynamic oscillator plays a role in the neuromotor execution of human locomotion. That oscillator may be due to a neural central pattern generator (CPG), the musculoskeletal periphery, or a combination of both, probably mediated by afferent feedback. However, we cannot rule out the possibility of supraspinally mediated adaptation. Entrainment to periodic mechanical perturbations supports a new exploratory strategy for locomotor rehabilitation that

may have promise: Based on a patient's performance, a robot may be programmed to entrain the patient's walking frequency and gradually "drag" it toward the normal walking frequency. The amplitude of mechanical perturbation as well as its frequency can be adjusted based on a patient's performance, providing assistance only as needed to promote the patient's participation, which is an essential element of neurorestoration [35, 36]. Further assessment of the feasibility of entrainment to mechanical perturbation as a therapeutic strategy for various impaired subjects is in progress, and we are designing clinical studies to determine whether we can harness the approach and improve patients' outcome.

14.6 Exploratory Study: MIT-Skywalker and Supraspinal Control for Stroke Rehabilitation

As discussed earlier, to employ mechanical devices to deliver therapy is not a new idea, with the most common mechanical device used in gait therapy being the treadmill. Treadmill training offers high-intensity task-oriented repetitive movements that can improve muscular strength and aerobic capacity [37]. Body-weight-supported treadmill training (BWSTT) has been proposed to improve gait and lower-limb motor function in patients with locomotor disorders [38, 39]. Initial studies suggested a positive impact on patients with stroke. More specifically, for hemiparetic patients, body-weight-supported treadmill training has been shown to improve balance, lower-limb motor recovery, walking speed, endurance, and other important gait characteristics, such as symmetry and stride length [39]. However, a recently completed large NIH-sponsored randomized clinical trial (RCT) with stroke patients casts significant doubt whether it offered any advantage over usual care (www.leaps.usc.edu; Principal Investigator: Pamela Duncan [5]). This raises significant questions about the likely effectiveness of attempts to automate BWSTT employing robotics. It is quite possible that these training approaches may be too limited to best promote recovery following a stroke. As with upper-extremity rehabilitation, supraspinally mediated processes may be critical elements required for effective recovery following a stroke. This may explain the surprising results favoring usual-care therapy.

We have recently introduced MIT-Skywalker to the clinic. This novel rehabilitation robot is unique and distinct from any other existing rehabilitation robotic devices for gait. It delivers safe and efficacious gait therapy inspired by the concept of passive dynamic walkers [40]. Contrary to gait robots based on restoring kinematics, MIT-Skywalker creates the ground clearance required for swing dynamically, exploiting gravity and inertial mechanics to assist swing-leg propulsion. Preliminary tests demonstrated its ability to provide therapeutic assistance without restricting the movement to any predetermined kinematic profile, providing ecological heel strike and hip extension to maximize patient participation during therapy. Moreover, since the working principle takes advantage of the natural dynamics of the leg, no mechanism attached to the patient's leg is needed. This maximizes safety by eliminating the possibility of exerting unwanted forces on the leg due to mismatch between the artificial (robot) and natural (human) degrees of freedom. Equally important, it significantly reduces the don and doff time required – a significant consideration for clinically practical designs.

In conventional gait physiotherapy, the therapist pushes or slides the patient's swing leg forward, either on the ground or on a treadmill. In kinematically based robot-assisted gait therapy, the leg is propelled forward by the robotic orthosis acting on the patient's leg (e.g., in Lokomat or Autoambulator). Instead of lifting the patient's leg manually or mechanically, we achieve forward propulsion during swing in MIT-Skywalker by lowering the walking surface at maximum hip extension. This provides swing clearance and takes advantage of gravity and the pendular dynamics of the leg to propel the leg forward, while allowing proper neural inputs due to hip extension near swing onset and ecological heel

strike at swing termination. Figure 14.6 provides a conceptual sketch of the device and illustrates several phases of the walking cycle. More details on the hardware architecture and characteristics of MIT-Skywalker can be found elsewhere [41, 42], as well as details of our control algorithm to track the patient's gait abilities and challenge them to increase participation and improve speed and symmetry [43].

In a study of unimpaired subjects, we used MIT-Skywalker to apply unilateral mechanical perturbations during gait and analyze the response of the contralateral unperturbed limb. Body weight was supported, the position of the body center of mass was constrained, and excitation of the vestibular system was minimal. We unexpectedly lowered the walking surface for one leg in two different gait phases of gait, namely, at terminal swing before heel strike and at midstance. Although the induced perturbation is similar to the kind used in previous studies [44–48], our experimental paradigm included full body-weight support and torso stabilization, thereby minimizing vestibular feedback and loading of the legs. The latency of the effect of the perturbations was larger in our experiments than in any previous work (Table 14.2). Our results indicate the participation of supraspinal pathways in regulating interlimb coordination, at least for the case of body-weight-supported gait. In other words, the experimental paradigm used in this study revealed an interlimb coordination mechanism that controlled the bilateral occurrence of walking phases and events, based mainly on proprioceptive responses, and this mechanism is more likely to reside in supraspinal levels. This further supports the need for more targeted research to enable proper redesign of high-intensity ambulation therapy delivered by therapists or by robots.

14.7 Anklebot-Mediated Assay

The ability to modulate ankle stiffness is a critical biomechanical factor in locomotion. Studies have shown that humans adjust leg stiffness to accommodate surface changes during hopping in place and forward running [49, 50], and there is increasing evidence that modulation of ankle stiffness is the primary mechanism for adjusting leg stiffness under a variety of circumstances [50]. Others have shown that the nondisabled human ankle appears to change stiffness characteristics as gait speed changes [51]. Further, there is evidence that adequate ankle joint stiffness is critical during the single-support phase to control forward and downward body momentum [52]. Ankle impedance (i.e., stiffness plus damping and any other dynamic factors) is also important for the role it plays in "shock absorption"; in particular, it has been suggested that the impact force at floor contact is attenuated by cushioning during the supination and pronation of the ankle joint [53].

Ankle stiffness is influenced by passive mechanisms, e.g., ligamentous stiffness, as well as active mechanisms and neuromotor mechanisms such as reflex and voluntary control. In neurologically impaired patients, spasticity (reflex hyperexcitability and hypertonus) might disrupt the remaining functional use of muscles [54]. It may be accompanied by structural changes of muscle fibers and connective tissue, which may result in alterations of intrinsic mechanical properties of a joint. Studies have shown, for example, that neurologically impaired individuals, e.g., those with spinal cord injury [55], spastic cerebral palsy [56], multiple sclerosis [57], or cerebrovascular accident [54] have abnormal passive ankle stiffness in addition to hypertonia (caused by spasticity, dystonia or rigidity, individually or in combination). Tracking such properties in neurologically impaired individuals over the course of a therapy or intervention program may yield better characterization and assessment of a patient's improvement [58]. Clinicians assess muscle tone in patients with the Modified Ashworth Scale (MAS) [59]. This scale requires the evaluator to rate ankle resistance subjectively while passively moving the joint through various ranges of motion at differing velocities. Objective quantitative techniques to estimate the ankle joint passive stiffness would significantly benefit characterization of patients' neurorecovery and may even serve as signatures of ankle pathology [60–64].

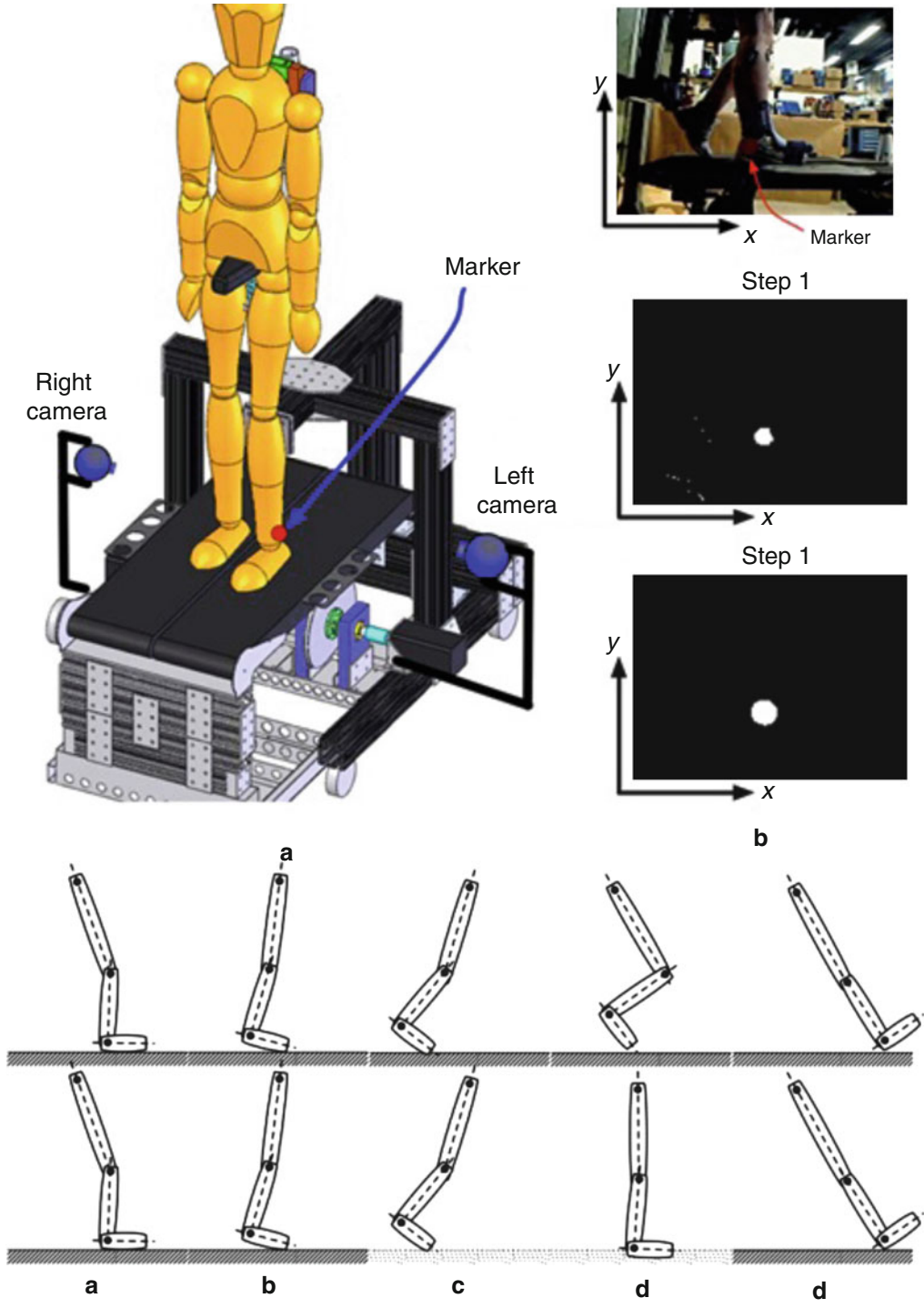

Fig. 14.6 The *top left panel* shows the MIT-Skywalker platform equipped with two cameras on the sides to monitor the position of red markers placed on the user's heels (**a**). The *topmost right panel* shows the marker position (highlighted in *red*). The other *top right panels* show captured frames from the right camera. Steps 1 and 2: Successive steps of the image processing used to detect the marker position in the camera frame. *White image* regions correspond to the selected infrared pixels belonging to the sets R and S, respectively. The *bottom panels* depict the gait phases for walking on a flat surface (*top row*) and a surface that drops between toe-off (**c**) and heel strike (**e**) (*bottom row*) (From: Artemiadis and Krebs [42]; used with permission, Courtesy IEEE)

Table 14.2 Response time for the unperturbed knee and hip joints

	Perturbation midstance	Perturbation heel strike
Contralateral knee response (ms)	120 (SD 22)	312 (SD 42)
Contralateral hip response (ms)	205 (SD 32)	325 (SD 54)

While the passive stiffness of the human ankle has been estimated and reported extensively, both in healthy as well as in neurologically impaired individuals, nearly all those measurements have been made in the sagittal plane, i.e., the dorsiplantarflexion degree of freedom (DOF) [54, 65–69], with the exception of only a few studies that report ankle joint stiffness in healthy individuals in the frontal plane (e.g., [70]) even though eversion–inversion DOF plays a critical role in maintaining balance under static and dynamic conditions. Most ankle sprains and injuries, in actuality, occur along the lateral ligament complex via an inversion mechanism [71]. Therefore, the ability to accurately estimate passive ankle stiffness in the frontal plane will improve our understanding of biomechanical stability and factors that influence it.

We can employ the wearable ankle robot, Anklebot, not only to deliver therapy but also to evaluate ankle impairment. Subjects were seated with their ankles clear of the ground in an anatomically neutral position, the sole at a right angle to the tibia, and instructed to relax while the robot moved their ankles. The protocol consisted of 24 movements along 12 equally spaced directions in IE–DP space, with a nominal displacement amplitude of 20° in each direction. Perturbations began with 0° and ended at 330° at 30° increments. Note that 0° and 180° correspond to eversion and inversion, 90° and 270° correspond to dorsiflexion and plantarflexion, respectively. The Anklebot displaced the ankle with low speed (5°/s), which was selected to avoid evoking stretch reflexes. Figure 14.7 shows the results estimating the passive ankle stiffness in sagittal and frontal planes for persons with foot drop due to chronic stroke (10 chronic, hemiparetic stroke survivors, 60 ± 8 year), as well as young and age-matched healthy controls at the Baltimore Veterans Administration Medical Center. The results of this study indicate that passive stiffness is strongly direction dependent in both planes of movement and that, compared to individuals of similar age without known pathology, individuals with stroke have increased passive ankle stiffness in dorsiflexion and inversion but are more compliant in eversion.

Conclusion

A recently completed NIH-sponsored randomized controlled trial (RCT) demonstrated that, contrary to expectations of its clinical proponents, body-weight-supported treadmill training administered by two or three therapists did not lead to superior results when compared with a home program of strength training and balance (LEAPS Study). This is a remarkable and extremely important result, one that must be acknowledged and explored further by roboticists: The goal of rehabilitation robotics is to optimize care and augment the potential of individual recovery. It is not simply to automate current rehabilitation practices, which for the most part lack a sound basis of scientific evidence. This is not a criticism of clinical practitioners, who must provide treatment as best they know how, but is primarily due to a lack of tools suitable to properly assess clinical practices themselves. To move LE robotics beyond its infancy, we have to determine what constitutes best practice. Here robotics offers tools to carefully and methodically build evidence- and science-based approaches that allow a patient to harness plasticity and recover within only the limitations of biology. In this chapter, we examined two alternatives, discussing our initial studies that aim to take advantage of the natural rhythmic dynamics of the neuromechanical system and that suggest the need to engage the supraspinal network explicitly – much like we do in upper-extremity robotic therapy and, we suspect, as occurs in usual-care gait training approaches.

Of course, these are only the initial, faltering steps toward our goal. We recognize the

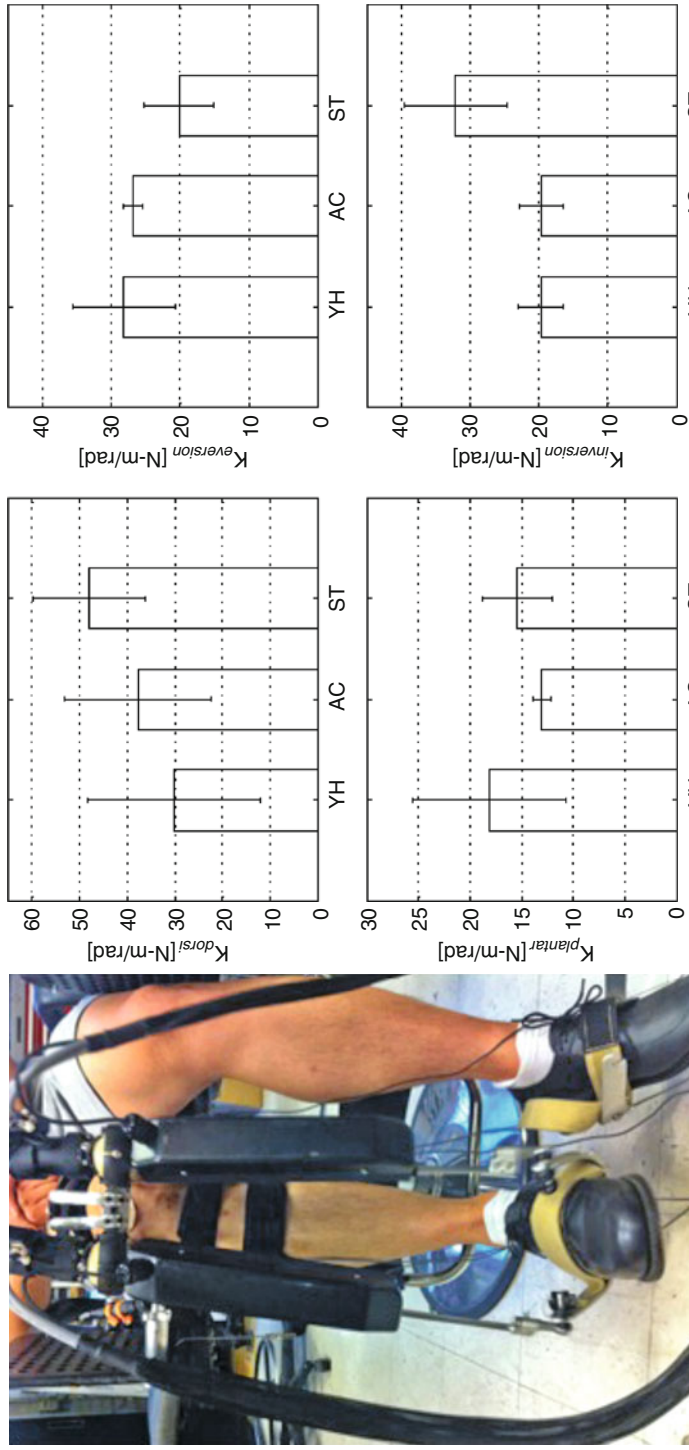

Fig. 14.7 Comparison of passive stiffness in seated position between healthy young (*YH*), healthy age-matched (*AC*), and stroke (*ST*) groups. *Left panel* shows the frontal view of a subject during testing. *Right panel* shows the passive stiffness measurements for dorsiflexion (Kdorsi), plantarflexion (Kplantar), inversion (Kinversion), and eversion (Keversion). The error bars represent variability across all subjects tested within a group

correctness of the conclusion of the American Heart Association's statement in its guidelines: "… robotics for the lower extremity (LE) still in its infancy…" We still do not know how to tailor therapy for a particular patient's needs. We do not know the optimal dose, or in cost-benefit terms: What is the minimum intensity to promote actual change? Is too much therapy detrimental? Should we deliver impairment-based approaches (as in seated "open-chain" ankle training) or functionally based approaches (as in body-weight-supported treadmill training) and to whom: severe, moderate, mild strokes? If impairment-based approaches, should therapy focus on each joint one at a time? If so, should therapy progress proximal to distal or the other way around? Should we assist as needed, resist, or perturb and augment error? Who might be the responders who benefit most from these interventions? How should we integrate the robotic gyms in therapy practices?

The challenge for the next 5 years is to focus on the multitude of variables that may influence outcome and to determine the interaction or independence among these variables and their actual impact on outcomes. If we can make significant inroads on this facet of the problem and avoid prematurely declaring victory, then we can rest assured that the 2015 guidelines from the American Heart Association, from the Veterans Administration, and the Department of Defense will endorse lower-extremity robotics as well.

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Part VI

Robotics for Lower Extremity (Locomotion): Clinical Applications

Robotics for Stroke Recovery

15

Carolynn Patten, Virginia L. Little,
and Theresa E. McGuirk

Abstract

The introduction of robotics into neurorehabilitation is a relatively recent phenomenon. To date, both their acceptance by the rehabilitation community and penetration of robotic devices into rehabilitation facilities have been limited. The majority of clinical studies evaluating the efficacy of rehabilitation robotics to date have framed the question in terms of superiority between robotic approaches and some chosen standard therapy. Not surprisingly, the results of many of these studies have revealed nonsignificant differences between robotic and traditional rehabilitation approaches, which clinicians generally interpret as failure of the robotic approach. Improvements in response to both traditional and robotic approaches yielding results of "no difference" could, however, be interpreted as a positive result. Considered in this light, robotic approaches may offer the opportunity for therapeutic intervention to more individuals and/or may extend the therapeutic opportunity (i.e., dose, time, repetitions) while practitioners focus on other critical aspects of rehabilitation. Here, it is

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important to recognize that many of the robotic approaches have been designed to mimic currently utilized rehabilitation interventions, at least as these interventions are currently understood. Thus, the modest efficacy of robotic approaches demonstrated to date may stem from limitations in our current understanding of the critical processes of neural recovery, and how to effectively induce neural recovery, rather than from limitations of robotic devices per se. This chapter considers the problem of walking dysfunction following stroke and offers perspectives on the use of the Lokomat to promote walking recovery.

Keywords
Biomechanics • EMG • Locomotion • Neurorehabilitation • Recovery • Sensorimotor integration • Stroke

15.1 Introduction

The introduction of robotics into neurorehabilitation is a relatively recent phenomenon. To date, both their acceptance by the rehabilitation community and penetration of robotic devices into rehabilitation facilities have been limited. These circumstances may reflect the state of rehabilitation practice, in general, rather than limitations of robotic approaches for rehabilitation. Among clinical practitioners, the reaction to rehabilitation robotics tends to be bimodal: either they are embraced for the potential opportunity to offer more therapy, more consistent therapy and perform the numerous repetitions required to induce neural plasticity; or they are met with suspicion and criticized for their limitations, expense, and attendant technical challenges. Indeed, at least in North America, many practitioners argue for the superiority of traditional, "hands-on" therapeutic approaches [1].

Of note, the majority of clinical studies evaluating the efficacy of rehabilitation robotics to date have framed the question in terms of superiority between robotic approaches and some chosen "standard" therapy. Perhaps not surprisingly, the results of many of these studies have revealed nonsignificant differences between robotic and traditional rehabilitation approaches [1–3]. Clinicians generally interpret these nonsignificant differences as failure of the robotic approach. Importantly, however, improvements in response to both traditional and robotic approaches yielding results of "no difference" could be interpreted as a positive result. Rehabilitation produces measurable effects! Considered in this light, robotic approaches may offer the opportunity for therapeutic intervention to more individuals and/or may extend the therapeutic opportunity (i.e., dose, time, repetitions) while practitioners focus on other critical aspects of rehabilitation. Here, it is important to recognize that many of the robotic approaches have been designed to mimic currently utilized rehabilitation interventions, at least as these interventions are currently understood. Thus, the modest efficacy of robotic approaches demonstrated to date may stem from limitations in our current understanding of the critical processes of neural recovery, and how to effectively induce neural recovery, rather than from limitations of robotic devices per se. This chapter considers the problem of walking dysfunction following stroke and offers perspectives on the use of the Lokomat (Hocoma, Volketswil, Switzerland) to promote walking recovery.

15.2 Statement of the Problem

Stroke is the leading cause of serious, chronic disability in adults worldwide. Each year, approximately 16 million strokes occur worldwide. As a

result of marked improvements in acute stroke management, the cohort of survivors now exceeds 62 million persons worldwide, a third of whom experience significant physical disability and functional impairment [4]. Because its risk doubles with each decade of age beyond 55 years, stroke has historically been considered a problem of an aging population. However, in the last decade, the representative demographics have shifted dramatically to reveal an emerging representation of younger individuals affected by stroke. Approximately half of total stroke costs [5] are now directed toward persons between the ages of 45 and 64 years. This demographic shift heralds an urgent and critical need to improve the efficacy and effectiveness of stroke rehabilitation. This need encompasses strategies not only to reduce stroke-related costs and disability but also to restore function for persons in the productive and vital years of their lives. Simply put, we need to increase our expectations of the outcomes attainable in stroke rehabilitation.

Walking dysfunction is one of the greatest physical limitations contributing to stroke-related disability. While two-thirds of persons who suffer a stroke regain ambulatory function, their gait is slow, asymmetrical, and metabolically inefficient [6–9]. These characteristics are associated with difficulty advancing and bearing weight through the more affected limb, leading to instability and an increased risk of falls [10]. Secondary impairments, including muscle disuse and reduced cardiorespiratory capacity, often contribute to further declines in gait function. Walking dysfunction restricts independent mobility, and autonomy, and therefore severely impacts quality of life for many stroke survivors and their families [11, 12]. Given this constellation of problems, it is not surprising that improved walking is one of the most frequently articulated goals of neurorehabilitation [13]. Interventions that effectively restore and promote meaningful recovery of walking function are needed to enable these persons to resume participation in their premorbid social roles. This challenge offers a significant opportunity for the area of rehabilitation robotics.

15.3 Walking Recovery Poststroke

Traditional approaches to gait therapy involve one-on-one treatment by a physical therapist using various forms of exercise, equipment, and feedback [14, 15]. However, because many hemiparetic persons are unable to bear weight normally through the paretic limb and lack normal tolerance to upright posture, such traditional gait training fails to establish the requisite biomechanical conditions for normal locomotion. Indeed, this traditional, clinical approach may engender, and even reinforce, compensatory movement strategies and dependence on assistive devices. Concern regarding traditional gait training approaches extends beyond compromised biomechanics to the sensory-perceptual aspects of locomotor control. Integration of inaccurate and inappropriate sensory information is disruptive and can interfere with positive effects of motor rehabilitation, especially at critical stages in the process of neural recovery [16].

Recent efforts have emphasized the need for a "task-specific" [17] approach to gait therapy based on fundamental concepts of motor learning [18] and specificity of training [19]. Indeed, the task-specific approach appears to produce somewhat greater gains in gait function than traditional therapy [20]. Of note, results reported by proponents of the task-specific approach reveal that persons in the subacute period poststroke demonstrating at least a minimal level of gait function pretreatment (i.e., ability to walk at ~0.3 m/s) are most likely to produce significant treatment-induced improvements in walking [21]. This observation suggests that baseline hemiparetic severity may be the fundamental determinant of locomotor outcome; that is, a critical level of function must be retained following stroke to benefit from gait rehabilitation. This perspective suggests a limited capacity for locomotor recovery in persons poststroke.

An emerging, contemporary approach to walking recovery involves partial body weight-supported treadmill training, also termed "Laufband" therapy [22, 23] or locomotor training [24]. The mechanics of locomotor training involve a

harness by which the patient is supported to partially unload his/her body weight while walking on a treadmill. Critical elements of this approach include: upright orientation relative to gravity, weight-bearing through both limbs, and the opportunity to utilize a bilateral, reciprocal gait pattern that involves hip extension [16, 22, 25]. Of note, each of these elements is a biomechanical characteristic of normal walking [26].

One of the major proponents of locomotor training [22] demonstrated remarkable and functionally significant improvements in walking function in hemiparetic individuals who initiated training from either a nonambulatory or minimally ambulatory state during the subacute period poststroke. These effects were observed in a series of single subject ABA designs where the A phases involved locomotor training and the B phase traditional, Bobath, gait therapy [27]. Improved walking ability and speed were observed in both locomotor training blocks but demonstrated a plateau in the traditional therapy block. These results illustrate the efficacy of the locomotor training approach, even in hemiparetic persons demonstrating extremely low levels of physiologic function. Further, they stand in contrast to those suggesting the need for minimal functional capacity to benefit from task-specific gait rehabilitation [21, 28].

15.4 Recipe for Success

15.4.1 Neuromechanical Constituents

Walking for successful community ambulation is a complex behavior requiring control to: (1) produce a bilaterally reciprocal stepping pattern with sufficient propulsion for steady-state ambulation, (2) maintain balance during forward propulsion/progression [29], and (3) adapt walking to the behavioral goals of the person and the constraints imposed by the environment [30]. All three of these subtasks of walking are compromised as effects of stroke. Locomotor training has been proposed as an effective approach to promote walking recovery because it offers the requisite task specificity to address these subtasks.

Locomotor training is based on a model for the neural control of walking and its functional requirements as described by Forssberg and adapted by Barbeau [31–33]. Locomotor training in neurorehabilitation originally emerged for persons with spinal cord injury (SCI). Motivated by relative similarities between animal and human models of SCI, much attention focused on the role of afferent information in generation of appropriate patterned muscle activity during stepping. Afferent signals from muscle spindles and load receptors are important for promoting a proper locomotor rhythm in the central nervous system [34, 35]. Animal models demonstrate that sensory inputs are both phase and task specific [36–38] and that loading and unloading cycles are important for activation of extensors during stance [39]. In human bipedal locomotion, the leg flexor and extensor muscles are differentially controlled with more centrally determined control of flexors and more peripheral afferent input influence on extensors [40]. The spinal locomotor pools are highly responsive to phasic segmental sensory inputs associated with walking and demonstrate evidence of learning during step training [41–44]. Walking speeds and postural challenges have proven essential to improve locomotor outcomes [31, 45], emphasizing the need for locomotor training to establish conditions that present and optimize the relevant and appropriate signals to the spinal locomotor pattern generators in order to induce activity-dependent plasticity.

A critical perspective of the locomotor training approach is recognition of the inherent capacity for plasticity, even following central nervous system insult. Locomotor training shifts the goal of the rehabilitation intervention from enabling compensatory mechanisms to promoting recovery of neurologic function [31, 33, 42, 46, 47]. Because the locomotor training approach focuses on restoring locomotor capacity [44, 48–53], it depends on establishing conditions in which the damaged nervous system can experience normalized movement patterns.

The combined efforts of both animal and human studies emphasize the importance of normalizing stepping kinematics to promote activation and relearning of appropriate motor patterns

in the spinal networks [16]. With increased limb loading, as provided through locomotor training, increased muscle activity (EMG) is observed in leg extensors during stance and, reciprocally, in contralateral leg flexors during swing [54, 55]. In the post-acute recovery period, continuous, nonspecific EMG patterns are typically observed during both standing and stepping [16, 56], but over time, by promoting appropriate stepping patterns through the physical assistance of partial body-weight support, treadmill, and manual advancement of paretic limbs, appropriately timed patterns of EMG bursting emerge. With training, these bursts become progressively refined and increasingly efficient, as they are specifically tuned to the gait phase. Sullivan and coworkers [56] observed both the emergence of phasic EMG patterns and significant reorganization of cortical activation [57] following locomotor training. These investigators observed reciprocal paretic limb dorsiflexion/plantarflexion in hemiparetic individuals was initially accompanied by weak cortical activation distributed diffusely across the leg and foot representation of sensorimotor cortex. Following locomotor training, central activation became more specific, as characterized by intense activation in a distribution focused on the contralateral foot region [57]. Related work using near infrared spectroscopy (NIRS) to monitor cortical activity during walking [58]. Miyai and coworkers [58] studied individuals poststroke and found that cortical activation during unconstrained treadmill walking was initially asymmetrical, favoring the contralesional hemisphere. With partial body-weight support, gait performance improved toward normal proportions of stance and swing phases and became more symmetrical between limbs. Concomitantly, cortical activation was globally reduced with improved hemispheric symmetry. Regionally specific effects included significantly reduced activation of sensorimotor cortex, somewhat reduced activity in supplementary motor cortex, and increased activity in premotor cortex. Thus, there is evidence to support that locomotor training affects not only the spinal locomotor pattern generators but provokes supraspinal reorganization specific to the differential control of flexor and extensor muscles that characterizes human locomotion.

15.4.2 Establishing the Appropriate Environment

The concepts that underlie locomotor training are relatively simple, but the pragmatics of its delivery are less straightforward. Several factors, which include: limb advancement during swing phase, effective loading, means to experience normalized movement patterns, and movement variability, interact with the fundamental components of body-weight support and treadmill speed to influence overall training efficacy. The majority of studies to date report adjustment of the two fundamental parameters, body-weight support and treadmill speed, empirically, without providing a clear rationale based on either the biomechanics of walking or physiological function [59]. Specific to persons poststroke, adjustments of body-weight support are noted to influence: single-limb support time – especially of the paretic limb, upright posture, maximal hip and knee extension angles, and plantigrade orientation of the foot–ankle complex at weight acceptance. Adjustments of treadmill speed are noted to influence: cadence, stride length, muscle activation, and heart rate, and in combination reveal greater metabolic efficiency of training at higher speeds (reviewed in [60]). Taken together, the available evidence suggests that optimal levels to promote interlimb symmetry range between 15% and 30% body-weight support. While specific recommendations for treadmill speed are less tangible, the objectives remain to improve the timing and magnitude of relevant muscle activation during walking and promote independent and efficient overground walking at physiologic speeds.

Limb advancement during swing phase is not specifically influenced by the basic locomotor training parameters. Various investigators have addressed this problem using: manual assistance of one or more therapists/trainers [22, 56, 61, 62], electrical stimulation to trigger a flexion withdrawal response [63], neuromuscular electrical stimulation [64], restraining the treadmill to

speeds that allow the patient to advance the limb independently [65, 66], and providing external support via handrail hold [67]. Robotic devices contribute in this regard, not only by assisting limb advancement during swing phase, but by inducing a physiologic gait pattern with appropriate timing of stance and swing phases [68–70] and phasing of interlimb coordination.

Understanding the relative and concurrent effects of adjusting parameters of the locomotor training environment is critical to the development of effective training paradigms for restoration of locomotor function. Here, it is important to recall that walking is a bilateral, cyclic behavior. Approaches that focus on particular gait deficit (i.e., so-called foot drop) or specific phase of the gait cycle (i.e., swing phase) may neglect effects elsewhere in the gait cycle. For example, ankle dorsiflexion is often deficient, or even absent, during swing phase in persons poststroke. However, singular focus on addressing deficient ankle dorsiflexion may neglect stance phase deficits that compromise the ability to position the limb effectively and achieve hip extension in terminal stance and ankle plantar flexion at the stance-to-swing transition. While a singular focus on promoting dorsiflexion during swing may address "foot drop," it is equally likely to induce compensatory movement strategies including excessive hip flexion, shortened step length, and increased cadence. In contrast, promoting appropriate hip positioning permits appropriately timed ankle power at the stance-to-swing transition and sets in motion a series of events that include normalization of paretic limb swing time and enables limb shortening via combined adjustments at the hip, knee, and ankle [7, 71]. Robotic approaches are unique in their capacity to address the multifactorial problem of human walking.

While there is enthusiasm for the locomotor training approach and the collective evidence to date suggests it promotes improved walking function, it is well recognized that locomotor training is labor intensive. As discussed previously, an important objective is to normalize the kinematics during bilateral stepping in order to elicit appropriate activity in the spinal circuitry [16]. However, it is difficult to produce repeatable kinematics within individuals during training, making it difficult to produce consistent results across individuals. Inconsistencies in motor performance of the therapists/trainers assisting movement impede presentation of normalized kinematics and repetition of consistent patterns during training. Indeed, the results of 15 randomized controlled trials comparing locomotor training and traditional gait training (i.e., overground gait training, motor relearning) in persons poststroke reveal conflicting evidence regarding the efficacy of locomotor training [3, 72]. Perhaps more importantly, these mixed results highlight the difficulty in interpreting the effectiveness of manually applied cues during repetitive stepping. Considered in combination with the costs of delivering locomotor training [73], these challenges contribute to its limited acceptance in the clinical setting to date. In response to these challenges, robotic devices, such as the Lokomat® (Hocoma, Inc., Zurich, Switzerland), have been developed in an effort to automate locomotor training and offer more cost effective and labor efficient locomotor rehabilitation [68].

15.5 Robotic Approaches

15.5.1 Design Considerations

Important to consideration of the role of robots in rehabilitation is the designed intent of the device. For example, one of the earliest reports of a robot designed for rehabilitation of walking was REHABOT [74]. This device addressed the challenge of early mobilization in patients with multiple traumatic or orthopedic injuries by providing secure postural support and reduced weight-bearing during ambulation. Robotic control of these two parameters alone permitted early partial weight-bearing and ambulatory training for several hours per day in the acute hospital setting, and facilitated early return to independent walking. While the REHABOT may have lacked sophistication in the actual walking pattern, it did facilitate graded weight-bearing and physical activity during a critical period when patients would otherwise remain minimally active.

Another early entry into the rehabilitation robotics was the electromechanical gait trainer developed by Hesse and coworkers who reported remarkable success at improving ambulatory capacity in low functioning, nonambulatory individuals poststroke [69, 75]. Likewise, the Lokomat, developed by Colombo and coworkers, targeted attainment of some level of ambulatory capacity for otherwise nonambulatory individuals with incomplete spinal cord injury (iSCI) [68]. Considered from this perspective (i.e., promoting ambulatory function in nonambulatory individuals), the outcomes of robotic locomotor training are remarkable and significant.

As discussed previously, a clear strength of robotic training approaches is the ability for simultaneous control of the multiple parameters of walking. The attendant challenge in robotic design is to identify important parameters involved in generating, controlling, and training the locomotor pattern and to prioritize these parameters appropriately. For example, the Lokomat was originally designed to mimic manual locomotor training for persons with iSCI and thus incorporated the key elements of walking: upright positioning relative to gravity, weight-bearing through both limbs, and a bilateral, reciprocal gait pattern incorporating hip extension. Given that the goal was to induce ambulatory capacity in nonambulatory individuals, the generic set of parameters incorporated into this design may have been sufficient.

The importance of mechanisms contributing to disordered locomotor control varies somewhat by pathology. For example, in nonambulatory individuals with iSCI, the first priority is generation of afferent signals that converge on the spinal locomotor circuitry to facilitate stepping. In contrast, persons poststroke retain some capacity for locomotion, including the ability to step. While, ostensibly, the spinal circuitry remains intact poststroke, descending motor drive to the spinal pools is compromised. Further, walking with an asymmetrical, hemiparetic gait pattern returns afferent signals to the spinal circuitry that are both diminished and anomalous. Dysregulated sensorimotor integration may thus be far more detrimental to locomotor recovery poststroke than the absence of sensory signals to activate the spinal circuitry as emphasized in iSCI. Reintegration of accurate afferent signaling and descending motor drive at the level of the bilateral spinal circuitry is likely an essential requirement for walking recovery poststroke. Thus, effective locomotor rehabilitation for persons post-stroke must explicitly establish the biomechanical conditions that normalize coordinated bilateral motor activity. Repeated expression of this coordinated bilateral pattern will ultimately induce activity-dependent neural plasticity. To meet these goals and inform robotic designs with greater sophistication, necessitates a depth of understanding of the neuromechanics of walking for each clinical condition.

Table 15.1 summarizes currently existing robotic devices developed for locomotor rehabilitation [68, 69, 76–84]. Of note are the various design approaches and the elements emphasized in these designs. Early approaches to rehabilitation robotics controlled few parameters and offered limited adjustability. As previously noted, the REHABOT was designed to enable upright posture and support partial weight-bearing. The AutoAmbulator incorporated these fundamental elements adding mechanically guided reciprocal stepping. However, it offered no ability to adjust walking speed, cadence, or step length. Motivated by the goal to address principles of task specificity, the electromechanical gait trainer and Lokomat built on these rudimentary design concepts and incorporated adjustability of multiple parameters. Numerous devices, including both stationary and wearable exoskeletons, and designs incorporating various theoretical approaches to restoring locomotor control, now represent the rapidly evolving field of rehabilitation robotics. As the technical aspects of robotic design become more tractable and the design expertise expands, it becomes more critical to understand the neural control of locomotion, which elements of locomotion should be controlled and when and how these controls should be adjusted. For example, the recently developed Anklebot focuses solely on restoration of ankle dorsiflexion during swing phase and uses backdrivability, meaning the participant experiences less resistance when

Table 15.1 Existing robotic devices for restoration of walking function

Device	Design	Number of studies	Theoretical approach	Authors	Pub Year
REHABOT	Automatic device suspends patient in standing, provides secure postural support, and prescribed weight-bearing. No forward propulsion	3/3	Accurate support of body weight. Simplify walking and allow early mobilization for individuals with multiple comorbidities and/or requiring use of orthoses or walking aids. Target individuals difficult to train using traditional gait approaches including parallel bars	Kawamura, Ide, Hayashi, Ono, and Honda [79]	1993
Lokomat	Exoskeleton, driven gait orthosis	47/17	Based on motor learning principles of task-specificity and repetition with less therapist effort to set paretic limbs; establish physiological pattern.	Colombo, Wirz, and Dietz [68]	2001
Electromechanical gait trainer	Movement of footplates simulates stance and swing with a 60/40 ratio. Ropes attached to the patient control vertical and lateral movements of the center of mass in a phase-dependent manner. Device enables nonambulatory subjects to practice gait-like movement with minimal assistance. Some adjustability now available in step length and training speed. Partial body-weight support provided as is support of hand rail in front of patient	22/20	Task-specific repetition with less therapist effort to set the paretic limb	Werner, von Frankenberg, Treig, Konrad, and Hesse [69]	2002
AutoAmbulator	Exoskeleton	None	Simple mechatronic device offers upright positioning and reciprocal gait pattern. Enables early mobilization and initiation of walking therapy	Information derived from HealthSouth resource materials [83]	2002
LoPeS	Powered exoskeleton, actuated degrees of freedom include pelvic translation in horizontal plane, hip ab/adduction, hip flexion/extension, knee flexion/extension	3/1	Impedence control, assist-as-needed	van Asseldonk, Veneman, Ekkelenkamp, Buurke, van der Helm, and van der Kooij [80]	2008
Haptic Walker	End-effector; programmable footplate concept	1/1	End-effector principle	Hussein, Schmidt, Volkmar, Werner, Helmich, Piorko, Kruger, and Hesse [81]	2008
Tibion PK100	Wearable exoskeleton robot	1/1	Intention-based assistance/resistance during stance phase only	Horst [82]	2009
Powered ankle exoskeleton	Pneumatically powered exoskeleton	10/0	"Pneumatic muscles" augment and effectively increase plantar flexor strength during walking	Ferris [84]	2009
ALEX	Active leg exoskeleton and force-field controller	1/2	Assist-as-needed paradigm. Undesirable gait motion is resisted. Assistance provided toward desired motion. Effective forces applied at ankle through actuators at hip and knee	Banala, Kim, Agrawal, and Scholz [77]	2009
Anklebot	3-Degree-of-freedom backdrivable, wearable robot, actuated in sagittal and frontal planes	1/1	Dorsiflexion assist	Khanna, Roy, Rodgers, Krebs, Macko, and Forrester [76]	2010
G-EO-Systems	End-effector; programmable footplate concept	1/1	End-effector principle	Hesse, Waldner, and Tomelleri [78]	2010

Current robotic devices including brief treatment of design approach and device intention. Devices listed by publication date. Citations found from pubmed using terms "robotics, rehabilitation, stroke, gait training". Number of studies reflects: total citations for a given device (numerator) and studies reporting applications with persons post-stroke (denominator).

performing the desired motion [76]. In contrast, the ALEX device focuses on endpoint control [77] of foot–ankle placement using force fields to actively resist undesired motion and offering assistance as needed toward desired motion at all three joints: hip, knee, and ankle. As the field of rehabilitation robotics has matured, devices themselves and the control strategies have grown more sophisticated to incorporate: multijoint control to reproduce full kinematic trajectories of normal walking, multiple degrees of freedom at single joints (Hocoma, Inc., Zurich, Switzerland), physiologic variability [85], and assistance as needed [77, 86]. However, many questions remain regarding the control strategies. Invoking the principle of Occam's razor, the relatively parsimonious approaches of the REHABOT or the first generation Lokomat addressed only global aspects of normal gait (i.e., upright posture, reciprocal stepping, appropriate proportions of stance: swing or loading:unloading). But how much is enough? Did these relatively simple approaches afford sufficient physiologic specificity? Alternatively, is it necessary to develop subject-specific templates of the locomotor pattern? [87] Is this degree of sophistication necessary for certain neurologic conditions?

15.5.2 Current Evidence

Table 15.2 presents a brief synthesis of studies that have investigated acute (i.e., immediate, single-session) effects of robotic-guided walking in nondisabled individuals and persons poststroke or spinal cord injury [76–78, 80, 81, 86, 88, 89]. While it is not surprising that the device itself affects the spatiotemporal and kinematic characteristics of walking, these observations are important for identifying specifically how a robotic device influences the gait pattern. Further, this information provides important context for interpreting the outcomes of subsequent intervention studies and serves to inform the ongoing process of device development. For example, Neckel et al. observed healthy individuals while walking in the Lokomat and found that hip and knee angles and swing time are reduced but hip extension is increased [88]. These observations quantify expected differences between robotic-assisted and unconstrained treadmill walking; that is, the normal walking pattern is affected by moving against the robotic device. They also confirm the ability of the Lokomat to emphasize hip extension in terminal stance, which is a key objective of the locomotor training paradigm. Subsequent studies performed by these investigators involved individuals poststroke and revealed few significant differences in either kinematics or kinetics between healthy, paretic and nonparetic limbs during robotic-assisted walking. These observations indicate the capacity for the Lokomat to induce similar biomechanical effects between nondisabled and hemiparetic individuals. In reviewing the studies in Table 15.2, a common theme across devices is that nondisabled individuals demonstrate reduced joint angle excursions and increased swing time. Both effects are consistent with walking slower against an increased load.

Summarized in Table 15.3 are 11 studies drawn from the current literature that compare robotic locomotor training to either conventional rehabilitation, including gait training, or manual locomotor training for persons poststroke [1, 3, 69, 78, 90–96]. Characteristic of the rehabilitation literature, the study designs, therapeutic prescription, participant characteristics, and outcome measures vary tremendously, making it difficult to identify either distinct differences between training approaches or key elements where training approaches induce differential effects. Nine studies [1, 3, 90–95, 97] involve experimental designs, one study [96] involved biomechanical analysis of a subset of participants from one of the experimental designs [1], and one is a single case report [78]. Three experimental studies [91, 92, 95] were conducted in the acute rehabilitation period (i.e., <60 days poststroke), four involved persons in the subacute period (i.e., 2–10 months postevent) [69, 90, 93, 94], and two studied chronic hemiparetic individuals (i.e., >2 years postevent) [1, 3].

Table 15.2 Neuromechanical effects of robotic guidance

Citation	Device studied and device function	Population	*n*	Prescription	Study design	Outcome measures	Results
Neckel, Wisman, and Hidler [88]	Lokomat	Healthy	1	No intervention	Comparison of lower limb kinematics between Lokomat and treadmill walking at matched speed	Maximum knee angle Maximum hip angle Minimum hip angle	Maximum hip and knee flexion significantly lower in Lokomat compared to treadmill Maximum hip extension significantly higher in Lokomat compared to treadmill Percent time spent in swing significantly lower in the Lokomat
Neckel, Blonien, Nichols, and Hidler [89]	Lokomat	Stroke Chronic	10	No intervention	Comparison between controls, unimpaired, and impaired legs poststroke	ROM ankle, knee, and hip Max vertical pelvic displacement from heel strike Time of minimum pelvic displacement Maximum vertical ground reaction force Maximum ankle dorsiflexion torque Knee extension torque at midpoint of initial swing Time of maximum hip extension torque Hip adduction torque at midswing	Kinematics: no significant difference between control limbs and unimpaired limb of stroke subjects; No significant difference between the impaired and control limb; 1 significant difference between impaired and unimpaired limb (ankle ROM was less in the impaired limb). Kinetics: no significant difference between control and unimpaired limb of stroke subjects; 3 significant differences between impaired and control limb (maximum ankle dorsiflexion, knee extension at initial swing, and hip adduction at mid swing); 3 significant differences between impaired and unimpaired limb (maximum ankle dorsiflexion, knee extension at initial swing, and hip adduction at midswing). Lokomat torques: no significant difference between induced Lokomat torques on the three limbs (control, unimpaired, impaired)
Hussein, Schmidt, Volkmar, Werner, Helmich, Piorko, Kruger, Hesse [81]	Haptic Walker	Healthy	9	1	Comparison of free walking and stair climbing to each of 2 training modes; Comparison between 2 training modes	Mean normalized muscle activations during floor walking and walking up stairs	*Floor*: decreased activation shank extensor and flexor muscles, prolonged activation of thigh muscles, delayed onset from biceps femoris; *Stairs*: decreased activation of the shank muscles, (to a lesser degree), decreased activation of the thigh muscles and erector spinae, stronger activation of major weight-bearing muscles (when compared to floor walking)

Citation	device function	Population	*n*	Prescription	Study design	Outcome measures	Results
Emken, Harkema, Beres-Jones, Ferreira, and Reinkensmeyer [86]	Ambulation-Assisting Robotic Tool for Human Rehabilitation (ARTHuR)	Spinal cord injury (SCI) American Spinal Injury Association (ASIA) B–D Chronic	6	7 experiments within 2-h session	Proof of concept	Electromyographic (EMG) profiles Step height (kinematic data) Step length (kinematic data) Tracking error (kinematic data)	Kinematic trajectories: mean position tracking errors were within one standard deviation of the desired kinematic trajectories during walking
van Asseldonk, Veneman, Ekkelenkamp, Buurke, van der Helm, van der Kooij [80]	LOPES	Healthy	10	1	Randomized block design Types of walking: free walking on treadmill vs. walking with LOPES Walking velocities: 0.5 m/s 0.75 m/s 1.25 m/s	Stride time Total stance time Swing time Step length Single stance time Double stance ratio Step width Knee ROM Sagittal thigh movements Frontal thigh movements Frontal trunk rotation	All comparisons represent walking with LOPES vs. free walking Stride time: no significant difference Total stance time: no significant difference Swing time: significant increase walking with LOPES Step length: no significant difference Single stance time: Double stance ratio: significant decrease walking with LOPES Step width: significant increase walking with LOPES Knee ROM: reduced with LOPES walking Sagittal thigh movements: smaller with LOPES walking Frontal thigh movements: reduced with LOPES walking Frontal trunk rotation: significantly increased with LOPES walking
Banala, Kim, Agrawal, and Scholz [77]	ALEX	Stroke Chronic	2	Three, 5-day training sessions	Proof of concept	Tolerable treadmill speed. Ability of participant to track trajectory template developed from speed-matched healthy control. Template size	Tolerable treadmill speed: both participants showed improvements reflected by increases in their tolerable treadmill walking speeds Template tracking ability: both participants showed significant improvements in ability to track healthy control template Template size: both participants showed considerable improvements in template size and approximated control values

(continued)

Table 15.2 (continued)

Citation	Device studied and device function	Population	*n*	Prescription	Study design	Outcome measures	Results
Khanna, Roy, Rodgers, Krebs, Macko, and Forrester [76]	Anklebot	Stroke Chronic	10	No intervention[a] Anklebot was unpowered	Treadmill vs. overground and with vs. without anklebot on paretic leg	Kinematics Step time (footswitch data) Percent stance (footswitch data)	Spatiotemporals: no significant differences between overground and overground with robot; No significant differences between treadmill and treadmill with robot; improved symmetry with treadmill vs. overground. Kinematics: significant decrease in maximum paretic dorsiflexion during overground with robot vs. overground; nonparetic knee flexion greater in treadmill vs. treadmill with robot condition; Maximum paretic hip flexion higher with treadmill than overground; Maximum paretic hip flexion higher with treadmill and treadmill with robot than overground with robot condition; Maximum nonparetic hip flexion greater in the treadmill vs. overground with robot condition. No other significant differences
Hesse, Waldner, and Tomelleri [78]	G-EO-systems Device based on end-effector principle	Stroke Ambulatory Subacute ≥20 m, ≥0.25 m/s, ≥10 stairs reciprocally; AD and handrails allowed 6–14 weeks	6	No intervention	Real vs. simulated floor walking and stair climbing	EMG	*Simulated floor walking*: delayed onset and prolonged activation of the vastus medialis and vastus lateralis, relative to real walking condition; gastrocnemius showed a phasic pattern in simulated walking vs. a tonic pattern in real floor walking; *Stair climbing*: activation patterns and amplitudes comparable across conditions for the thigh muscles, shank muscles demonstrated timely activation in the simulated condition for 3 participants, and the gastrocnemius pattern became more phasic

[a]Goal of this study was observation of potential effects due to mass of the device

Table 15.3 Effects of robotic devices on walking function and recovery post-stroke.

Citation	Device studied and device function	Population	*n*	Prescription	Study design	Outcome measures	Results
Werner, von Frankenberg, Treig, Konrad, and Hesse [69]	Electromechanical gait trainer enabled nonambulatory subjects to practice gait-like movement with minimal assistance; movement of 2 footplates simulated stance and swing inducing timing of a physiological gait pattern; ropes attached to the patient controlled vertical and lateral movements of	Stroke	30	30 sessions	Randomized controlled study with crossover design	Functional ambulation categories (FAC)	FAC: Group A improved more than group B;
		Nonambulatory		5× per week	A-B-A vs. B-A-B	Rivermead motor assessment(RMA) score (gross functions and leg and trunk section),	RMA: Both groups improved over time, no group differences;
		Subacute		6 weeks	A = 2 weeks of gait trainer therapy (0–2.5 km/h)	Modified Ashworth (mAshworth) (ankle DF)	mAshworth : No group differences;
				Net walking time: 15–20 min in addition to other therapies	B = 2 weeks of treadmill therapy with BWS (0–5 km/h)	Gait velocity: (10-m overground, maximum speed)	Gait velocity: Both groups improved over time, no group differences
Tong, Ng, and Li [90]	Electromechanical gait trainer	Stroke	46	20 sessions	Randomized controlled trial	5M Walking speed	5M: Significantly faster following EGT-FES than CGT at 2 weeks and following EGT and EGT-FES rather than CGT at 4 weeks
		Subacute		5× per week	Control: Conventional gait therapy (CGT)	Elderly Mobility Scale (EMS)	EMS: Significantly higher scores following EGT and EGT-FES than CGT at 4 weeks
				4 weeks	Experimental Groups: Electromechanical gait trainer + Conventional Gait Therapy (EGT)	Berg Balance Scale (BBS)	BBS: No significant differences between control and experimental groups
				20 min of gait training as part of 1.5 h of interdisciplinary rehabilitation program	Electromechanical gait trainer with Functional Electrical Stimulation + Conventional Gait Therapy (EGT-FES)	FAC	FAC: Significant difference between CGT vs. EGT and CGT vs. EGT-FES at 2 and 4 weeks; control group did not show comparable improvements to experimental groups
						MI (leg)	MI: Significantly higher strength score from EGT-FES than CGT at 4 weeks
						Functional Independence Measure (FIM)	FIM: No significant differences between control and experimental groups
						BI	BI: No significant differences between control and experimental groups
							No significant differences between EGT and EGT-FES. However, effect sizes demonstrate differences in favor of EGT-FES

(continued)

Table 15.3 (continued)

Citation	Device studied and device function	Population	*n*	Prescription	Study design	Outcome measures	Results
Pohl, Werner, Holzgraefe, Kroczek, Mehrholz, Wingendorf, Holig, Koch, and Hesse [91]	Electromechanical gait trainer	Stroke Nonambulatory Subacute (<60 days)	155	20 sessions 5× per week 4 weeks 45 min	Randomized controlled trial Group A: 20 min Electromechanical gait trainer+25 min conventional physical therapy (PT) Group B: 45 min conventional PT	FAC Barthel Index (BI) Gait velocity: (10-m overground, maximum speed)walking endurance: 6 min walk test Mobility: Rivermead Mobility Index Leg power: Motricity Index (MI)	FAC: Significantly greater number of *group A* could walk independently at tx end and 6 month f/u; BI: Significantly more people in *group A* attained ≥75 at tx end. Difference not maintained at follow-up. *Group A* performed significantly better on walking velocity, endurance, mobility, leg power at tx end, but not at f/u
Husemann, Muller, Krewer, Heller, and Koenig [92]	Lokomat	Stroke Subacute (≥28, ≤200 days)	30	20 sessions 5× per week 4 weeks 60 min	Randomized controlled pilot study Control: 60 min conventional PT Experimental: 30 min robotic training+30 min conventional PT	FAC Gait velocity (10-m overground, maximum speed) Spatiotemporals (cadence, stride duration, stance duration, single support time for both legs) Body composition Muscle tone (mAshworth) Leg power (MI) BI	FAC: Both groups improved over time, no group differences; Gait speed and cadence: increased while stride duration: decreased over time, no group differences; Paretic single support time: Experimental group showed significant increase over control group; BI and MI: Increased over time, no group differences; mAshworth: No change, no group differences; Body composition: Control group increased body weight and fat mass, experimental group did not change body weight, but exchanged fat mass for lean body mass

Mayr, Kofler, Quirbach, Matzak, Frohlich, and Saltuari [93]	Lokomat	Stroke 0.5–10 months	16	45 sessions 5× per week 9 weeks Up to 30 min	Prospective, randomized, blinded, parallel-group trial ABA vs. BAB A = 3 weeks Lokomat B = 3 weeks conventional PT	Modified EU-Walking Scale RMA (gross function), Gait velocity: 10-m overground 6MTWD Muscle strength (Medical Research Council Scale (MRC) and MI) Muscle Tone (Ashworth)	Group 1 (ABA): Improved EU-Walking Scale, RMA, MRC, 6MTWD, following Lokomat (phases I and III), MI improved after phase I, Ashworth improved after phase III; no significant improvements noted during phase II Group 2 (BAB): Improved RMA, 6MTWD, MI following phase I, improved EU-Walking Scale, MRC, 6MTWD, and Ashworth following phase II, and 10 m walk time following phase III; walking speed did not significantly improve from baseline to end of treatment No significant differences noted between groups at baseline; therefore, differences result from differential training modes. Training with the Lokomat produced improvements in EU-Walking Scale, RMA, MRC, 6MTWD, MI, and Ashworth score; whereas training with conventional PT produced improvements in only RMA, 6MTWD, MI, and 10 m walk time
Hornby, Campbell, Kahn, Demott, Moore, and Roth [1]	Lokomat	Stroke Ambulatory Chronicity Robotic-assisted: 50 (+/-) 51 months Therapist-assisted:73(+/-) 87) months Baseline SSWS Robotic-assisted: 0.45–0.19 m/s Therapist-assisted: 0.43–0.22 m/s	48	12 sessions 3× per week 4 weeks 30 min	Randomized controlled study Control: Therapist-assisted locomotor training Experimental: Lokomat	Gait velocity (SSWS and FAST measured with Gait Rite) Single-limb stance% (Gait Rite) Step length asymmetry (Gait Rite) 6MTWD – overground distance covered walking at SSWS for 6 min Modified Emory Functional Ambulation Profile (mEFAP) BBS Frenchay Activities Index SF36 – physical component	*By Group*: Control group revealed larger gains than experimental group for SSWS, FAST, and single-limb stance%-FAST. Differences were not maintained at 6 month f/u No group differences detected for single-limb stance%-SSWS, step length asymmetry-SSWS, and step length asymmetry-FAST. *By Severity*: Participants with moderate deficits made greater improvements than participants with severe deficits in SSWS following treatment. Participants with severe deficits demonstrated greater improvements in step length asymmetry-SSWS. No differences detected for single-limb stance%.

(continued)

Table 15.3 (continued)

Citation	Device studied and device function	Population	*n*	Prescription	Study design	Outcome measures	Results
Hidler, Nichols, Pelliccio, Brady, Campbell, Kahn, and Hornby [94]	Lokomat	Stroke: 0.1–0.6 m/s <6 months	63	24 sessions 3× per week	Randomized clinical trial Control: Conventional therapy	Self-selected walking speed (SSWS) – 5-M overground Cadence (Gait Rite)	SSWS: control group improved more than experimental group;
		<6 months		8–10 weeks 45 min	Experimental: Lokomat	6MTW BBS FAC National Institute of Health Stroke Scale (NIHSS) Motor Assessment Scale (MAS) RMA Frenchay Activities Index SF-36	6MTW: control group improved more than experimental group; No group differences detected for FAC, RMA, BBS, MAS, cadence
Lewek, Cruz, Moore, Roth, Dhaher, and Hornby [96]	Lokomat	Stroke	26	12 sessions	Randomized clinical trial	Hip and knee average coefficient of correspondence (HK-ACC)	No group differences detected for SSWS, cadence, stride length, kinematics, and extent of limb circumduction.
		Ambulatory; able to walk ≥10 m without physical assistance; self-selected gait speed <0.8 m/s		3× per week	Control: Therapist-assisted locomotor training	SSWS	No group differences noted for HK-ACC in either paretic or nonparetic legs.
		Chronic (>6 months) (subset from Hornby et al. 2008)		4 weeks 30 min	Experimental: Lokomat	Cadence Stride length Kinematics Extent of limb circumduction	Within-group improvement noted for HK-ACC paretic in the control group

Westlake and Patten [3]	Lokomat	Stroke Ambulatory Chronicity Lokomat: 43.8–26.8 months Therapist-assisted: 36.8–20.3 months Baseline SSWS Lokomat: 0.62–0.31 m/s Therapist-assisted: 0.62–0.28 m/s	16	12 sessions 3× per week 4 weeks 30 min	Parallel, randomized design (pilot study) Control: Therapist-assisted locomotor training Experimental: Lokomat	Gait velocity (SWSS and FAST measured with Gait Rite) Step length asymmetry 6MTWD Fugl-Meyer Short Physical Performance Battery (SPPB) BBS Late Life Function and Disability Instrument (LLFDI)	By Group: No significant differences between experimental and control group for SSWS, absolute paretic step length ratio, Fugl-Meyer, SPPB, BBS, LLFDI. Experimental group: significant *within-group* improvements for SSWS, FAST, absolute step length ratio, Fugl-Meyer, SPPB, BBS; Control group: significant *within-group* improvements detected for only BBS. *By Training Speed*: No significant differences noted between fast- and slow-trained groups on primary or secondary measures

(continued)

Table 15.3 (continued)

Citation	Device studied and device function	Population	*n*	Prescription	Study design	Outcome measures	Results
Schwartz, Sajin, Fisher, Neeb, Shochina, Katz-Leurer, and Meiner [95]	Lokomat	Stroke Severity: 6–20 (NIHSS) <3 months	67	30 sessions 5× per week 6 weeks ~48 min	Nonblinded prospective, randomized, controlled study Control Group: Conventional physical therapy Experimental Group: Lokomat	Ability to walk independently according to FAC scale NIHSS FIM Stroke activity scale (SAS) Gait velocity – 10-m overground, maximum speed Timed Up and Go (TUG) Exercise tolerance – 2 min walk test Number of stairs climbed test	FAC: Experimental group showed significant improvement in ambulation ability (achieving FAC score ≥3). Control group did not. NIHSS: Both groups improved, greater improvement revealed in the experimental group. FIMcognitive: Both groups improved, no group differences detected. FIMmotor: Experimental group improved greater than control group. SAS: Both groups improved, no group differences. Tested for differences in gait velocity, TUG, exercise tolerance, and number of stairs climbed only in participants who achieved FAC ≥3. Only stair climbing revealed significant differences with the experimental group demonstrating greater improvement than the control group
Hesse, Waldner, and Tomelleri [78]	G-EO-systems	Stroke	1	25 sessions	Clinical case report	FAC	FAC: Improved from level 1 at baseline to level 4 at the end of 5 weeks; able to walk 20 m with a quad cane, without physical assistance
	Device based on end-effector principle	Nonambulatory		5× per week 5 weeks 25–30 min		MI RMA BI	MI: Improved from a score of 22 at baseline to a score of 59 at the end of 5 weeks RMA: Improved from a score of 3 at baseline to a score of 7 at the end of 5 weeks BI: Improved from a score of 25 at baseline to a score of 65 at the end of 5 weeks

Synthesis of studies investigating acute (n = 6) and intervention-related effects (n = 12) of robotic locomotor trainers/training.
Abbreviations: w/c - wheelchair, FAC – Functional ambulation categories, RMA – Rivermead motor assessment, mAshworth – modified Ashworth score, BI – Barthel Index, MI – Motricity Index, tx – treatment, f/u – follow-up, PT – physical therapy, CGT – Conventional Gait Therapy, EGT – Electromechanical Gait Trainer, EGT-FES – Electromechanical Gait Trainer with Functional Electrical Stimulation, EMS - Elderly Mobility Scale, BBS – Berg Balance Scale, FIM – Functional Independent Measure, MRC – Medical Research Council Scale, SSWS – self-selected walking speed, NIHSS – National Institute of Health Stroke Scale, MAS – Motor Assessment Scale, mEFAP – modified Emory Functional Ambulation Profile, SPPB – Short Physical Performance Battery, LLFDI – Late Life Function and Disability Instrument, HK-ACC – hip and knee average coefficient of correspondence, ARTHuR – Ambulation-Assisting Robotic Tool for Human Rehabilitation, SCI – spinal cord injury, ASIA – American Spinal Injury Association, EMG - Electromyography

15.5.3 Robotic Training Versus Conventional Therapy

Robotic training and conventional therapy were compared in six studies, all of which were conducted in the acute to subacute period of stroke recovery (i.e., range 28 days–10 months) [90–95]. The inclusion criteria for one study extended to the period from 6–10 months poststroke [93]. The robotic devices studied included the electromechanical gait trainer (EGT) [75] and the Lokomat [98]. Clinical measures of *impairment* [99] including the Rivermead Motor Assessment [100], Fugl-Meyer Test of Motor Function [101], NIH Stroke Scale, and either the Ashworth or modified Ashworth scale [102] reveal equivocal differences between training approaches. Two studies report no differences between groups [92, 94], while two studies favor robotic training [93, 95]. Indicators of *walking ability* including the: Functional Ambulation Categories (FAC) [103], EU-Walking Scale [104], Elderly Mobility Scale [105], and timed walking tests (6MTWD [106]) favor robotic training in four studies [90, 91, 93, 95], while two studies reveal no difference between robotic and conventional training [92, 94]. Three studies report improved *walking distance or endurance* following robotic training [90, 91, 93], while conventional therapy produced greater effects in one study [94]. Improvements on other indicators such as disability and activities of daily living (ADL) are difficult to assess and have not been consistently evaluated across studies. Nonetheless, two studies report gains following robotic training [91, 95], while two studies report no differences between approaches [90, 92]. Specific *gait parameters* also reveal mixed results. Two studies report greater improvements in walking speed following conventional therapy [93, 94], while Pohl [91] reported greater effects following training with the EGT and Husemann's investigation [92] revealed improvements following both approaches. Of note, following Lokomat training, Husemann [92] reported improved paretic single-limb support time during gait while Schwartz [95] reported improved ability for stair climbing. Both of these findings suggest improvements in strength, or power, particularly in the paretic limb. In this light, strength, broadly defined, using assessments including the Motricity Index [107], MRC Scale [108], or direct measurement of strength/power clearly favor robotic training [90–93]. In addition, Husemann's finding of increased lean body mass following robotic, but not conventional, training are noteworthy [92].

An important detail to note in the studies comparing robotic gait training to conventional therapy is that in many of these studies [90–92, 95], the experimental treatment involved both conventional gait therapy and robotic training. Thus, the comparison in these studies was not truly between robotic and conventional therapy. Rather, the study designs held the time in therapy constant and compared conventional therapy, including gait training, to a similar amount (i.e., time) of combined robotic and conventional therapy. Recognizing this critical detail, it is important to note that the actual amount of robotic therapy in these studies was half, or less than half, of the full time spent in each therapy session. Clarifying these parameters underscores the efficacy of robotic training and further confirms that the combination of robotic training and conventional physical therapy or gait training increases the likelihood of regaining independent ambulatory status [109]. These findings suggest that by combining robotic and conventional therapy, participants may be better able to consolidate and generalize locomotor adaptations, at least as probed by the clinical measurements used. Related to this point Mayr [93] used an alternating treatment design (i.e., ABA and BAB), which also combined robotic and conventional therapies, although presentation of the treatments was interleaved in blocks rather than within sessions. While Schwartz [95] compared robotic (Lokomat) to conventional gait training, the study design involved gait training sessions (3 per week) in addition to regular physical therapy daily for 6 weeks. Again, the significantly greater gains in neurologic status, ambulation capacity, and motor function revealed by the Lokomat-trained group were attained in conjunction with a regime of regular, conventional physiotherapy.

In a true parallel design, Hidler and coworkers [94] compared conventional therapy to robotic locomotor training with the Lokomat. While similar to studies discussed above, participants were in the subacute phase poststroke, but an important difference is that ability to walk without physical assistance was required for study inclusion. In contrast to studies discussed thus far, the conventional therapy group outpaced the Lokomat group on the primary outcome, overground walking speed. Secondary outcomes including walking ability, balance, and motor impairments revealed no differences between groups. These findings emphasize two important points regarding the efficacy of robotic locomotor training poststroke: first, robotic approaches demonstrate efficacy for improving ambulatory capacity; second, the strongest effects of robotic training have been demonstrated in participants with low levels of walking function (i.e., gait speeds <0.3 m/s [21]).

15.5.4 Robotic Training Versus Locomotor Training

A second set of studies involves comparisons between locomotor training, either with or without therapist assistance, and robotic locomotor training. Werner [69] utilized multiple ABA or BAB designs, where "A" phases involved the electromechanical gait trainer (EGT) in comparison to treadmill therapy with body-weight support ("B" phases) and revealed greater improvements in functional ambulation categories, but not walking speed, following training with the EGT in persons in the subacute phase poststroke [69]. In a study design with little contrast between experimental and control treatments, Hornby and coworkers [1] found that manual, or therapist-assisted, locomotor training revealed greater improvements in both self-selected and fast overground walking speed compared to an equivalent dose of locomotor training with the Lokomat. Of note, participants were in the chronic phase poststroke, and demonstration of ability to walk >10 m without physical assistance was required for study eligibility. Secondary outcomes revealing differences between treatment approaches include single-limb stance time in the fast walking condition and the physical function dimension of the SF-36. While statistical differences in single-limb stance were detected, it is important to note that the improvement reported was a 2% change, representing 20–22% of the gait cycle, while single-limb stance in healthy individuals is 39% of the gait cycle [110]. Taken together, these results suggest that both manual and robotic locomotor training improved walking speed, but did not appear to induce significant changes in the gait pattern. Instrumented gait analysis of a subgroup performed by Lewek and coworkers [96] revealed lack of change in kinematics, spatiotemporal parameters including cadence, step and stride length, and paretic limb circumduction in either group. Interjoint coordination, quantified using the hip–knee average coefficient of correspondence [111] (HK-ACC), revealed improved consistency following therapist-assisted locomotor training. While improved HK-ACC consistency was interpreted to reflect superior motor learning and skill acquisition and attributed to greater variability in the therapist-assisted condition, this interpretation warrants caution [112]. A higher HK-ACC indicates greater consistency in the interjoint coordination pattern, which may reflect strengthening of dysfunctional or aberrant locomotor coordination. Westlake [3] compared Lokomat and manually assisted locomotor training in chronic individuals poststroke. While the study design was quite similar to that utilized by Hornby, results of this pilot study revealed significant within-group differences favoring Lokomat training on primary outcomes of self-selected overground walking speed, fast walking speed, and step length symmetry. Potentially important differences between Westlake's and Hornby's studies include both chronicity poststroke and baseline walking function. Additional factors include specific training parameters. The Lokomat used by Westlake and coworkers was capable of attaining normal, physiologic walking speeds (i.e., 5 km/h or 1.4 m/s) [3]. Training in the range of speeds exceeding the standard Lokomat (i.e., 3.3–5 km/h) may have contributed to positive gait speed outcomes in the robot-trained group. Additionally, participants in

this study were trained without ankle–foot orthoses that alter ankle joint range of motion and affect plantigrade orientation during limb loading, and when safely possible, Lokomat elastic foot lifters were removed to enable normal foot–ground interaction at loading and terminal stance. All means were observed to optimize position and load-related sensory signals that may influence the gating of spinal locomotor patterned activity.

Three of these studies tested persistence of treatment effects at times distal to the intervention. In all three cases, significant differential effects were detected immediately posttreatment [1, 91, 94], favoring robotic training [91], conventional therapy [94], and manual locomotor training [1] in one case each. Pohl's study, in subacute individuals, revealed differential treatment effects that were lost at follow-up 6 months postintervention [91]. It is important to note that treatment-related gains were retained, and even somewhat advanced, during follow-up, however, due to intersubject variability, statistical differences between groups were not detected at follow-up. Such results are quite typical of clinical research in rehabilitation. In contrast, Hornby's study involved individuals in the chronic phase poststroke (i.e., 4–6 years postevent). While revealing modest gains in gait speed and differential treatment effects immediately following locomotor training, these gains dissipated and differential treatment effects were no longer manifest at the 6 month follow-up evaluation [1]. Differences between conventional and Lokomat training were both greater and maintained statistical significance at 3 month follow-up in subacute individuals studied by Hilder [94]. Taken together, the available evidence demonstrates a robust biological effect of improved walking capacity that appears to be mediated by training and persists, to some degree. These effects are considerably greater when intervention occurs earlier in recovery. Robotic approaches appear to be particularly beneficial for promoting ambulatory ability in low level, or nonambulatory, individuals, especially in the acute phase of recovery. Once ambulatory capacity has been achieved, improvements in locomotor function, including changes in the locomotor pattern, have not been well investigated.

An additional detail to consider is that the majority of these studies involved greater, and more consistent, therapeutic doses relative to those offered in the typical clinical setting. Independent of chronicity poststroke, the doses tested in these studies reveal robust biological effects of improved walking speed and walking function generally consistent with fundamental principles of neural plasticity [113]. Given the fundamental rationale to offer more repetition and contextualized in the overall developmental timeline, these cumulative findings using rehabilitation robotics are encouraging. Devices have been developed. Their feasibility, safety, and fundamental efficacy have been demonstrated. Having attained these milestones, the challenge for the next generation of rehabilitation robotics is development of approaches that optimize therapeutic efficacy. Rather than mimicking current, conventional therapies, robotics holds potential to produce better, longer lasting effects more efficiently. But we need to understand the unique opportunities and parameters afforded by the robotic environment.

15.6 Can We Change the Fundamental Locomotor Pattern?

The capacity to restore the fundamental locomotor pattern in persons poststroke remains an unanswered question in neurorehabilitation. Once this capacity is revealed, there is a need to understand the most effective approach to locomotor restoration, and this information will inform the next generation of robotic designs.

15.6.1 Task-Specific? How Specific?

As discussed above, a critical perspective of the locomotor training approach is recognition of the inherent capacity for plasticity, even following central nervous system insult. Because locomotor training shifts the goal from attainment of

walking capacity regardless of locomotor strategy, it is critical to establish conditions in which the damaged nervous system can experience normalized movement patterns. Locomotor training has been proposed as an effective approach to promote walking recovery because it offers the requisite task specificity to address the functional and biomechanical subtasks of walking.

Here, it is important to note that the current evidence remains inconclusive regarding whether locomotor training produces superior outcomes to traditional therapeutic approaches for persons poststroke [1, 94, 114, 115]. This lack of conclusive findings suggests the three putative walking functions: stepping, balance, and adaptability, as identified for animal and spinal cord injury models and described above, may not encompass all critical elements of the locomotor training paradigm as it relates to persons poststroke. Because both supraspinal and spinal segmental structures remain at least partially intact and patent, dysregulated sensorimotor integration may be far more critical than generation of sensory signals to activate the spinal circuitry, as is the goal in models of spinal cord injury. Our perspective thus holds that integration of afferent signaling and descending motor drive at the level of the bilateral spinal circuitry represents a fourth essential requirement for walking. Because the neural mechanisms controlling sensorimotor integration are disrupted poststroke, effective locomotor rehabilitation must explicitly establish physical and biomechanical conditions that normalize coordinated bilateral motor activity. Repeated expression of the coordinated bilateral pattern is necessary to induce activity-dependent neural plasticity. We assert that robotic approaches afford means to control the requisite physical and biomechanical parameters of walking and present normalized movement patterns to the damaged nervous system.

15.6.2 The Robot Is Not Passive

Contrary to prevailing expectation, robotic-guided locomotion is not passive. While EMG patterns differ somewhat between unconstrained walking and walking in the Lokomat, these differences are understandable given constraints of both treadmill walking and the presence of the robotic exoskeleton [116]. Speed-related modulation of EMG patterns during Lokomat walking in healthy individuals up to and including physiological walking speed (i.e., 1.4 m/s) [116] is consistent with speed-related scaling of EMG patterns during unconstrained treadmill walking [117]. Importantly, patterns at slow walking speeds (<3.5 km/h or 0.9 m/s) illustrate prolonged, and often ill-timed, muscle activation. However, as physiologic walking speeds are attained (>3.5 km/h), EMG patterns become progressively tuned and appropriately timed to the specific biomechanical functions of gait. Additionally, distal muscles, both tibialis anterior and gastrocnemius, are activated appropriately; thus, lack of actuation at the ankle does not impair the normal control strategies or the foot–ground interaction.

Our early experiences with the Lokomat revealed EMG activity generally consistent with expected timing of muscle activation patterns fulfilling biomechanical functions of gait. Of note, however, is an incidental observation illustrated in Fig. 15.1. Our data illustrate that muscle activation at, or below, self-selected walking speed is markedly asymmetrical with substantially less activity in the paretic relative to the nonparetic limb. This finding was not surprising and consistent with our earlier research [118] that revealed profound, disruptive influences of the nonparetic limb on paretic limb activation during bilateral, reciprocal locomotor activity. However, with progressive increases in walking speed in the Lokomat, paretic limb activation systematically increased, while nonparetic limb activation systematically decreased. These observations illustrate three salient points. First, robotic-assisted locomotion is not a passive phenomenon. Second, EMG is actively modulated during a single session of robotic-assisted walking indicating that the locomotor pattern is influenced by adjustments in the biomechanical parameters, including walking speed. Third, the symmetry of EMG activity between the paretic and nonparetic limbs improves markedly with increased stepping speed. This increased activation may exert, at least partial, inhibition on the nonparetic motor

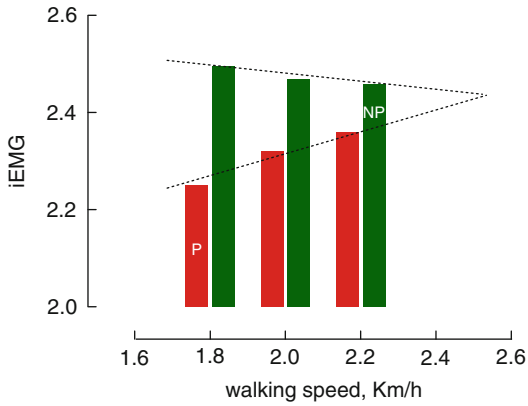


Fig. 15.1 Walking speed improves neuromotor symmetry. EMG data obtained from the vastus medialis of a chronic hemiparetic individual walking in the Lokomat at progressively increasing speeds. The Lokomat was operated using the default (bilateral position control) mode with 30% body-weight support. Foot lifters were used to assure limb/foot clearance. Treadmill speed was adjusted as tolerated. Quadriceps activity (integrated EMG per stride) becomes more symmetric with increased walking speed. Importantly, improved symmetry results from both increased paretic leg activity and reduced nonparetic leg activity and suggests a speed at which EMG will reach symmetry between limbs. These data clearly demonstrate that robotic-driven locomotion is an active, rather than passive, process

pools [119], producing a net normalizing effect on activation of the bilateral motor pools revealed as more symmetrical motor output. Of note, this phenomenon occurs simultaneously in multiple muscles at the same speed. Fundamentally, it is now possible to identify the subject-specific range of speeds where symmetrical neuromuscular activation is restored. Locomotor training in this range of speeds is likely to produce restorative effects on the locomotor pattern.

Another point related to activity during robotic walking was elegantly illustrated by Israel et al [120] in comparing metabolic cost (VO_2) between walking in the Lokomat and walking with manual assistance in persons with iSCI. Metabolic cost was markedly reduced while walking in the robot. This finding has been interpreted in favor of manual locomotor training, arguing that the intensity of exercise is greater during manual training and, further, that robotic-assisted walking is passive. However, considered in combination with changes in body composition reported by Husemann [92], these findings suggest that the lower metabolic cost of robotic-assisted walking may support sustained bouts of stepping with greater likelihood of inducing physiologic training effects. Moreover, metabolic cost was compared at matched speeds between manual and robotic-assisted walking. Manual locomotor training is typically conducted at the participant's "comfortable" walking speed. The ability to train for either sustained periods or at higher speeds, approaching normal walking speed, is limited by the capacity of therapists/trainers and, to some degree, discomfort of the participant. In this light, reduced metabolic cost during robotic-assisted locomotion offers: the potential to train at higher speeds, approaching physiologic walking speed; to experience more normal neuromotor patterns; and to sustain continuous stepping. It is noteworthy that Husemann found the control group (conventional therapy) increased body weight and fat mass over the 4 week (20 sessions) intervention, while the experimental (combined conventional and robotic training) group maintained body mass and exchanged fat mass for lean body mass. This difference may not be surprising, especially having made the point that studies investigating robotic training involve both increased dosage and consistency of dose, at least as defined by training time and, ostensibly, repetitions (steps), for all participants.

15.6.3 Altering the Biomechanical Environment

Spatiotemporal asymmetry between limbs is a hallmark of hemiparetic walking dysfunction. Illustrated in Fig. 15.2 [1, 3, 110] are differences in paretic single-limb support (expressed as percent gait cycle, SLS%) from 12 hemiparetic individuals during overground, treadmill, and Lokomat walking at the same speed. While it has been reported that treadmill walking, in and of itself, improves spatiotemporal symmetry [67], these data reveal that treadmill walking – without support of handrail hold – not only fails to improve SLS% symmetry but actually exacerbates asymmetry in some individuals. In contrast, walking with guidance of the Lokomat normalizes SLS% of both paretic and nonparetic limbs. Husemann's

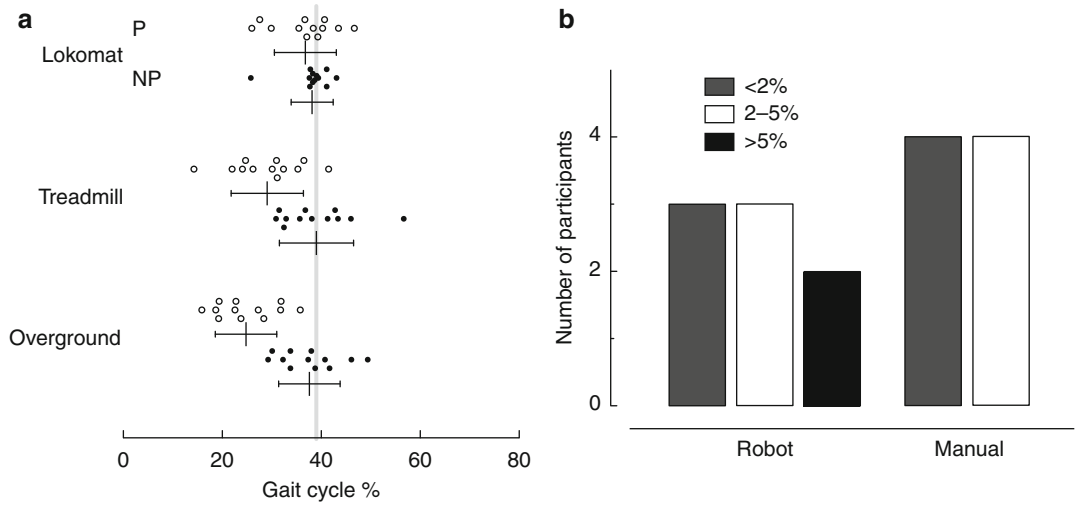


Fig. 15.2 (**a**) Single-limb support time across walking conditions. Single-limb support expressed as percent gait cycle for both paretic (*solid*) and nonparetic (*open circle*) legs in 12 chronic hemiparetic individuals during overground, treadmill, and Lokomat walking at matched speeds. Vertical cursor line at 39% of gait cycle denotes SLS% for normal, adult gait [110]. Individual subject data are presented with group mean (standard deviation) designated below each cluster. Asymmetry between paretic and nonparetic legs is obvious, and unchanged ($p > 0.05$) between overground and treadmill conditions. During Lokomat walking, nonparetic limb SLS% is markedly normalized, clustering around 39% gait cycle. While variability among individuals remains present in the paretic leg, the group mean is markedly shifted toward normal ($p < 0.01$), and means between limbs are similar ($p > 0.05$). Note that 9/12 participants reveal P-SLS% near 39% gait cycle. (**b**) Changes in SLS% posttraining. Frequency counts of participants producing minimal (<2%), small (2–5%), or modest (>5%) improvements in P-SLS% (Data from Westlake and Patten [3], with eight participants per group (Lokomat and manually trained). Consistent with observations from Hornby et al. [1] changes following manual training are distributed between minimal and small magnitude improvements. The Lokomat-trained group demonstrated fewer individuals in the minimal change group and more improving P-SLS% >5%)

comparison of conventional gait training to combined Lokomat and conventional training revealed significant improvements in paretic single-limb support (P-SLS%) in the Lokomat-trained group [92] consistent with repetitive experience of loading the paretic limb for normal duration of SLS. While statistically significant differences between groups were not detected in the sample reported by Westlake [3], our data reveal more large improvements in P-SLS% (i.e., >5% of gait cycle) in participants who trained in the Lokomat (Fig. 15.2b). This finding is consistent with the biomechanical task specificity of normalized SLS% and loading experienced during Lokomat-guided training.

15.6.4 Are We Measuring the Right Outcomes?

Addressing the question of capacity for neuromotor recovery assumes we are measuring the appropriate outcomes. Few studies to date have probed beyond gross measures of walking speed or clinical outcome scales of gait ability, to determine whether, and how, locomotor training affects the neurobiomechanical walking pattern [22, 56, 65, 69, 112, 121]. The overwhelming majority of rehabilitation studies use overground walking speed as their primary outcome [3, 62]. While overground walking speed does reflect certain aspects of hemiparetic severity and functional capacity, its use as a primary outcome can be problematic because many factors contribute to walking speed. Improved walking speed can result from: physical conditioning, acquisition of compensatory movement strategies or genuine changes in locomotor function – either changes in coordination or neuromechanical function. Further, while many studies report small, perhaps clinically meaningful [122, 123], changes in overground gait speed, it is important to recognize the heterogeneity of response contributing to these

group effects. Any of the existing literature reporting gait speed changes is likely reporting combined effects of responders, nonresponders, and even negative responders. Mixing these patterns of response obscures the ability to identify actual physiologic changes. To identify these differences requires measures with greater sensitivity.

15.6.5 Vertical Ground Reaction Forces

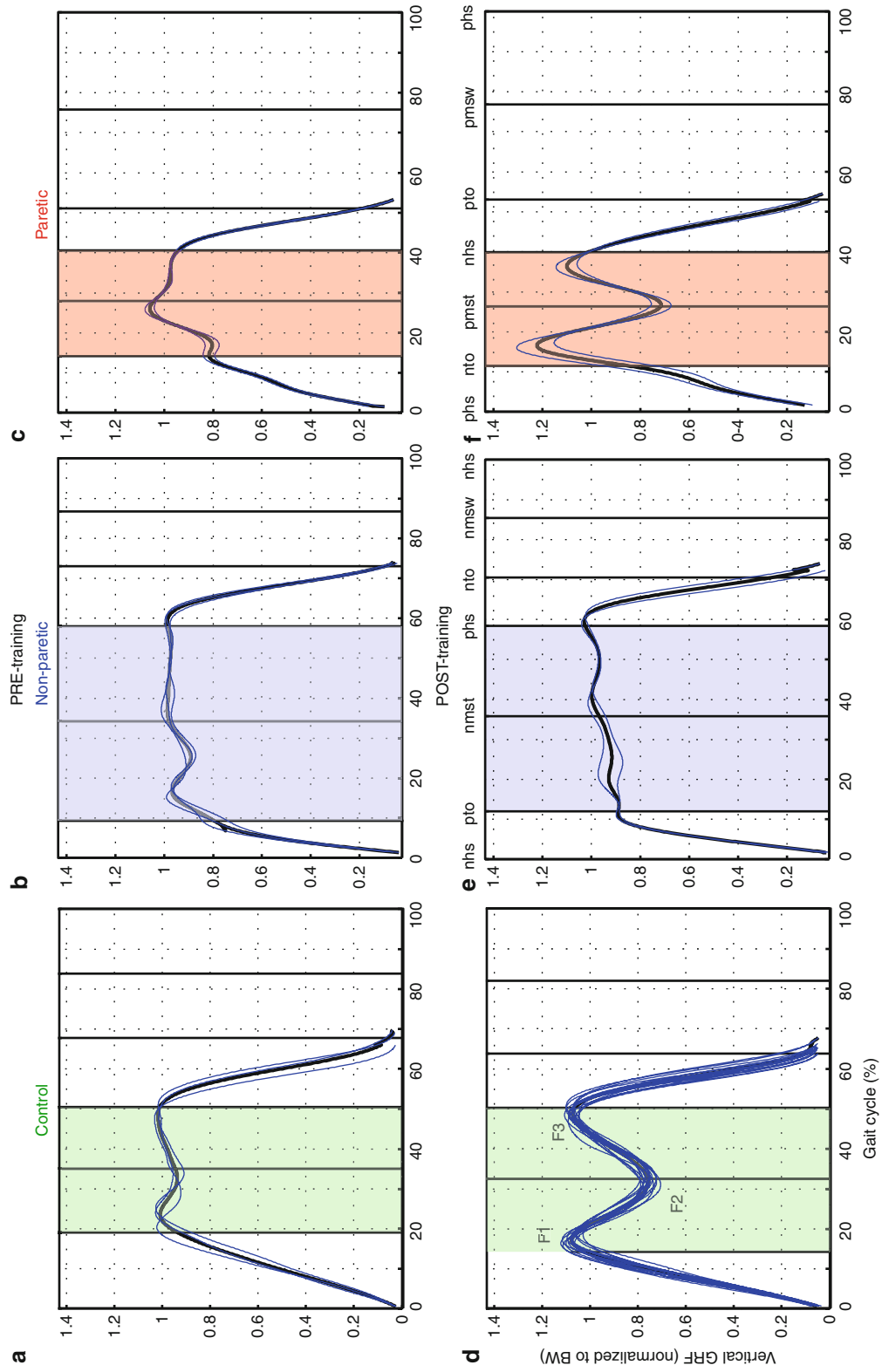
While it is important to understand effects induced while walking in the robot, it is critical to determine whether these produce persistent effects during unconstrained voluntary activity outside of the robot. Prior to and following our pilot study comparing robotic and manual locomotor training [3], we conducted instrumented gait analysis to characterize the gait pattern (pretraining) and identify changes (posttraining). Importantly, all participants were studied walking overground. Posttraining studies were conducted within 1 week following completion of locomotor training. Both pre- and posttraining data are interpreted relative to reference normal by making comparisons between individuals with hemiparesis and nondisabled individuals walking at matched speeds.

Vertical ground reaction forces (Fig. 15.3) revealed some improvements consistent with not only increased and more symmetrical single-limb support, as described above, but improved loading and transfer of body weight between limbs. In addition to comparison between manual and robotic locomotor training, our study examined the effect of training speed. Half the sample was randomized to slow (<2.5 km/h or 0.69 m/s), while the other half was randomized to fast (>3.0 km/h or 0.83 m/s) training speeds. While our primary outcome (gait speed) did not reveal a significant effect, changes in the vertical ground reaction forces revealed improved symmetry between limbs, especially in individuals who trained either at fast speed or in the robot. For overall assessment of interlimb symmetry, we defined improvement as improved symmetry in at least 2 of the 3 peaks that characterize the vertical ground reaction force (i.e., F1, F2, and/or F3). Using this definition, the majority of participants who trained robotically demonstrated quantitative improvements in interlimb symmetry. Additionally, the majority of fast-trained participants demonstrated improved symmetry, while few such improvements were observed in slow-trained individuals. We also assessed intralimb changes in loading and unloading. Consistent with the interlimb effects discussed above, a greater number of improvements were observed in both paretic and nonparetic limb loading in the fast-trained individuals (Fig. 15.4a) [3]. Limb unloading patterns also improved somewhat in fast-trained individuals, although these effects were less dramatic (Fig. 15.4b). Although we anticipated the paretic limb would produce the greatest number of changes in vertical ground reaction force, our data revealed bilateral adaptations resulting from locomotor training. Training at fast speeds induced the greatest magnitude and number of improvements. Robotic configurations enable training at physiologic walking speeds for sustained periods and thus are critical to eliciting these effects.

15.6.6 Interjoint Coordination Patterns

We also investigated interjoint coordination patterns between the hip and ankle during overground walking to determine whether locomotor training alters the coordination pattern. Figure 15.5 illustrates our method for quantifying interjoint coordination (IJC). We compared IJC patterns in hemiparetic participants to control participants walking at similar speeds and identified positive changes when the hemiparetic subject's pattern became more similar to control between pretest and posttest. Likewise, we identified negative changes when subjects' patterns became more dissimilar to controls.

Tracking the centroid location of the hip–ankle angle–angle plot revealed that the majority of individuals demonstrated improved IJC in both nonparetic and paretic limbs. Interestingly however, nonparetic limb improvements appear to predominate from the hip. Further, our analysis detected differential patterns of improved IJC between Lokomat and manually trained individuals. Across all participants, we found that Lokomat-trained individuals improved IJC more


a
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significantly than manually trained individuals. While our analysis detected roughly an equal number of beneficial and detrimental changes in IJC patterns among manually trained individuals, these changes were equally distributed across both the paretic and nonparetic limbs. We were surprised to find detrimental changes (i.e., worse IJC) bilaterally at the ankle suggesting a loss of normal coordinated ankle motion following manual locomotor training. Most notably, however, improved paretic limb IJC in Lokomat-trained individuals resulted from concurrent hip–ankle contributions. This pattern of concurrent joint contributions suggests that robotic training promoted reacquisition of the coordinated motor pattern rather than compensation for hemiplegic gait with exaggerated single joint contributions to IJC.

15.7 Conclusions – Ongoing Development and Future Thinking

Current perspectives in neurorehabilitation recognize the inherent capacity for neuroplasticity, even following central nervous system insult. Therefore, it is critical to establish conditions in which the damaged nervous system can experience normalized movement patterns, especially the sensory experience that stems from appropriate mechanical loading and movement. Robots could be used to our advantage in this regard, but to date, this has not been the overriding perspective. Our initial experiences with the Lokomat afford optimism that it is indeed possible to change (improve) the fundamental locomotor pattern in persons poststroke. More importantly, these findings belie capacity for neuromotor recovery that has otherwise gone unrecognized due to use of suboptimal outcome measures and has remained untapped due to inability to effectively induce appropriate neuromechanical conditions. As rehabilitation robotics move to the next generation of development, there are opportunities for continued technological advancements. Rather than replication of clinical effects, the goal and expectation of these future designs is neural recovery and restoration.

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Fig. 15.3 Representative vertical ground reaction forces (*vGRF*) during overground walking. Patterns in nondisabled individuals (**a** and **d**) illustrate a positive peak (F1) at ~12% of the gait cycle, representing the beginning of single-limb support (*SLS*), as the contralateral limb initiates swing, the negative peak (F2) occurs at midstance as the contralateral limb is in midswing; the second positive peak (F3), occurring at ~50% of the gait cycle, represents the end of SLS, as the contralateral limb begins stance. The shaded area in each plot represents SLS. The epoch between F1 and F2 represents limb loading as the center of gravity (*COG*) moves over the support limb. The epoch between F2 and F3 represents limb unloading as the COG translates forward of the support limb in preparation for swing. The magnitude of the F1, F2, and F3 peaks results from differences in walking speed, (**a**) (0.7 m/s) and (**d**) (1.16 m/s) correspond with walking speeds produced by a hemiparetic individual who participated in robotic locomotor training. (**b**) (nonparetic limb) and (**c**) (paretic limb) illustrate vGRFs at self-selected walking speed (*SSWS*, 0.66 m/s) prior to LT. Following LT in the Lokomat distinctive peaks in the paretic limb vGRF at SSWS are illustrated (**f**) indicating normalization relative to nondisabled individuals (Abbreviations: *nhs* nonparetic heel strike, *pto* paretic toe off, *nmst* nonparetic midstance, *phs* paretic heel strike, *nto* nonparetic toe off, *nmsw* nonparetic midswing, *pmst* paretic midstance, *pmsw* paretic midswing)

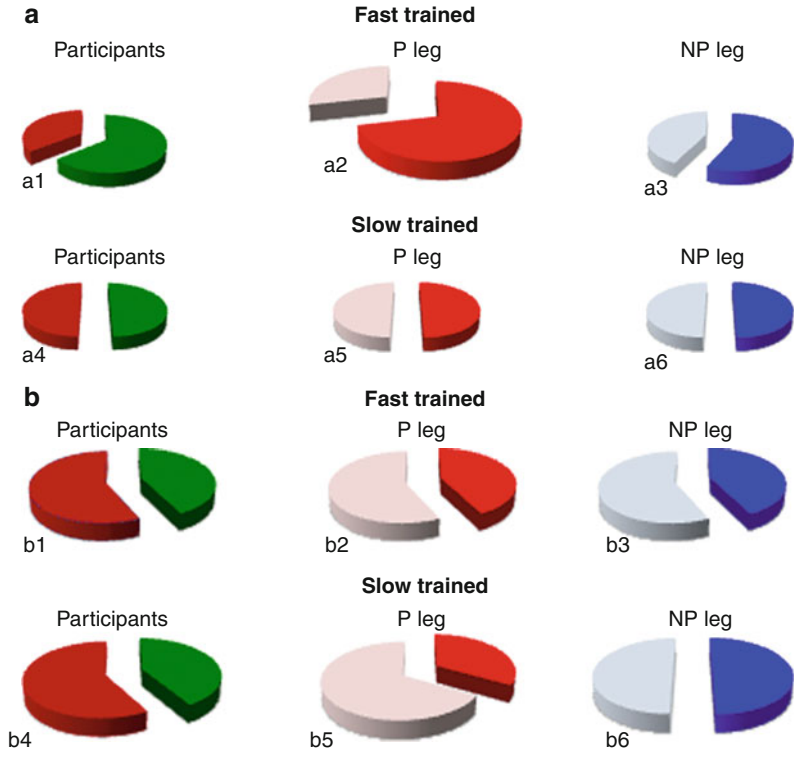

Fig. 15.4 (**a**) Limb loading (F2/F1). Changes in limb loading identified by analysis of vertical ground reaction forces (*vGRF*) obtained during overground walking following locomotor training in persons with chronic post-stroke hemiparesis (results reported in Westlake and Patten [3]). The ratio of the F2/F1 vGRF peaks characterizes loading and transfer of body weight onto the stance limb during the single-limb support phase of gait. Participants were stratified to slow (<2.5 km/h or 0.69 m/s) vs. fast (>3.0 km/h or 0.83 m/s) training speeds. Independent of manual or robotic training mode, the majority of fast-trained participants (64%) demonstrated improvements in limb loading (*a1*) which were noted more frequently in (*a2*) paretic (71%) vs. (*a3*) nonparetic (57%) legs. Fewer improvements in limb loading were observed in slow-trained individuals (50%) (*a4*) and were equally distributed across (*a5*) paretic and (*a6*) nonparetic legs. While improvements in limb loading were observed in fast-trained individuals following both manual and robot training modes, robotic training offers a clear advantage to achieve physiological walking speeds and maintain a coordinated stepping pattern. (Legend: *a1* and *a4 green* – improved vs. *red* – nonimproved; *a2*, *a3*, *a5*, and *a6* solid – improved vs. shaded – nonimproved) (**b**) Limb unloading (F2/F3). Changes in limb unloading identified by analysis of vertical ground reaction forces (*vGRF*) obtained during overground walking as described above in Fig. 15.3. (Data from participants as reported in Westlake and Patten [3]). The ratio of the F2/F3 vGRF peaks captures the single-limb support phase of gait from mid- to late stance and characterizes acceleration of the center of mass and transfer of body weight onto the contralateral limb. Improvements in limb unloading were revealed in both the (*b1*) fast (43%) and (*b4*) slow-trained (42%) individuals and were observed equally in (*b2*) paretic and (*b3*) nonparetic legs in fast-trained individuals. In slow-trained participants (*b5*), the paretic leg showed fewer improvements than the (*b6*) nonparetic leg. Across both fast and slow training speeds, the majority (82%) of improvements in limb unloading were revealed following robotic training. (Legend: *b1* and *b4 green* – improved vs. *red* – nonimproved; *b2*, *b3*, *b5*, and *b6* solid – improved vs. shaded – nonimproved)

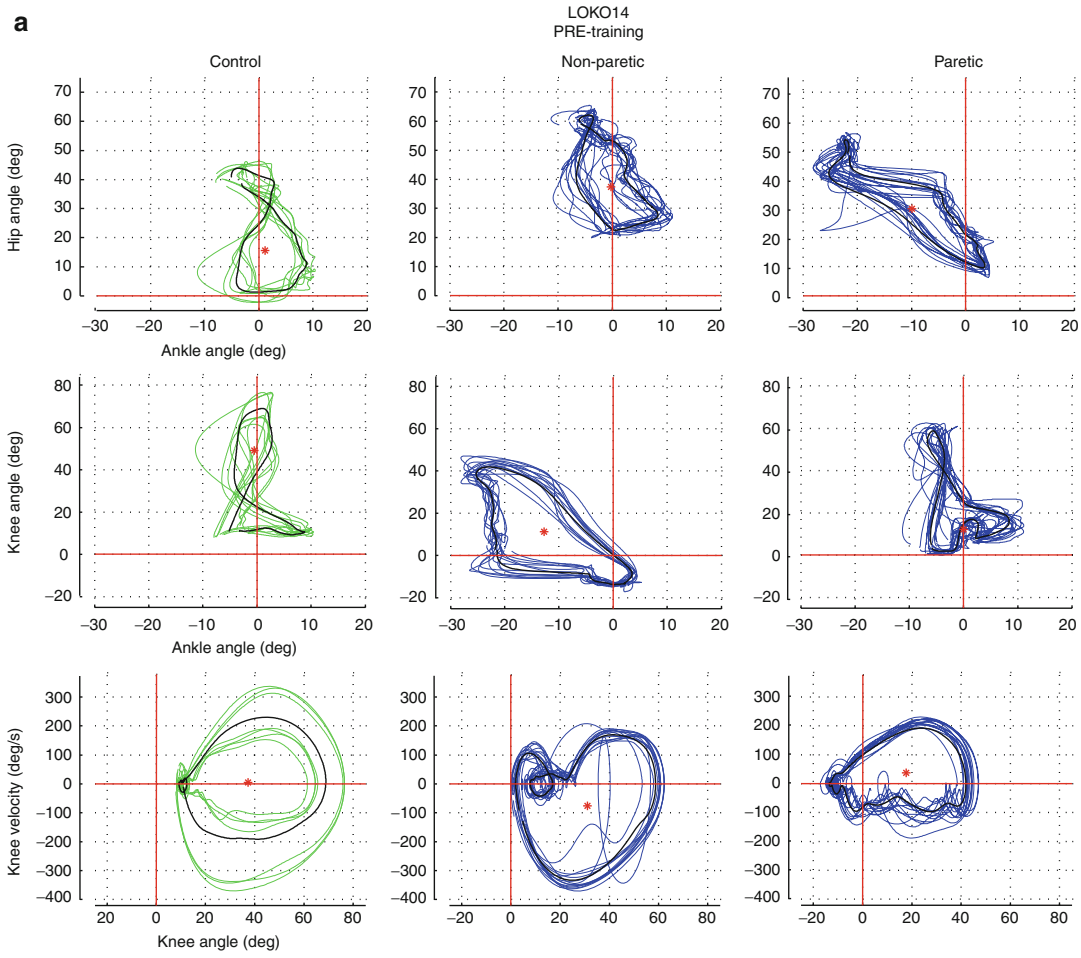

Fig. 15.5 Interjoint coordination. Coordination patterns derived from kinematics obtained during overground walking at self-selected walking speed. Top row: Hip–ankle angle–angle plots representing the excursions (*deg*) of the hip (*y-axis*) and ankle (*x-axis*) joints, respectively. Middle row: Knee–ankle angle–angle plots representing the excursions (*deg*) of the knee (*y-axis*) and ankle (*x-axis*) joints, respectively. *Bottom row*: Phase planes representing the angular velocity (*y-axis*, *deg/s*) vs. excursion (*x-axis*, *deg*) of the knee joint. Individual traces represent gait cycles and illustrate similarity of the coordination pattern over repeated cycles. *Left column*: Representative data from a control participant, walking at speed matched to hemiparetic participant, illustrated in green. *Middle and right columns*: Data from the nonparetic and paretic legs, respectively, of a hemiparetic participant. Calculation and interpretation of centroid location: The outer perimeter of the shape was used to calculate the centroid location (illustrated in red) and determine its coordinate location and distance from the origin. The absolute magnitude of the difference of centroid distance from origin is used to compare a participant to an individual, speed-matched control and to evaluate changes from pre- to posttraining. Movement of the centroid location toward control values is defined as a positive change. The centroid location can be decomposed into contributions from the x- and y-axes enabling identification of which joints (or joint) are deficient in their motion throughout the gait cycle and whether locomotor training induces changes in coordination.

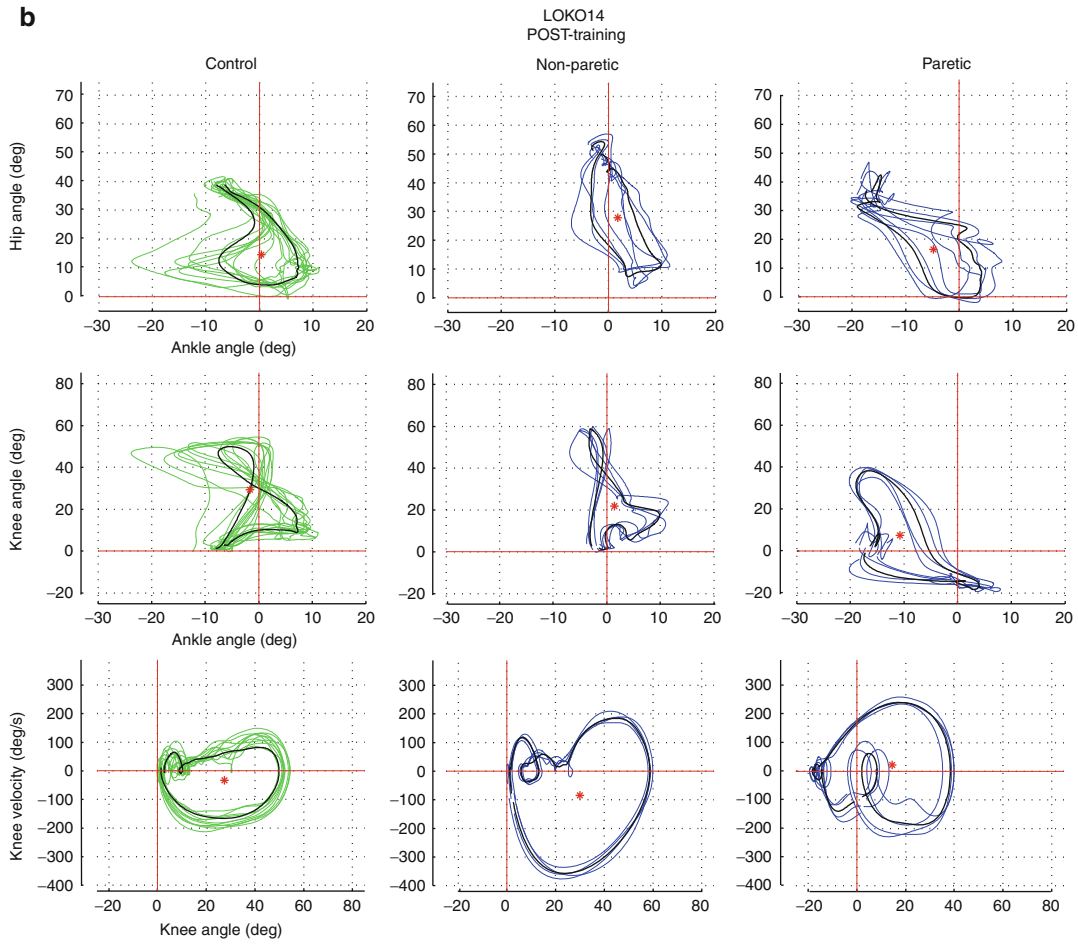

Fig. 15.5 (continued) (**a** and **b**) Interjoint coordination (*IJC*) patterns from a hemiparetic individual who trained with manual assistance. Self-selected walking speed (*SSWS*) = 0.44 m/s, absolute step length ratio (*SLRabs*) = 0.22. IJC patterns prior to LT (Fig. 15.5a) reveal bilateral deficiencies of knee and ankle excursion, compensated by exaggerated hip flexion, and compression of the knee joint phase plane. Posttraining, self-selected walking speed (*SSWS*) = 0.55 m/s, absolute step length ratio (*SLRabs*) = 0.14. Nonparetic limb IJC patterns reveal subtle improvements at the hip and marked improvements in knee–ankle coordination toward normal. However, paretic limb patterns reveal coordinative changes that suggest reduced excursion and poorer coordination across all joints. (**c** and **d**) Interjoint coordination (*IJC*) patterns from a hemiparetic individual who trained with the Lokomat. Self-selected walking speed (*SSWS*) = 0.69 m/s, absolute step length ratio (*SLRabs*) = 0.24. IJC patterns prior to LT (Fig. 15.5c) reveal minimal hip–ankle dyscoordination resulting from deficiencies of ankle excursion. Knee–ankle patterns are more aberrant with contributions from both joints. Posttraining (Fig. 15.5d), self-selected walking speed (*SSWS*) = 0.75 m/s, absolute step length ratio (*SLRabs*) = 0.17. Centroid shifts in the hip–ankle IJC pattern reveal contributions from both hip and ankle with ankle excursion in the range of normal. Changes in the knee–ankle IJC centroid location result primarily from improved ankle excursion

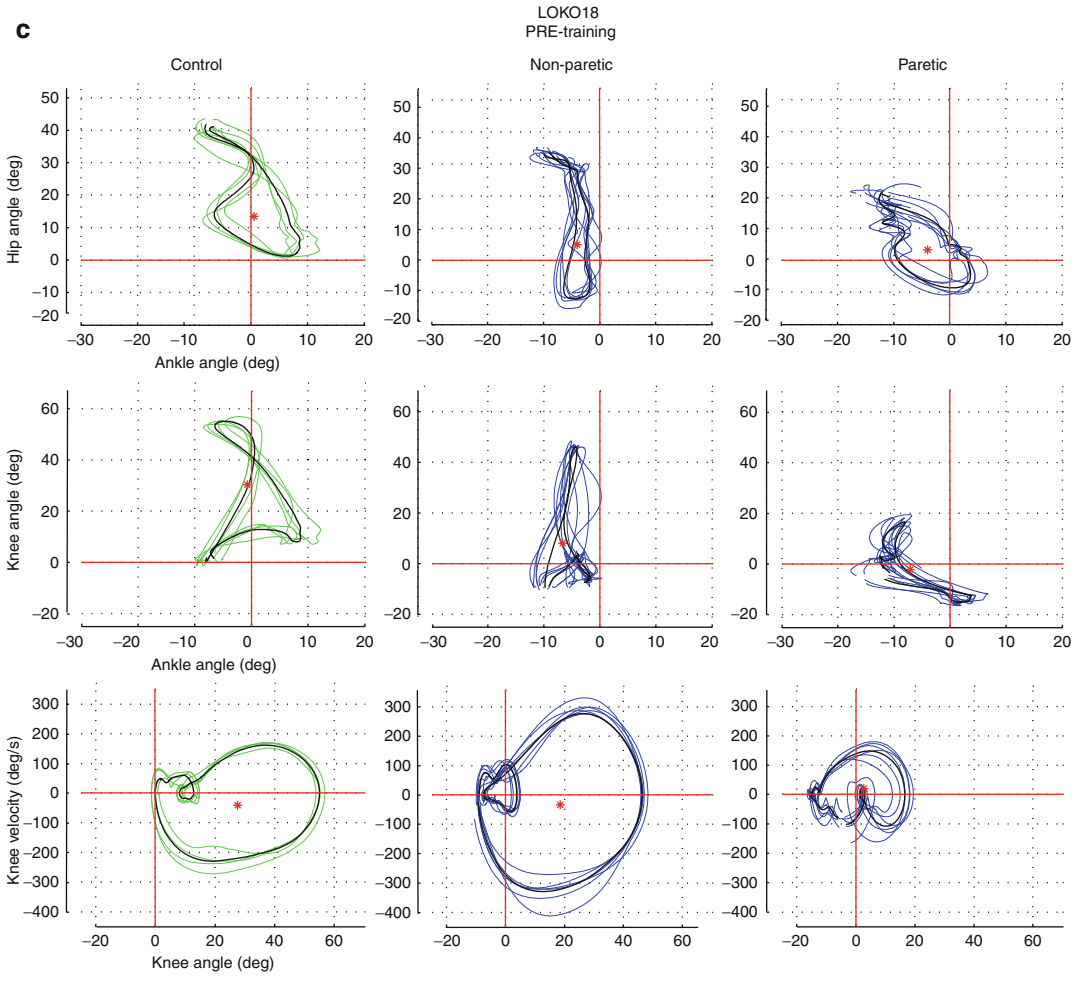

Fig. 15.5 (continued)

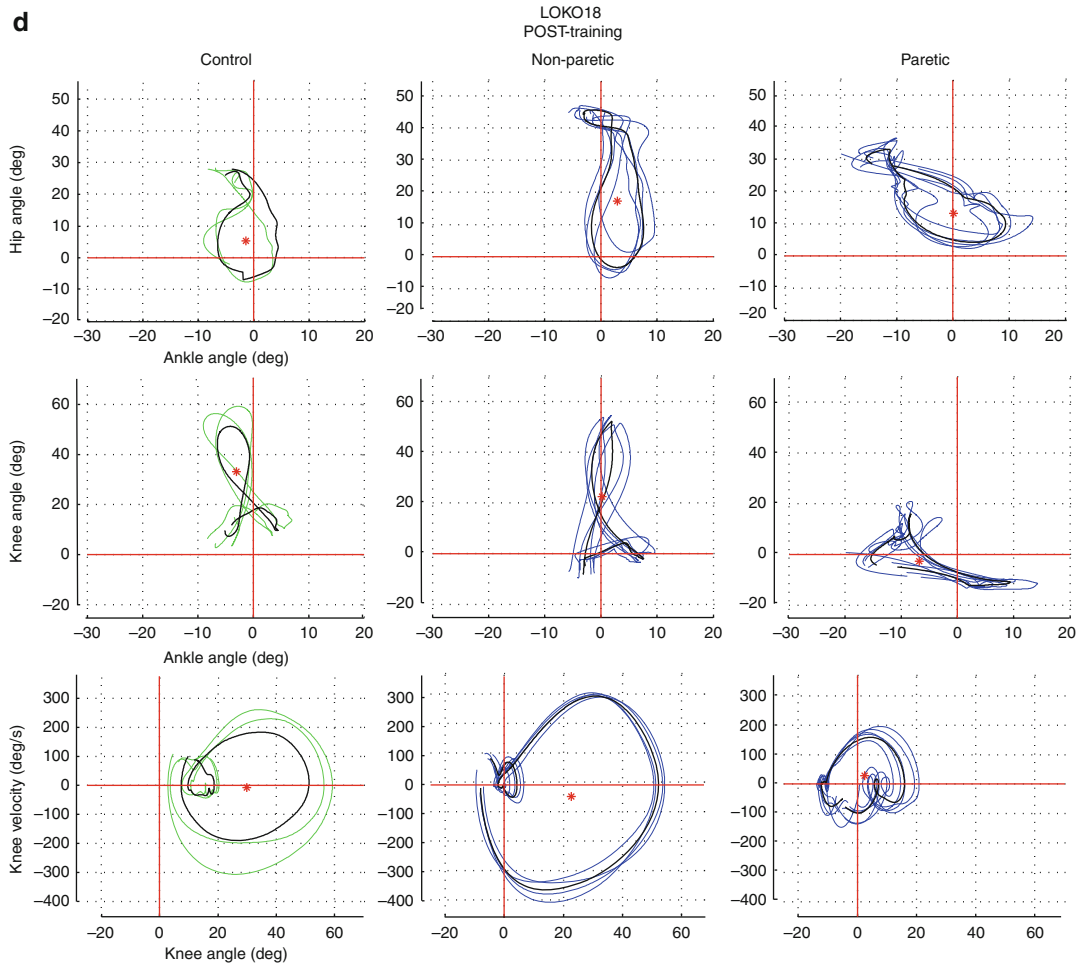

Fig. 15.5 (continued)

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Clinical Aspects for the Application of Robotics in Neurorehabilitation

16

Volker Dietz

Abstract

In patients suffering from a movement disorder after a stroke or spinal cord injury (SCI), improvement in walking function can be achieved by providing intensive locomotor training. After a stroke or an SCI, neuronal centers below the level of lesion exhibit plasticity that can be exploited by specific training paradigms. In these individuals, human spinal locomotor centers can be activated by an appropriate afferent input. This includes assisting stepping movements of the affected legs and providing body-weight support (BWS), while the subjects stand on a moving treadmill. The stroke and SCI subjects benefit from such locomotor training that enables them to walk over ground.

Load- and hip-joint-related afferent input seems to be of crucial importance for the generation of a locomotor pattern and, consequently, the effectiveness of the locomotor training. In severely affected stroke/SCI subjects, rehabilitation robots enable longer, more intensive training than can be achieved by conventional therapies. Robot-assisted treadmill training also offers the ability to standardize training approaches and obtain objective feedback within one training session. This allows clinicians to monitor functional improvements over time. This chapter provides an overview of the clinical aspects available for the application of robotic devices in the neurorehabilitation of stroke and SCI subjects. First, background information is given for the neural mechanisms of gait recovery. Findings from clinical studies are presented covering the feasibility and efficacy of robot-assisted locomotor training.

Keywords

Stroke • Spinal cord injury (SCI) • Locomotion • Locomotor training rehabilitation robotics • Assessment • Robot-assisted training

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16.1 Introduction

The loss of the ability to walk represents a major disability for subjects suffering a spinal cord injury (SCI) or a stroke [1, 2]. Almost two-thirds of all stroke survivors cannot walk without assistance in the acute phase following the incident [3]. Therefore, one major goal of rehabilitation for these patients is recovering locomotor function. One approach frequently applied over the past 20 years for retraining of gait is locomotor training on a treadmill combined with partial body-weight support [4–9].

In typical movement disorders following a lesion of the central nervous system (CNS), such as stroke or SCI, there is increasing evidence that a defective utilization of afferent input, in combination with secondary compensatory processes, is involved (cf. [10]). The secondary compensatory processes include the development of spastic muscle tone that is required to support the body during stepping movements [11].

In cat (for review, see [12]) and human (for review, see refs. [13, 14]) experiments, neuronal networks underlying the generation of movement patterns show considerable flexibility after central or peripheral neural lesions. Therefore, rehabilitation procedures should concentrate on improving function by taking advantage of the plasticity of neuronal centers and should less be focused on the correction of isolated clinical signs, such as reflex excitability or muscle tone.

A limitation of manual-assisted, body-weight-supported treadmill therapy (BWSTT) is that training sessions rely on the ability and availability of physical therapists to appropriately assist the patient's leg movements through the gait cycle. Robotic devices can eliminate this problem through a mechatronic system that automates this assistance [15, 16].

This chapter summarizes the neuroscientific rationale for robot-assisted therapy. Research findings will be presented covering the neuronal mechanisms of functional movements, the basic mechanisms of neuroplasticity underlying behavioral recovery after stroke or an SCI, and the feasibility and functional improvements achieved in response to robot-assisted functional training after a CNS lesion [17].

16.2 Neuroplasticity: Basic Research

There is convincing evidence from research with spinal animals that a use-dependent plasticity of the spinal cord exists [18, 19]. When stepping is practiced in a spinal cat, this task can be performed more successfully than when it is not practiced [20, 21]. The training of any motor task provides sufficient and appropriate stimuli to initiate a reorganization of neural networks within the spinal cord and, for example, to generate and train locomotion after a stroke or SCI. Consequently, the loss of motor capacity following neural injury can become exacerbated when locomotor networks are no longer used, for example, following a stroke [18]. By contrast, a greater level of functional recovery might be possible if a functional, use-dependent approach is applied in both clinical and rehabilitative settings [18].

A considerable degree of locomotor recovery in mammals with SCI can be attributed to a reorganization of spared neural pathways ([22, 23]; for review, see [24]). It has been estimated that if as little as 10–15% of the descending spinal tracts are spared, some locomotor function can recover [25, 26]. The neuronal networks below an SCI can be activated to generate locomotor activity even in the absence of supraspinal input [25–29].

In cats, recovery of locomotor function following spinal cord transection can be improved using regular training even in adult animals [4]. When stepping is not stimulated, the cat loses the ability to step spontaneously. During such a locomotor training, the animal is supported. Locomotor movements of the hindlimbs are induced by a treadmill while the forelimbs stand on a platform. With ongoing training, body support can be decreased, associated with improving locomotor abilities. Later on, the cat can completely take over its body weight and perform well-coordinated stepping movements [30]. The locomotor pattern at this stage closely resembles that of a normal cat. Furthermore, after hindlimbs exercise in adult rats after spinal cord transection, the excitability of spinal reflexes becomes normalized [31].

It can be concluded that assisted training represents an important factor in the recovery of locomotor function. Stepping movements can also be released in a monkey after transection of the spinal cord, suggesting that the isolated primate spinal cord is capable of generating hind limb stepping movements [32].

16.3 Effects of Locomotor Training in Stroke/SCI Subjects

Human locomotion is basically similar to that described for the cat, i.e., it is based on a quadrupedal neuronal coordination (for review, see [33]). Step-like movements are present at birth and can be initiated spontaneously or by peripheral stimuli, e.g., ground contact by the foot sole. The electromyographic (EMG) activity underlying this newborn stepping is centrally programmed, and since it has also been observed in anencephalic children [34], it is likely that spinal mechanisms generate the EMG activity. The apparent loss of locomotor movements in accidentally spinalized humans has been suggested to be due to a greater predominance of supraspinal over spinal neuronal mechanisms [35].

Nevertheless, there are indications that human spinal interneuronal circuits exist that are involved in the generation of locomotor EMG activity (cf. Fig. 16.1; [37] similar to those described for the cat [30]).

Stroke and SCI in human subjects are frequently associated with impaired or total loss of locomotion. Patients primarily show flaccid paresis and, later, spasticity in one or both legs. Repetitive execution of the impaired functional movement (with external help) in these patients can improve motor function of the affected limbs [4]. This improvement is based on the neuroplasticity of the CNS at several levels and results in some compensation for the loss in function resulting from lesioned brain or spinal cord areas [14, 38, 39]. In SCI, the supraspinal control over the neural circuitry in the spinal cord is impaired, while the spinal and supraspinal neural centers responsible for locomotion remain intact. Evidence for the existence of a human spinal central pattern generator (CPG) is seen through

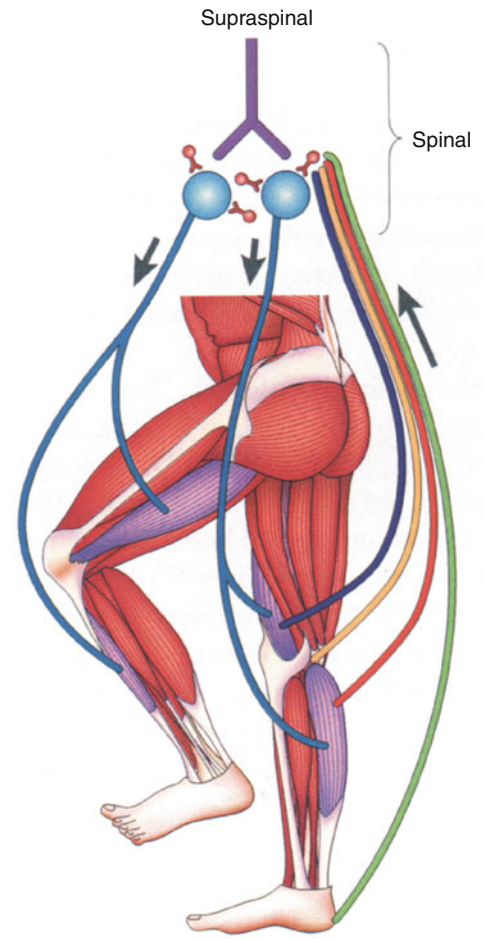

Fig. 16.1 Schematic drawing of the neuronal mechanisms involved in human gait. Leg muscles become activated by a programmed pattern that is generated in spinal neuronal circuits. This pattern is modulated by multisensory afferent input that adapts the pattern to meet existing requirements. Both the programmed pattern and the reflex mechanisms are under supraspinal control. In addition, there is differential neuronal control of leg extensor and flexor muscles. While extensors are primarily activated by proprioceptive feedback, the flexors are predominantly under supraspinal control [36]

spontaneously occurring step-like movements [40], myoclonus [13], and the appearance of late flexion reflexes [13] in tetraplegic subjects as well as from locomotor movements induced in body-weight-supported SCI subjects walking on a moving treadmill [5, 41].

A locomotor pattern can even be induced and trained in complete SCI subjects when leg movements are assisted externally and when an

appropriate afferent input to the spinal cord is provided [5, 10, 41–43]. Nevertheless, the amplitude of leg muscle EMG activity in severely affected patients is small compared to healthy subjects but increases during the course of locomotor training sessions [5]. The generally smaller EMG amplitudes in patients with complete paraplegia may be due to a loss of input from descending noradrenergic pathways to spinal locomotor centers [3].

When the EMG of antagonistic leg muscles of such patients is analyzed over the step cycle in this patient group, it becomes evident that leg muscle EMG activity is roughly equally distributed during muscle lengthening and shortening in both healthy subjects and complete SCI subjects during assisted locomotion. Furthermore, imposing locomotor movements in complete paraplegic patients with full body unloading does not lead to a significant leg muscle activation [44]. This indicates that stretch reflexes are unlikely to play a major role in the generation of the leg muscle EMG pattern in these patients, but that it is rather programmed at a spinal level.

In a successful training program for stroke and SCI subjects, spastic muscle tone must be present as a partial compensation for paresis [11], and the spinal central pattern generator must be activated by the provision of an appropriate afferent input and proprioceptive feedback to induce plastic neuronal changes [45]. Body unloading and reloading are considered crucial to inducing training effects on the neurological locomotor centers because the afferent input from receptors signaling contact forces during the stance phase (corresponding to the initiation of newborn stepping by foot-sole contact, see above) is essential to activate spinal neuronal circuits underlying locomotion [46]. Therefore, a cyclic loading is considered essential for achieving training effects in cats [47] and humans [45, 48]. Overall, observations of healthy subjects [46, 47], small children [49], and patients with paraplegia [44, 50] indicate that afferent input from load receptors and hip joints essentially contribute to the activation pattern of leg muscles during locomotion (Fig. 16.2). This suggests that proprioceptive input from extensor muscles, and probably also from mechanoreceptors, in the foot

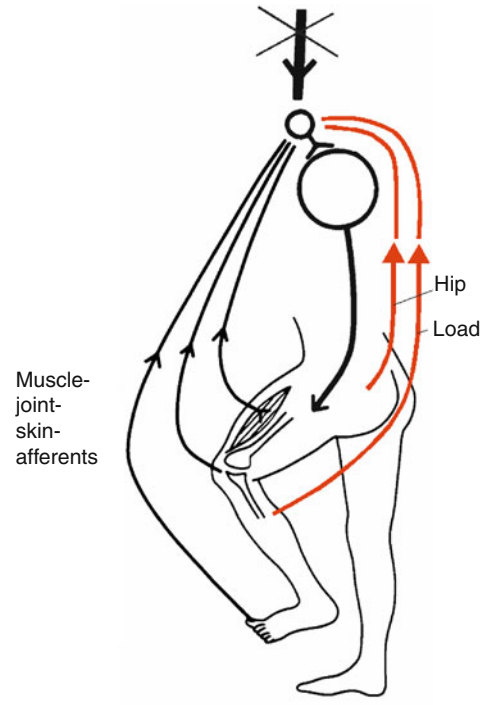

Fig. 16.2 Essential afferent input for the generation of a locomotor pattern. To evoke a locomotor pattern in complete SCI subjects, load- and hip-joint-related afferent input were shown to be crucial

sole provides load information [10]. This afferent activity is to shape the locomotor pattern, to control phase transitions, and to reinforce ongoing activity. Short-latency stretch and cutaneous reflexes may be involved in the compensation of irregularities and in the adaptation to the actual ground conditions.

In severely affected subjects, the muscle force produced by the leg muscle activation (small EMG amplitude) is insufficient to support the body during walking at the initial stage after stroke or SCI. Therefore, partial body-weight unloading is necessary to allow for the performance of stable stepping movements. During daily locomotor training, the amplitude of leg extensor EMG activity increases during the stance phase, while an inappropriate tibialis anterior activation decreases [45, 48]. This is associated with a greater weight-bearing function of the leg extensors, i.e., body unloading during treadmill locomotion can be reduced. These training effects

are seen in both incomplete and complete paraplegic patients. However, only SCI subjects with incomplete paraplegia benefit from the training program insofar as they learn to perform unsupported stepping movements on solid ground. Nevertheless, patients with complete paraplegia experience positive effects on the cardiovascular and musculoskeletal systems (i.e., they suffer less from the spastic symptoms). Several studies indicate that following an acute, incomplete SCI in humans, an improvement of locomotor function can be attributed to the locomotor training [39, 44] in addition to the spontaneous recovery of spinal cord function that occurs over several months following an SCI [22, 23, 40, 50].

Years ago, a score was developed relating to function. Locomotor ability in SCI subjects has been classified into 19 items [51]. A current study indicates that a close relationship between motor scores and locomotor ability exists only in patients with moderately impaired motor function. Patients with a low motor score undergoing a locomotor training can improve locomotor function without or with little change in motor scores [36, 52, 53]. In these cases, a relatively low voluntary force level in the leg muscles (reflected in the ASIA score) is required to achieve the ability to walk.

16.4 From Manual to Robotic Gait Training

Over the last two decades, there has been growing support for applying the functional training approach in neurorehabilitation programs for stroke [54] and SCI [8, 39, 43, 55] subjects. Some studies showed stronger improvement in functional walking ability following BWSTT compared to conventional gait training [54, 56], whereas other groups did not report better functional outcomes [8, 57, 58]. This is unsurprising since, with both approaches, a functional locomotor training is performed. However, with BWSTT, the support can be adjusted to the patient's stepping ability, i.e., to the severity of paresis. In addition, in severely affected SCI/stroke subjects, manually assisted BWSTT involves assistance while the patient is stepping on a moving treadmill and with simultaneous unloading of body weight (up to 80%). Manual assistance is provided as necessary to enable upright posture and to induce alternative leg movements (Fig. 16.3a).

Although an improvement in locomotor function is achieved following manually assisted treadmill training, its practical implementation in the clinical setting is limited by the labor-intensive nature of the approach. Specifically, training sessions tend to be short because of the physical demands and time costs. In SCI subjects, usually two therapists must assist leg movements on both sides [59]. This resource constraint limits access to and the duration of the therapy and, consequently, the effectiveness of the therapeutic approach. Particularly, in individuals with severe motor deficits and/or a high degree of spasticity, appropriate manual assistance is difficult to provide over longer times. The success and promise of BWSTT and the limitations and resource constraints in the therapeutic settings have inspired the design and development of robotic devices to improve the rehabilitation of ambulation in patients following stroke or SCI.

The research team of the Spinal Cord Injury Center of the University Hospital Balgrist in Zurich, Switzerland, an interdisciplinary group of physicians, therapists, and engineers, began to work on a driven gait orthosis (DGO) in 1995 that was intended to partially replace the arduous physical labor of therapists in locomotor training [15]. The "Lokomat" (Hocoma AG, Volketswil, Switzerland) consists of a computer-controlled robotic exoskeleton that moves the legs of the patient in an adjustable configuration with a body-weight-support system (Fig. 16.3b). Later on, other exoskeletal systems were developed for functional gait training (e.g., [12, 16, 49, 60]).

16.5 Clinical Effects of a Robotic Gait Training

Several studies have investigated the feasibility and benefits of a robotic-assisted treadmill training provided, for example, by the Lokomat system [15, 44, 61–74]. So far, it is still difficult

Fig. 16.3 Locomotor training of stroke/SCI subjects. (**a**) Conventional locomotor training using body-weight support and subjects standing on a moving treadmill. (**b**) Current version of the Lokomat system (2007) (Photo **b** – Hocoma AG; courtesy of Hocoma AG, Switzerland)

to draw general conclusions about effectiveness due to the small numbers of participants enrolled in the studies and heterogeneous selection criteria (e.g., acute and chronic stroke/SCI subjects, different pathologies/severities) involved [75]. Furthermore, robotic training is performed in rather variable terms of training onset, duration, specific parameters (e.g., walking speed, level of body-weight support, amount of assistance), as well as the conventional physiotherapy which the patients receive in parallel with the robotic locomotor training. Nevertheless, it is commonly accepted that robotic training can be integrated into the normal neurorehabilitation program and has proven feasible for the treatment of a number of different neurological deficits such as SCI [15, 44, 67, 76], stroke [65, 66, 68, 70, 73, 74], multiple sclerosis [61, 69], and cerebral palsy [62–64, 71, 72]. Beneficial effects of robot-assisted training are quite diverse, ranging from gains in walking velocity and endurance to an improvement in walking tests [44, 61, 63, 67, 69–72, 74]. Some benefits are associated with changes in gait characteristics [61] such as a better walking quality [68, 77] or a better control of voluntary leg movements [78]. In addition to improvements in walking ability, positive influences on abnormal reflex function [63, 70], respiration [79], and cardiovascular response [80, 81] have also been reported.

A number of studies were undertaken to compare the efficacy of robot-assisted locomotor training with conventional training [65, 66, 68, 70, 71, 73, 74]. It became apparent that, especially for those with severe neurological deficits, patients benefit from robot-assisted treadmill training [68, 70, 73], while manually assisted gait training or additional therapies including balance and strength training are more appropriate for stroke/SCI subjects with some preserved walking ability [65, 66]. This is reasonable since a robotic device such as the Lokomat is designed to be applied in stroke/SCI subjects suffering severe sensory-motor deficits including a reduced ability to support body weight, problems in movement control, and high demands on therapists for physical assistance.

For example, the "Lokomat" was developed to enable longer training periods in severely affected subjects that could lead to better outcomes [82]. An increase in muscle mass associated with cardiovascular training [68] and enhanced oxygen consumption due to the partial body-weight support [83] indicate that even training within a robotic device requires an active movement performance [45].

16.6 Future Developments

Patients with some ability to walk profit from gait training that does not require robotic assistance. Future technical improvements of robotic devices should also include a challenging training of coordination and balance. Some studies report higher inconsistencies in intralimb coordination [84] and reduced EMG activity during robot-assisted therapy compared to therapist-assisted walking [81]. However, stepping quality was improved by locomotor training in SCI subjects regardless of training approach [77]. These observations illustrate the importance of minimizing robotic assistance but to enhance patient's participation and to challenge the training of balance and movement control during relearning of walking [84]. Multicenter clinical trials are required to ascertain appropriate patient selection for optimal treatment programs and training intensity.

Future clinical and basic research is needed to investigate a range of topics to optimize training paradigms such as training duration and protocol, parameters for objective metrics, and best combinations with conventional therapies. In addition, robotic devices should also be designed to serve as diagnostic tools, e.g., muscle voluntary force or muscle tone. In the future, robotic devices might help monitor the course of rehabilitation including the outcome of lower limb dysfunction. Research groups have already started to use robotic devices as diagnostic and experimental tools for a better understanding of the mechanisms, leading to improvements of functional outcomes, such as the provision of appropriate afferent input [42]. In addition, a supraspinal plasticity and increased activation of the cerebellum

could be demonstrated as a consequence of a robotic-assisted locomotor training [76].

Robotic devices have further been employed to investigate the effects of locomotor training on corticospinal excitability [85, 86], spinal reflex modulation [42, 87], muscle activation patterns in incomplete and complete SCI subjects [45, 81], and spinal neuronal function in chronic complete SCI [88] as well as changes in cardiovascular, metabolic, and autonomic responses [80, 89, 90]. In the future, collaborations between clinical and basic researchers are required to further improve robotic functions (e.g., proprioceptive feedback, stepping velocity, and amount of challenge) and individual training protocols to achieve the best functional outcomes.

Modern robotic devices already allow quantitative assessments of the locomotor ability of stroke/SCI subjects. The advantage of such a quantitative assessment is that the course of rehabilitation can be monitored. In the future, this approach may be refined to pinpoint factors responsible for the improvement of a movement disorder. Such an analysis has revealed, for example, that the development of spastic muscle tone after stroke or SCI is advantageous, in that it provides body support during stepping movements [11]. This knowledge has, of course, consequences for therapy and drug applications.

For future application in the rehabilitation field, standardized gait analysis may help to select the most effective pharmacological and physiotherapeutical/training approaches. This may not only be of benefit for the patient but also could lead to reduced costs as most therapeutic approaches are not yet based on controlled studies and their effectiveness has not yet been convincingly demonstrated. For future application in the clinical diagnosis, gait analysis may help to achieve an early diagnosis and detection of subtypes of a movement disorder with the consequence of an early onset of an appropriate training (for review, see [36]).

In severely affected stroke or SCI subjects, the strength of leg muscle activation is insufficient to build enough muscle tone to support the body or to control leg movements for locomotion. In these patients, the search for substances that influence the gain of leg muscle EMG activity is essential.

However, the most promising approach may be to induce partial regeneration of the lesioned spinal cord tract fibers. Recent experiments in rats and monkeys have indicated that, after inhibition of neurite growth inhibitors, a partial regeneration can occur [91] (for review, see [92, 93]). Connected with an appropriate locomotor training, this approach may improve functional mobility even in complete paraplegic/tetraplegic subjects. Electrophysiological and biomechanical recordings of locomotion in rats with spinal cord lesions have provided information that this animal model can be applied to humans with SCI [26].

Conclusion

Functional training represents an established approach for the rehabilitation of stroke and SCI subjects [10]. Robotic rehabilitation devices have become increasingly important and popular in clinical and rehabilitation settings for standardized assessments and functional training. Such devices allow lengthier training periods, increased repetitions of movements, improved patient safety, and fewer physical demands of therapists. Novel sensor-, display-, control-, and feedback-information technologies have led to an improvement of training effects. By increasing the patient's challenge and participation and by improving the assessment of clinical measures and performance, robots have successfully become an essential component of neurorehabilitation. Standardized assessment tools and therapies provided by robots are an important prerequisite for intra- and intersubject comparisons to evaluate and monitor the rehabilitation process of stroke/SCI patients and to assess the effectiveness of new therapies. In the future, rehabilitation robots offer a platform for implementing advanced technologies that provide new forms of training for patients with movement disorders. With the use of cooperative control strategies, e.g., virtual reality technologies, not only is the patient's engagement (especially for children) enhanced during training sessions but also the motivation to participate in the training can improve.

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Transfer of Technology into Clinical Application

17

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Abstract

Robots for neurorehabilitation have been designed to automate labor-intensive training techniques and to optimally support therapist and patients during different stages of training. Devices designed for body-weight-supported treadmill training, for example, have become a promising, task-oriented tool in order to restore gait function. At an early stage, these robots provide the ability to secure and stabilize the patient and guide trunk and legs through a normal gait trajectory with a high number of repetitions. At later stages, more sophisticated control strategies, virtual environment scenarios, or possibilities to exercise specific gait parameters and tasks extend their application to more experienced patients. Clinical evidence for feasibility and effectiveness of these devices exists; however, their advantages in comparison to conventional therapies are still under debate. This might be due to the fact that currently reliable parameters for appropriate selection of locomotor training parameters basing on functional impairments are lacking. Despite this fact, robotic devices are already successfully integrated into clinical settings with promising results.

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Appropriate use is dependent on the therapist's knowledge about the value and limits of different devices as well as the ability to utilize the device's technical means, thereby allowing patients to benefit from robot-aided gait training until they are able to perform safely and efficiently overground walking training. This chapter will provide an overview on the rationales of introducing robots into a clinical setting and discuss their value in different pathologies. In addition, recommendations for goal setting and practice of robot-assisted training based on disease-related symptoms and functional impairment are summarized together with reliable functional assessments.

Keywords

Best practice • Gait training • G-EO • Lokomat • Neurorehabilitation • Robot-assisted treadmill training

17.1 Introduction

Increasing evidence within the last 20 years has shown that the injured central nervous system (CNS) has the ability to reorganize. The potential for reorganization is in particular high within a plastic phase early after injury but also possible to a limited degree at later stages. Reorganization in a functional meaningful way is dependent on motor activity as executed during rehabilitative training and followed by functional improvements [1, 2]. A high number of task-oriented, repetitive movements based on the principles of motor learning can improve muscular strength and movement coordination in patients with impairments due to neurological or orthopedic disorders [3, 4]. Training furthermore prevents secondary complications such as muscle atrophy, osteoporosis, and spasticity [5].

Robots for neurorehabilitation were designed as a possible tool for therapist to automate labor-intensive training techniques, especially at an early stage where patients require a high amount of support. Because of their programmable force-producing ability, robotic devices can apply task-oriented movements, thereby providing correct afferent feedback. They can furthermore increase the duration and number of training sessions while reducing the number of therapists required for each patient. Robots can replicate some features of a therapist's manual assistance, allowing patients to semiautonomously practice their movement training. Besides enhancing the rehabilitation process and improving therapeutic outcome, they have the potential to support clinical evaluation, precisely control and measure therapy, implement novel forms of mechanical manipulation impossible for therapists to simulate, and provide different forms of feedback, thereby increasing patient's motivation [6, 7]. Within the last 15 years, the number of research groups developing robotic therapy devices for upper and lower extremity has rapidly increased including devices where limbs are passively stabilized, fixed, or limited in their range of motion [8].

17.2 Robot-Assisted Treadmill Training

One example for successful integration of technology into clinical application is robots designed for body-weight-supported treadmill training. Human gait is a typical repetitive functional movement, and locomotor training with treadmill and harness support has become a promising, task-oriented approach to restoring gait function. A number of studies indicate that positive therapeutic effects are obtained for patients with spinal cord injury (SCI) [9–16], subacute and chronic hemiparesis [17–23], traumatic brain injury (TBI) [24], and children suffering from cerebral palsy (CP) [25].

Fig. 17.1 Exoskeletal systems like the Lokomat (Hocoma AG, Switzerland) apply exoskeletons that move the patient's legs in the sagittal plane in conjunction with a body-weight support system

Positive therapeutic effects are also obtained in patients with neurological pathologies, such as multiple sclerosis (MS) [26–29] and Parkinson disease (PD) [30–32]. Depending on the patient's abilities and preconditions, up to four therapists can be required in order to secure and stabilize the patient and guide trunk and legs through a normal gait trajectory. Over the past years, several robotic devices have been developed to assist patients in gait performance and relieve therapists from their labor-intensive work. Exoskeletal systems like the Lokomat (Fig. 17.1) (Hocoma AG, Switzerland) [33], LOPES (University of Twente, Netherlands) [34], ALEX (University of Delaware, USA) [35], and the ReoAmbulator (Motorika, USA) [36] apply exoskeletons that move patient's legs in the sagittal plane in conjunction with a body-weight support system. End-effector-based systems like the Gait Trainer GT I (Reha-Stim, Germany) [37], G-EO Systems (Fig. 17.2) (Reha Technologies, Bozen, Italy) [38], HapticWalker [39], or LokoHelp [40] work like conventional elliptical trainers: the subject's feet are strapped to two footplates moving along a gait-like trajectory. All these robotic devices offer ideal training conditions for the enhancement of neuroplastic changes in patients with acquired or congenital central gait impairment as intensity, repetition, and task specificity are met with this training option.

As kinematic variability, active participation, and motivation are important preconditions of motor learning, rehabilitation robots that replay a gait pattern as accurately as possible are considered not ideal, especially in functionally more advanced patients [41]. In order to optimally support patients in their training progression up to a point where they can safely and efficiently perform overground walk training, different possibilities can be applied. Some robotic devices offer patient-cooperative control strategies that allow kinematic variability and increase active participation of patients while still guaranteeing successful task execution [34, 42, 43]. Other devices allow training of additional tasks, for example, stair climbing [38]. Patient's active participation can also be encouraged by providing feedback and instructions

Fig. 17.2 End-effector-based systems like G-EO Systems (Reha Technologies, Bozen, Italy) work like conventional elliptical trainers, where the subject's feet are strapped to two footplates moving along a gait-like trajectory (Photo courtesy of Reha Technologies, Bozen, Italy)

derived from precise measurements taken by the system [44–46]. The goal of this feedback is to quantify the patient's activity in relation to the target gait function such that the patient can improve muscle activity toward a more functional gait pattern. Furthermore, combining robots with advanced virtual reality technologies seems to be a promising option for rehabilitation therapy as it allows controlling and manipulating feedback parameters and leads to more challenging training situations followed by increased participation [47–49].

17.3 Clinical Evidence

The Lokomat, the ReoAmbulator, and the Gait Trainer have been in clinical use for several years. A growing number of studies have shown that robot-assisted gait training is feasible and effective in numerous pathologies and results in functional improvements [38, 50–54]. Value and limits of different devices or robot-assisted gait training in comparison to conventional training, however, are still under debate [41]. A number of studies aiming to directly compare efficacy of robot-assisted treadmill training with conventional therapy resulted in equivocal findings [21, 41, 53, 55–58]. Some of these studies found advantages of robot-assisted treadmill training compared to manual-assisted therapy [21, 53, 56–58]; others found conventional therapy to be more effective [41, 55]. Between studies, considerable variability existed in the functional impairment of patients, ranging from nonambulatory [56–58] to ambulatory patients [41, 53, 55]. The application of robots was also variable in terms of number of training

sessions, training duration, and technical possibilities applied. Patients were either trained in the position control mode where the robot does not allow deviation from the predefined gait pattern [41] whereas other studies increased the challenge by adapting training parameters over training progression [53, 55, 58]. Conventional training on the other side also varied between studies from stance and balance training with step initiation [57, 58] to manual-assisted treadmill training [41, 53].

17.4 Experience Versus Evidence

As the selection of specific training parameters can influence treatment outcomes [4, 21–23, 59, 60], well-designed, randomized multicenter clinical trials with large, strictly selected samples, relevant control groups and standardized training parameters are required to separate general effects of locomotor training from true automated training effects. Unfortunately, no objective basis for the proper selection of locomotor training parameters currently exists. However, a growing number of clinicians and therapists already successfully integrate robotic devices into their clinical setting. Effective integration is dependent on the therapist's knowledge about a patient's level of functional impairment and pathology-specific symptoms dependent on time after injury, potential for recovery, and selection of specific training goals over time. Furthermore, the therapist's knowledge about the value and limits of different devices, as well as their ability to utilize the devices' technical means in order to optimally support patients, allows the patients to benefit from robot-aided treadmill training through different stages of recovery up to the point where they can safely and efficiently perform overground walk training.

In the following sections, we provide an overview about a number of pathologies where manual-assisted gait training has been applied, functional impairment and specific symptoms over time, and potential for functional improvements. We further provide insight into the training parameters applied during robot-assisted gait training at an early phase as well as overtraining progression. Recommendations provided are based on experience gathered with Lokomat training over the last 10 years but may also provide guidelines for robot-assisted gait training with other devices.

Providing general recommendations on how to train upper limb function with the assistance of new technology is currently difficult due to the large number and variability of devices and therefore not included as it would exceed the scope of this chapter. Recommendations on how to apply these devices are, however, necessary for successful integration into clinical practice and will follow in the near future.

17.5 Pathology-Specific Motor Impairment and Training Goals over Time

17.5.1 Stroke

Stroke causing an ischemic or hemorrhagic brain lesion frequently leads to hemiparesis and other movement deficits that persist in a large proportion of patients so that at 6 months, about half of the surviving patients remain disabled [61–63]. Recovery occurs depending on the intensity of motor training, and no specific rehabilitation program has so far stood out as being most effective [64]. The brain bears a potential for reorganization that compensates for the loss of tissue in motor networks. This potential is exploited by repetitive and active exercises, the intensity, complexity, and timing of which mainly determines their effectiveness. Intense training as part of a rehabilitation program is more effective than no training [65] (often regarded as "spontaneous recovery" although it is unknown whether this recovery stems from the patient's self-training by being active in daily life or from an indigenous brain repair process that is use-independent). Earlier training seems better than late [66] although physical therapy exercises in the chronic stage clearly remain effective [67]. The time period in which training is most effective is debated. Reduced mobility as well as falling or the fear thereof remains a prominent problem of

the stroke survivor [68]. Therefore, specific interventions that improve mobility and reduce the risk of falling are desperately needed.

Walking is just one, but one of the most important activities, for stroke patients as it permits independence in their social environment. The aim of rehabilitation is to advance their overground walking ability in terms of safety, energy efficiency and endurance, balance, speed, and the quality and symmetry of the gait pattern. The main focus of rehabilitative training at an early stage is to incorporate gait activities as early as possible in order to avoid learned nonuse of the correct gait pattern as well as the appearance of compensatory walking strategies. Motor input provided by cerebral cortex, basal ganglia, midbrain, cerebellum, pons, and spinal cord may compensate for diminished motor commands from the cortex and help reestablish the ability of bipedal locomotion, including gait control. In this phase, the patient profits from sensory information during walking in a gait-like pattern, appropriate afferent input of muscle and joint receptors and foot soles, and rhythmic acoustic input. Gait training targets the stroke survivor's mobility. Treadmill training has proven effective [69]. Robotic gait training may be effective, but optimal training protocols remain to be developed [55, 70]. However, to participate in daily life, the patient also has to relearn house-walking abilities, which are mostly dual or multitask activities (e.g., walking and looking around, walking and holding something or someone, walking and talking, walking and adapting to changes on the ground, etc.).

At later stages, there is still a chance to overcome learned nonuse and enable the patient to advance overground walking ability in terms of energy efficiency and endurance, speed, and the quality and symmetry of gait pattern. By providing intensive and repetitive stimulation through walk training, patients – even with cognitive deficits – can enhance existing but nonused movements and integrate them in their compensatory gait pattern. Providing a save and stabile training situation enables patients to concentrate and further improve specific components of their gait.

Nonambulatory chronic stroke patients, however, might never regain independent walking ability, and it is therefore important to avoid false expectations. Training goals have to be adapted to the specific needs of patients and their caregivers. Preventing pain, stiffness, and contractures, as well as the regulation of muscle tone, is essential. Another goal is to reinforce muscle strength in order to stabilize the patient's head and trunk in an upright and dynamic therapy position.

17.5.2 Spinal Cord Injury

The spinal cord can be acutely narrowed or distorted due to major physical impact along with a trauma. An accident with a consecutive SCI is associated with severe mechanical impact and a loss of the stability of the spine. Often, additional lesions of the extremities and the thorax are present [71]. Nontraumatic causes for SCI include tumors, ischemia, hemorrhages, or infections.

The sequelae of SCI are partial or complete loss of motor, sensory, and vegetative function below the level of the lesion. A lesion to the cervical spinal cord affects all four extremities while lesions below that level affect the legs only. Based on the clinical examination of motor and sensory function, SCI can be classified using the widely established Standard Neurological Classification of the American Spinal Injury Association (ASIA) [72]. It ranges from a motor and sensory complete (ASIA A) to a complete restitution of all symptoms (ASIA E) (Table 17.1).

In addition, there are six special forms of SCI clinical syndromes [73], of which two are important pertaining to the recovery of locomotor function: the central cord syndrome (CCS) and the Brown–Sequard syndrome (BBS). The CCS describes a lesion of the central matter of the cervical spinal cord. Here, arm and hand functions are severely impaired whereas leg functions are less affected. The BBS describes a unilateral damage of the spinal cord followed by spinal hemiparesis. Due to the remaining functions below, the level of the lesion CCS and the BBS can be considered as an incomplete SCI.

Table 17.1 Standard neurological classification of a spinal cord injury from the American Spinal Injury Association

A = complete	No motor or sensory function is preserved in the sacral segments S4-S5
B = incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5
C = incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3
D = incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more
E = normal	Motor and sensory function are normal

S4-S5 represents the lowest spinal segments of the spinal cord
Muscle grading 3 means active movement through full range of motion against gravity

Spontaneous recovery can be observed within the first 2 years after injury [71]. Extent of recovery is dependent on the severity of the lesion. Patients with a complete injury (ASIA A) might recover function over one or two segments but remain paralyzed below the level of lesion [74, 75], whereas patients with an incomplete injury recover function below the neurological level of injury to various degrees. The range of recovery in terms of ambulatory function varies from 50% for ASIA B to over 90% for ASIA D patients [71]. Both CCS and BBS also have favorable prognosis pertaining to motor and walking function [73, 75]. In the beginning, patients with an incomplete SCI, CCS, or BSS present severe loss of neurological functions which can recover and convert to less severe ASIA impairment scale over time [76].

Even though patients classified as incomplete have a good prognosis to recover walking function, they usually cannot stand or walk at an early stage due to the acute posttraumatic condition as well as paralysis of their leg muscles. At an early stage of rehabilitation, patients are therefore very much dependent on assistance for almost all of their activities. That assistance is provided by specialized nurses or therapists as well as mechanical devices, e.g., a wheelchair, as well as support during walk training. The rehabilitation of walking function is shaped according to the actual state of the patients in a way that they are challenged by the exercises without being overextended. As the amount of expected recovery is difficult to forecast, rehabilitation should not only focus on regaining ambulation but also on the use of a wheelchair in case this will be the main mode of mobility. With increasing recovery of lower extremity muscle strength, patients can be further challenged during training and additionally start to walk without the assistance of a robotic device, either on a treadmill still using body-weight support, in a rehabilitation pool, or overground using a specific walking aid (e.g., parallel bars, walking frames, etc.). At later stages and when the rate of recovery took place accordingly, further goals are highly skilled coordinative tasks like running, jumping, carrying weights while negotiating obstacles, etc.

17.5.3 Multiple Sclerosis

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) with a variable disease pattern (relapsing–remitting, secondary progressive, primary progressive) and various pathological features (inflammation, demyelination, axonal loss, and degeneration). In the long term, a major part of MS patients gradually accumulate pathological changes at different sites of the CNS leading to a broad range of symptoms, functional deficits, and disabilities. Different disease-specific pathophysiological disturbances may influence physical performance in MS patients. Uhthoff's phenomenon (deterioration of symptoms with increasing body temperature induced by physical activity or high ambient temperature) and activity-dependent conduction block in central pathways (induced by high-frequency discharges during strenuous activities) are the main factors responsible for motor fatigue and fatigability in MS patients. Together with changes of central recruitment, these specific phenomena are limiting longstanding physical strain in MS patients.

Gait disturbances are common in MS patients, affecting up to 80% in the long term, typically with a spastic ataxic gait pattern. Walking impairments have a high negative impact on different personal activities, social participation, and physical quality of life. MS patients with walking disabilities are at a high risk for secondary complications (especially falls, osteoporosis, de-conditioning), and total costs of disease rise steeply after losing walking abilities. Therefore, maintaining or improving walking abilities is a key issue in rehabilitation of MS patients.

There is a good evidence for the beneficial effect of physical training (physical therapy, resistance training, and aerobic training) on mobility in MS. Physical therapy has been shown to be effective in improving gait and mobility and reducing the risk of falls. In patients with more severe gait disabilities, however, overground walking training becomes difficult or even impossible. Physical effort and motor fatigue are increased due to spastic ataxic gait, limiting effective treatment time and treatment effects. Thus, reducing physical effort by body-weight support or robot-assisted gait training (RAGT) may be particularly useful in MS patients, avoiding motor fatigue and increasing treatment effect by more efficient gait training. There is some evidence that body-weight-supported treadmill training (BWSTT) reduces physical effort and that robot-assisted gait training, providing a high amount of support, might be more beneficial than overground walking training in MS patients with severe walking disabilities.

17.5.4 Children with Central Gait Impairments

Robot-assisted gait training in children can be applied for various diagnoses leading to central motor impairments such as cerebral palsy, spina bifida, traumatic brain injury (TBI), stroke, intracranial hemorrhage, MS, and SCI (Fig. 17.3). The indication for as well as the goal of rehabilitation arises from the individual functional impairments rather than from the diagnosis itself. RAGT offers an early verticalization and gait training in patients with acute cerebral lesions as seen, e.g., in stroke or TBI. In these patients, RAGT should be ideally combined with conventional physiotherapeutic treatments and also include training for recovery of positional changes, trunk stability, and transfer. The possibility of achieving gait (with or without walking aids) is the main indication for BWSTT. However, there are other indications, like the improvement of tone regulation or improving transfer function, depending on the special needs of each individual child.

17.6 Recommendations of Best Practice for Robot-Assisted Walk Training

17.6.1 Patient Selection

In general, robot-assisted gait training is suitable for male as well as female patients. Just as during manual-assisted walk training with an unloading system, special attention has to be given to a proper fit of the harness, especially in the crutch for male patients; for female patients, problems can arise at the breast area. Patients can be trained at almost all ages; inclusion criteria at an early age are leg length as well as minimal body weight (recommended 15 kg). Some devices offer pediatric modules adjustable to smaller leg and foot length. At older ages, an increasing occurrence of osteoporosis has to be taken into account. Patients with severe osteoporosis and/or a recent history of a lower extremity and pelvic fracture may not train in robotic devices.

Training is in particular suitable for patients with severe walking disabilities; however, achieving the ability of overground walking (with or without assistive devices) should be a realistic goal of rehabilitation. Acute as well as post-acute stroke patients up to 6 month after injury benefit from high-frequency robot-assisted gait training, always in addition to overground gait training if applicable. Incomplete SCI patients profit most from repetitive locomotor movements, i.e., patients with an acute or chronic SCI classified as ASIA C or D. Training is also suitable for ASIA B patients when assessed within 8 weeks after SCI, as well as

Fig. 17.3 Robot-assisted gait training offers an early verticalization and gait training in children and can be applied for various diagnoses leading to central motor impairments (Photo courtesy of Spaulding Rehabilitation Hospital, USA)

MS patients with severe walking disabilities, for example, limited walking distance of few steps up to 100 m with and without walking aids (EDSS 6.0–7.5). RAGT can be applied in children with severe motor impairment (GMFCS IV); however, a recent study has shown that patients with GMFCS I-II benefit most due to a longer training duration and walking distance [77].

Even though the possibility of achieving gait (with or without walking aids) is considered the main indication for RAGT, severely affected and chronic patients with little potential of regaining independent walking ability may also benefit from repetitive gait-like movements. Here, training can focus on specific training goals (i.e., tone regulation and prevention of secondary complications) depending on the special needs of each patient. In children, it offers a possible therapy method after orthopedic or neurosurgical interventions like selective dorsal rhizotomy in order to train the new biomechanical situation and regain muscle strength after immobilization periods. In any case, a medical consultation should address the expectations of the caregivers. Also, time and effort in comparison to expected outcome ought to be considered carefully and discussed frankly before training is started. Initially, a neurological examination followed by a first robotic-assisted training trial may provide information about the rationale and feasibility for this kind of training in chronic, nonambulatory patients. In general, the indication for robot-assisted gait training follows the individual goal setting (for example, improvement of walking ability, mobility, tonus regulation, etc.) and may also depend on the economic and time resources of families and the patients, respectively, as well as the organization of a particular health system.

Training is suitable for patients in the acute, subacute, or chronic state. Stroke and SCI patients can be trained very early after injury within a professional setting in an acute hospital state. In children with acquired brain injuries like TBI or stroke, an early mobilization and verticalization is also essential. Here, it is of particular importance to consider the compliance of patients. Besides the device-specific contraindications provided by the manufacturer, a number of points should be taken into account before applying robot-assisted body-weight-supported gait training in patients with different pathologies.

To be suitable for training, patients must be able to signal discomfort, fear, and exhaustion. Severe cognitive or psychiatric problems as well as incontinence might be contraindications to start training with a robotic device. In order to benefit most from training session, it is advantageous if patients are cognitively able to follow therapist's instructions, cooperate, and participate during the training procedure.

Patients must be able to stand upright for at least 20 min without experiencing a drop in blood pressure. Training is strenuous, and patients must tolerate the corresponding exertion. Before each training session, the skin needs to be controlled for lesions, especially around the area where the machine transfers forces to the trunk and legs of the patient (i.e., the groin, thigh, shin, and ankles). Pressure sores, as well as acute lesions or inflammation of soft tissue which interferes with harness support, robotic leg cuffs, or loading, preclude the training. In order to avoid friction and irritation due to pleats, recommended clothes for training are long tights, cycling shorts, or tight-fitting gymnastic clothing. In the authors' clinical experience, a careful adaptation of the exoskeleton by a well-trained and experienced therapist is indispensable (Fig. 17.4). The time required for a careful patient setup has to be included in the schedule of each robotic-assisted training session [77].

Musculoskeletal stability has to be warranted to allow for upright position, loading, and movement of the lower extremities. Very low head control or trunk instability might lead to a discontinuation of therapy. In cases of distinct leg length

Fig. 17.4 A careful adaptation of the harness as well as the exoskeleton by a well-trained and experienced therapist plays a prominent role for the success of all further training sessions (Photo courtesy of Spaulding Rehabilitation Hospital, USA)

asymmetry, correction using insoles is required; in patients with severe asymmetries of more than 4 cm, training might be impossible. Training should also be reconsidered in patients with major orthopedic pathologies and contractures of the lower limbs. After orthopedic or neurosurgical procedures in children (i.e., hip reconstructions, osteotomies or soft tissue surgery and selective dorsal rhizotomy), specific training paradigms may be applied which have to be developed in closed cooperation with the surgeon in charge. To date, the authors would not recommend RAGT in children with progressive neuromuscular disorders like Duchenne muscular dystrophy, etc.

Passive range of motion of the hips, knees, and ankles must be sufficient to allow normal kinematics consistent with upright gait. Especially, limited range of motion in the knee and hip joints

can have an impact on the feasibility of RAGT. Joint stability must be warranted to allow weight bearing. Severe and fixed contractures of the lower extremities (more than 20° extension deficit) make it difficult to allow a proper stance phase and thus a proper weight loading on the corresponding leg.

Abnormal muscular tone expressed by spasticity, hypotonus, or dyskinetic movements need to be considered carefully and individually before, during, and after the training [78] as they might require specific adjustments and training parameters for initial as well as subsequent training sessions (see below). Medication or Botox injection, carefully adjusted to the patient's needs, might also be useful prior to the training session, especially for patients with severe spasticity.

17.6.2 Training Initiation and Adjustments over Time

17.6.2.1 Training Goals

The aim of the first training session is to accustom patients to robot-assisted gait training. In some cases, the challenge might be to reduce patients' depreciative or anxious attitude toward new technologies; in other patients, it might be important to lower disproportional expectations. Therapists as well as patients can concentrate on the right setup and adequate training parameters in order to reduce the required time for further trainings, thereby increasing the actual walking time. The goal is to establish a comfortable natural walking pattern as far as possible by the patients' symptoms and conditions in order to establish initial training paradigms that can be adjusted over consecutive therapy sessions.

Within the course of therapy, patients are likely to improve in motor function, so training procedures and goals should change in accordance with training progression. At this stage, robot-assisted training provides a safe environment where a reduced fear of falling might enhance patient's ability and motivation to concentrate on specific training goals. On the other hand, walking in a stereotypic gait pattern might become rather restrictive, and training parameters have to be adapted in accordance with each patient's progress to control his/her own movements. Today's robotic devices provide a number of possibilities for therapist and patients to keep training at a challenging level and further improve motor function. In order to implement new challenges, the therapist can also combine different devices dependent on the technical features and training possibilities provided and has to decide on when and how to gradually replace robotic training by overground walk training.

17.6.2.2 Number of Training Sessions

At an early stage of rehabilitation, gait training should be applied as often as possible; two to three or even up to five training sessions a week have been suggested, depending on the patients' disease characteristics, functional abilities, and training goals. RAGT should always be combined with other physical exercises like aerobic, resistance, and balance training and be applied in addition to physiotherapeutic overground walk training as soon as possible. In chronic stroke patients, continuous training one to two times a week is required to hold the steady state and may also be beneficial in MS patients in order to maintain walking abilities.

17.6.2.3 Setup and Training Duration

For the first training session, 60 min should be scheduled. Patient setup will take longer in order to define the proper adjustments of harness as well as the orthosis. In severely affected patients with little trunk control, the harness should be adjusted while the patient is in a laying position (Fig. 17.5). As mentioned earlier, a careful adaptation of the harness as well as the exoskeleton by a well-trained and experienced therapist plays a prominent role for the success of all further training sessions. To maintain the patient's (in particular children's) cooperation, the phase of total unloading during device attachment should be kept rather short in order to avoid discomfort, in particular on the crutch.

During the first training session, patients have to be carefully observed concerning clinical symptoms of cardiovascular instability, fatigue, exertion, or pain. It is recommended to keep the

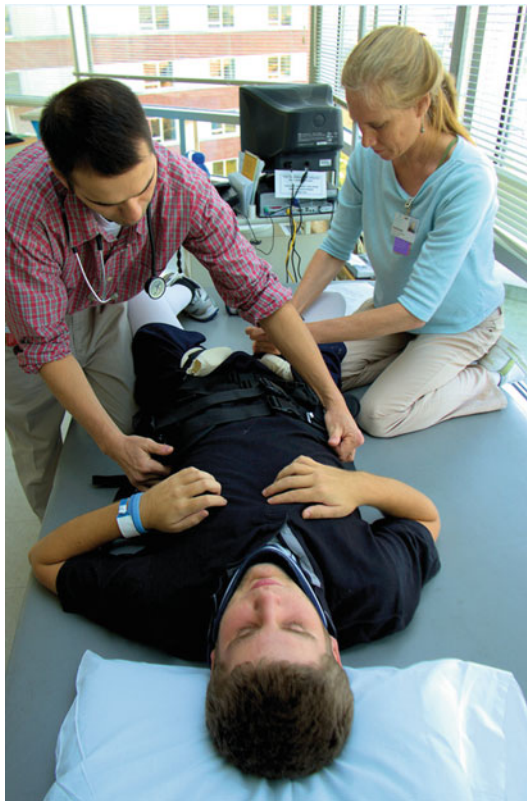

Fig. 17.5 In severely affected patients with little trunk control, the harness should be adjusted while the patient is in a laying position (Photo courtesy of Spaulding Rehabilitation Hospital, USA)

walking duration rather short during the first training session; adult patients should not walk longer than 20–30 min and children for 5–20 min. MS patients in particular tend to be very motivated, which may overstrain their abilities; it might help to instruct them to walk rather passively during their first training session to experience the effects. Even if patients seem to tolerate the training very well, reactions like pain, hypertonus, and muscle soreness may appear later. Pressure marks due to friction from harnesses and cuffs might become obvious only later due to the reduced sensibility of patients. Therapists should be on the alert for any indication of friction and interrupt the training and check the respective locations of the body thoroughly.

After the first training session, when the time for setup is reduced to a minimal amount and the patient is accustomed to the training procedure, the duration of training sessions can be gradually increased – but not more than 10 min from one session to the next. The goal is to advance the patient up to 45–55 min of continuous walking with minimal breaks throughout. In MS patients (up to 30 min) and children (20–45 min), the training duration might be shorter depending on fatigue or motivation. Training should also contain a ramp-up period in order to prevent overexhaustion of soft tissue structures like joints or tendons. The last 2–3 min of training can be used as a cool-down period, where body-weight support can be increased, thereby reducing the effort of the patient. For setup and take down, a training session of 60 min should be generally foreseen.

17.6.2.4 Body-Weight Support

In stroke and MS patients, it is not recommended to apply the highest possible amount of body weight within the first session. Predictor for the correct amount of body-weight support is the appearance of the foot and/or knee during walking, which is often affected by paralysis or muscle hypertonus. At an early stage, patients might not yet be aware on how they are able to influence their leg movements, and therefore, therapists need to regulate loading in order to establish a physiologic knee extension in alignment to hip and foot. In SCI, the maximum possible load can be applied. If the patient is unable to achieve good knee extension during stance, body-weight support should be increased. Based on the literature and the experience, initial unloading will probably range from 40% to 80% of the subject's weight. It might be better to initially provide the subject with a bit more support than required. For children, a body-weight support of at least 60% is recommended in order to walk the first steps; more support might be required for children who are not yet able to bear their own body weight. Unloading can be decreased with proper knee extension during stance phase. The ultimate goal for all patients should be to train with maximal possible load, eventually carrying their own body weight. Training therefore has to be adapted in accordance with the patient's ability of accepting more weight while keeping control

of their movements during training. Body-weight support can be gradually reduced within and over training sessions according to the patient's tolerance. Therapists can use a ladder approach, where the patient may be able to tolerate a reduced amount of body-weight support only for a brief time and must then return to the higher level of support. The goal should be to gradually increase the amount of time a patient can tolerate higher amounts of body weight until he/she can maintain that weight for the entire session. However, an adequate loading response with good knee extension during stance phase has to be assured at all times, as well as the ability to walk with this amount of loading during most of the training session.

17.6.2.5 Speed

During the first training sessions, training should start rather slow, at approximately 0.5–1.0 km/h in children, 1.0–1.5 km/h for stroke and MS patients, and up to 1.6–2.0 km/h in patients with SCI. Patients should have the opportunity and time to adjust to the new training situation, experience the device, adapt their gait pattern, and even concentrate on specific gait parameter. Once the patient starts to demonstrate improvements in confidence and comfort with the device and is able to carry a large amount of body weight over the duration of one training session, speed can be gradually increased. An average speed of 0.8–1.8 km/h in children, 1.5–2.5 km/h in stroke or MS, and 2.5–3.2 km/h in SCI patients has been recommended. As soon as patients walk very fast carrying at least 80% of their body weight, therapists have to control for heart rate to ensure an aerobic training situation. Whereas high functional, ambulatory patients might be able to tolerate even higher speeds, for children, a maximum speed of 1.8 km/h is recommended as here, maximum walking speed is defined by the leg length, and an appropriate stance phase can no longer be assured at higher training speeds. Another predictor for the correct speed might be by specific symptoms, i.e., dystonia or marked spasticity. Ataxic patients with stable muscle function can be trained fast whereas fatigue or hypertonus requires slower training.

With an increase in speed, gait parameters are changing, and it is required to make the necessary adjustments, e.g., provide higher range of motion during hip extension. Hip fixation can be slightly loosened in order to provide more range of motion in the hip joint. As the variability of gait is important in terms of motor learning, the therapist can challenge patients by changing speed within one training session, either manually or with specific software programs. In order to keep training at a challenging level, the therapist can also vary step length in accordance with changes in speed and implement dual-task training situations like reciprocal arm movements, using the handrails, or pretending to kick a ball during walking. A comfortable walking speed, good loading during stance phase, and a harmonic gait pattern are important at any time. Decrease during swing phase might reflect patients' inabilities to deal with the higher speeds and reflect the need to make further adjustments.

17.6.2.6 Guidance Force

Within the first training session, guidance force should be kept at 100% and should not be decreased before an individual is able to walk at a very high speed under minimal body-weight support. Once the patient has progressed, the amount of guidance force should be progressively reduced in order to further challenge the subject. In MS patients, this can already be the case after two to three training sessions. The amount of guidance force should be reduced so that the patient can still maintain proper gait trajectories, clear toes during swing phase, and adequately extend knees during stance phase but is constantly challenged during the training session. For hemiparetic patients, the guidance force can be reduced specifically on the impaired leg in order to force the patient to train this leg in accordance with force-induced therapy. In children, training below 50% guidance force is not recommended.

17.6.2.7 Biofeedback

Some devices provide a biofeedback system with detailed information for patient and therapist about active participation within the gait cycle, for example, swing and stance phase.

Fig. 17.6 Biofeedback systems provide detailed information for patients and therapist about active participation. They furthermore allow therapists to give detailed training instructions in order to achieve specific training goals whereas the patient receives immediate feedback on his/her performance (Photo courtesy of Spaulding Rehabilitation Hospital, USA)

This allows the therapist to give detailed training instructions in order to achieve specific training goals whereas the patient receives immediate feedback on compliance with these instructions (Fig. 17.6). Once patients have been introduced to the biofeedback system and have a clear understanding on how to influence biofeedback values, they can gradually adjust their gait pattern or start focusing on specific training paradigms.

The decision if and when additional information via biofeedback systems might become beneficial and how it should be applied during the training session depends on therapist evaluation based on patient's abilities. For patients with mild functional impairments, biofeedback values might be a useful training tool whereas in patients with basic troubles in alertness and vigilance, walk training itself is quite demanding and, by providing biofeedback values, the requirement of therapy might become too complex and thereby aggravating progress.

Due to limitations of alertness and perception in severely affected stroke patients, training of one specific gait parameter at a time, for example swing or stand phase of one hip or knee joint, might be recommended so as not to overstrain the patient. These patients often need manual or verbal feedback in addition to the biofeedback values presented by the device. The therapist may furthermore have to facilitate knee or foot during walking to provide additional afferent feedback, for instance, support during knee extension or facilitation of plantar flexion in late midstance. If the training goal is to change an already established compensatory gait pattern, the patient requires clear instructions by the therapist on what parameters of gait he should specifically concentrate on, for example, achieving proper knee extension or concentration on correct positioning of the foot during stance phase. Hemiparetic patients can also concentrate on biofeedback values displayed by the less affected side as active participation of the stronger leg during stance phase might reflect a more active swing phase of the paretic side. Until subjects get used to how their efforts affect their biofeedback values, walking speed should be rather slow. Reduced walking speed with slower step cycles also provides more time for patients to concentrate on coordinated activation and relaxation of antagonistic muscle groups during stance and swing phase thereby preventing muscle co-contractions. Increased spasticity might be observed if patients get overexcited or overmotivated during training, and in this case, training without displaying biofeedback values might be required for a time.

In children, patient adaptive control strategies and an adapted biofeedback system are of particular importance to assure maximum participation, especially in young children. Simple feedback mechanisms can only be used for a limited period of time in order to improve selective muscle control, i.e., hip flexion or knee extension. Current projects aim to expand the existing biofeedback system integrating technologies that allow walking

Fig. 17.7 Augmented feedback allows walking in a motivating and patient-friendly virtual reality-based environment and results in good compliance, increased attention, and high muscle activity

in a motivating and child-friendly virtual reality-based environment (Fig. 17.7). Interactive virtual realities like soccer games or collecting games are motivating, especially for young patients, and result in good compliance, increased attention, and high muscle activity [47]. Children should, however, still react to verbal input provided by their therapist.

17.6.3 Specific Training Goals

17.6.3.1 Achieve Body Alignment and Trunk Control

In some patients, verbal feedback and manual facilitation might be required in order to keep trunk and head in upright position and symmetric alignment. Patients might furthermore benefit from visual feedback provided by a mirror placed in front of the treadmill during walking in order to adjust their trunk and maintain a correct position. Different devices positioned at a slightly elevated place (i.e., balloons, bells, or computer screens displaying biofeedback values or augmented feedback) encourage patients to walk in an upright position.

One more challenge is to integrate paretic or hypertonic arms in a correct alignment. Therapists have the ability to adapt the parallel bars of the treadmill in order to position hands and arms on the bar. Special attention is required to place the arms correctly to prevent shoulder pain. In some cases, it might be necessary to place the arm in a sling during training, whereas paraplegic SCI patients can be encouraged to swing their unaffected arms during walking.

17.6.3.2 Decreasing High Muscle Tone

Patients that exhibit strong spasticity in their legs might be difficult to train as increased forces acting on the drives can trigger safety mechanisms that continuously stop the machine, thereby interrupting the training procedure. In order to reduce high muscle tonus, training should be started in the air with minimal afferent input at a decreased range of motion and a very slow walking speed, if necessary, even without foot lifters. Stroke patients that suffer from muscle hypertonus only in one paretic leg can start walking with a smaller range of motion in the affected leg. Additional input provided by the augmented feedback can further increase muscle tonus and should be abandoned. Once a patient is able to walk and movements continue to be appropriate, the therapist can slowly lower the patient on the treadmill. If the foot displays clonus, he can facilitate it with his hands, carefully adapting gait. As soon as patients continue to walk with an undisturbed gait pattern, the therapist has the ability to slowly increase the range of motion thereby establishing a normal or, in hemiparetic patients, more symmetric gait pattern over time.

However, even though decreasing high muscle tone might be one of the goals in

Fig. 17.8 The use of elastic foot lifters is strongly recommended in robotic devices without footplates or boots due to safety reasons as obtaining ankle dorsiflexion for a whole training session will be difficult for most patients (Photo courtesy of Spaulding Rehabilitation Hospital, USA)

rehabilitation therapy, one has to take into account that secondary changes in mechanical muscle fiber, collagen tissue, and tendon properties result in spastic muscle tone that can, in part, compensate for paresis and allow functional movements. Antispastic interventions (for example, drugs) can accentuate paresis and therefore should be applied with caution in mobile patients [79].

17.6.3.3 Increasing Range of Motion

Chronic patients might suffer from restrictions of hip or knee joints leading to a decreased range of motion. In order to obtain a physiological gait pattern, one of the main training goals is to increase the range of motion by walking with smaller steps at initial training, slowly adapted by the therapist in order to obtain a larger range of motion over time. However, in SCI patients, compensatory movements, for example in the lower spine, can cause pain and should be prevented. The optimal range of motion allows an adequate step length in order to achieve symmetrical gait and balanced stance-to-swing phase.

17.6.3.4 Improving Ankle Control

Correct positioning of the foot is of special importance in order to obtain a physiological gait pattern and appropriate afferent feedback and requires adjustments by an experienced physiotherapist. The use of elastic foot lifters is strongly recommended in robotic devices without footplates or boots due to safety reasons, as obtaining active ankle dorsiflexion for a training session of 35–55 min will be difficult for most patients (Fig. 17.8). Depending on the functional abilities and restrictions (i.e., hypo- or hypertonus, clonus) of ROM in any of the joints, the foot can be properly adjusted with the foot lifters. Preliminary studies suggest that the muscular activity of shanks is not affected when wearing foot lifters [80]. As soon as the patient shows an increasing ability to control his/her ankle movements, the therapist can concentrate on further increasing ankle control by loosening the straps. Walking with dynamic splints is also possible during robot-assisted training. Within a training session, the therapist has to continuously monitor if the splint is still useful, otherwise it might be removed. The therapist also has to be aware that this might require additional adaptations of foot lifters or cuffs. If, in contrast, shoes and splints that completely fix the upper angle are required, body-weight support, step length, and the amount of knee flexion have to be adapted in order to establish a comfortable gait pattern.

Fig. 17.9 The G-EO systems (Reha Technologies, Bozen, Italy) allow training of additional tasks, for example, repetitive practice of stair climbing (Photo courtesy of Reha Technologies, Bozen, Italy)

17.6.4 Integration into the Clinical Path

Robot-assisted gait training should be integrated as an additional treatment option in a comprehensive rehabilitation program with specific goals. A therapy setting starting with safe, intensive robot-assisted gait training from two up to five times a week as soon as the patient's general health conditions allow for upright standing for a certain amount of time seems beneficial. In addition, patients have to be mobilized and stretched during conventional physiotherapy; exercises can aim at improving muscular strength, trunk control, joint mobility, and activities of daily life (for example, transfer in and out of bed). In addition, patient and therapist can train balance and controlled weight shift from one leg to the other, important for transition from stance to swing phase. At later stages, technical features of specific devices can be used to keep training at a challenging level (Fig. 17.9) and train specific gait parameters, while integrating proper strength, stance, balance, and walk training during individual therapy sessions. Therapists might decide to gradually integrate/replace one robotic device with another, thereby offering more degrees of freedom in the hip and knee joint in order to further improve postural stability, strength, and balance. As soon as no further improvements can be observed, he might also cease robot-assisted training and concentrate on manual-assisted gait training and overground walking alone. Robotic training can then be applied in specific training sessions to reduce secondary complications or specifically train strength as well as specific gait parameters. To appropriately support the patient at any functional stage, keep training at a challenging and motivating level and train specific gait parameters. Patients' progression should be assessed on a regular basis.

Conclusion

In parallel with an increasing number of robotic devices for neurorehabilitation, the demand for clinical evidence to proof their

efficacy as well as recommendations of best practice has been increasing. Clinical evidence in the future will require large multicenter studies with standardized patient populations and training parameters. These parameters can potentially be based on experience collected over the last 10 years, which have led to a better understanding on how robots can successfully be integrated into the clinical path. Devices for automated walk training have been applied in clinical settings all over the world, and patients can be trained as soon as they meet the required inclusion criteria concerning their cardiovascular stability, cognitive abilities, and muscular and skeletal performance. Training parameters applied during early sessions focus on a large number of repetitions in order to use the plastic potential of the injured CNS at an early stage, reestablish a normal gait pattern, and prevent the occurrence of compensatory movements. Locomotor performance can be enhanced by training patients in a challenging and motivational environment provided through different technical features and continuously adapted by the therapist based on the patient's improvements over time. In chronic patients, robots can support therapist and patient in working toward specific training goals, enhanced by immediate feedback about the quality of movements and a decrease in secondary complications. Close collaboration and constant knowledge sharing between basic scientists, clinicians, therapists, and engineers will further enhance and perhaps even ensure a safe and efficient integration of robotic devices into the rehabilitation process to the patients' benefit.

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Part VII

Specific Aspects of Neurorehabilitation Technology: Robots Versus Passive Systems

18 Functional Assisted Gaming for Upper-Extremity Therapy After Stroke: Background, Evaluation, and Future Directions of the Spring Orthosis Approach

David J. Reinkensmeyer

Abstract

We describe the use of a passive, spring-based orthosis approach (as exemplified by T-WREX and Armeo®Spring) to enhance upper-extremity movement therapy after neurologic injury. This approach incorporates an arm exoskeleton that assists a patient in moving his or her weakened arm by using springs to support the weight of the arm: a grip sensor that can sense minimal grasp forces, and thus allows even very weak patients to practice integrating hand movement with arm movement; and a suite of computer games that simulate functional, whole-arm activities and provide objective feedback on performance. This chapter first traces the development of the spring orthosis approach to upper-extremity arm therapy within the context of the development of robot-assisted therapy. Then, this chapter evaluates the spring orthosis approach in light of recent evidence concerning the role of functional exercise, external assistance, and gaming in promoting movement recovery of the arm and hand after stroke. The chapter concludes by analyzing possible future directions for technology for upper-extremity movement therapy relative to the spring orthosis approach.

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18.1 Introduction: From the Appearance of Robot-Assisted Movement Therapy to the Development of the Spring Orthosis Approach

Beginning in the late 1980s, engineering and rehabilitation research groups identified the potential to develop new technologies for upper-extremity rehabilitation in neurologic disorders. A key realization was that rehabilitation technology had not yet taken full advantage of computers and robotic technology. Existing therapeutic equipment allowed people with arm weakness to practice arm movement, but it did so with limited flexibility, feedback, and engagement. For example, devices such as overhead slings, mobile arm supports, or simply a towel on a tabletop provided assistance in moving the arm against gravity, and devices such as elastic bands and hand exercise bicycles provided resistance for specific arm movements. Yet they had limited adjustability in the pattern of assistance, they could apply relative to that which was possible with a robotic device. Further, upper-extremity rehabilitation technology that was routinely used in clinics lacked sensors, with the notable exception of dynamometers. Adding sensors and then connecting the sensors to a computer would allow measurement and recording of arm movement ability, providing feedback to both the patient and therapist about progress. Further, once the sensed information was in the computer, then it could be used to control computer games, which allowed for the possibility of improving patient engagement in the exercises performed with the device.

Out of this rationale came several new robotic devices, including the MIT-Manus [1], the MIME [2], the ARM-Guide [3], and the BiManuTrac [4]. Each device took the approach of assisting patients in making movements with the arm or forearm as they played simple computer games. Twenty years later, hundreds of patients have been involved in randomized controlled trials with these earlier devices, and two of these original devices are commercially available (MIT-Manus and BiManuTrac). The studies indicate that people with an acute or chronic stroke can recover additional movement ability if they exercise for tens of hours with these devices; the transfer to functional movement is typically small [5–7]. Exercise with a robotic device has also been found to be as effective or, in some cases, more effective than a matched amount of exercise performed with a therapist [2, 8, 9], or a matched amount of exercise performed with another rehabilitation technology, such as electromyogram-triggered functional electrical stimulation [10] or sensor-based approaches to range of motion exercise [11].

Given these limitations in outcomes, developers of next generation technology for upper-extremity therapy asked the question "How can we improve upon these initial robotic designs?" Many possible pathways have emerged, but three stood out to my group in the early 2000s. First, robotic devices were at the high end of complexity in the spectrum of therapeutic technology. While these devices were powerful tools for studying rehabilitation therapy, it was unclear whether their therapeutic benefit justified their cost. What had been demonstrated was the importance of repetitive practice of movement attempts, with or without robotic guidance present [12]. Further, installing motors on an orthosis or manipulandum (making the device robotic) increased cost and complexity and decreased safety. Therefore, we asked whether it would be possible to gain the benefits of robotic assistance without the robot.

The second new pathway emerged out of the observation that initial robotic therapy devices did a relatively poor job of training functional

movements. Functional movements are characterized by three features. First, they are oriented at achieving activities of daily living: prevailing robot therapies focused on simple range of motion and tracking games rather than simulating activities of daily living. Second, they often involve the use of many or all joints of the arm simultaneously; existing robots typically offered one or two degrees of freedom, with the exception of the MIME device, but this device relied on an industrial robot that did not match the workspace of the human arm. Third, functional movements typically require coordination of the hand with the arm to achieve a meaningful goal; existing robots typically worked on the arm or forearm in isolation. At the same time, the importance of functional training was also being promoted by the broader field of rehabilitation science. This position was influenced by both occupational therapy models in which functional practice is noted to hold greater meaning for a patient and by motor learning models in which transfer of learning is noted to be limited, and therefore, functional transfer would theoretically be maximized if patients spent therapy time practicing the activities they actually needed to relearn to do.

In addition, our thinking about the desirability for a functional focus was influenced by the development and pilot testing we had done with a very low-cost, web-based system for facilitating repetitive movement training called "Java Therapy." [13] Java therapy required users to log into a website and then play through a customized program of movement training games using a mouse or joystick as the input device. In pilot testing, people with a chronic stroke responded enthusiastically to the objective feedback the system provided about their movement performance, and accessed the system frequently from home. However, the use of a standard mouse or joystick as the input device meant that users could only practice mouse-like or joystick-like movements, and while we measured improvements in the ability to perform these movements, we found no functional improvements in movement ability.

Third, initial robotic devices used only crude video games typically involving movement of a cursor to a target with a simplistic graphical reward given upon success. Given the sophistication and complexity of modern video games, there was clearly significant potential to improve the challenge and engagement provided by the game interface.

My group moved along these three pathways by developing a new device called T-WREX (or "Therapy-Wilmington Robotic Exoskeleton"), which was described in the doctoral dissertation research of Dr. Robert Sanchez [14]. First, we designed T-WREX to be nonrobotic but to still allow severely weakened patients to move by providing gradable assistance against gravity with elastic bands. To achieve this, we collaborated with Dr. Tariq Rahman of the A.I. duPont Institute for Children, who with National Institute of Disability and Rehabilitation Research (NIDRR) support had developed the innovative arm support called WREX to assist children with weakened arms in moving their arms [15]. We scaled up the WREX design to be large enough and strong enough to support movements by adults with a stroke (Fig. 18.1). Second, we designed T-WREX to support functional movements. The use of WREX helped achieve this goal in part because WREX allowed a large range of motion and had been explicitly designed to allow feeding and other functional movements (Fig. 18.1b). But we also developed and integrated a grip sensor that allowed detection of even trace amounts of hand grasp, thus allowing people with weakened, essentially "useless" hands to practice using their hands in a meaningful way in a virtual world, in coordination with their arms. Third, we developed a suite of computer games that were easy to learn yet engaging and which approximated the movements needed for activities of daily living. These games included activities such as cooking, shopping, bathing, and cleaning (Fig. 18.1c).

18.1.1 Clinical Testing with T-WREX

We performed a pilot study with T-WREX at UC Irvine [14]. In this study, we first quantified the effect of the gravity balance provided by

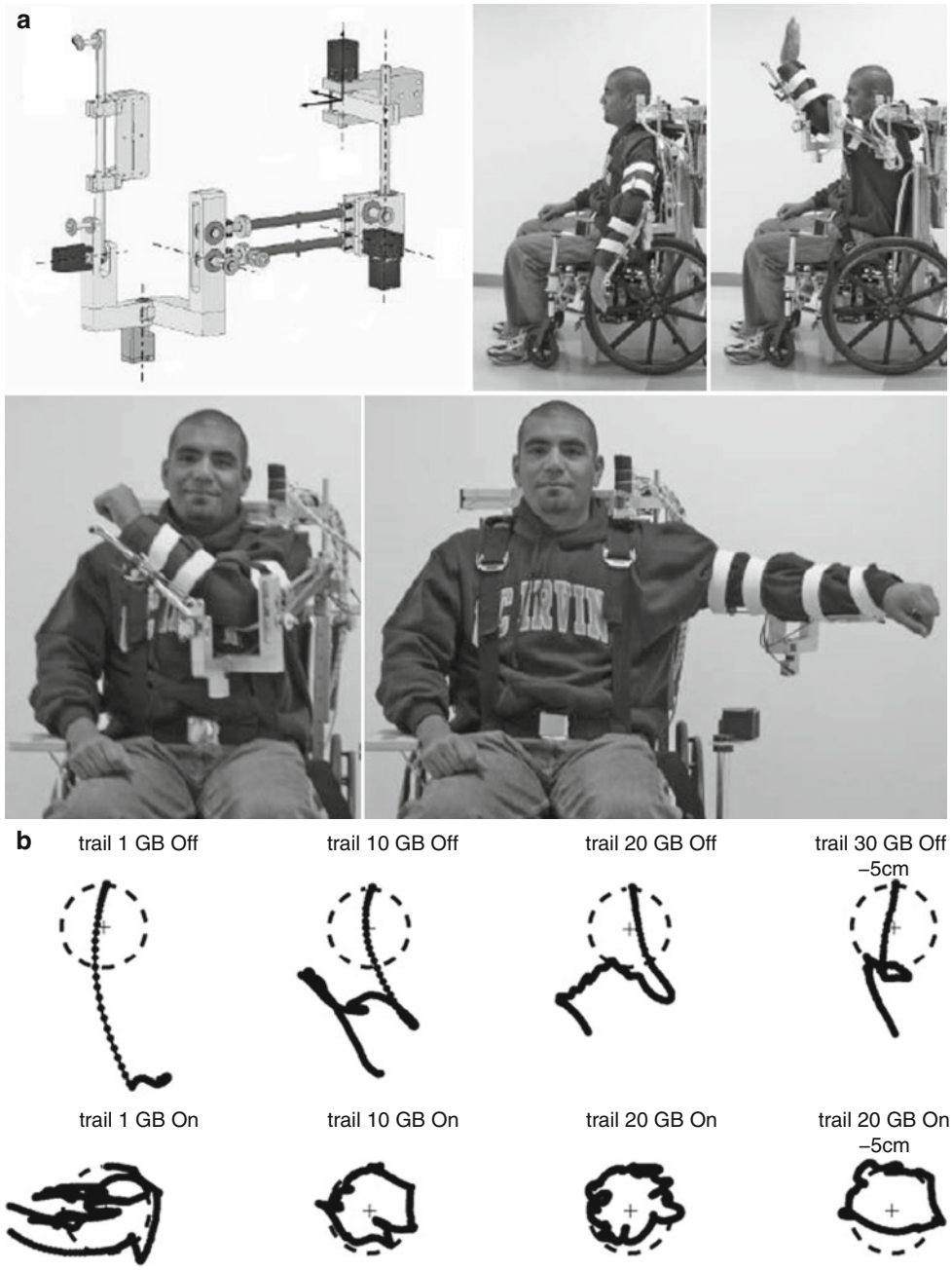

Fig. 18.1 (**a**) The T-WREX arm support exoskeleton was based on WREX and relieves the weight of the arm while allowing a wide range of motion of the arm. (**b**) This sequence of plots shows the hand trajectory when a person with severe paresis after chronic stroke tried to trace a circle in the frontal plane, without and with arm support from the T-WREX device. Without arm support (*top row*), the arm dropped, and the person was only able to hold it at the bottom of the circle. With arm support (*bottom row*), the person could begin to draw a circle, and the quality of the circle improved notably after 30 attempts, indicating that even a person who had not drawn a circle in years can quickly relearn how to, given an enabling dynamic environment. (**c**) Example of original T-WREX games, which all simulated activities of daily living. In the shopping game, the user reaches for items on the shelves, squeezes to grip the object, moves to the shopping cart, and releases to drop the object. The egg-cooking game is a similar pick-and-place task but requires control of the peak grip force as well as the minimum grip force. Other games simulate driving, cooking, cleaning, self-care, and sports (Adapted from Sanchez et al. [14]; © 2006, IEEE)

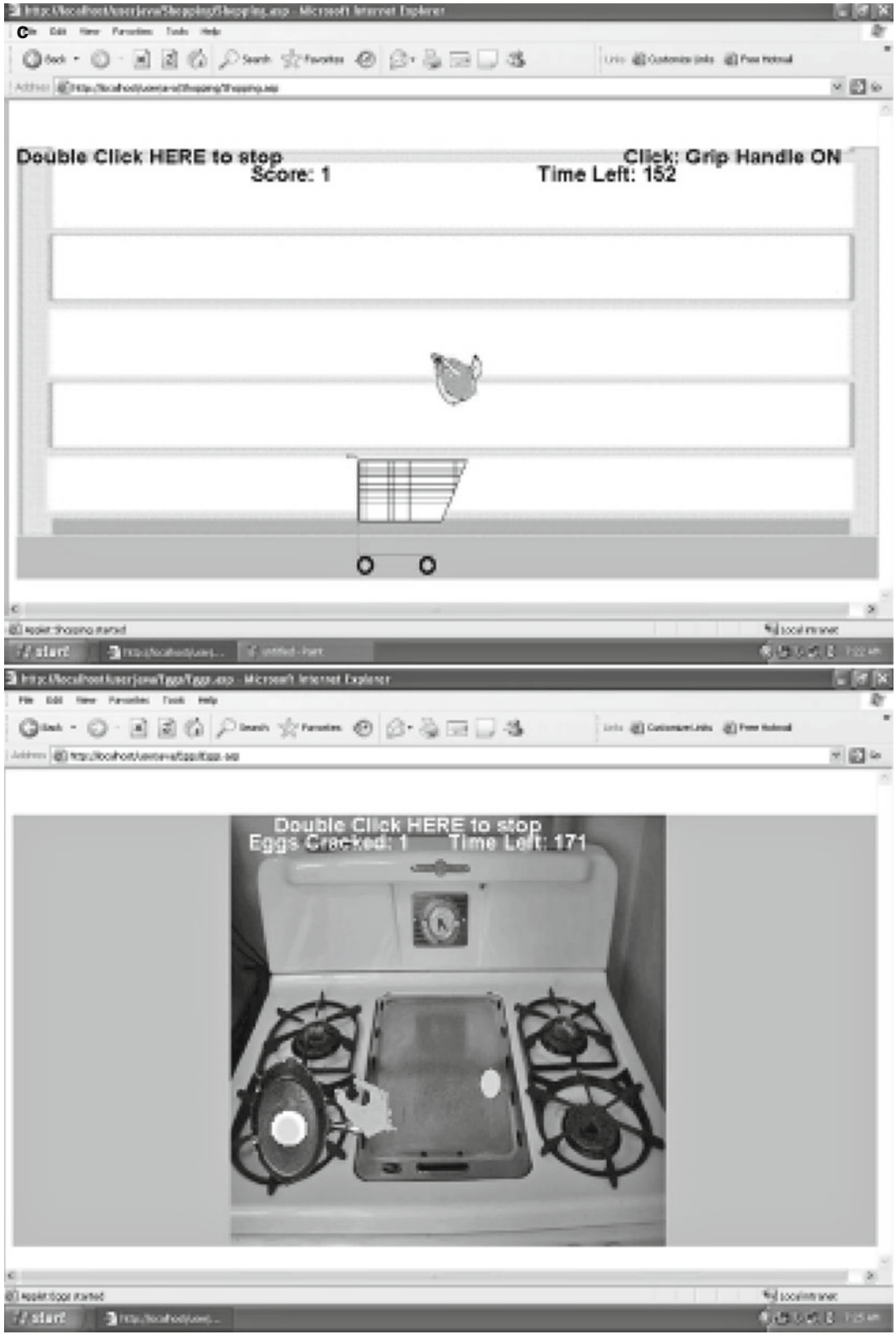

Fig. 18.1 (continued)

T-WREX on voluntary arm movements by measuring how well volunteers with moderate-to-severe stroke (mean Fugl–Meyer upper-extremity score 25, $n = 9$) could perform various arm movements while they wore the orthosis with and without gravity balance. The users first performed a version of the Fugl–Meyer test that measured 14 tasks with a possible total score of 28. The gravity balance improved the FM score by about 1 point on average, a small change. They then reached to two targets, one ipsilateral and one contralateral to their impaired arm. Gravity balance significantly improved reaching to the contralateral target but not to the ipsilateral target. The most dramatic results came when the volunteers attempted to trace the outline of a large plastic disk placed in the frontal plane about 20 cm in front of their torso. The gravity balancing provided by T-WREX significantly improved the accuracy of the drawn circles for those who were able to draw a circle (Fig. 18.1b). Most strikingly, it also improved the ability of the volunteers to draw circles for those subjects who could not draw them without assistance (i.e., for those volunteers who could not hold their arms at the top of the circle against gravity). Thus, provision of gravity compensation allowed people who had not made certain movements (i.e., frontal-plane circles) for years to quickly relearn how to make those movements (Fig. 18.1b). Subsequent testing with T-WREX showed that the device improved quality of movements of people with stroke, as measured by smoothness and timing as well [16].

We also performed a pilot therapeutic test of T-WREX at UC Irvine [14]. Volunteers with moderate-to-severe arm impairment after chronic stroke (mean starting FM score 22) practiced moving with T-WREX three times per week, 45 min per session, over an 8-week period. They improved their movement ability as quantified by an average change in Fugl–Meyer score of 20% compared to baseline, hand grasp strength by 50%, as well as unsupported and supported reaching range of motion by 10%. They achieved these improvements with approximately 6 min of direct contact with a rehabilitation therapist per 45 min of training. This interaction was necessary to help the volunteer to attach and detach his arm from the device.

Encouraged by these results and with the support of the NIDRR MARS (Machines Assisting Recovery in Stroke) RERC (Rehabilitation Engineering Research Center) led by Drs. Zev Rymer and Jim Patton, we refined T-WREX and performed a single-blind, randomized controlled trial of it at the Rehabilitation Institute of Chicago, under the supervision of the occupational therapist Sarah Housman [17]. We compared movement training with T-WREX against the standard approach for semiautonomous exercise at RIC, which was to train the weakened arm by using a tabletop to support the arm and a towel to remove the friction between the arm and the table (Fig. 18.2a) [18]. Twenty-eight chronic stroke survivors were randomly assigned to the experimental (T-WREX) or control (tabletop exercise) treatment. A blinded evaluator rated upper-extremity movement before and after 24 1-h treatment sessions and at 6-month follow-up. The volunteers were also asked to rate their preference for T-WREX versus tabletop exercise after a single-session crossover treatment. The volunteers significantly improved upper-extremity motor control (Fugl–Meyer), active reaching range of motion (ROM), and self-reported quality and amount of arm use (Motor Activity Log). Improvements in the T-WREX group were better sustained at 6 months (improvement of 3.6 ± 3.9 versus 1.5 ± 2.7 points, mean $\pm$ SD, $p = 0.05$, Fig. 18.2b). The volunteers reported a strong preference for the T-WREX training compared to the tabletop training (Fig. 18.2c). The amount of supervision time required for both groups was about 3 min, following an initial training period of three sessions.

These results were encouraging: training with T-WREX produced detectably better results than a matched duration of the tabletop exercise and was substantially preferred by patients but required minimal direct supervision time, in an amount comparable to the time

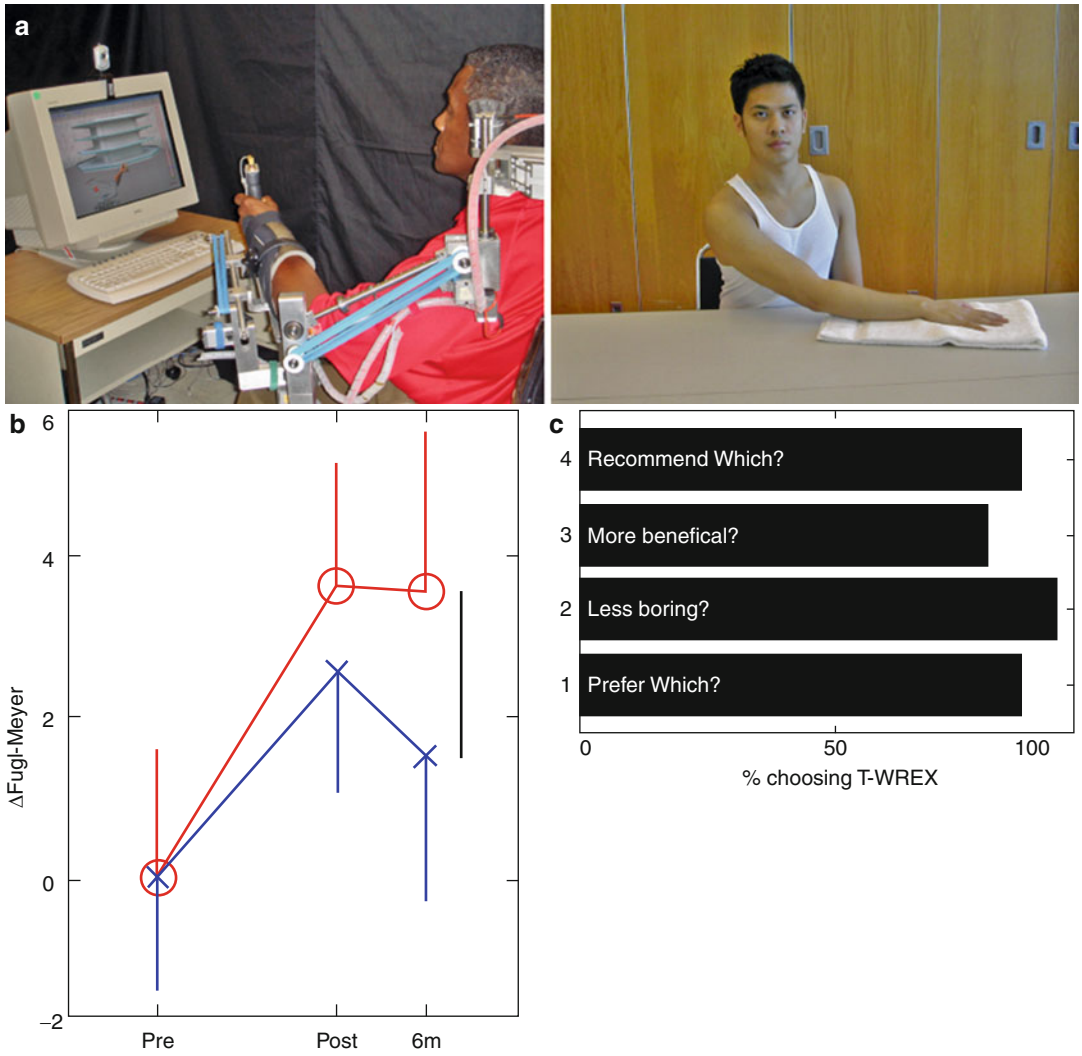

Fig. 18.2 (**a**) In a single-blind randomized controlled trial of T-WREX, we compared training with T-WREX to training of the arm on a tabletop with a towel. (**b**) Improvements in upper-extremity (UE) movement ability as measured with the UE Fugl–Meyer (FM) scale [18] following chronic stroke with 2 months of T-WREX therapy ($n=14$) and conventional tabletop exercise ($n=14$) were significantly different at 6-month follow-up ($p=0.05$). (**c**) Percentage of subjects preferring T-WREX therapy, compared to conventional, self-directed tabletop exercise, measured in our study. Subjects in both groups were given a chance to try each therapy and then select which one they preferred in ten categories, of which four are summarized here (From Housman et al. [17] © 2009; reprinted by permission of SAGE Publications)

required for a simple form of semiautonomous exercise (tabletop exercise with a towel). In addition, another group showed also that computer game–driven movement practice with the arm supported by a different spring-based arm support could improve arm motor recovery after chronic stroke [19].

Hocoma AG licensed the intellectual property for T-WREX from the University of California at Irvine then substantially improved

Fig. 18.3 Armeo, developed by Hocoma AG based on T-WREX, is designed to be more quickly adjustable than T-WREX for easier clinical use (Courtesy Hocoma AG)

the mechanical, electrical, and software designs of T-WREX for usability and manufacturability. The resulting ArmeoSpring device (Fig. 18.3) is now being used in approximately 200 clinics around the world.

18.2 Reevaluating the Conceptual Framework for Spring-Based Orthoses: Status of Functional, Assistive, Computer Gaming in Upper-Extremity Motor Recovery

T-WREX was based on the rationale that functionally oriented activities, physical assistance, and computer gaming and feedback would best promote movement recovery of the upper extremity, without need for use of robotics. In this section, we review recent research findings that both support and challenge the three components of this rationale.

18.2.1 Is "Functional" Training Better Than "Nonfunctional" Exercise?

One characteristic of functional movement training is that it often involves the coordinated use of many joints in the upper extremity. Remarkably, some of the best clinical results gained with robot-assisted therapy have come from two studies that used devices that only assisted in few degrees of freedom of motion. The first study was performed with the BiManuTrac, a device that assists unilateral and bilateral forearm supination/pronation or wrist flexion/extension movements [10]. Robotic training of the forearm and wrist using the BiManuTrac device produced greater improvements than EMG-triggered FES of the wrist in

subacute stroke patients ($n=44$). The FM score was 15 points higher at study end and 13 points higher at 3-month follow-up than the FES group, a larger difference noted than in any other study of robot-assisted therapy. In this study, the activities performed might be characterized as "non-functional," involving rotation of the wrist or forearm in order to track computer targets.

The second study was done with the HWARD device, which allows hand opening and closing by assisting in finger extension and flexion around the metacarpophalangeal (MCP) joint, along with wrist flexion/extension and simple thumb movement [20]. Chronic stroke patients who received robot assistance using the HWARD device for all of their training movements ($n=7$) recovered significantly more hand function than patients who received robot assistance for only half of their training movements (i.e., for only the last 7.5 sessions of a 15-session protocol, $n=6$). The increase in FM score was 9.1 versus 5.8 points, for the two groups, which again were large changes. In this study, it should be noted that the training activities were designed to simulate hand functional activities. However, the device ignored use of the arm, and functional use of the upper extremity typically requires coordinated arm and hand use.

One might use these two studies to suggest an approach to robotic therapy for the upper extremity that focuses on the hand only, with a reduced number of degrees of freedom and possibly a limited use of functional games. But the picture is still far from conclusive. For example, another study compared functional and impairment-based robotic training in volunteers with severe-to-moderate chronic stroke [21] and found that addition of hand therapy to arm therapy reduced recovery; that is, arm training alone was best. A total of 47 people were randomized into three groups: one that trained just the arm; one that trained the hand with the arm using the hand to transport objects to targets; and one that trained the hand with the arm, using the hand to grasp and release a simulated object. All three groups improved, but the group that focused on arm movement alone had significantly better outcomes in the Fugl–Meyer score. Thus, focusing on distal function may not always bring more benefit.

More studies are needed to clarify how the various components of a functional emphasis during training modulate upper-extremity recovery. Spring-based or robotic orthoses can serve as tools for these studies because they can measure both proximal (shoulder and elbow) and distal (forearm, wrist, and hand) joint movements and can incorporate games that focus training proximally, distally, or on a combination of both, including both more "functional" activity of daily living and less "functional" tracking-type games.

18.2.2 Is Physical Assistance Beneficial for Promoting Motor Recovery?

Consistent with the original implementation of robotic therapy devices, spring-based orthoses take the approach of providing physical assistance to help the patient move his or her arm. The role of different forms of physical assistance in promoting motor recovery after stroke remains unclear, but new insights are being gained, as we review in this section.

How does the motor system modulate muscle activity in response to physical assistance? For unimpaired adult volunteers, we found that the motor system adapts to robot-applied force fields by minimizing a cost function that includes error and effort terms (in a greedy or steepest descent fashion) [22]. The motor system achieves this minimization by an error-based adaptation algorithm that contains a forgetting term. Essentially, the motor system applies slightly less force than it predicts is necessary for a given force field environment. The effect of this forgetting is that the motor system "slacks," reducing its force output when kinematic errors are small. In other words, the human motor system seems to be fundamentally organized to minimize its motor output when given a chance by a robotically assisting device. We have confirmed that individuals with a stroke exhibit this same slacking behavior during reaching movements assisted by a robotic orthosis [23].

But does slacking affect motor learning and recovery? The answer is still unclear, but there is evidence from motor learning, strength training,

and rehabilitation studies that suggest that slacking does have an impact on these activities.

Motor learning studies in healthy adults have found that learning is typically reduced or entirely absent if the trainee is passive during training, demonstrating the importance of voluntary drive for brain plasticity [24–26]. As an example, Lotze and colleagues [25] compared motor performance gains after a training period of either subject-driven (i.e., active) or robot-driven (i.e., passive) wrist movements. Motor performance, measured as the number of movements that hit a target window duration, was significantly better after active training than after passive training. Passive training did not lead to significant behavioral gains. In addition, the magnitude of cortical reorganization and the size of the engaged brain areas were each larger with active than with passively elicited movements. Likewise, active training of repetitive thumb movements resulted in persistent changes in the primary motor cortex, accompanied by characteristic changes in corticomotor excitability, whereas passive training did not [26]. Guiding unimpaired subjects along the path needed to compensate for a visuomotor rotation reduced the rate of learning of the perturbation, compared to experiencing errors, with the least learning when the subject was passive during guidance [27]. All of these studies suggest that slacking will diminish motor learning.

In a neurologic rehabilitation context, a recent study showed that robotically assisting wrist movement while the patient remained passive reduced spasticity at the wrist but also significantly reduced the movement gains achieved compared to a patient active approach [28]. In this study, 27 hemiparetic volunteers with chronic stroke were randomly assigned to receive 20 sessions of wrist training with an electromyogram (EMG)-driven robot or a passive motion device (passive group, $n = 12$). The EMG-driven group exhibited significantly greater improvements in Fugl–Meyer scores. Both groups exhibited reduced spasticity of the wrist muscles. This study indicates that slacking to the point of passivity is undesirable, except possibly that such training might still help reduce spasticity.

For the Lokomat gait training robot, motor output was about 50% of that compared to when a human therapist assisted spinal cord injured patients with the desired gait motion, measured by energy expenditure gauged by oxygen uptake [29]. This decreased motor output may help explain why motor gains with robotic gait training that did not reinforce patient effort with any feedback were about 50% less than with therapist-assisted gait training, for patients who were ambulatory at study start after chronic stroke [30, 31].

Notably, intensity of motor output matters for strength training, an important consideration for stroke given that studies that have compared a range of impairment measures with upper-extremity functional activity after stroke find that weakness produces the strongest correlations [32–35]. Weakness following stroke primarily has a neurologic rather than muscular origin, as, for example, electrical stimulation can produce near normal muscle forces after stroke [36]. But strength in health also has a large neurologic component, as, for example, initial increases in force production cannot be explained by muscle hypertrophy which requires time-delayed protein synthesis and imagined contractions alone can improve maximum force output [37]. In health and after stroke, the strength training literature indicates that larger intensity motor output more rapidly increases strength through both neurologic and muscular pathways [38, 39]. It is thus rational to expect stroke patients to exercise at relatively high output levels to better stimulate mechanisms responsible for strength increases, i.e., motor output matters.

Besides encouraging slacking, physical guidance also has the effect of reducing the experience of error, which may diminish learning. Reduced variability has been hypothesized to explain the reduced effectiveness of rigid robotic gait training in rodents and humans [40–42]. In the motor learning literature, the guidance hypothesis suggests that providing guidance too frequently, whether physical assistance or detailed knowledge of results, can create an environment in which problem-solving skills are not learned [43]. Thus, when the guidance is removed, learning is reduced, although for some tasks, this may not be true [44–47].

If assistance has unexpected drawbacks in that it can cause slacking, increase passivity, and reduce errors or variability needed for learning, are there benefits to assistance? In the HWARD study described above, the act of physically finishing the movement for the patient appeared to have a benefit, as the group that received assistance for all training sessions recovered significantly more, suggesting that afferent input caused by moving the hand provoked plasticity in sensory motor brain areas. This HWARD study was also unique because the hand contacted physical objects as it closed during training, providing increased tactile input. The idea that helping a patient finish a movement will promote recovery is consistent with a Hebbian concept of sensory motor rehabilitation in which sensory information that is enhanced by the robot and coordinated with motor output drives plasticity. This concept requires future testing.

Assistance also likely serves two practical functions that enhance practice. Assistance can make movements that are impossible for a patient to practice independently, now possible to practice. This function of assistance may be more important for gait training as compared to upper-extremity training, as safely practicing gait requires a greater level of baseline ability than safely practicing simple arm and hand movements. But assistance can also make practice more motivating. In the words of a volunteer in a T-WREX study, "If I can't do something once, why would I do it a hundred times?" Assistance appears to increase "self-efficacy" or "functional causality," and this may increase desire to practice [48].

How does this information relate to the spring orthosis approach? As noted above, spring orthoses take the approach of providing physical assistance to help the patient move his or her arm yet provide a tangibly different form of assistance compared to the standard approaches developed for robotic therapy devices [49]; that is, they typically provide static gravity balancing alone rather than active guidance. Thus, unlike most robotic therapy devices, spring orthoses will not move unless the patient initiates movement, and this feature likely mitigates against slacking. Further, spring orthoses have very low impedance – just their inertia – and thus, they do not constrain the user to any particular movement, allowing variability in movement trajectories and thus, presumably, the experience of error.

To summarize, spring orthoses preclude high levels of slacking by requiring the patient to generate movement, allow the experience of error and variability, and enhance active range of motion and thus self-efficacy. Whether more elaborate forms of assistance, as can be provided with robotics, will produce better outcomes remains unanswered. A key consideration in future studies will be to evaluate devices that tailor the assistance to the ability level of the patient. Intriguingly, more capable patients may even benefit from robotic amplification of movement errors to speed learning [47, 50, 51]. Conversely, whether less elaborate forms of assistance, or no assistance at all, will produce as good of outcomes as assistance-oriented approaches is also unanswered. Effort will need to be given not only to testing the Hebbian-like concept that rationalizes the provision of assistance but also to answering the pragmatic question of whether patients who are extremely weak will actually engage in practice without physical assistance.

18.2.3 Can Computer Games and Quantitative Feedback Improve Recovery?

A third premise of the spring orthosis approach, as well as much other robotic and nonrobotic upper-extremity therapeutic technology, is that engaging patients in computer games will improve recovery. This premise was recently directly tested by measuring changes in gait biomechanics when people with hemiparesis due to a stroke exercised with a robotic ankle device, either performing the ankle exercises in the context of a computer game or to a metronome [52]. The computer game required the volunteers to use the foot movements to navigate a plane or boat through a virtual environment that contained a series of targets. Participants in the gaming group demonstrated significantly better gains in ankle power generation at push-off and in ankle

and knee range of motion. This is a compelling result because the investigators controlled for the number of movements performed by each group by using the metronome in the nongaming environment.

Providing objective feedback, measured with a sensor, to patients about their movement ability also appears to improve recovery. In a recent multisite trial, 179 people with stroke were randomized to two groups [53]. One group of participants was informed of their self-selected walking speed immediately after a single, daily 10-m walk, while the other group performed the walk but was not informed of their speed. The group that received objective feedback improved walking speeds significantly more by about 25%. This result supports the use of objective feedback of motor performance to motivate and enhance training.

18.3 Perspectives and Conclusion

Spring-based orthoses, such as T-WREX and ArmeoSpring, are based on the rationale that functionally oriented activities, physical assistance in the form of gravity balance, and computer gaming and feedback will best promote movement recovery of the arm that is severely to moderately impaired after stroke. Initial clinical testing of T-WREX with 28 patients with chronic stroke supported this rationale: the patients recovered significantly more arm movement ability than a control group that practiced tabletop exercises, a form of exercise which had diminished functional relevance, less-sophisticated mechanical assistance, and no gaming or objective feedback aspects. Further, the patients significantly preferred exercising with T-WREX and could perform the exercises with only brief interaction with a supervising therapist. These results indicated that the starting rationale had at least some validity. In addition, T-WREX was simpler, less expensive, and safer than a robotic device because it did not require actuators.

Clearly, however, randomized controlled trials are still needed to compare the spring orthosis approach to the large number of possible alternate technology-for-therapy approaches. In thinking about what trials might provide the most useful information, it is perhaps helpful to think of the data that both supports and challenges the starting rationale for T-WREX, as we reviewed above. For example, as explained above, while functionally oriented activities produce benefits, less-functional exercises may also be effective, allowing simpler, lower-cost technology to be developed and more widely used. Thus, my group and others (e.g., [54–58]) are developing mechanical devices and sensor systems to enhance therapy, and these provide interesting targets for comparison with spring orthosis therapy. The advent of motion-control technology for commercial videogames, including the Nintendo Wii, Sony Move, and X-box Kinect, is exciting as they provide low-cost hardware platforms to test the efficacy of sensor-only rehabilitation systems.

The picture with physical assistance is also unresolved, with some forms of assistance having a negative effect apparently because they cause slacking and reduce movement variability. The use of a gravity balance approach to provide assistance seems to strike a good compromise of improving self-efficacy and sensory input by allowing greater active range of motion for weakened patients, while limiting slacking and still allowing trajectory variability. However, this approach needs to be tested rigorously by comparing it to full assistance and no assistance approaches.

Because distal exercise appears important for recovery, enhancing the distal function spring orthoses seems like an important direction to pursue. We have developed a robotic forearm/wrist orthosis for Armeo. We chose to pursue a robotic approach (versus a passive measuring system) because we believe it is helpful to assist patients in actually moving the hand so that the therapy is not frustrating. Our target population is people with moderate and severe arm weakness, which means that the users will typically have only small amounts of wrist and hand movement. As noted above, asking people to practice moving without any sort of positive reinforcement of a resulting, tangible movement is very challenging, even if a therapist is present. We seek to develop a system for which the user will be motivated to

practice moving even without direct therapist presence. Developing a passive counterbalancing system for the hand/wrist/forearm is problematic because the restraining forces on the hand and wrist are primarily due to muscle tone and soft tissue stiffness, and it is difficult to passively compensate for these forces, although some progress has been made in this direction with the hand [57, 59]. We have programmed our device to quickly measure the passive tone of the forearm and wrist, then to provide gravity and tone counterbalancing. We are testing whether the addition of such compensation for distal movement improves functional recovery.

Simpler forms of gravity balance that do not assist or measure individual joint movement, but can still expand active range of motion [60], are also important to test, as are robotic devices that can prove a wide range of forms of assistance [61, 62]. Different training environments (inpatient, outpatient, home) and different stages of recovery (acute, subacute, chronic) might benefit from different forms of assistance, not only in terms of a cost perspective, but also in terms of what might be necessary to optimize neurologic recovery.

Ultimately, the role of assistance in promoting motor recovery and learning is a fascinating topic that will require carefully planned trials of many forms of assistance, including not only robotic assistance but also alternate techniques like robotics and orthotics combined with functional electrical stimulation-based assistance [63, 64] and robotic error amplification [50]. These trials will provide insight into motor system organization, which will further aid the design of rehabilitation technology. Further, much of the emphasis in developing assistive/therapeutic technology has been on chronic stroke, but there are other disabling conditions in which its role remains to be explored, including high-level spinal cord injury, multiple sclerosis, traumatic brain injury, muscular dystrophies, amyotrophic lateral sclerosis, and cerebral palsy. Training with ArmeoSpring was recently shown to improve functional movement for people with a substantial level of arm impairment due to multiple sclerosis [65].

Initial controlled studies on the role of computer-based games and objective feedback in movement rehabilitation support the idea that these features are beneficial for recovery. Key areas for future research are identifying games that provide the most motivation for and relevance to rehabilitation, determining how to adapt those games to provide optimal challenge for training, and designing simple and effective feedback for the patient. My group and others are investigating technology-mediated sports and dance to motivate rehabilitation practice and the design of algorithms for automatically controlling challenge levels. Design of appropriate activities, challenge levels, and feedback will advance as the mechanisms of reward-modulated control of brain plasticity are elucidated.

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19 Implementation of Impairment-Based Neurorehabilitation Devices and Technologies Following Brain Injury

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Abstract

The implementation of electromechanical devices for the quantification and treatment of movement impairments (abnormal muscle synergies, spasticity, and paralysis) resulting from brain injury is the main topic in this chapter. The specific requirements for the use of robotic devices to quantify these impairments as well as treat them effectively are discussed. A case is made that electromechanical devices not only generate a vehicle to augment treatment intensity but more importantly allow for the precise measurement and treatment of specific impairments using scientifically underpinned approaches. Acceptance of these new technologies is dependent on proof of their effectiveness in treating movement impairments and on future clinical trial evidence for accompanying improvements in activities of daily living and quality of life. Furthermore, the need of a concerted effort to simplify these new technologies, once essential treatment ingredients have been determined, is seen as being a key component for their acceptance in the clinic on a large scale. Finally, it is crucial that we demonstrate that electromechanical technologies are indeed more effective in delivering rehabilitative care, by reducing required treatment time in

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expensive clinics while maintaining, and even improving, functional outcomes. This is a requirement for future technology development and acceptance in the clinic and at home, especially in a health care environment where rehabilitation costs become more and more prohibitive.

Keywords
Brain injury • Stroke • Rehabilitation • Robotics • Technology • Spasticity • Synergies • Movement impairment

19.1 Introduction

Sensorimotor deficits and restricted mobility are among the more prevalent problems encountered by individuals following brain injury such as stroke. While the expression of stereotypical muscle synergies, spasticity, and paralysis are common to many forms of brain injury, it is only in recent years that we have begun to understand how each of these sensorimotor deficits may impact movement. It is with the advent of rehabilitation robotics and associated robotic technologies that scientists have begun to rigorously study both the specific impairments and their contribution to movement dysfunction. Additionally, as understanding of sensorimotor deficits has increased, new knowledge has been applied to the development of rehabilitation interventions capable of directly targeting fundamental impairments. In recent years, widespread use of rehabilitation robotics has demonstrated improvements in motor function and strength in the paretic upper limb. However, all of these interventions have fallen short of generating significant improvement in activities of daily living (ADL) [1–3]. The lack of significant results in the area of ADL can be attributed to numerous factors such as low resolution of ADL measurements and small sample sizes in early investigational clinical trials. However, the most likely explanation may be that most robotic interventions lack a solid scientific underpinning. For example, many rehabilitation robotic therapies aim to reproduce existing therapeutic approaches such as practicing functional tasks but with the added benefit of greater intensity and duration [1–3]. Reproduction of existing hands-on rehabilitation approaches ignores the quantitative strength of robotics to identify the impairments responsible for movement dysfunction (scientific underpinning) and therefore will not likely advance neurorehabilitation beyond its current state. On the other hand, recent work has demonstrated that robotic devices can characterize fundamental impairments such as the presence of abnormal muscle synergies [4], weakness [5, 6], or spasticity [7–15] and has demonstrated their relationship to functional movement [16]. With quantitative identification of impairments, a robotic rehabilitation approach can be developed, intervening in a specific and rigorous fashion directly targeting the impairments that are responsible for ADL limitations. Early evidence for the use of robotics in providing high-resolution measures of motor impairment in the upper limb of individuals with stroke will be provided, as well as preliminary results from novel robot-mediated interventions that can complement conventional neurotherapeutic interventions. In short, we will show that new robotic technologies are ideal for the delivery of novel science-underpinned therapeutic interventions that can be implemented in current rehabilitation clinics as well as provide such interventions in a more controlled fashion and with greater intensity than conventional rehabilitation. Furthermore, considerations for successful transition to clinical practice will be highlighted including methods to increase acceptance by the therapist and patient such as merging entertainment with impairment-based rehabilitation robotics through the implementation of virtual gaming environments.

19.2 Quantification of Impairment

19.2.1 Quantification of Abnormal Synergies and Weakness Using Electromechanical Devices

A central abnormality in unilateral hemispheric brain injury is the loss of independent control of joint movement that is evident in the form of stereotypic movement patterns [17–19]. It is believed that these stereotypic movement patterns are an expression of abnormal muscle coactivation patterns or muscle synergies. We have presented quantitative evidence for the existence of abnormal muscle coactivation patterns using electromyography (EMG) from elbow and shoulder muscles in the paretic arm of individuals with stroke during static force exertions in various directions and of various magnitudes [20]. Using static or isometric mechanical measurements, we were able to improve the quantification of abnormal muscle coactivation patterns with a six-degree-of-freedom load cell [21, 22]. Using this approach, we studied the expression of isometric elbow and shoulder torque patterns during the generation of maximum voluntary torques one direction at a time. During the execution of this single-task protocol in a primary direction, we observed relative weakness in the paretic limb compared to the contralateral limb, and we found strong abnormal coupling between elbow flexion and shoulder abduction/extension/external rotation and elbow extension and shoulder adduction/internal rotation in the paretic limb of individuals with stroke [22, 23]. Conversely, control subjects, and individuals with stroke in their nonparetic arm, only generated nominal torques in secondary degrees of freedom. In subsequent studies, we measured maximum voluntary elbow torques under three different conditions: in combination with 10% and 50% of maximum shoulder abduction torque and in combination with 10% of maximum shoulder adduction torque [21]. The torque combinations most affected were those that required the subject to deviate from the abnormal torque patterns observed during the single-task paradigm. Specifically, individuals with stroke exhibited an impaired ability to generate elbow extension torque with the paretic limb when increasing shoulder abduction (i.e., the 50% shoulder abduction level). The opposite trend was observed for elbow flexion torque. Individuals with stroke exhibited an enhanced ability to generate elbow flexion torque in the paretic limb with increasing levels of shoulder abduction torque. These abnormal torque patterns are analogous to the abnormal upper extremity movement synergies described in the clinical literature (see Table 19.1) [17]. These results demonstrated the existence of a strong and abnormal linkage in the paretic limb between elbow flexion and shoulder abduction and between elbow extension and shoulder adduction. Quantification of this fundamental impairment was only possible through the implementation of multi-degree-of-freedom force/torque sensing technologies. Application of these new technologies would then set the stage for the execution of dynamic experiments and subsequent robotic development.

Table 19.1 Upper limb synergies in hemiparetic stroke [17]

Flexor synergy	Extensor synergy
Flexion of the wrist and fingers	Extension of the wrist and flexion of fingers
Flexion of the elbow	Extension of the elbow
Supination of the forearm	Pronation of the forearm
Abduction of the shoulder	Adduction of the arm in front of the body
External rotation of the shoulder	Internal rotation of the shoulder
Shoulder girdle retraction and/or elevation	Shoulder girdle protraction

Our first dynamic study investigated the effect of synergies on movement as a function of support condition (supported versus unsupported) on planar reaching and retrieval movements by comparing the kinematic and kinetic characteristics of gravity-eliminated (supported on a frictionless table) and free (unsupported) upper limb movements [23–25]. Support of the upper limb in the supported condition was provided by a low-friction air-bearing apparatus and by activation of the shoulder musculature in the unsupported condition.

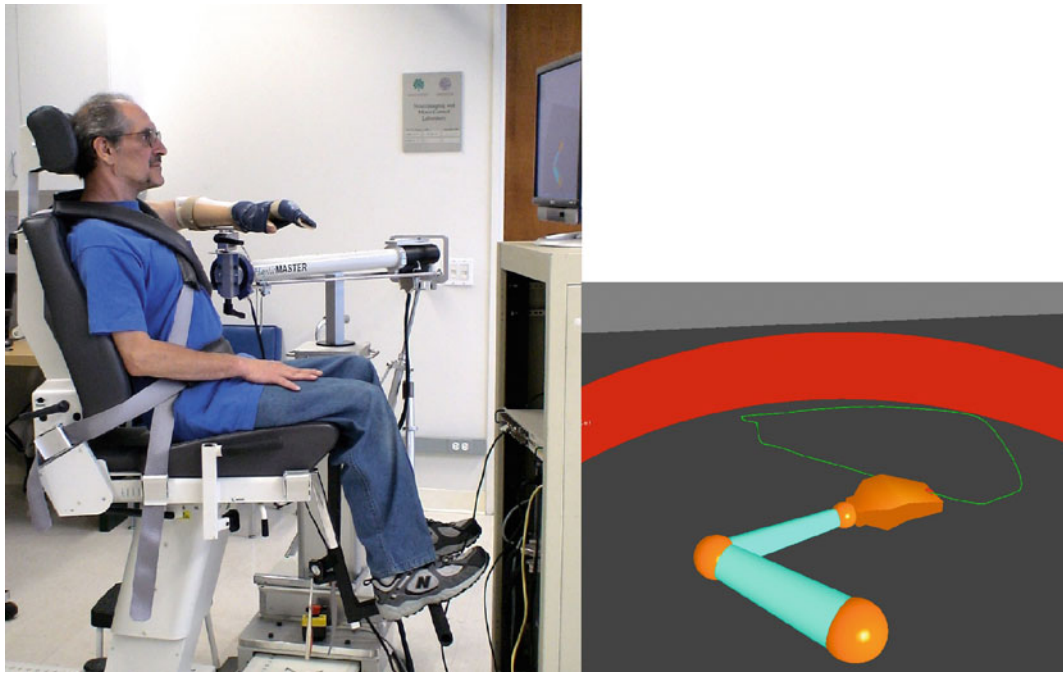

Fig. 19.1 (*Left*) Illustrating ACT-3D robot with gimbal and orthosis. (*Right*) Example of the visual feedback. The haptic table is shown by the *darker gray*, which the arm is resting on. In the envelope protocol (see measurement of work area below), subjects will use the *red arc* as their goal, with the *green tracer* shown to give them a reference to their performance in previous circles (With kind permission from Springer Science + Business Media: Sukal et al. [4])

For either limb of control subjects, as well as the nonparetic limb of individuals with stroke, we found that movement parameters were broadly invariant with the support condition. In contrast, movements of the paretic limb exhibited a strong dependence on the supported condition. Specifically, active support of the paretic limb resulted in significant reductions in estimated peak dynamic joint torques for targets requiring elbow extension or shoulder flexion, while the peak elbow flexion and shoulder extension joint torques associated with the acquisition of proximal targets were relatively unaffected. The clinical implication of these findings is that a target-dependent restriction in the work area of the hand exists and reflects a reduced range of active elbow extension that is linked to the unsupported state of the limb. We concluded that the target-dependent effect of the support condition on movements of the paretic limb reflects the existence of abnormal coactivation of the elbow flexors and shoulder extensors, abductors, and external rotators in individuals with chronic hemiparesis. These findings led to the realization that implementing variable shoulder loading conditions would be crucial to fully quantifying the effects of abnormal elbow–shoulder coupling on the functional workspace of the hand.

In an effort to implement variable load conditions at the shoulder, a HapticMASTER robot (Moog Inc., The Netherlands) was modified by adding a gimbal with position sensors and a six-degree-of-freedom load cell to its end effector. The individual's forearm and hand are attached to the gimbal using a hand–forearm orthosis (Fig. 19.1). The modified HapticMASTER robot was then integrated with a Biodex experimental chair (Biodex Medical Systems, Shirley, NY) to form the first-generation Arm Coordination Training 3-D (ACT-3D) device shown in Fig. 19.1. This unique combination of technologies allows for the measurement of shoulder abduction loading and induced shoulder and elbow coupling during reaching. It provides a

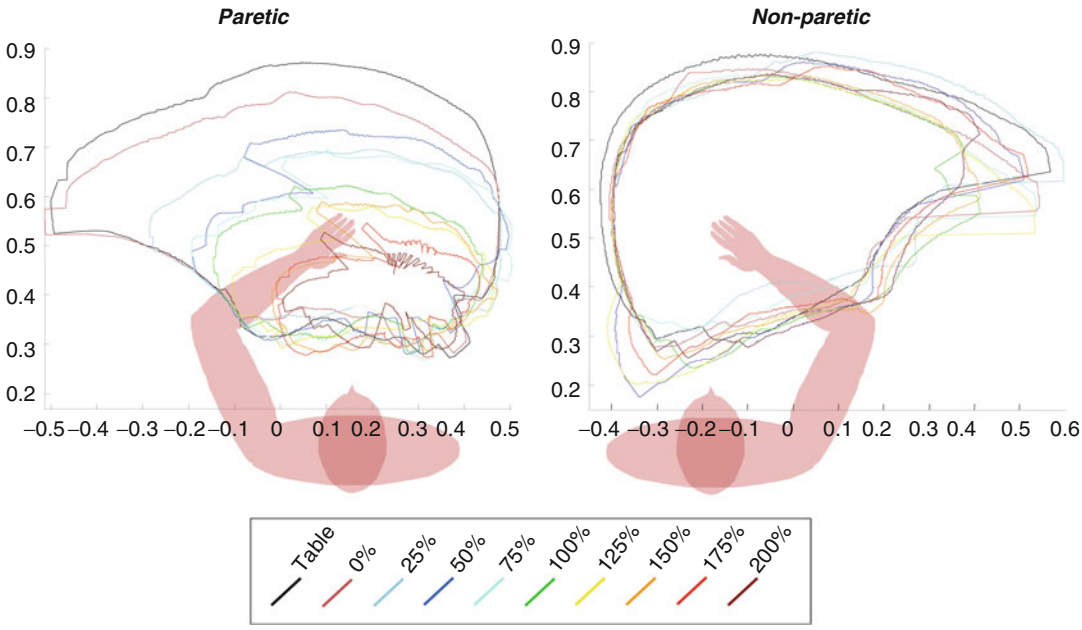

Fig. 19.2 Envelope traces consisting of shoulder/elbow flexion/extension combinations during various levels of limb support in the paretic limb (left arm) of a single subject. Conditions listed in the legend are percentages of limb weight. Note the significant reduction in work area for increasing levels of shoulder abduction/external rotation. Axis units are in meters (With kind permission from Springer Science + Business Media: Sukal et al. [4])

sophisticated quantification tool to characterize movement disabilities in individuals who have had brain injury resulting from a stroke. The advantage of this system is that it incorporates the ability to control the level of shoulder abduction/adduction loading while measuring movement abilities in the 3-D workspace, features unavailable in the early isometric and dynamic studies [21–24]. In an unprecedented way, the ACT-3D has allowed us to investigate the progressive debilitating impact of shoulder abduction loading on reaching range of motion. When quantifying the effect of shoulder abduction loading on the work area of the hand, individuals with stroke and control subjects were asked to slowly trace with their hands the largest possible envelope on a horizontal plane (at shoulder level) by moving their arm several times in a clockwise and counterclockwise direction. The largest work area for each level of abduction loading was calculated from multiple trials. Subjects performed the reaching movements while sliding over a haptically rendered table or under conditions where the virtual effect of gravity was enhanced or reduced by providing forces along the vertical axis of the ACT-3D. The direction of these forces dictated the amount of resulting shoulder abduction loading and was varied from 100% of limb support to 100% or more of limb weight added to the shoulder load.

An example of work area resulting from a single moderately to severely affected subject (Fugl-Meyer upper extremity score 23/66, and Chedoke–McMaster Arm Scale 3/7) is shown in Fig. 19.2. The different lines correspond to the percentage of limb weight the subject was required to lift during the generation of the envelope. This ranged from 0% where the robot was compensating for the entire weight of the limb to 200% where the subject had to generate abduction torques twice the size of those required to lift the limb against the normal gravitational load. The left panel in Fig. 19.2 shows the reduction in work area in the paretic limb (left arm in this subject) with the greatest work area reduction in the ipsilateral and forward reaching portion of the envelope; this area coincides with the direction requiring primarily elbow extension (the upper

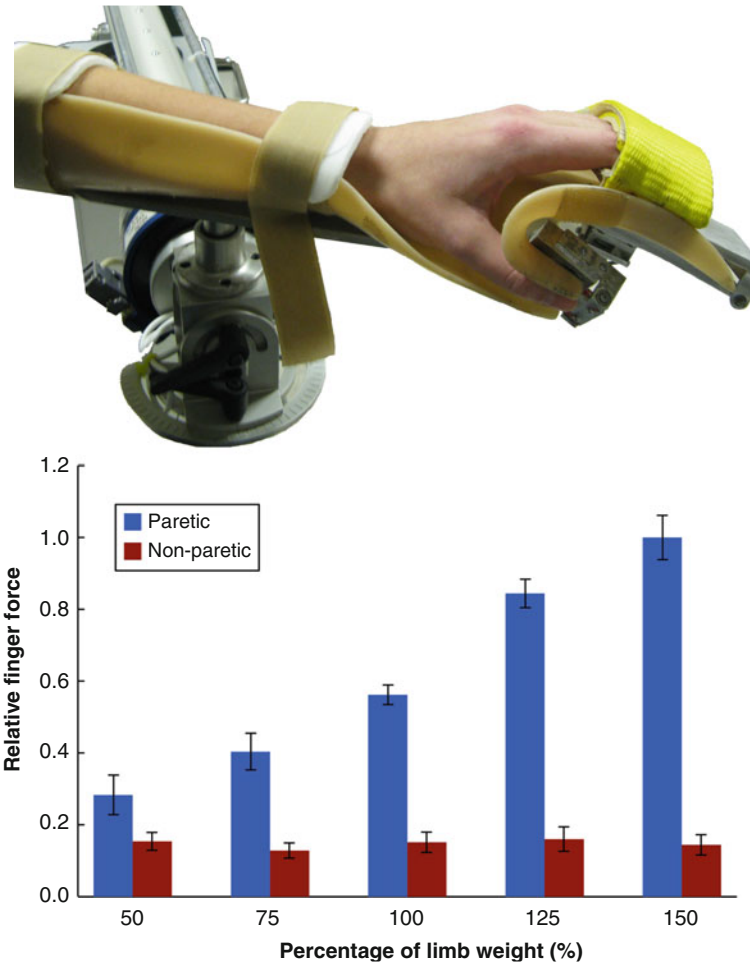

Fig. 19.3 *Top*: Instrumented hand finger orthosis [29]. *Bottom*: Relative level of finger force (normalized for each subject by the largest forces measured over the five limb weight conditions) generated for increasing levels of limb weight. This demonstrates that increasing levels of shoulder abduction generate involuntary increases in finger flexion in the paretic hand. The error bars represent intersubject standard errors (*Top* – From Miller et al. [29]; used with permission)

left portion of the envelopes). This is consistent with the expression of the flexion synergy that dictates the presence of greater coupling with elbow flexion torque for increasing levels of shoulder abduction. The reduction in work area for the same subject is displayed as a function of mean area versus percentage of active limb support. These results are in stark contrast to the nonparetic side, where no change or effect of abduction level related to shoulder and elbow range of motion is observed (see Fig. 19.2). The reductions in upper limb workspace as a function of shoulder abduction load have been shown to exist in individuals with moderate to severe motor impairments following hemiparetic stroke [4]. This is a result of the abnormal coupling between shoulder abduction and elbow flexion or the flexion synergy. This synergy has been reported to also include more distal joints of the paretic arm, namely the wrist and fingers [17].

The paretic wrist and fingers have also been the focus of extensive research [26–28]; however, they have been examined most frequently in isolation from the rest of the upper limb, without consideration for the effect of the flexion synergy. The addition of a wrist/finger force sensing device [29] (Fig. 19.3, top) to the ACT-3D robot has allowed us to study the effect of shoulder abduction loading on wrist and finger forces in both adults and children with spastic hemiparesis. As can be appreciated from the results shown in Fig. 19.3 (bottom), secondary finger/wrist forces increase as shoulder abduction loads increase in individuals with adult-onset stroke.

Future research using the wrist/finger force sensing device will allow for the continued characterization of abnormal coupling at the hand and wrist during 3-D movements. This is likely to result in the development of a progressive shoulder abduction loading rehabilitation protocol focused on the improvement of hand function. The integration of functional electrical stimulation of wrist/finger extensors can also be investigated using this device that allows for the measurement of extension forces generated by various electrical stimulation parameters and with various shoulder abduction loads encountered during activities of daily living.

19.2.2 Quantification of Spasticity Using Electromechanical Devices

Spasticity, defined as an increased velocity sensitive stretch reflex [30], has been studied using electromechanical devices for four decades [8, 10, 12, 13, 31–35]. Using robotic devices, spasticity or reflex hyperexcitability has primarily been studied in resting limbs, yet its clinical management has been directed mainly at an assumed impact on active movement. Current directions in the treatment of spasticity include stretching, serial casting, and the use of antispastic agents such as botulinum toxin and baclofen to reduce overactive muscle activity. The rationale for this approach is that by reducing spasticity, movement performance will improve. This conventional approach persists despite the lack of evidence demonstrating that reflex hyperexcitability (measured on a resting limb) actually impacts active movement. Numerous studies on resting limbs have reported increased mechanical resistance (reflex torques) and augmented stretch reflexes during passive joint rotation imposed by single-degree-of-freedom robotic devices, particularly after stroke [7–12, 31–35]. Under passive or resting conditions, spastic limbs can be clearly distinguished from normal limbs where slow stretches generally fail to elicit signs of significant levels of stretch reflex activity [36, 37].

Relatively little is known of spasticity in active contracting muscle despite its obvious relevance to active movement and subsequent treatment. Even a small voluntary background contraction leads to prominent reflex activity and increased passive resistance in normal limbs [35, 38]. Additionally, there is no clear demonstration that reflex EMG and torque magnitude are significantly higher in spastic limbs under analogous background activation conditions [7, 12, 31, 32, 39–41]. Hence, it is unclear how, or if, spasticity contributes to the movement disorder in the affected limbs. It is possible, without clear evidence to the contrary, that the defining features of spasticity are a phenomenon confined to resting limbs. More detailed knowledge of the properties of spastic muscle during active movement is needed to resolve this issue. With the use of robotic technologies, we now have the capability to investigate the impact of spasticity, or hyperactive stretch reflexes, on active movement.

Most of the spasticity quantification literature to date considers hyperactive stretch reflex activity at the single-joint level with the subject relaxed and does not consider its potential effects on multijoint movements such as reaching or retrieval motions. If we hypothesize that spasticity expresses itself as a hyperactive stretch reflex during passive conditions only (i.e., with the subject relaxed) and does not affect stretch reflex activity during active (i.e., movement) conditions [7], then multijoint movements may still be affected. This is especially true during multijoint reaching where elbow extension is the result of coupling or interaction torques generated during shoulder flexion movement and not due to elbow extensor muscle activation [25]. It is likely that under such conditions, abnormal hyperactive stretch reflex activity of "relaxed" elbow flexors (which are not reciprocally inhibited by triceps activity because of the effect of coupling torques) could limit the upper extremity workspace, especially at higher movement velocities. In addition to the role that spasticity may play when joint movement is driven by coupling or interaction torques, as occurs during multijoint movements, it may also be affected by the expression of abnormal muscle synergies (see section above). Spasticity quantification studies at the elbow have been done with the weight of the paretic limb

supported by the measurement system [7, 8, 10, 12, 40]. The effect of shoulder abductor activity to lift the arm against gravity and the resulting expression of the abnormal flexor synergy have been shown to impact the stretch reflex excitability in elbow flexors for a single posture and shoulder abduction load level [13]. State-of-the-art robotic technologies, some of which are currently under development in our laboratory, are required to fully elucidate the interaction between stretch reflex excitability and impairments such as abnormal synergies during multiple postures, abduction levels, and movements. Depending on the specific application, robotic devices must possess certain key design characteristics. First, these devices must be capable of rendering haptic environments within which users can interact with desired forces. For example, to investigate the flexion synergy, robotic devices must be capable of providing forces to simulate abduction loading and unloading of the shoulder muscles. These devices must also be capable of switching between compliant and stiff modes, enabling low-impedance movements throughout the workspace while simultaneously providing the capability to apply precise position or speed-controlled perturbations to the user. Additionally, robotic devices seeking to measure the relationship between stretch reflexes and abnormal muscle coactivation patterns must possess an adequate number of degrees of freedom to capture functional behaviors. For planar movements of the upper limb, this translates to at least three degrees of freedom: two for the shoulder and one for the elbow. Finally, an important consideration for robotic devices seeking to capture functional movements is workspace volume. If, for instance, the desired task is a center-out reaching task in multiple directions, it may be necessary to permit full extension of the arm, which will require both shoulder flexion as well as elbow extension and a larger workspace. If however the goal is only elbow extension, a smaller workspace volume may be acceptable.

Ultimately, with careful design considerations and a working knowledge of the relevant physiology, robotic devices can be designed and implemented that allow investigators to answer specific questions in terms of the mechanisms underlying movement impairments. In addition, the same robotic devices can be used for subsequent development of effective robotic treatments that complement conventional neurorehabilitation approaches.

19.3 Impairment-Based Robotic Interventions

19.3.1 Introduction to a Scientifically Underpinned Concept

Impairment-based interventions for individuals with stroke have gone by the wayside over the last decade, in part, due to the success of functional task practice and forced-use paradigms [42] in individuals with mild stroke. However, these approaches do not benefit individuals with more substantial impairment [43]. Individuals with moderate to severe stroke, therefore, need an innovative solution that allows for the amelioration of fundamental impairments such as abnormal synergies and weakness in order to experience functional gains. Recent basic science research discussed above has demonstrated that unavoidable and debilitating distal arm and hand flexion occurs during progressively greater shoulder abduction loads in individuals with moderate to severe stroke. This phenomenon is attributed to abnormal coactivation of groups of muscles and results in stereotypical movements and postures, making it impossible to complete functional upper extremity tasks such as reaching out to pick up a glass of water. Only within the last few years, utilizing new robotic rehabilitation technology like the ACT-3D, has it been possible to design an intervention that directly targets this impairment. Directly targeting abnormal muscle synergies and associated loss of independent joint control with an impairment-based intervention is the most likely avenue for achieving functional restoration in this population. This impairment-based approach represents a scientifically underpinned rehabilitation strategy since the neural mechanism of the impairment is well investigated and its relationship to functional movement is

known. Recent evidence from our laboratory supporting this approach will be discussed below and appears to elevate the prognosis of even the most severely impaired individuals with stroke.

19.3.2 An Isometric Impairment-Based Approach

Our initial and foundational intervention work [44] sought to determine the amenability of abnormal flexion synergy to an impairment-based intervention. The intervention entailed intensive practice of an isometric multijoint (shoulder and elbow) task comprised of both a multijoint coordination element and a resistance element that ultimately proved to be successful in reducing the impairment but difficult in interpreting the relative importance of therapeutic elements responsible for the observed improvement [44]. The abnormal flexion synergy impairment was directly targeted by having individuals generate multijoint torque patterns outside of the flexion synergy. This was accomplished by maintaining a submaximal percentage of their maximum shoulder abduction while maximally generating shoulder flexion or elbow extension. The involvement of two concurrent torque directions was the multijoint coordination element of the exercise, while the resistive element was the requirement of maximal isometric torque generation. Individuals practiced these multijoint isometric tasks three times per week for 8 weeks. The primary outcome measure was the magnitude of abnormally coupled isometric elbow flexion occurring during maximum isometric shoulder abduction (abnormal flexion synergy). The secondary outcome measure was single-joint isometric strength.

Ultimately, the study demonstrated the effectiveness of implementing an intervention at the level of impairment as opposed to gross function. All participants showed a decrease in the amount of abnormal flexion synergy that was congruent with progressive improvements in generating torque patterns outside of the flexion synergy throughout the course of the intervention. A second meaningful improvement was an increase in single-joint isometric strength for the torque directions comprising the practiced tasks. Participants became stronger following the intervention for shoulder abduction, shoulder flexion, and elbow extension. The concurrent increase in multijoint coordination and increase in single-joint strength offered two inextricable explanations for the measured improvements in arm function. Future work from our laboratory discussed below began utilizing robotics in an attempt to more specifically target abnormal flexion synergy by removing the resistance component from the intervention.

19.3.3 Targeting the Loss of Independent Joint Control with the ACT-3D

Our robotic intervention for individuals with severe stroke sought to identify the effect of the multijoint coordination element without the confounding effects of other potential therapeutic elements such as resistance training as incorporated in our initial isometric intervention work [45, 46]. Utilization of the robotic device, ACT-3D, allowed us to target the flexion synergy and associated loss of independent joint control through the implementation of a dynamic multijoint coordination task that did not involve a resistive element. In a randomized controlled design, 14 participants were assigned to one of two intervention groups. While both groups practiced reaching with the ACT-3D over 8 weeks emulating traditional therapy, only the experimental group was required to support the arm against specified submaximal abduction (vertical) loads. The control group practiced the same reaching tasks but was fully supported on a horizontal haptic table. Therefore, only the experimental group was practicing movement outside of or against the abnormal flexion synergy. Participants in the experimental group were required to support greater percentages of arm weight (corresponding to greater shoulder abduction loads) as reaching abilities improved beyond standardized kinematic performance thresholds. For example, if a participant could reach 80% of

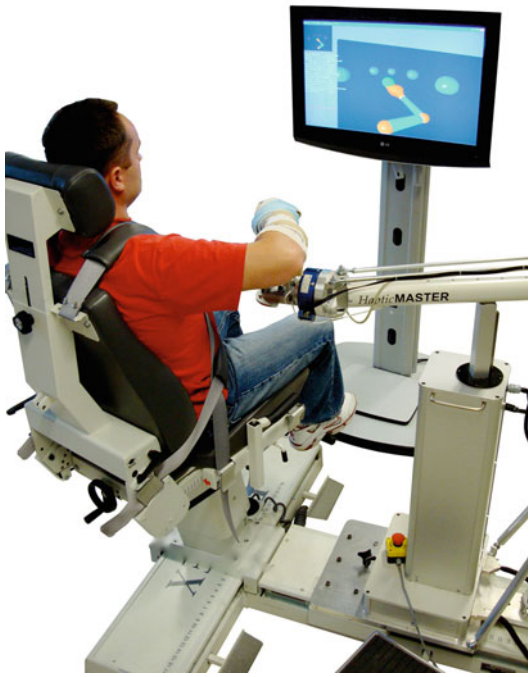

Fig. 19.4 Example of a research participant positioned with the ACT-3D showing the five reaching targets (From Ellis et al. [46]; used with permission)

the distance to the practiced target for 8 out of 11 trials in one set for a given abduction load, the load would be increased by one increment of 25% of limb weight. The same procedure was followed independently for all five of the targets that spanned the reaching work area of each participant based on standardized joint angles (Fig. 19.4). The primary outcome utilized to demonstrate effectiveness was total reaching work area as a function of abduction loading, measured by the ACT-3D, and the secondary outcome was isometric single-joint strength.

We found significantly greater increases in work area for the experimental group. Importantly, the greatest improvements in total reaching work area were at abduction loading levels equivalent to and beyond limb weight such as experienced during the transport of an object during a functional task. The results of the secondary outcome measure of strength were important to the interpretation of why improvements were observed in work area as a function of abduction loading. We found that there was no improvement in single-joint maximum strength, indicating that a reduction of flexion synergy and associated increase in multijoint coordination must have occurred [46]. This research indicated that the abduction loading element was effective in improving arm function. Most importantly, it demonstrated the capacity of a scientifically underpinned impairment-based approach to achieve gains in individuals with chronic severe stroke whom conventional care had failed.

19.4 Successful Translation to Clinical Practice

19.4.1 Device Design That Facilitates Translation

Recent advances in robotic technology have given rise to multiple systems for upper extremity rehabilitation in stroke [4, 47–54]. Such systems combine robotics with computer graphics for delivery of a rehabilitation protocol. Systematic reviews of the effect of robotic-based therapy on upper limb recovery following stroke [1–3] suggest significant improvement in motor control of the paretic upper limb but no significant improvement on functional abilities or activities of daily living.

The majority of these rehabilitation systems are based on traditional therapeutic approaches. Most groups have implemented a task-oriented approach where, for example, subjects complete a pick-and-place or grasp-and-release virtual task [3, 55–65] not unlike conventional therapeutic strategies [66–69]. A few groups have implemented systems based on a more hands-on approach where the reaching movement or task is guided by a predefined trajectory or set of rules [70–72], again, not unlike traditional interventions where the movement is guided by the therapist(s). Some of these systems provide robotic assistance to the task or movement being performed either by moving the arm in a programmed trajectory or by supporting the weight of the limb [60, 64, 73–79], thus taking advantage of the unique features of their device which cannot be mimicked by a person.

Fig. 19.5 The ACT-4D robotic device allows for single-joint perturbations at the elbow combined with adjustable shoulder abduction loading to study the relationship between synergies and abnormal stretch reflex or spasticity following brain injury

The common theme from all of these therapeutic robotic systems is their ability to reproduce traditional-type therapies in order to reduce the workload of the clinician and allow for greater repeatability and increased repetitions. Device design was therefore driven by these needs without specific regard for identifying novel and potentially more effective means of reducing impairments and increasing function in comparison to conventional strategies. The Dewald laboratory has taken a radically different approach based on years of research of the mechanisms underlying upper extremity movement impairment in individuals with brain injury. Based on results from previous studies [6, 20–25, 74], we have designed robotic systems to directly target the fundamental impairments impacting upper extremity function. Attempting to ameliorate the contributing impairments may be a more effective strategy in improving arm function during activities of daily living in individuals with moderate to severe hemiparetic stroke. The ACT-3D [4, 16], which is based on the HapticMASTER (Moog, Inc., The Netherlands), a commercially available haptic device, was designed to allow adjustable shoulder abduction loading, a required attribute to directly target the flexion synergy impairment. Previous studies have demonstrated the effectiveness of targeting the flexion synergy impairment with the ACT-3D and increasing the work area of the upper limb at greater shoulder abduction loads (see previous section) [45, 46]. Although other systems like the T-WREX, ARMin, L-EXOS, and Freebal [4, 49, 53, 58] have adjustable limb weight support abilities, only the ARMin and the ACT-3D systems are able to generate loads in the vertical direction to allow simulation of increased limb weight or object handling. This is a key component for therapeutic interventions attempting to improve arm function during activities of daily living because it allows for continued targeting of the flexion synergy impairment even at higher functional levels such as during object transport.

Based on the promising results obtained with the ACT-3D, our laboratory has continued to design robotic devices that target specific impairments present in individuals with brain injury such as weakness, synergy, and spasticity. A new device, the ACT-4D, was designed to further our understanding of spasticity during movement in stroke (see Fig. 19.5). Concurrently, a new version of the ACT-3D was designed to augment its capabilities both in workspace and strength to allow not only implementation of impairment-based interventions but also investigations of the complex interactions between weakness, synergy, and spasticity in order to better understand the mechanisms underlying movement dysfunction in this population (see Fig. 19.6). In doing so,

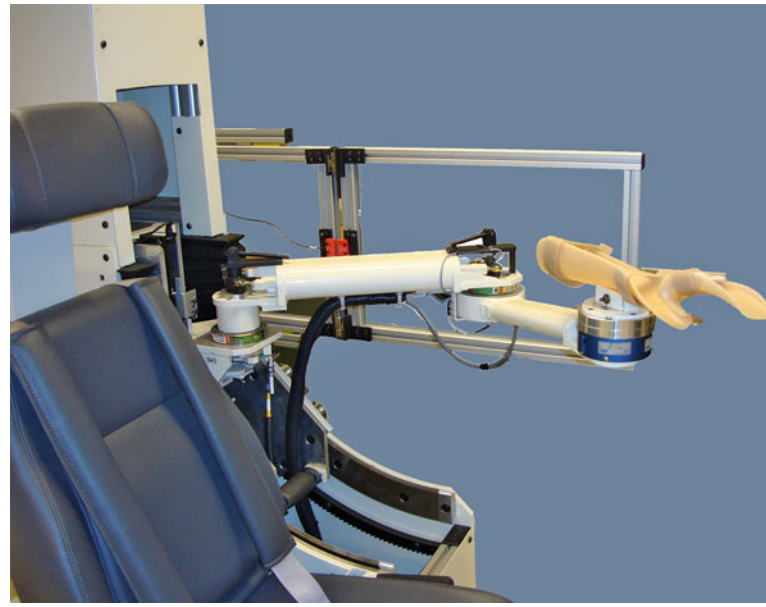

Fig. 19.6 New version of the ACT-3D, designed to allow greater workspace measurements as well as the application of multijoint perturbations in the plane of movement

standardized protocols for the quantitative evaluation of each impairment are being developed and will provide a tool for clinicians to immediately augment conventional qualitative methods of clinical evaluation. Currently, initial efforts are underway to design and implement an affordable passive device that will facilitate translation to practice and even utilization at home.

19.4.2 Acceptance by the Rehabilitation Specialist

Despite exciting advancements in rehabilitation robotics regarding quantitative evaluation of movement impairments and impairment-based interventions, translation to clinical practice has been slow and incremental. The rate of translation can be improved by increasing the quality of evidence made available to practicing clinicians. The field of rehabilitation will readily accept new technologies, such as the impairment-based robotics approach, given that quantitative data of impairment reduction is provided. Recent evidence from our lab supports an impairment-based approach showing that amelioration of flexion synergy and improvement in reaching function are possible [45, 46]. As impairments are remedied, normal movement is restored, and thus, function in everyday activities improves. This represents a methodical, scientifically underpinned strategy to achieving improved function that is in stark contrast to the conventional approach of blindly practicing functional tasks in hopes of unexplained functional improvement. Educating clinicians will need to go beyond marketing tutorials describing bells and whistles of robotic devices and include evidence of how the device is grounded in medical science both in concept, design, and implementation. Convincing evidence from large-scale clinical trials are necessary to demonstrate that an impairment-based robotic intervention is superior to conventional care not just in improving function but in restoring normal movement through impairment reduction. Additionally, improvements observed should be explained by the underlying neurophysiological mechanism. Our laboratory recently has made substantial efforts to merge quantitative evaluation of movement with high-resolution neuroimaging to meet this requirement [80]. With convincing quantitative evidence and sound scientific underpinning, the rehabilitation specialist will readily accept the impairment-based approach catalyzing the translation to clinical practice.

19.4.3 Motivation, Ease of Use, Practical Implications, and Translation into Rehabilitation Clinics

The issue of patient motivation in rehabilitation robotics is one that can be addressed by combining impairment-based robotics with video games. Combining science-underpinned haptic environments with a game has the potential to motivate patients to participate in therapy sessions and push themselves to greater performances. Recent advances in robotic and video game technology have given rise to multiple systems for upper extremity rehabilitation in stroke [4, 47–54]. Such systems combine robotics with computer graphics for delivery of a rehabilitation protocol. An increasingly common approach is the use of virtual reality (VR) games that allow interaction with a 3-D environment simulated in a computer and integrated with haptic feedback. Reviews on the effectiveness of virtual reality programs for stroke rehabilitation [81–83] support their application albeit with limited evidence. All of these reviews recognize the potential for these therapeutic modalities, encouraging further research to establish their validity and provide evidence of their advantages over conventional therapy. The lack of directly targeting specific impairments in current gaming approaches may explain the limited improvements in arm function during activities of daily living. Preliminary results from our laboratory suggest that the combination of video games and robotics to create a haptic interface should emphasize the design of games that include specific reaching targets in the workspace compromised by the expression of the loss of independent joint control following stroke [84]. Therefore, the ultimate goal will be to develop video games that, in combination with state-of-the-art robotic devices, directly address movement impairments while providing a fun and challenging experience.

Another important element that needs to be considered for the ultimate success of robotics in the clinic and possibly at home is its ease of use. Once the necessary ingredients have been determined to measure and reduce movement impairments resulting from brain injury, simple actuated or possibly passive devices should be developed. Setup time for use of such devices should be fast, and measurement and treatment approaches, incorporating gaming, should provide intuitive interfaces that can be ultimately utilized by the individual receiving therapy.

Finally, to facilitate translation of impairment-based electromechanical devices to clinical practice, they should offer evaluation and treatment approaches that are not readily reproducible by rehabilitation specialists. Electromechanical devices must provide for a precise quantitative evaluation of movement impairments resulting from brain injury such as the loss of independent joint control, weakness, and spasticity. Furthermore, devices must utilize standard quantitative measurements of impairment to initiate and progress the intervention. With these attributes, clinicians will be better informed of the impairments causing movement dysfunction and the response of the patient to rehabilitation.

Conclusion

This chapter discusses the use of impairment-based rehabilitation technologies and provides examples of device development that allows both for the evaluation and treatment of movement impairments. Evidence is provided, demonstrating that electromechanical devices have the unique ability to measure loss of independent joint control, weakness, and spasticity following brain injury. In addition to the quantification and study of mechanisms underlying the expression of these impairments, evidence was also provided, demonstrating the effectiveness of specifically targeting fundamental impairments in order to improve arm function during activities of daily living. The novelty of impairment-based robotics was contrasted with the currently advocated use for robotics that is based on its ability to provide greater intensity of existing rehabilitation approaches. Finally, successful translation to clinical practice was discussed, pointing to several key attributes that will facilitate both clinician and patient acceptance. From this chapter, we hope

to have demonstrated that new robotic technologies are ideal for the delivery of novel science-underpinned therapeutic interventions that can be implemented in current rehabilitation clinics as well as provide a tool for clinicians to better evaluate and treat patients in a more controlled fashion and with greater specificity and intensity than is currently possible with conventional rehabilitation.

The successful application of impairment-based rehabilitation technologies will depend on two factors. First, robotic devices must prove to provide a quantitative evaluation that precisely defines movement impairments that can serve both as indicators for prognosis and response to rehabilitation. Wielding powerful diagnostic and prognostic tools, rehabilitation specialists will make more informed clinical decisions and achieve better clinical outcomes. Second, the future of rehabilitation robotics lies in our ability to demonstrate the effectiveness of robotic devices in delivering interventions that result not only in amelioration of impairments but also in clear gains in arm function during activities of daily living. This will require implementation of large-sample Phase III and IV clinical trials that encompass controlled impairment-based rehabilitation robotic interventions and conventional care. These trials will have the statistical power necessary to detect significant clinical effects utilizing outcomes measuring activity of daily living that are unavoidably limited by low-resolution ordinal scales of measurement. Additionally, it is with these large Phase III and IV clinical trials that cost-benefit analyses can be completed, demonstrating the fiscal utility of these exciting new impairment-based technologies in a changing health care environment.

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Part VIII

Specific Aspects of Neurorehabilitation Technology: Lower Extremity Robots

Lower Extremity Flexible Assist Devices for Locomotion

20

Ming Wu and Jill M. Landry

Abstract

A cable-driven locomotor training system (CaLT) has been developed to improve locomotor function in individuals following hemispheric stroke or spinal cord injury (SCI). A key component of this new system is that it is highly backdrivable, which allows for variation to occur in the trajectory of the gait pattern. The new robotic trainer uses a lightweight cable driven with controlled forces applied to the leg (rather than a controlled trajectory). The refore, the CaLT is compliant, and gives patients the freedom to voluntarily move their legs in a natural gait pattern while providing controlled assistance/resistance forces during body weight supported treadmill training (BWSTT).

Fourteen individuals poststroke and nine patients with SCI were recruited to participate in this pilot study to test the feasibility of using the CaLT for gait training. For our stroke survivors, locomotor training was provided using robotic-assisted, body weight supported treadmill training three times a week for 6 weeks. Single training sessions lasted up to 45 min with body weight support provided as necessary. The treadmill speed was consistent with the subject's maximum comfortable speed. Primary outcome measures were evaluated for each participant prior to training, after 6 weeks of training, and at 8 weeks after training was completed. Primary measures were participant self-selected and fast overground walking velocity, collected on a 10-m instrumented walkway, and walking distance assessed through the 6-min walk. Secondary measures included clinical assessments of balance, muscle tone, and strength. A similar protocol was used for patients with SCI, but locomotor training was provided three times a week for 8 weeks, and outcome measures and clinical assessments

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were evaluated prior to training, and after 4 and 8 weeks of training. Results from this study indicate that locomotor gait training using the CaLT resulted in a significant improvement in walking function in individuals poststroke or with SCI. Thus, it is feasible to use a flexible cable-driven robotic system, i.e., CaLT, to improve locomotor function in individuals poststroke or with SCI.

Keywords
Locomotion • Treadmill training • Cable-driven robot • Spinal cord injury • Stroke

20.1 State of the Art in the Respective Field

20.1.1 Relevant Pathophysiology Background

20.1.1.1 Stroke

Stroke is currently the leading cause of disability in the United States with approximately 1.1 million individuals currently living with stroke-related disabilities. A stroke is the clinical consequence of neuronal death, related to either bleeding or a blockage in one of the two main supplying arteries or their branches. About 80% of stroke cases are induced by ischemia, which may result from vascular embolism or thrombosis. The remaining 20% result from hemorrhage, arising within cerebral tissues or into surrounding spaces. The consequence of either one or more etiology is often cell death, which results in a loss of brain function. As a result, patients may experience hemiplegia, sensory loss, visual impairments, cognitive difficulties, and speech and language difficulties [1].

Impaired mobility is an important factor in determining the degree of physical disability after stroke [2]. While up to 80% of individuals with stroke may ultimately recover the ability to walk a short distance [3], most of them do not achieve the locomotor capacity necessary for community ambulation. Limited community walking reduces the probability of successful return to work and decreases participation in community activities [4].

Walking ability poststroke is characterized primarily by reduced walking speed [5] and endurance [6], residual spatial and temporal left-right asymmetry [7], and impaired postural stability [8]. Patients suffer a greatly reduced knee flexion at toe off and during swing of the paretic leg, as compared to the intact leg, which is usually associated with compensatory movement such as pelvic hiking and limb circumduction [9]. The impaired hip and knee flexion during swing may result in a decreased forward progression and gait velocity, shortened step length, and toe drag at initial swing [10]. These impairments restrict independent mobility and severely impact quality of life of individuals poststroke.

20.1.1.2 Spinal Cord Injury

The estimated prevalence of spinal cord injury (SCI) in the United States is approximately 262,000, with an incidence of approximately 12,000 new cases every year [11]. While the incidence of SCI is considered low compared to stroke, the personal and social-economic consequence of SCI can be severe. For instance, most patients with SCI are young men (in their teens, twenties, or thirties) [12]. Many of them are at their most productive age when injured. After injury, they have to rely increasingly on support from the health-care system, and many have to switch jobs or may not be able to work at all after their injury. A major goal of patients with SCI is to regain walking ability [13, 14], as limitations

in mobility can adversely affect most activities of daily living [15, 16].

Following SCI, descending spinal motor pathways are usually damaged. The loss of descending input to spinal neurons may reduce synaptic drive to locomotor networks and also compromise the ability to produce voluntary movements of the limbs. In addition, there is often impaired control of balance, and this impairment, together with associated weakness of lower extremity muscles, may adversely impact walking. Specifically, individuals with SCI may suffer difficulties supporting their body weight during the stance phase and moving their legs forward during the transition to swing. As a consequence, patients with SCI walk with reduced speed and shorter stride length [17], require assistive devices, such as rolling walkers, and spend more of the gait cycle in double limb support [18]. In addition, subjects with SCI may demonstrate excessive pelvis and trunk motion to compensate for the lower limb deficits due to the spinal cord lesion [19], resulting in an abnormal gait pattern.

20.1.2 Rationale for Application of Current Technology (The Role of Neural Plasticity)

20.1.2.1 Neuroplasticity of Individuals Poststroke and SCI

Although the loci of neuraxis lesions obviously differ between stroke and SCI, the extent of injury to the motor system and to motor-related cognitive networks often overlaps. In particular, the mechanisms of the neural adaptations that accompany training and learning are not dependent on the disease (i.e., stroke or SCI) as much as they rely on the available plasticity in relevant neural networks [20]. The neural reorganization achieved during rehabilitation is highly dependent on the magnitude and specificity of neural activity. Thus, increasing intensity of neural activity during locomotor training should improve the training effect, consistent with use-dependent synaptic plasticity, as expressed in "Hebb's Rule" [21]. Observations in spinalized cats in which targeted standing training or locomotor training produced only task-specific improvements in motor function demonstrate that practice is more effective when it is task specific [22, 23]. Furthermore, motor training paradigms that emphasize active movements are more effective in producing plasticity in spinal circuits and should increase volitional locomotor performance when compared to passive movement training [24, 25]. Thus, to maximize locomotor recovery, rehabilitation after stroke and SCI should emphasize active, repetitive, task-specific practice that maximizes neuromuscular activity.

20.1.3 Therapeutic Action/Mechanisms and Efficacy

20.1.3.1 Task-Oriented Practice in Individuals Poststroke

To improve gait performance and functional outcomes following neurological injury, rehabilitation efforts have been focused on reestablishing normal walking patterns [14]. Toward this end, the use of body weight supported treadmill training (BWSTT) has demonstrated significant improvements in walking capability in individuals poststroke and SCI [26] and is becoming increasingly popular. Use of a treadmill (with or without body weight support) permits a greater number of steps to be performed within a training session. That is, it increases the amount of task-specific walking practice. For instance, previous studies indicated that stroke patients can perform up to 1,000 steps in a 20-min treadmill training session but can only perform 50–100 steps during a 20-min session of conventional physiotherapy [27]. By providing partial body weight support over a treadmill and manual facilitation from therapists, previous research has demonstrated improvements in temporal-spatial gait patterns, including gait velocity [28–31], endurance [32], balance [29], and symmetry [33, 34]. For instance, previous studies in nonambulatory hemiparetic subjects revealed that BWSTT was superior to conventional physiotherapy with regard to

restoration of gait ability and improvement of overground walking velocity [28]. In addition, a large study involving 100 acute stroke patients compared the effect of treadmill therapy with and without body weight support [29]. The results of this randomized clinical trial indicated that subjects with stroke who received 6 weeks of gait training with body weight support recovered better balance and walking abilities, such as overground walking speed and endurance, than those who received similar gait training while bearing full weight on their lower extremities. Changes in impairments and functional limitations observed with intensive BWSTT are often greater than that achieved during conventional or lower intensity physical therapy [30, 31].

However, two randomized, controlled trials in acute stroke survivors failed to show a superiority of BWSTT compared with conventional physical therapy focusing on overground training [35, 36]. For instance, results from a multicentre trial in 73 hemiparetic patients indicated that there was no significant difference between the BWSTT and the control group (who completed overground walking training) with regard to Functional Independence Measures (FIM), walking velocity, Fugl-Meyer Stroke Assessment, and balance assessments [35]. Although, in a subgroup of severe stroke subjects, the BWSTT group demonstrated a greater improvement of walking speed and endurance compared to the control group [36]. In addition, in studies that have employed high-intensity walking regimens in individuals with chronic stroke (i.e., those without presumed spontaneous recovery), the average increase in walking speed ranges from 0.09 to 0.13 m/s following 1–6 months training [30, 32]. While significant statistically, these changes are relatively small considering the effort required to perform such training.

20.1.3.2 Task-Oriented Practice in Humans with SCI

BWSTT with manual assistance given to the legs and the pelvis has also been used as a promising rehabilitation method designed to improve motor function and ambulation in people with SCI [37–42]. For instance, BWSTT has been shown to provide significant improvements in locomotor ability and motor function in humans with SCI [43]. Specifically, 89 patients with incomplete SCI underwent BWSTT and were compared with 64 patients treated conventionally. The results indicated that the BWSTT group improved their mobility more than the control group (i.e., conventional treatment group). For the acute patients, 92% of those initially wheelchair bound became independent walkers following BWSTT, while only 50% were able to walk independently following conventional therapy. For chronic patients, 76% of those initially wheelchair bound learned to walk independently following BWSTT, while only 7% returned to walking following conventional therapy [43].

Conversely, results from a recent large multicenter randomized clinical trial with acute incomplete SCI patients indicated that both groups improved their outcome measurements related to walking performance, but no significant differences were found between the BWSTT and the conventionally trained groups [41]. Specifically, a total of 146 subjects within 8 weeks of spinal cord injury were entered into a single-blinded, randomized clinical trial. Subjects received 12 weeks of equal time of BWSTT or conventional overground mobility intervention. No significant differences were found at entry between treatment groups or at 6 months for FIM, walking speed, and 6-min walk distance.

Even though BWSTT may only be as effective as conventional training, it is still a valuable technique for locomotor training in humans with SCI. The technique may be safer and more convenient for assisting ASIA A and B subjects to stand and step when compared with conventional physical therapy [41]. Also, it may allow for earlier gait training in patients with limited locomotor capabilities, allowing them to repeat a gait-like motion and alternative loading of the lower limbs [37, 43]. Despite this, BWSTT often requires the effort of multiple physical therapists (generally up to three) to assist with leg movement and control trunk movement. It can be a labor-intensive work for physical therapists, particularly for those patients who require substantial walking assistance following SCI. This suggests that there is a need to improve the current BWSTT system.

20.2 Review of Experience and Evidence for the Application of Specific Technology

Due to the high effort level required by therapists to assist patients during BWSTT, several robotic systems have been developed for automating locomotor training of individuals poststroke or SCI, including the Lokomat [44], the Gait Trainer (GT) [45], and the AutoAmbulator [46]. The Lokomat is a motorized exoskeleton that drives hip and knee motion in the sagittal plane with a fixed trajectory using four DC motors [44]. The GT rigidly drives the patient's feet through a stepping motion using a crank-and-rocker mechanism attached to foot platforms [45]. The AutoAmbulator is a body weight supported treadmill robot system with robotic arms strapped to the patient's leg at the thigh and ankle, which move the legs in a quasi-normal walking pattern. These robotic systems had at their initiation the basic design goal of firmly assisting patients in producing correctly shaped and timed locomotor movements. This approach is potentially effective in reducing therapist labor in locomotor training and increasing the total duration of training. For instance, while a manually assisted treadmill training session usually lasted up to 20 min, the robotic BWSTT could be performed up to 60 min [47], depending on the tolerance of the patient. Also, the number of therapists required to provide robotic BWSTT is significantly less than that required for manually assisted treadmill training [48].

20.2.1 Robotic Gait Training in Individuals Poststroke

While robotic gait training relieves the strenuous effort of the therapists, the functional gains are limited for some patients [49, 50]. For instance, results from a study using the Lokomat with 30 acute stroke patients indicated that there was only 0.06 m/s gait speed improvement following 4 weeks of training, and there was no significant difference between the therapy on the Lokomat and gait training overground [49]. In particular, in a study with 63 subacute stroke patients, results indicated that participants who received conventional gait training experienced significantly greater gains in walking speed and distance than those trained on the Lokomat [51]. In addition, results from a study with 48 chronic ambulatory stroke survivors indicated that robotic-assisted BWSTT with a fixed trajectory control strategy is less effective in improving walking ability in individuals poststroke than physical therapist–assisted locomotor training [52]. In contrast, results from a study with 155 nonambulatory subacute stroke patients show that robotic-assisted gait training (using the Gait Trainer) plus conventional physiotherapy resulted in a significantly better gait ability compared with conventional physiotherapy alone [53].

20.2.2 Robotic Gait Training in Human with SCI

Similar results have been observed in humans with SCI [54]. For instance, results from a randomized study with 27 chronic SCI patients indicated that all modalities of locomotor training were associated with improved walking speed, and there were no significant differences between the group with robotic gait training using the Lokomat and other groups [42]. Similarly, in a study with 30 acute SCI patients randomly assigned to three groups: robotic-assisted BWSTT using the Lokomat, therapist-assisted BWSTT, and overground ambulation with a mobile suspension system used for safety and support as necessary, results indicated that there were no significant differences in the rate and extent of motor and functional recovery among the three groups [48], although the total distance ambulated during robotic BWSTT was significantly greater than that with overground training (i.e., 2859 ± 111 vs. 1282 ± 666 m). Such results suggest that current robotic-assisted BWSTT methods may reduce the requirements and labor effort for the physical therapist, but it does not necessarily offer an advantage in terms of regaining gait function in individuals poststroke or in humans with SCI.

20.2.2.1 Limitations of the Current Robotic System

While these first generation robotic systems are effective in reducing therapist labor in locomotor training, they have obvious limitations [55]. For example, due to the limited degrees of freedom of the standard Lokomat (i.e., the sagittal plane), the device essentially eliminates, or at least minimizes, lateral and rotational movement of the pelvis. This may have an adverse impact on walking, given that even small, but timely, right/left shifts in the pelvis can greatly facilitate leg swing [55, 56]. In addition, a fixed trajectory control strategy may encourage passive rather than active training. During robotic BWSTT, the driven gait orthosis passively moves the legs in a kinematically correct pattern. The robot essentially takes over the movement task, sharply reducing the patient's participation level [57]. A fixed-trajectory training eliminates the variability in kinematics of the lower limbs, which may be critical for successful motor learning as demonstrated in animal studies [58].

Another limitation of current robotic gait training systems is the relatively expensive cost, which may be a significant barrier to widespread clinical application and use. For instance, the cost of the Lokomat is about four times the annual stipend of a physical therapist. With such a high cost, many rehabilitation settings will be unable to deliver this type of therapeutic intervention to a larger patient population. As a consequence, there is a need to develop new cost-effective techniques of robotic BWSTT in order to produce greater functional improvements in individuals poststroke or SCI.

In an attempt to improve the efficacy of robotic BWSTT, we have developed a novel cable-driven gait training system (CaLT) [59]. This new robotic trainer uses a lightweight cable driven with controlled forces applied to the legs. A key component of this new system is that it is highly backdrivable, which means that the patient can readily overcome the forces and torques generated by the robot. This unique feature offers key advantages over both the ball-screw mechanisms used in the Lokomat [44] and the crank-and-rocker mechanism, as used in the Gait Trainer [45] in that it allows for variation in lower limb kinematics and increases active participation of the patient during training. As demonstrated in previous studies, these components of gait training are critical to maximize motor learning and functional improvements in both individuals with stroke and humans with SCI.

In the current design, four nylon-coated stainless steel cables (1.6 mm diameter), driven by four motors (AKM33H, Kollmorgen) through four cable spools and pulleys, are affixed to custom cuffs that are strapped to the legs (routinely around the ankles) to produce an assistance/resistance force of up to 45 N (see Fig. 20.1). Four one-degree-of-freedom (DOF) reaction torque load cells (TRT-200, Transducer Techniques, Temecula, CA) are integrated between the output shafts of the motors and the cable spools to record the applied torques. Ankle kinematics of both legs are recorded using two custom, three-dimensional position sensors. Each sensor consists of a detection rod and two universal joints (U-joints) attached to the two ends of the rod. The ankle position signals are used by the operator to control the timing and magnitude of applied forces, at targeted phases of gait.

Control is implemented through a custom LabVIEW program, which sends control signals to the motor drives through an analog output to set the applied forces. The controller automatically adjusts the load provided by the cables based on the kinematic performance of the subject. The load is applied starting at preswing (10% gait cycle prior to toe off) through midswing of gait [60]. Two control algorithms were designed for either an assistance or resistance strategy. For the assistance paradigm, the force applied to the legs was determined in real time using the following equation:

$$F_a(t) = -k_P(x(t) - x_d(t)) - k_D(\dot{x}(t) - \dot{x}_d(t)) \quad (20.1)$$

where t is time; k_P and k_D are the position and velocity gains (e.g., k_P and k_D are adjustable depending the tolerance of the subject); $x(t)$, $\dot{x}(t)$, $x_d(t)$, and $\dot{x}_d(t)$ are the measured and desired

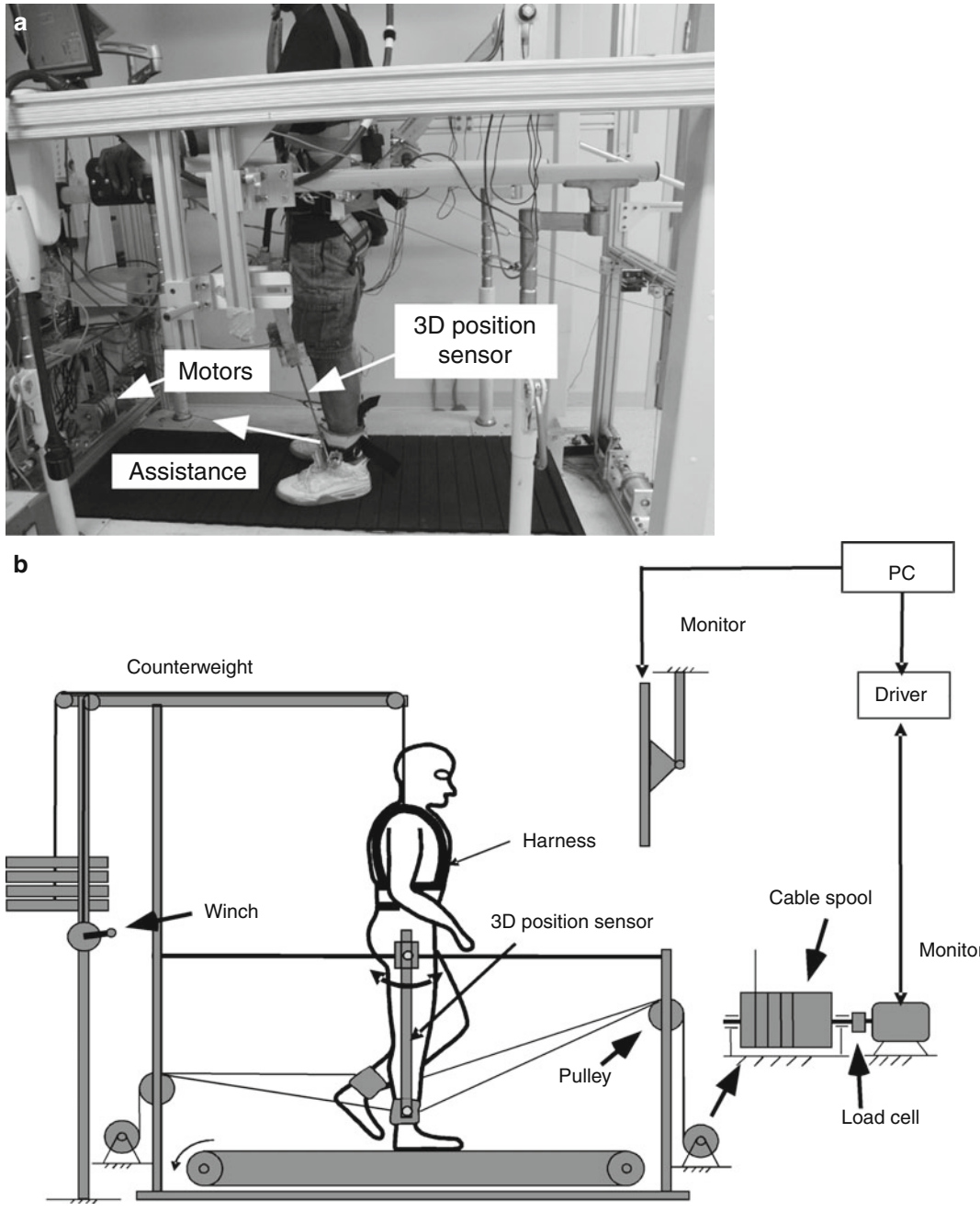

Fig. 20.1 Photo (**a**) and drawing (**b**) of the cable robot, a motor-driven cable apparatus that was used with a treadmill and body weight support system. Four cables driven by four motors, pulleys, and cable spools were used to apply resistance/assistance loads during the swing phase of gait. A personal computer was used to control the load produced by the four motors, applying targeted assistance or resistance loads

ankle horizontal position and velocity during the swing phase. The desired positions were determined from the mean recorded ankle trajectory using the position sensor for two healthy subjects walking on the treadmill. For the resistance paradigm, a similar equation was used to determine the amount of force, but a resistance load was applied.

20.3 Current Developments and Ongoing Testing

20.3.1 Locomotor Training in Individuals Poststroke

20.3.1.1 Subjects

Fourteen individuals with chronic hemiparetic stroke were recruited to participate in this pilot study. Mean age at the time of study enrollment was 53.6 ± 9.4 years old. The average interval between stroke and the onset of robotic BWSTT was 7.5 ± 5.3 years (range 2–21 years). Specific inclusion criteria for the participation in the study included: (a) age between 21 and 75 years old; (b) >6 months duration after unilateral, supratentorial, ischemic, or hemorrhagic stroke with lesion location confirmed by radiographic findings; (c) no prior stroke; (d) demonstration of impaired walking function (self-selected walking speed ≤0.99 m/s); (f) ability to stand and walk (>10 m) without physical assistance, with the use of assistive devices or orthoses (below knee) as needed. Subjects were further stratified according to initial overground gait speed. Those who ambulated <0.5 m/s were classified with severe locomotor impairments, and those with moderate impairments ambulated >0.5 and ≤0.99 m/s.

Exclusion criteria included significant cardiorespiratory/metabolic disease, or other neurological or orthopedic injury that may limit exercise participation or impair locomotion; scores on the mini-mental status examination (MMSE) [61] <24; stroke of the brainstem or cerebellar lesions; and uncontrolled hypertension (systolic >200 mmHg, diastolic >110 mmHg). All subjects required medical clearance prior to participation. Subjects were excluded if they were unable to tolerate 30 min of standing or undergoing concurrent physical therapy. In addition, subjects who were receiving pharmacological treatment for spasticity using oral medications were included but were requested to maintain their antispastic medication dosage throughout the training sessions. All procedures were approved by the Institutional Review Board of the Northwestern University Medical School. Written informed consent was obtained for all subjects.

20.3.1.2 Training Protocol

For each training session, subjects were fitted with an overhead harness attached to a counterweight support system, with the counterweight providing as much support as necessary to prohibit knee buckling or toe drag during stepping. The treadmill speed was consistent with their maximum comfortable walking speed, determined on the treadmill at each training session. Blood pressure and heart rate were assessed during treadmill training and were maintained below 220/110 mmHg and 85% of age-predicated maximum heart rate. Short rest breaks were provided as necessary during the course of training. Total training time, speed, distance, and the amount of unloading were recorded during each session.

At the initiation of locomotor training, the load was applied to the ankle of the paretic leg through the cable robot. For the assistance group, only an assistance load was applied, and for the resistance group, only a resistance load was applied. At the beginning of each training session, a physical therapist determined the position and velocity gains based on the tolerance of subject. Then, the amount of the load was real -time controlled by the controller, based on the kinematic performance of the subject using the control algorithm described above. Verbal encouragement from the physical therapist was provided as necessary.

20.3.1.3 Outcome Measures

Primary outcome measures were evaluated for each participant prior to training, after 6 weeks of training, and at 8 weeks after training was completed. Primary measures included self-selected and fast overground walking velocity collected on a 10-m instrumented walkway (GaitMat II, E.Q. Inc, Chalfont, PA) and walking distance assessed through the 6-min walk [62].

Secondary measures included clinical assessment of balance, muscle tone, and strength. Balance, a clinical measure of postural stability during specific standing tasks, was assessed using the Berg Balance Scale [63]. Maximum voluntary isometric joint torques were tested at each of the three evaluation sessions. Specifically, the hip (flexion/extension), knee, and ankle joints were

aligned to a six-degree-of-freedom load cell (Model 3550, ATI Industrial Automation, Inc., Garner, NC), which was affixed to the output axis of the motor of a Biodex Rehabilitation/Testing System (Biodex Medical Systems, Inc., Shirley, NY). Subjects were asked to perform three maximum voluntary extension/flexion contractions. The average of the isometric torque recordings was calculated.

20.3.1.4 Data Analysis

Data were analyzed using scores at pre vs. post 6 weeks training, and pre vs. 8 weeks follow-up assessment. Only data for subjects who completed all training and evaluation sessions were used for analysis. Overground gait speed and 6-min walk distance were analyzed using repeated measures ANOVAs for the effect of training (pre vs. post training, pretraining vs. follow-up), with significance noted at $p<0.05$. In addition, balance (Berg Balance Scale), strength, and other clinical assessments were also analyzed using repeated measures ANOVAs, with significance noted at $p<0.05$.

20.3.1.5 Results

Twelve patients finished 6 weeks of robotic treadmill training, and 11 patients completed testing at the 8 weeks follow-up session. One patient dropped out due to an illness not related to the treadmill training. One patient was excluded because his self-selected overground gait speed was greater than the inclusion criteria after retest at the first training session. Subjects were randomly assigned to assistance or resistance groups after the first evaluation (seven subjects participated in the resistance group and five subjects in the assistance group). All subjects finished 18 sessions of robotic treadmill training. Partial body weight support was provided for two subjects (starting at 32% and 23%, and decreased to 16% and 12%, respectively).

In this pilot study, we summarized the results of all subjects from both the assistance and resistance training groups. A significant improvement in walking function in individuals poststroke was observed following 6 weeks of robotic BWSTT using the CaLT. Specifically, self-selected overground walking speed significantly increased from 0.65 ± 0.21 m/s at the baseline to 0.77 ± 0.26 m/s post training ($n=12$, one-way repeated measures ANOVA, $p=0.002$). Fast walking speed significantly increased from 0.89 ± 0.33 m/s at the baseline to 1.04 ± 0.37 m/s post training ($n=12$, ANOVA, $p=0.001$) (see Fig. 20.2a). Further, the improved walking speeds were partially retained at 8 weeks follow-up. For instance, fast walking speed at the follow-up was significantly higher than that at the baseline (0.87 ± 0.33 vs. 0.99 ± 0.38 m/s, $n=11$, one-way repeated measures ANOVA, $p=0.004$). Self-selected walking speed at the follow-up was also greater than that at the baseline (0.63 ± 0.21 vs. 0.69 ± 0.23 m/s), although no significant difference was obtained ($n=11$, ANOVA, $p=0.07$). In addition, the 6-min walk distance significantly increased after training (238 ± 81 vs. 250 ± 79 m, for pre and post training, $n=12$, ANOVA, $p=0.03$), although no significant change was noted at 8 weeks follow-up (237 ± 81 m, $n=11$) (see Fig. 20.2b). Balance also improved following robotic treadmill training. For instance, the Berg Balance Scale score significantly increased from 48 ± 5 at the baseline to 50 ± 5 post training ($n=12$, ANOVA, $p=0.02$), but slightly declined to 49 ± 5 ($n=11$) at 8 weeks follow-up (see Fig. 20.3). There was no significant change in muscle strength following robotic BWSTT.

20.3.2 Locomotor Training in Human with Incomplete SCI

20.3.2.1 Subjects

Nine individuals with chronic incomplete SCI (i.e., >12 months post injury) with an injury level from C2 to T10 were recruited to participate in this study. Mean age at the time of study enrollment was 46 ± 8 years old. The average interval between SCI and the onset of robotic BWSTT was 5.6 ± 4.3 years (range 1–14 years). All subjects were classified by the American Spinal Injury Association (ASIA) as ASIA grade D. Specific inclusion criteria for participation in the study included: (a) age between 16 and 65 years; (b) medically stable with medical clearance to

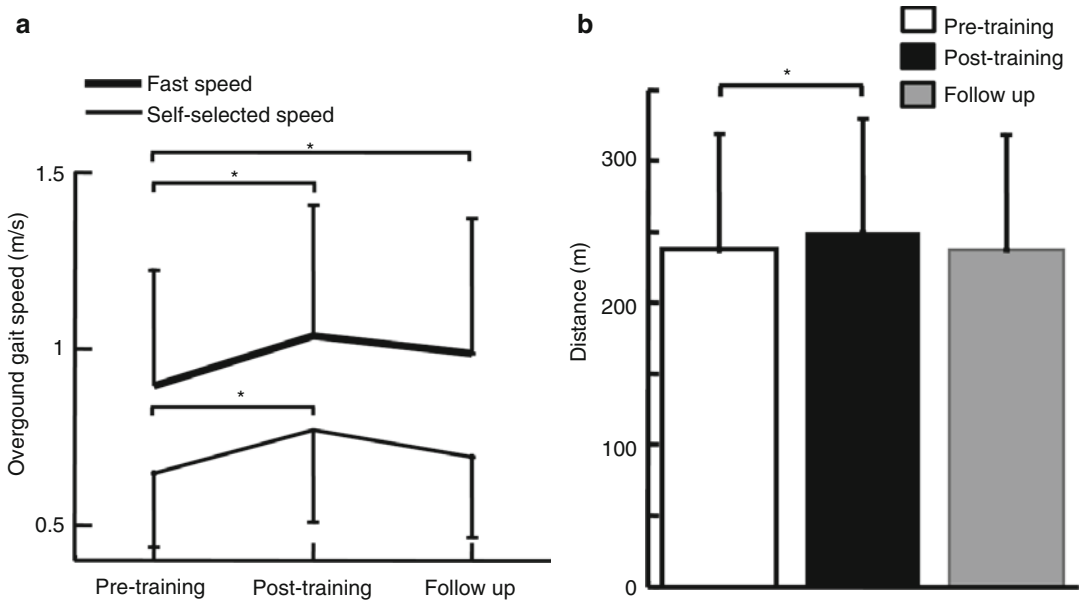

Fig. 20.2 Overground gait speed (**a**) and 6-min walk distance (**b**) at pre, post 6 weeks robotic treadmill training, and 8 weeks follow-up in individuals poststroke. The *bar and error bar* indicate the mean and standard deviation of gait speed and walking distance across 12 subjects for pre and post training, and for 11 subjects at follow-up. *Asterisk* (*) indicates significant effect of treatment

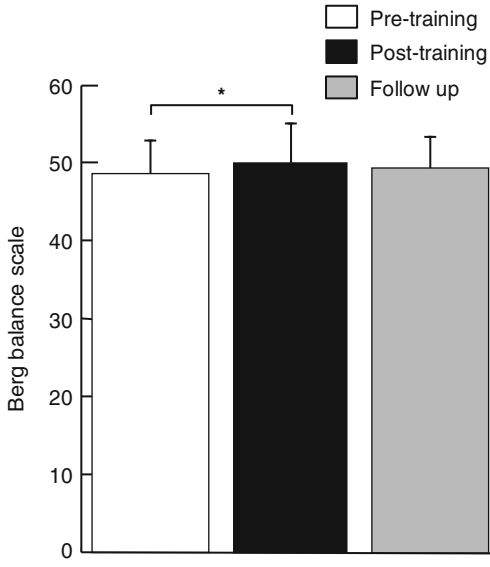

Fig. 20.3 Berg balance scale at pre, post 6 weeks robotic treadmill training, and 8 weeks follow-up in individuals poststroke. The *bar* and *error bar* indicate the mean and standard deviation across 12 subjects for pre and post training, and for 11 subjects at follow-up. *Asterisk* (*) indicates significant effect of treatment of robotic gait training

participate; (c) level of SCI lesion between C1 and T10; (d) passive range of motion of the legs within functional limits of ambulation (i.e., ankle dorsiflexion to neutral position, knee flexion from 0° to 120°, and hip from 10° extension to 90° flexion); (e) ability to walk on a treadmill for more than 30 min with partial body weight support as needed; (f) ability to stand and walk (>10 m) without physical assistance with the use of assistive devices or with orthotics that do not cross the knee.

Exclusion criteria included the presence of unhealed decubiti, existing infection, severe cardiovascular and pulmonary disease, concomitant central or peripheral neurological injury (e.g., traumatic head injury or peripheral nerve damage in lower limbs), history of recurrent fractures, and known orthopedic injury to the lower extremities. Subjects receiving pharmacological treatment for spasticity were included but were requested to maintain their antispastic medication dosage throughout training sessions. All research on human subjects was conducted with

authorization of the Northwestern University Medical School Institutional Review Board.

20.3.3 Training Protocol

In order to test the locomotor training effect of the cable-driven robot in the SCI population, an 8-week training trial was conducted using a randomized crossover schedule. Specifically, subjects were blocked by gait speed into slow (<0.5 m/s) or fast (>0.5 m/s) subgroups and then randomized to either the assistance or resistance training first. After the first 4 weeks of training, subjects from both groups were switched from assistance to resistance or from resistance to assistance training and completed another 4 weeks of training. Three assessments of gait were used to determine the training effects. Gait speed, endurance, and clinical measures of functional ambulation and static isometric measurements of strength were made at the beginning, the middle (post 4 weeks of training), and at the end of the training period (following 8 weeks of training).

A training protocol similar to the one in the study with stroke patients was used. Training was performed three times per week for 8 weeks with the training time for each visit set to 45 min as tolerated, excluding setup time. At the initiation of locomotor training, controlled assistance (for assistance training group) or resistance (for resistance training group) loads were applied at the ankle of both legs. The amount of the load was controlled by the controller and was based on the kinematic performance of the subject.

20.3.3.1 Data Analysis

In this pilot study, data from all subjects who completed all training and evaluation sessions were analyzed using scores at pre and post 8 weeks training. Improvement in overground gait speed and endurance (6-min walk) was analyzed using repeated measures ANOVAs for the effect of training (pre vs. post training), with significance noted at $p<0.05$. In addition, improvements in balance (Berg Balance Scale), strength, and other clinical assessments were also analyzed using repeated measures ANOVAs, with significance noted at $p<0.05$.

20.3.3.2 Results

In this pilot study, seven out of nine subjects finished 8 weeks of robotic treadmill training, with two subjects dropping out the study. One subject dropped out due to increasing knee and low back pain, and the other was unable to continue with the study secondary to difficulty with transportation. For the seven patients that finished 8 weeks of robotic gait training, we found a significant improvement in self-selected overground walking speed ($p=0.03$, one-way repeated measures ANOVA), i.e., gait speed improved from 0.69 ± 0.21 to 0.79 ± 0.23 m/s (see Fig. 20.4a). Fast walking speed also improved from 0.99 ± 0.31 to 1.11 ± 0.32 m/s, although no significant difference was obtained due to the small sample size ($p=0.20$, one-way repeated measures ANOVA). In addition, scores on the Berg Balance Scale significantly improved from 42 ± 13 at pretraining to 45 ± 13 post 8 weeks robotic gait training (see Fig. 20.5). There was no significant change in walking distance at the pre and post robotic training evaluation sessions ($p=0.2$), although averaged 6-min walk distance increased from 233 ± 82 m at pretraining to 253 ± 93 m at post training (see Fig. 20.4b). We found all subjects in this study had no change in their WISCI II scores at pre and post robotic treadmill training (17 ± 4). In addition, there was no significant change in muscle strength following robotic BWSTT.

20.3.3.3 Discussion

The purpose of these pilot studies was to test the feasibility of using the CaLT and determine whether intensive locomotor training using the CaLT would improve ambulatory and functional capabilities in people with chronic stroke or motor incomplete SCI. We found that it was feasible to use the cable-driven robotic system to improve locomotor function in individuals post-stroke or with chronic SCI. Specifically, significant changes were observed in self-selected

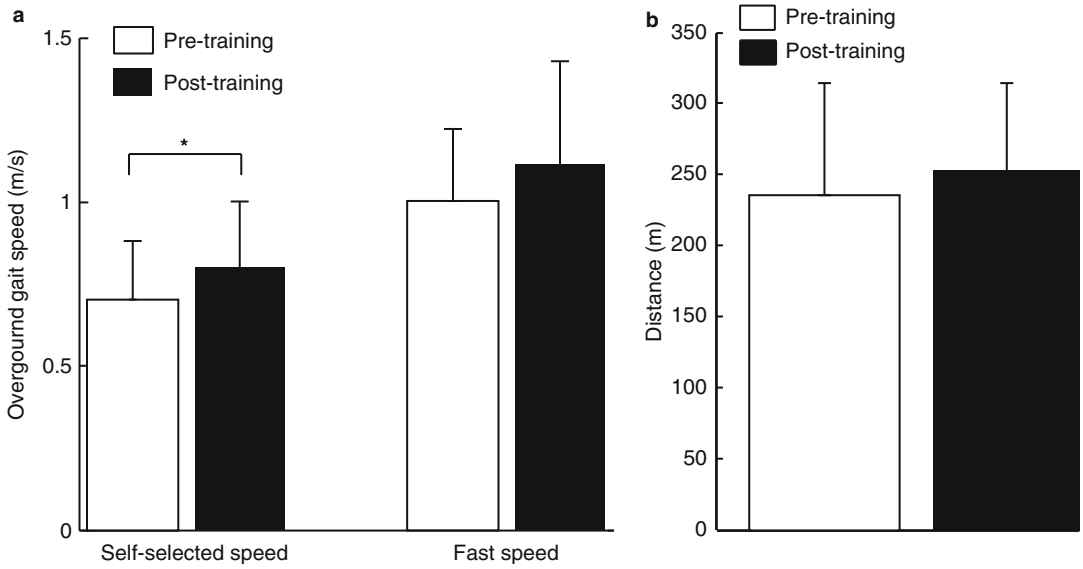

Fig. 20.4 Self-selected overground gait speed (**a**) and 6-min walk distance (**b**) at pre and post 8 weeks robotic treadmill training in human SCI. The *bar* and *error bar* indicate the mean and standard deviation of the gait speed and walking distance across seven subjects for pre and post training. *Asterisk* (*) indicates significant effect of treatment

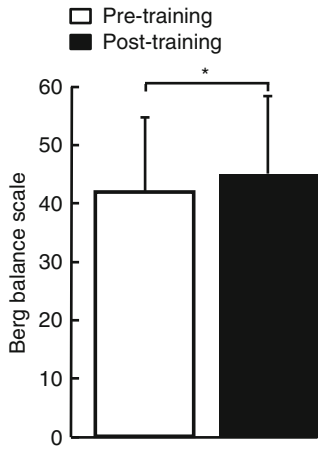

Fig. 20.5 Berg balance scale at pre and post 8 weeks robotic treadmill training in humans with SCI. The *bar and error bar* indicate the mean and standard deviation across seven subjects for pre and post training. *Asterisk* (*) indicates significant effect of treatment of robotic gait training

overground gait speed and balance (BBS). Further, the improvements in walking were partially retained at 8 weeks post training in individuals poststroke, indicating a clinical significance of this intervention.

20.3.4 Improved Walking Function in Individuals Poststroke

The walking functional gains of individuals poststroke obtained in the current study with cable-driven robotic gait training are comparable to outcomes following physical therapist assisted BWSTT, i.e., 0.12 ± 0.11 vs. 0.13 ± 0.11 m/s for self-selected walking speed and 0.14 ± 0.11 vs. 0.13 ± 0.12 m/s for fast walking speed [52], but larger than the outcomes following robotic gait training with a fixed trajectory control strategy, i.e., 0.12 ± 0.11 vs. 0.07 ± 0.07 m/s for self-selected walking speed and 0.14 ± 0.11 vs. 0.06 ± 0.08 m/s for fast walking speed [49, 52]. In addition, balance significantly improved following cable-driven robotic training, while no significant changes were obtained following robotic training using the Lokomat, which only allows for movement in the sagittal plane. Specifically, the BBS score increased from 48 ± 5 to 50 ± 5 following cable-driven robotic training and from 43 ± 10 to 44 ± 10 following robotic training using the Lokomat [52]. These functional improvements may be due to the features of the cable-driven robotic system, which is designed

to mimic the way in which a physical therapist would provide an assistance force to the paretic leg during treadmill training in individuals poststroke.

Maintaining variation in kinematics during BWSTT is considered to be critical in improving the locomotor function in individuals poststroke. For instance, results from animal experiments show that motor learning is more effective with a robotic algorithm that allows for variability in the stepping pattern than with a fixed trajectory paradigm [58]. In addition, results from human study have shown that intralimb coordination after stroke was improved by physical therapist assisted BWSTT, which allowed for kinematic variability, but not robotic gait training with a fixed trajectory, which reduces kinematic variability [64].

In the current study, the cable-driven robotic system, which is highly backdrivable, has limited constraint on leg kinematics during treadmill training [59]. The cable-driven system can be moved by the patient with smallest possible resistance opposed by the robot. Thus, the cable system allows patients greater flexibility in controlling their gait pattern. The robot can also apply an assistance force to the legs if the patient lacks enough motor output to actively step forward during treadmill walking. As the patient recovers, the assistance force can be gradually reduced or even changed to a controlled resistance force to improve the efficacy of robotic BWSTT. This type of training appears to be more effective than fixed trajectory training in improving locomotor function in individuals poststroke.

Results from basic neuroscience studies have indicated that motor learning is more effective when human subjects actively practice movement rather than being passively moved [24, 25]. In this study, a controlled assistance or resistance load was applied to the paretic leg during treadmill training through the cable-driven robotic system. Thus, subjects were more actively involved during training with the cable-driven robot, which served to increase the efficacy of robotic BWSTT in individuals poststroke. In contrast, currently available robotic systems, such as the standard Lokomat, use a fixed trajectory control strategy. With this type of control strategy, it is easier for the patient to passively allow the robot to move their legs for them [57]. Results from this study suggest that a robotic system that encourages active involvement of patients during training would be more effective in improving locomotor function in individuals poststroke.

The subjects who participated in the current study were all ambulatory chronic (>6 months post-stroke) patients with self-selected walking speeds ranging from 0.23 to 0.89 m/s. Nine out of 12 subjects were limited or community walkers (i.e., self-selected walking speed >0.5 m/s). For these patients, cable-driven robotic gait training appeared to be effective to improve locomotor function. However, it remains unclear whether cable-driven robotic gait training will be as effective in improving the locomotor function of individuals who are more severely affected.

20.3.5 Improved Walking Function in Humans with SCI

The locomotor functional gains obtained using the cable-driven robotic gait training system are comparable or even greater than that of using currently available robotic systems with a fixed trajectory control strategy. For instance, in a randomized trial involving 27 participants with SCI, the use of robotic-assisted BWSTT with a fixed trajectory did not significantly increase walking velocity (mean difference was −0.05 m/s) [42, 65]. However, in another study with 20 subjects with chronic SCI, results indicated that the use of robotic-assisted treadmill training with a fixed trajectory may significantly improve walking speed in the SCI population [40]. The functional gains were 0.11 ± 0.11 m/s following robotic gait training, which is comparable to the results obtained in the current study.

In addition, results from the current study indicate an improvement in balance control in human SCI following cable-driven robotic gait training, i.e., Berg Balance Scale scores increased 3.4 ± 2.4. This is a functional gain not previously seen in studies with the Lokomat. The current Lokomat only allows movement in the sagittal

plane due to the limited degrees of freedom. The unnecessary medial-lateral support may reduce the potential functional gains in balance control following robotic gait training using the Lokomat. Recent studies indicate that there is a strong relationship between balance and walking capacity in patients with SCI [66, 67]. Thus, training stereotypical gait patterns in human SCI without challenging balance control may squander training time by focusing training on the impairment that is not the bottleneck for achieving a greater walking speed [68].

The effect of BWSTT in enhancing motor recovery and improving ambulation in human SCI has been studied intensely for the past two decades [69]. Specifically, it has been shown that BWSTT may increase lower extremity motor strength, walking ability, and postural stability in people with motor incomplete SCI in the acute or chronic stages of recovery. However, the primary limitation of such a therapy is the labor-intensive effort required of a physical therapist. Manual facilitation of the lower extremities and trunk to generate appropriate kinematics associated with stepping behaviors may require substantial effort by the physical therapist, especially for those patients with significant weakness or spastic motor behaviors. Indeed, for patients with little voluntary muscle strength, but high spastic muscle forces, the training duration is often limited by the fatigue of the therapists rather than the SCI patient [70]. As the therapist fatigues, maintaining an appropriate spatial and temporal gait pattern for the patient becomes increasingly difficult. In addition, two or even three physical therapists are often needed to assist the patient's legs and torso during BWSTT, which may limit the extent to which such therapy is given in the clinical setting.

In contrast, intensive task-specific walking practice may be delivered through a cable-driven robotic-assisted BWSTT system with the help of only one therapist and can be performed for a longer duration (dependent upon the tolerance of the patient), thereby increasing the amount of practice of stepping behaviors. While the sample size is small, our results indicate that the improvements in locomotor function in our ambulatory subject population were statistically significant, with self-selected gait speed and Berg Balance Scale scores increasing by 0.10±0.10 m/s (14%) and 3.4±2.4 m/s (8%), respectively, post robotic training. These improvements were qualitatively similar to those achieved by people with a similar diagnosis and chronicity of injury who performed therapist-assisted BWSTT [42]. Thus, the cable-driven robotic BWSTT may achieve comparable functional gains when compared to therapist-assisted BWSTT, but can substantially reduce the labor effort and personnel cost of physical therapists.

The patients who participated in the current study were all ambulatory (with or without an assistive device). Initial self-selected overground gait speed ranged from 0.27 to 0.90 m/s. It remains unclear whether cable-driven robotic gait training will be effective in improving locomotor function in humans with SCI who are more severely impaired and cannot ambulate. The injury level of participants ranged from C3 to T10. Six out of seven subjects who completed all training and evaluation sessions had an injury at the cervical level. In addition, three out of seven subjects were taking antispastic medications during the training sessions. These two confounding factors may have influenced the results of the robotic-assisted treadmill training. For instance, antispastic medications may affect locomotor activity in humans with SCI [71] and may alter the rate of locomotor recovery with robotic gait training. However, due to the small sample size of the current study, there was no conclusion about the effect of injury level and antispastic medications on locomotor recovery following robotic training in this population. In addition, a randomized controlled study is ongoing to determine whether cable-driven robotic-assisted BWSTT can produce greater functional improvements than those achieved through manually-assisted BWSTT in humans with SCI.

20.3.6 Other Advantages of the Cable-Driven Robotic System

The cable-driven robot system can apply compliant assistance as needed or even resistance as tolerated to the paretic leg (s) during treadmill training. The cable-driven robot system is easy to set up compared

to an exoskeleton robot system, such as the Lokomat, which requires the rotation center of robotic arms to be aligned with the patient's hip and knee joints [44]. The setup time of the cable-driven system is shorter than that of the exoskeleton systems, which is critical to consider for the efficacy of long-term treadmill training. In addition, the cost of the cable-driven robot system is less expensive than the current robotic systems, such as the Lokomat or AutoAmbulator. Also, it would be possible to install multiple sets of cable-driven robotic systems within a clinic and allow therapists to treat more than one patient at the same time. Thus, the cable-driven robotic system has multiple potential advantages to allow for delivery of this type of therapy to a larger patient population.

20.3.7 Development of Other Robotic Systems

In an attempt to improve the efficacy of robotic BWSTT, several other robotic gait training systems, such as PAM and POGO [72], LOPES [73], and Haptic Walker [74] have been developed. The PAM and POGO is a pneumatic-driven gait training robot that allows for a full range of natural motion of the legs and pelvis during treadmill walking and provides compliant assistance at both the pelvis and legs [72]. The LOPES is an eight-degree-of-freedom lightweight impedance controlled exoskeleton robot developed for gait training [73]. It consists of two actuated pelvis segments and three actuated rotational joints for each leg (i.e., two at the hip and one at the knee). The joints of the robot are actuated with Bowden cable-driven series elastic actuators and impedance controlled to allow bidirectional mechanical interaction between the robot and the training subject. The Haptic Walker is an updated design of the GT I with programmable footplates [74]. It allows the footplates to move along arbitrary foot trajectories (e.g., even ground, stair climbing up/down, perturbations like stumbling/sliding). A prototype machine has been built and tested on healthy subjects [75].

In addition, new control algorithms have been tested to improve the efficacy of the Lokomat. For instance, patient-cooperative control strategies have been tested to improve the active participation of the patients and allow for more kinematic variability during robot-assisted treadmill training through the Lokomat [76, 77]. The new design of the Lokomat also allows for hip joint abduction and adduction movement, and lateral movement of the pelvis. While these sophisticated robotic gait training systems and control algorithms are promising, it still remains unclear whether these are more effective than current robotic systems or conventional interventions to improve locomotor function in individuals poststroke or SCI. In addition, there are several other passive devices that deliver assistance to the leg during treadmill walking [78, 79], but no clinical results have been reported.

Robotic-assisted treadmill systems provide for training of a repetitive walking pattern that is critical for locomotor recovery in individuals poststroke or with SCI. However, the sensory feedback provided to the patients who are trained on the treadmill is distinct from overground walking. For instance, the optical flows are different for these two walking conditions. Visual cues are in conflict with proprioceptive signals from the legs during treadmill walking, which is not experienced during overground walking [80]. Such factors may limit the transfer of the motor skill learned on the treadmill to overground walking. For instance, a previous study showed a partial transfer of motor adaptation obtained from split-belt treadmill training to overground walking [81]. As a consequence, several overground robotic systems, such as ReWalk (Argo Medical Technologies Ltd., Haifa, Israel) and the Tibion Bionic Leg (Tibion Corporations, Sunnyvale, California), have been developed, although the clinical results have not been reported.

20.4 Perspectives and Conclusions

The cable-driven locomotor training system proposed in this study provides a promising adjunct for treatment of patients poststroke or for patients with incomplete SCI through robotic-assisted

treadmill training. This system is highly backdrivable, compliant, and allows patients the freedom to voluntarily move their legs during BWSTT. In addition, the cable-driven robot is easy to set up and cost-effective to allow for delivery of this type of therapeutic intervention to a larger patient population. Results from this pilot study indicate that it is feasible to improve locomotor function in individuals poststroke or with incomplete SCI using the cable-driven robotic gait training system.

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Robot-Aided Gait Training with LOPES

21

Edwin H.F. van Asseldonk and Herman van der Kooij

Abstract

Robot-aided gait training in stroke survivors and spinal cord injury patients has shown inconclusive effects on walking ability. It is widely acknowledged that the control and design of the robotic devices needs to be further optimized to be able to provide training that fits better into modern insights in neural plasticity, motor learning, and motor recovery and in doing so improves its effectiveness. We will go more deeply into the need and scientific background for improvements on active participation, task specificity, and the facilitation of different recovery mechanisms. Subsequently, we will discuss recent advances that have been made in the control and design of robotic devices to improve on these aspects. Hereby, we will focus on the robotic gait training device LOPES that has been developed within our group. We will discuss how its design and control approach should contribute to improvements on all of the aforementioned aspects. The feasibility of the chosen approach is demonstrated by experimental results in healthy subjects and chronic stroke survivors. Future clinical testing has to demonstrate whether the outcome of robot-aided gait training can indeed be improved by increasing its task specificity, by the active contribution of the patient, and by allowing different movement strategies.

Keywords

Impedance-controlled exoskeleton • Assist-as-needed • Recovery and compensation • Task specific • Stroke • Spinal cord injury

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21.1 State-of-the-Art Robot-Aided Gait Training

Robotic gait training devices have been on the market since the start of the millennium. Currently, the mechanized gait trainer (Reha-Stim, Berlin, Germany) [1], the Autoambulator (HealthSouth, USA), and the market-leading Lokomat (Hocoma AG, Volketswil, Switzerland) [2] are commercially available. In addition, different research institutes and companies are developing robotic gait trainers, among which are ALEX (Active LegEXoskeleton) [3], a combination of PAM (Pelvic Assist Manipulator) and POGO (Pneumatically Operated Gait Orthosis) [4], and LOPES (Lower Extremity Powered Exo-Skeleton) [5]. All these devices support the patients during treadmill walking. There are also developments in the design of wearable exoskeletons that can be used as assistive or therapeutic devices. The BLEEX (BerkeLEy EXoskeleton) [6], originally developed for military purposes, has been redesigned into a medical exoskeleton called eLEGS. The HAL (Hybrid Assistive Leg) [7] and ReWalk (Argo Medical Technologies, Israel) are other examples of medical wearable exoskeletons that assist during overground walking.

All these devices widely differ in their design and control. The most distinctive feature regarding the design is the number of assisted, free, or constrained degrees of freedom (DOF). Table 21.1 provides an overview of the DOFs of the aforementioned devices. Notably, all commercially available devices only assist movements in the sagittal plane and constrain all the movements out of the sagittal plane, even though these movements are natural to human gait. Regarding the control of the devices, the most distinctive feature is whether the devices control/enforce positions of the limbs or control the interaction forces between the robot and the limbs. Again, the commercially available robotic gait training stands out, as they are position controlled (the new Lokomat is impedance controlled), whereas the other devices are mostly force-controlled.

The effectiveness of robot-aided gait training has only been assessed in clinical trials using the commercially available gait trainers. The first effect studies showed fairly positive results in that training with these devices was at least as effective as manual training while the physical load on the therapists was reduced [8, 9]. Some studies even showed an increase in the number of subjects that could ambulate independently after receiving robot-aided gait training [10]. However, recently, two large randomized clinical trials, one in chronic stroke survivors [11] and one in subacute stroke survivors [12], demonstrated that walking velocity and endurance improved significantly less after robot-aided gait training compared to conventional training. Subacute stroke survivors improved their walking velocity with 71% after conventional training and only 35% after robot-aided training [12]. These latter studies clearly indicated that robot-aided gait training needs to be further optimized to improve its efficiency. Clinicians, (neuro)scientists, and engineers have put forward different ways to advance robotic gait trainers and make robot-aided gait training better fit in with new insights in neural plasticity, motor learning, and motor recovery. In short, the therapeutic benefit of robot-aided gait training might be increased by making the training more task specific, encouraging the patients to actively participate, and facilitating functional improvement by using recovery as well as compensatory strategies.

Advances on these aspects require changes in the mechanical design of the devices and in the control of these devices. The general shift from position to force control and the addition of DOFs in the research devices aim at improving on one or more of these aspects. The robotic gait training device LOPES was specifically developed to improve on all of these aspects. In the following paragraphs, we will first elaborate more on the need to improve on the different aspects to increase the efficiency of robot-aided gait training. Next, we will shortly discuss what achievements have been made in the field of robotic gait training devices, and we will describe the LOPES device into more detail and introduce its mechanical design and control. We will discuss the results that were obtained with the LOPES device and elaborate on the future perspectives.

Table 21.1 Overview of the major features of the mechanical design and control for different robotic devicesa

		Mechanized gait trainer	Lokomat	Autoambulator	ALEX	PAM/ POGO	LOPES	eLEGS	HAL	ReWalk
Mechanical design										
Type[b]		EE	EX	EX	EX	EX	EX	EX	EX	EX
Supports walking on		TR	TR	TR	TR	TR	TR	OG	OG	OG
Degrees of freedom										
Pelvis	Vertical translation	–	F	F	F	A	F	F	F	F
	Horizontal translation	–	C	C	C	A	A	F	F	F
	Rotations	C/–	C	C	C	A	C	F	F	F
Hip	Flexion/ extension	–	A	A	A	A	A	A	A	A
	Abduction/ adduction	C	C	C	C	F	A	A	F	C
	Exoration/ endoration	C	C	C	C	F	C	F	C	C
Knee	Flexion/ extension	–	A	A	A	A	A	A	A	A
Ankle	Plantar flexion/ dorsiflexion	–	F	F	F	F	F	F	F	F
Foot	Vertical translation	A	–	–	–	–	–	–	–	–
	Forward/ backward translation	A	–	–	–	–	–	–	–	–
Control		Pos	Pos/for	For	For	For	For	Pos/for	For	Pos

The device type is either an exoskeleton (*EX*) or end-effector (*EE*). The device is meant to support gait during treadmill (*TR*) or overground (*OG*) walking. The DOFs are actuated (*A*), free (*F*), or constrained (*C*). A dash (–) indicates that the DOF can be indirectly influenced by the provided assistance at the other DOFs

[a]Every year, several new devices are developed and introduced. This table does not give a complete overview of all existing devices

[b]In a pure "end-effector" robot, the interaction of the robot with the human is limited to the "end-effector" of the extremity, the foot. In exoskeleton-type robots, the robot is attached to the controlled limb at several places, and the robot moves in parallel with the segments of the limb

21.2 Background and Rationale for Advancement in Robot-Aided Training

21.2.1 Task-Specific Training Needed for Transfer of Learned Abilities to Overground Walking

Task specificity of training has been shown to be a crucial factor in facilitating functional improvement [13, 14]. Task specificity in this respect means that the trained task should closely resemble the real-world task that needs to be improved. The larger the resemblance, the larger is the likelihood that improvement during training will generalize to the daily task. The task specificity of training in the currently commercially available robotic gait training devices is questionable. This is mainly due to the fact that DOFs that are used while walking overground are constrained in these devices. Although movements in the constrained DOFs are not possible, subjects can still generate torques in those DOFs. For instance, Neckel and colleagues [15] demonstrated that chronic stroke survivors still generated considerable abduction torques during swing when they were walking in

a robotic gait trainer that constrained hip abduction movement. These abduction torques reflected that these stroke survivors actually employed a circumduction strategy, but the device was constraining this strategy. When subjects generate the same activity while walking overground, this will result in a hip abduction during swing and a completely different walking pattern. So by constraining important DOFs, learned muscle activity patterns in the device might not result in a suitable overground walking pattern, which will decrease the likelihood of transfer of the relearned abilities to overground walking.

Moreover, the therapeutic spectrum reduces when DOFs that are characteristic of (impaired) human gait are constrained. Commercial devices actuate DOFs in the sagittal plane and focus on weight bearing and making an appropriate forward step. Training of balance control is not possible as the devices impose stability by constraining pelvic movements and hip abduction/adduction. Kollen and colleagues [16] demonstrated that improvement of balance control is the most important determinant in regaining walking ability, even more important than an increase in leg strength or decrease of synergies. So including the DOFs that allow the subject to actively practice his balance control during walking makes training in a robotic device more task specific and probably has a favorable effect on the outcome of robot-aided gait training.

21.2.2 Recovery as Well as Compensation Contributes to Functional Improvement

In clinical practice, a physical therapist focuses the therapy on achieving recovery of the paretic leg or on learning compensatory strategies that overcome the limitations due to impairments in the paretic leg. Recovery can be defined as restoring the ability to perform a movement in the same manner as it was performed before injury, whereas compensation can be defined as the appearance of new motor patterns resulting from the adaptation of remaining motor elements or substitution [17]. For example, in achieving an appropriate foot clearance during swing, a decreased ability to flex the knee can be compensated for by using a hip circumduction strategy constituting of increased hip abduction and pelvic rotation. However, most robotic gait training devices limit the therapeutic spectrum, since these devices focus on recovery to gain improvements in walking ability and do not allow to train compensatory strategies The robotic devices focusing on recovery direct their support at restoring a "normal" walking pattern and furthermore do not have the appropriate DOFs to allow or train compensatory strategies.

Currently, there seems no solid scientific evidence to favor the one recovery mechanism over the other. Several recent studies have demonstrated the importance of compensation in (the improvement of) functional walking ability in stroke survivors: stroke survivors using compensatory strategies can attain similar gait speeds as stroke survivors with "normal" movement patterns [18], a limited amount of generated propulsion (coordinated output) by the paretic leg does not necessarily restrict the gait speed [19], and improvements in walking ability during recovery are not accompanied by a restoration of the paretic muscle coordination patterns [20]. An often-heard argument against the use of compensation is that, in the long run, it might impede gains in other functional tasks. In the above-mentioned example, a circumduction strategy would, in all likelihood, not positively contribute to improving stair walking, whereas a recovery of knee flexion could. There is also accumulating evidence that targeted intervention results in recovery of the paretic leg: an intervention aimed at increasing ankle function results in specific increases of ankle power and an accompanying increase in gait speed [21]. So, recovery and compensation can both contribute to functional gains observed in stroke survivors. The contribution of each mechanism in bringing about functional improvements will probably depend on the patient's impairments, their severity, and the time post-stroke.

To improve the outcome of robot-aided gait training, the devices should be directed not only at recovery but also at allowing and potentially even training compensatory strategies. This requires

that the number of assisted and free DOFs of the robotic device should be larger than the number of DOFs of the task at hand, so the device provides redundancy. Attaining enough foot clearance while making a forward step can be regarded as a task with two DOFs. Allowing and/or actuating hip flexion and knee flexion suffices to perform the task. Yet adding hip abduction results in a redundant number of DOFs and makes compensatory strategies possible.

The need to allow compensatory strategies also has consequences for the control of robotic gait trainers. The control of the robot should allow the patient with sufficient freedom in how to move. This implies that we cannot define subject-independent reference trajectories for each DOF. Instead, these reference trajectories should be subject-dependent or should be defined in a coordinate system that allows the subject to choose his own strategy.

21.2.3 Active Training Required to Induce Cortical Plasticity

In the first instance, robotic gait training devices were developed for spinal cord–injured subjects and were designed to provide the spinal cord with the appropriate sensory information by imposing a normal walking pattern upon the subject. The legs were moved according to this pattern whether the patient was active or passive, and consequently, patients were not encouraged to actively participate. This approach was built upon scientific evidence from animal models that locomotor activity can be evoked by appropriately timed sensory information [22]. This information would drive central pattern generators, which are an ensemble of spinal cord neural networks that can generate basic rhythmical motor patterns involved in walking. Although similar central pattern generators likely exist in humans, there is growing evidence that the bipedal nature of human walking requires an important contribution of supraspinal structures in controlling walking. This evidence could be gathered through advances in brain imaging and electrophysiological techniques that allowed investigation of supraspinal control of walking. Miyai and colleagues [23] measured the brain activity of healthy subjects during gait and showed that the medial sensorimotor cortices and the supplementary motor cortical areas were involved in the control of walking.

The supraspinal involvement in the control of walking implies that brain plasticity can contribute to improvements of walking ability, which has major consequences for the design of (robot-aided) gait training. Indeed, several studies using different technologies showed that changes at a cortical level and also on subcortical level correlated with locomotor recovery in stroke survivors [24–26]. Also, in spinal cord injury, subject brain plasticity contributes to locomotor recovery. After 3–5 months of treadmill training, SCI subjects showed an increase in evoked muscle responses from TMS to the leg area of the motor cortex that were related to locomotor recovery and could not be explained by increased spinal excitability [27].

The process underlying this brain plasticity/reorganization is driven by self-generated activity, which stresses the need of a subject to actively participate in the training and not being passive. The importance of self-generated activity over passive guidance was emphasized in a study by Lotze and colleagues [28] in healthy subjects. They showed that a training period consisting of voluntary induced (active) wrist movements resulted in larger performance improvement and cortical reorganization than passively induced movements. These results were later replicated for the lower extremities by Perez and colleagues [29], who also showed that not just repetitively performing a movement induces cortical plasticity but that the generated activity should be part of a skill. They compared the changes in corticomotor excitability in subjects who received skill training consisting of a pursuit tracking task by performing ankle plantarflexion and dorsiflexion, passive training in which subjects were assisted in the pursuit tracking task, or nonskill training consisting of just voluntary performing plantarflexion and dorsiflexion. Only subjects receiving the skill training showed an increase in cortical excitability that was accompanied by an improved performance.

These studies show that neurological patients should be encouraged to actively contribute in robot-aided gait training (and not to rely on the robot) in order to facilitate plasticity-induced improvements in walking ability. The tasks given during training should be clearly related to the skills that are important in walking, like balancing and foot placement. Additionally, the patients should not only be promoted to actively participate, but they should also be allowed to experience errors in the task execution as in the end task execution errors drive motor learning [30].

21.3 Mechanical Design of LOPES

Robotic gait training devices differ widely in their (actuated) DOFs and how they are controlled (see Table 21.1). The choice of which DOFs to restrain, actuate, or let free depends on the underlying view on neurorehabilitation and on the nature and control of human walking. Arguments can be given for more DOFs, but these are balanced by the consequence that the device will be more complex and expensive. At this moment, there is no solid evidence which DOFs to actuate or not since no comparative studies have been performed between devices with different DOFs. In the next paragraphs, we will provide the arguments for the chosen DOFs of LOPES.

The DOFs of LOPES and how they are actuated (see Table 21.1 and Fig. 21.1) are chosen in such a way that they allow unhindered walking in the device (transparent mode), allow the use of compensatory strategies and to selectively support the essential aspects of walking. A prerequisite for selective support is that the device itself is transparent. The transparent mode is needed at the end of the training program, when the subject only requires little support, since the device should resemble normal walking as close as possible to facilitate the transfer of the learned abilities to overground walking. Another argument for the importance of this transparent mode is that in hemiparetic gait, only the affected leg needs support while the unaffected leg should be able to move freely. We will first exemplify the choice of the DOFs in the light of the requirement that the essential aspects of gait should be selectively and partially supported.

Fig. 21.1 Subject attached in the first prototype of the LOPES device. The eight actuated DOFs are schematically indicated

When determining the essential aspects that need to be supported, we paid great attention to the inherently unstable dynamics of walking. Walking can be considered as controlled falling in a desired direction. The lateral and forward foot placement is used to stabilize gait and control balance [31, 32]. Therefore, hip flexion/extension and hip abduction/adduction are actuated. Also, horizontal pelvis motions are actuated as constraining or reducing pelvis motion would externally stabilize gait. Different studies have shown that constraining pelvis movements affects foot placement and increases trunk motion [33, 34]. Other essential aspects that need to be supported are foot clearance during swing and

weight bearing during stance, which require actuation of knee flexion/extension. Also, the propulsion is an important aspect of gait. Hip extension during initial stance contributes to propulsion [35], but the main contributor is plantar flexion at the ankle. Still, we decided not to actuate the ankle to reduce mass and complexity of the device. Different actuated orthoses have been developed to specifically support the ankle during gait [36, 37]. Future clinical testing with these devices has to show the additional value of incorporating ankle plantar flexion.

The DOFs needed to support the essential subtask also suffice in meeting the other abovementioned requirements. The inclusion of the hip abduction/adduction degree of freedom allows for using one of the most often used compensatory strategies, the hip circumduction. The total set of DOFs allows all major movements of gait to be made with the device, so walking with the device can resemble walking outside the device as long as the dynamics of the exoskeleton does not influence walking with the device too much.

Another important requirement for the mechanical design of LOPES is related to the dynamics of the exoskeleton. For LOPES, and generally for force-controlled devices, it is important to minimize the inertia of the device since control algorithms can only partly compensate for the inertia. Therefore, we build a lightweight exoskeleton that has the heavy motors and gearing detached from the exoskeleton. Newly designed Bowden-cable-driven series elastic actuators are used to transmit the mechanical power of the motors via Bowden cables to the actuated joints [38]. This actuation also resulted in the required high torque control bandwidth that is needed for impedance-controlled devices. The torque control bandwidth of LOPES is 16 Hz [39].

21.4 Control of LOPES

The control of robotic devices greatly determines whether patients are encouraged to actively participate in the training but also whether patients are allowed to use alternative movement strategies. The first generation of robotic gait training devices mainly used position control to move the patient's legs through a prescribed gait pattern, irrespective of the patient's self-generated activity, and not allowing the patient to use compensatory strategies. To increase the active participation, more and more robotic devices control the interaction forces by using impedance or admittance control algorithms. Mostly, reference position trajectories are still used in this approach to determine the amount of force to apply. The control of interaction forces brings along new challenges, as how and when to support the patient, and to decide how large the amount of support should be.

By controlling the interaction forces, the amount of support can be adapted to the patient's needs and abilities: the robot can still be very stiff and practically enforce a gait pattern when the patient is not capable of generating any appropriate activity, can be very compliant and move with the patient when the patient is generating the appropriate movement, and everything in between. One of the biggest challenges is how to determine the appropriate amount of support for each specific patient. Different algorithms have been developed to automate this process. Emken and colleagues [40, 41] developed and evaluated an error-based algorithm with a forgetting factor based on motor adaptation experiments in healthy subjects. One term in this assist-as-needed algorithm increases the support when deviations from the reference trajectories become larger, whereas a second term gradually reduces the support from step to step. The resulting support is the equilibrium between these two terms. They showed that the support was shaped to the patient's specific needs. An appropriate choice of the parameters of this algorithm would not only assure automatic adaptation of the support but would also prevent reliance on the robotic support to occur. Hitherto, this latter aspect has only been shown in experiments with healthy subjects and in simulation studies and not in experiments with neurological patient.

Another challenge is in the timing of the robotic support. When using reference trajectories, these trajectories should be synchronized with the movements of the subjects. Lowering the stiffness/impedance increases the likelihood

that the reference and actual movement are not in phase. This phase difference can grow rapidly over different steps and turns the robot's supportive forces into uncomfortable and unwanted perturbations. Different algorithms have been proposed and evaluated to synchronize the robot's actions with the actual movements. Aoyagi and colleagues [4] proposed and demonstrated the appropriate working of an algorithm that continuously adapts the "replay" speed of the reference trajectory to minimize the difference between the timing of reference pattern and the patient's movements. Duschau-Wicke and colleagues [42] proposed a method in which variation in timing is allowed within a specified time window. When the timing error exceeds the window, the robot will apply additional torques to slow down or speed up the movements of the patient.

The control approach is also important in allowing or even training alternative movement strategies, given that the used robotic device provides redundancy in the DOFs. Most robotic devices are controlled at a joint level, and reference patterns are also defined at a joint level. This complicates the definition of reference patterns for alternative movement strategies. Although compensatory strategies can be classified into a limited number of widely used strategies, there still is considerable variation between patients within a "class," as the actual strategy is highly dependent on the patient's impairments. As such, it is hard to define appropriate reference patterns that can be generally used but also to define subject-specific patterns. Still, the latter can be done by using a teach-and-replay approach [4]. In this approach, the robot is first controlled in such a way that it does not actively assist the movement. The necessary guidance is provided by a physical therapist who moves the leg through the desired pattern, and the robot records these movements. Subsequently, this recorded trajectory is used as a reference to what amounts to an endless repetition of the therapist's actions.

For LOPES, we developed and applied an alternative approach to tackle the previously described challenges. The core of this approach is that we divide human gait in different subtasks, and the performance on each of these subtasks is evaluated and controlled separately. These subtasks are: attaining sufficient foot clearance during swing, making a forward step, weight bearing, weight shifting, stance preparation, and balance control. This approach is called selective subtask control. Each subtask is controlled in parallel by using virtual models, like virtual springs and dampers, which are defined between the actual performance and the defined reference on the concerned subtask. The forces in these virtual models are transformed into the required robotic joint torques which are exerted by LOPES on the human limb. Recent simulation and experimental studies [43, 44] have provided evidence that humans also control walking in a modular approach as the muscle activity during walking can be decomposed in different modules associated with different subtasks.

In our approach, the amount of support can be adapted to the patient's needs in two different steps (see Fig. 21.2). First, the therapist selects the subtasks, which are impaired in the subject, to be controlled by LOPES [45]. Second, the amount of support in each of the controlled subtasks is adapted to the patient's needs by using an adaptive algorithm. In this way, patients are supported as much as necessary on the impaired aspects of gait while they have to generate all the activity for the unimpaired aspects by themselves [46]. Synchronization problems are prevented because the support is gait phase dependent. This means that a specific subtask is only controlled during the phases in which the subtask should be performed (see Fig. 21.2), and the control is actually reset for every gait cycle. The control on a subtask level also leaves room for compensatory strategies. Subjects can use different strategies to accomplish a certain subtask as the reference pattern is not defined on a joint level but on a subtask level. For instance, the patient can use a hip circumduction strategy instead of regular knee flexion to get enough foot clearance. If by using this strategy the patient indeed succeeds in attaining appropriate foot clearance, no support will be provided. If not, the support can either be directed at improving knee flexion or at using a compensatory strategy.

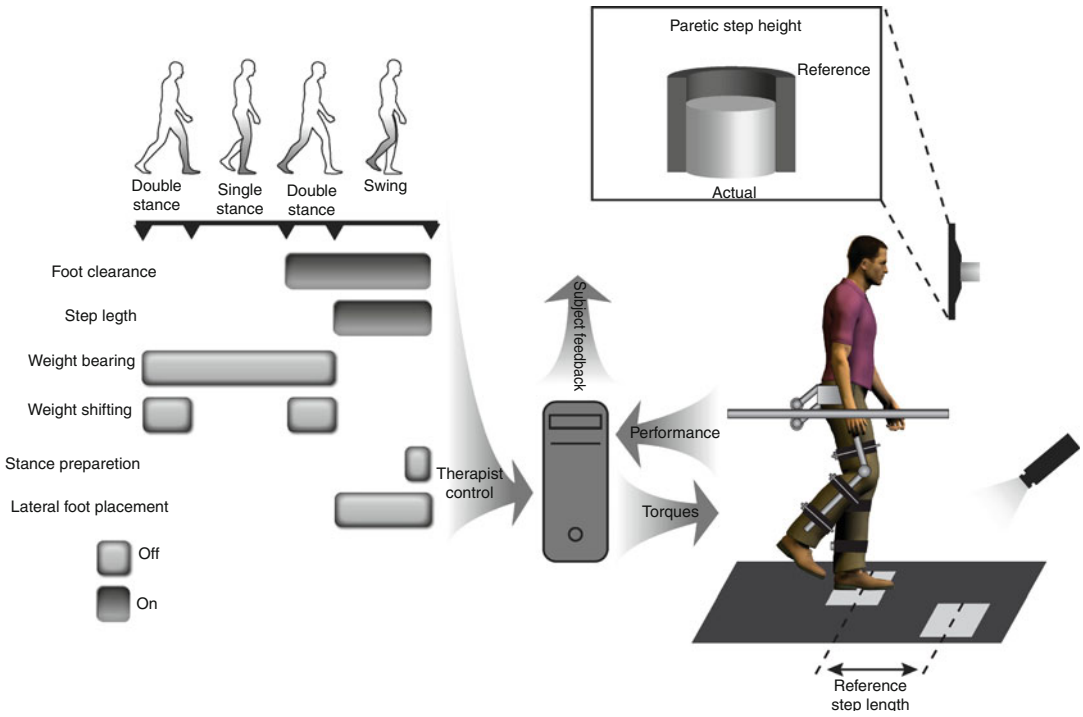

Fig. 21.2 Schematic overview of the used approach to selectively support different subtasks of gait with LOPES. This control allows for an intuitive control for the patient and therapist. The therapist decides on which aspects of gait the patient needs support. Based on this selection, the implemented control algorithms calculate the required supportive torques. The level of support is automatically adapted to minimize the robotic support and maximize the patient's participation by using an assist-as-needed algorithm. The reference or target values for each subtask are displayed on a screen in front of the patient or on the treadmill (by using a beamer). To stimulate the active participation of the patient its actual performance on each subtask can also be displayed

Another advantage of using selective control of subtasks is that it allows to provide intuitive feedback about the performance on each of the subtasks to the subject and therapist and that target values on each of the subtasks can be presented to the subject (see Fig. 21.2). Our experience is that setting the targets and providing feedback on gait parameters like step length and height are easier to interpret for patients as well as therapists than feedback in terms of joint angles or torques.

21.5 Experience with and Feasibility of LOPES

Only providing assistance as the patient needs it, not only requires that the robot is able to provide the necessary assistance but also that the robot does not hinder the motion of the subject when no assistance is required. As a first step in implementing LOPES into gait training, we evaluated this latter requirement by comparing the gait parameters, kinematics, and muscle activity of ten healthy subjects while walking with LOPES attached to their pelvis and limbs and while walking freely on a treadmill [47]. In this study, LOPES was controlled to provide no assistance (transparent mode). Overall, the patterns of the joint and segment movements and those of muscle activity while walking with LOPES resembled those of free walking. However, various changes did occur, which could be mainly ascribed to the mere fact that the attached exoskeleton added inertia to the subject's legs which needed to be accelerated and decelerated by the subject. Muscles involved in accelerating the leg during initial swing, like the rectus femoris, and

muscles involved in decelerating the leg during terminal swing, like the biceps femoris, both showed an increase in activity (see Fig. 21.3). In addition, the added inertia resulted in a decreased knee flexion during swing which on its turn likely induced the increase in tibialis anterior activity to achieve appropriate foot clearance. Apart from the inertia of the exoskeleton legs, the subject experienced some resistance in moving the pelvis, which caused a significant increase in the frontal trunk rotations. All in all, the results were satisfactory in that the walking pattern with the device was similar to the normal walking pattern. However, they do show the importance of reducing the inertia of the exoskeleton or developing algorithms to compensate for it when one wants to achieve unhindered walking in a robotic device.

In a subsequent study, we determined whether ambulatory chronic stroke survivors were able to make use of the DOFs of the device. The included stroke survivors had a decreased amount of knee flexion during the swing phase, which is an often-reported gait abnormality in stroke survivors and is also referred to as stiff knee gait. They walked with LOPES when again it was controlled to provide no assistance, so they were not forced to a certain pattern and were free to adopt their own walking pattern. When walking in LOPES, subjects indeed showed a marked lower knee flexion range in the paretic leg compared to the nonparetic leg (see Fig. 21.4). Most subjects compensated for this by using a hip circumduction strategy which was reflected in the large amount of hip abduction during swing. There seemed to be a trend in that the lower the knee flexion range, the larger is the amount of hip abduction. Subjects using a hip circumduction strategy in LOPES also used this strategy while walking overground. These results demonstrate that subjects can use their own movement strategy in the device and that they experience the result of their self-generated activity.

The feasibility of the selective support of subtasks has been demonstrated in experiments with healthy subjects for several subtasks, among which are attaining sufficient foot clearance, making a (larger) step, and weight bearing. In these experiments, subjects walked with LOPES, and the support on a specific subtask or combination of subtasks was switched on during selected steps, whereas during the other steps and on the other subtasks, no support was provided. In general, the feasibility was assessed by determining how well the set reference values were attained and how the support affected the remaining of the walking pattern. For the step height and step length, the reference values were set at a 15% increase with respect to their normal values. The support of step height resulted in an increase of the step height that was caused by an increase of the knee flexion during swing (see Fig. 21.5). The use of a stiff virtual spring in the controller resulted in a significant closer approach of the reference value compared to using a compliant spring. This support was selective in that it did not affect the other basic gait parameters like step length or cycle time. The support of step length resulted in a less selective effect as not only the step length showed a significant increase but also the step height showed a significant decrease. The accompanying decrease in step height could be explained from the exerted robotic torques to increase the step length, as to increase the step length, the robot exerted hip and knee extension torques. The support of step length also showed to be less dependent on the used virtual stiffness. When the support of step length was combined with the support of step height, the effects of the separate support algorithms were combined, and the increase in step length was accompanied by an increase in step height.

Weight bearing during stance can also be considered as a subtask of walking. Using a robotic gait trainer to support weight bearing might have considerable advantages over typical overhead suspension systems. These latter systems are often used in gait training to provide the patients with the required amount of body weight support, but do have some disadvantages. Over the last years, different studies [48, 49] have demonstrated that this form of body weight support considerably influences the spatial, temporal, and kinematic gait parameters in healthy subjects. Although some more advanced systems [50] allow the modulation of the amount of support

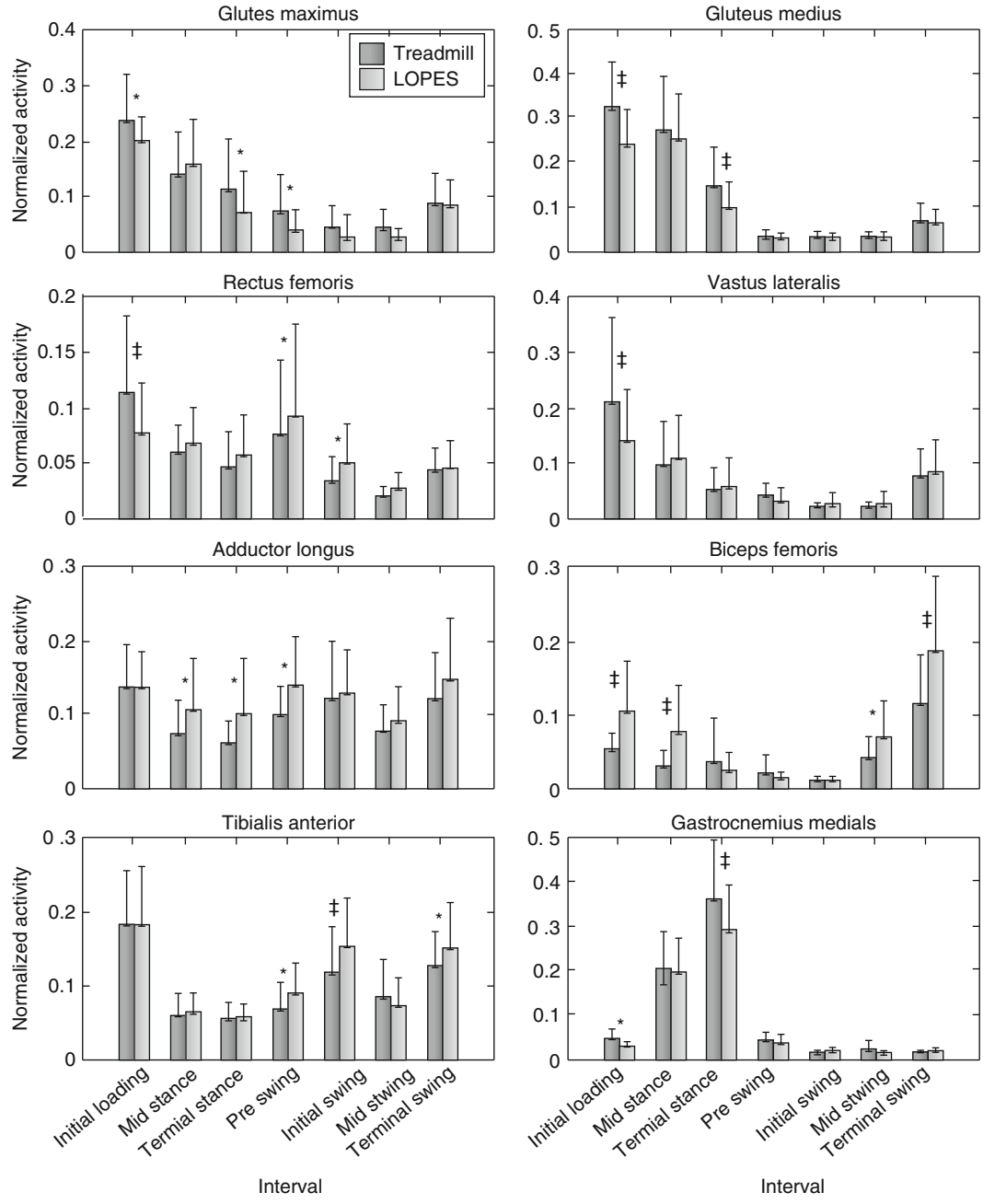

Fig. 21.3 Muscle activity of healthy subjects walking in LOPES when it is controlled to provide no assistance. Mean normalized integrated activity for eight leg muscles over seven gait intervals for LOPES walking and treadmill walking. The *vertical bars* indicate the standard deviation over the different subjects. Significant differences between LOPES walking and treadmill walking are indicated with an * for $p<0.05$ and with a ‡ for $p<0.001$ (Reprinted from van Asseldonk et al. [47]; with permission. © 2008 IEEE)

between the different legs, most systems support an equal amount of body weight support during stance of both legs, whereas hemiplegic subjects only need the support during the stance phase of the affected leg. Additionally, typical systems do not provide a force in the pure vertical direction

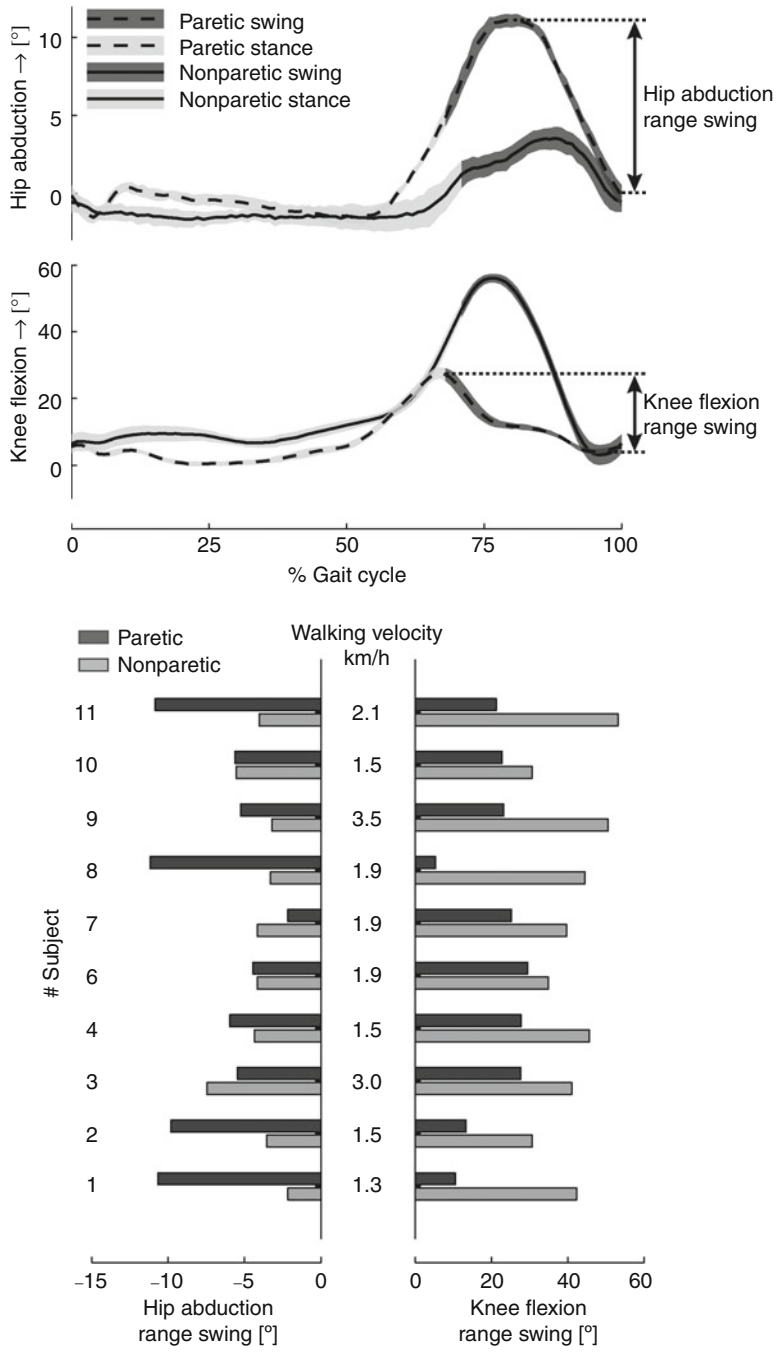

Fig. 21.4 Compensatory strategies of chronic stroke survivors walking with LOPES. The *upper graphs* show averaged trajectories of hip abduction/adduction and knee flexion/extension of a typical chronic stroke survivor (subject 11) walking with LOPES, which is controlled to provide no assistance. The *shaded areas* indicate the standard deviation. The *lower graphs* show averaged ranges of hip abduction and knee flexion during the swing phase of ten ambulatory, chronic stroke survivors with stiff knee gait walking in LOPES

but also in the horizontal plane that helps subjects to maintain their balance. This implies that the amount of support on weight bearing and balance control cannot be independently varied, whereas the amount of impairment on each of these tasks varies widely within and between subjects.

The aforementioned disadvantages can be overcome by using a robotic exoskeleton. We have assessed the feasibility of a control algorithm to support the subject in weight bearing by exerting torques on the joints to overcome the gravitational torques and to prevent knee buckling [51]. This

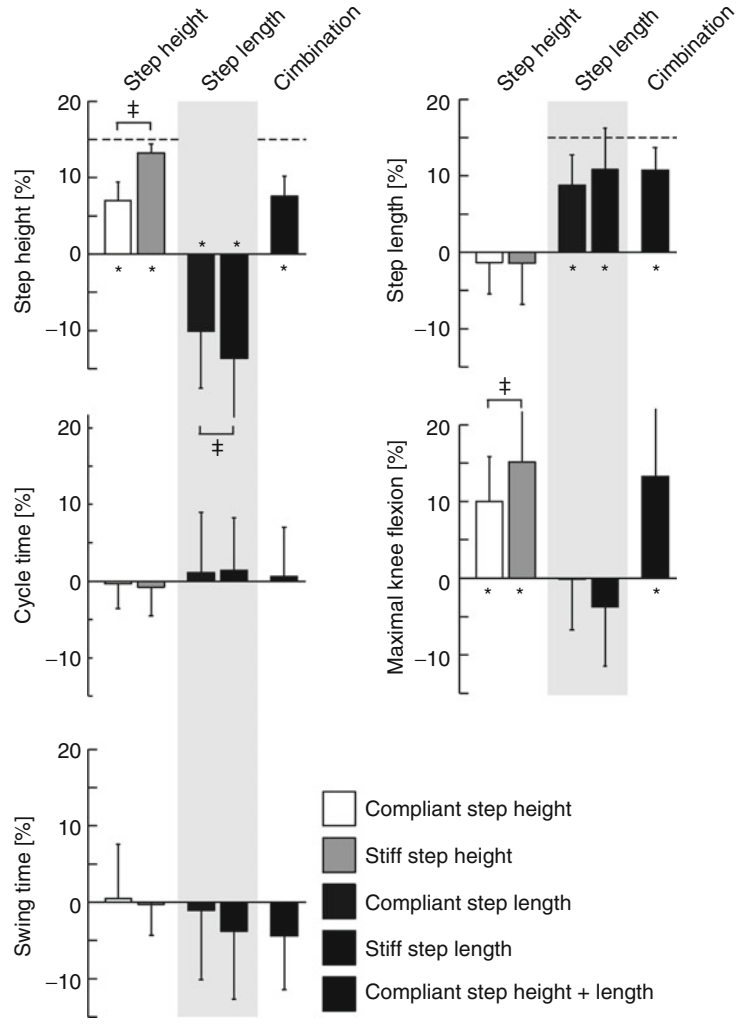

Fig. 21.5 Effects of exposure to selective subtask control on different spatiotemporal gait parameters. The *bars* indicate relative average (across six subjects) changes in gait parameters with respect to a baseline measurement. The *vertical lines* indicate the standard deviation. Subjects were being exposed to selective control of step height with a compliant (600 N/m) and stiff (1,200 N/m) virtual spring, selective control of step length with a compliant (400 N/m) and stiff (800 N/m) virtual spring, and a combination of the step height and step length support with compliant springs. The reference values during support were set to 115% of the baseline values. An * indicates significant difference with zero (the value is changed due to the support), and a ‡ indicates a significant difference between the compliant and stiff condition. The *dashed gray horizontal lines* indicate the set reference values

algorithm allows for independent control of weight support during stance of the different legs and does not interfere with balance control. Results showed that the algorithm was effectively supporting weight during loading as the muscle activity of important knee extensors decreased, whereas the pattern and range of angular movements resembled those of walking without the support.

All in all, these results showed that the different aspects of gait can be supported separately but not always selectively. A combination of selective controllers can be used to provide support on multiple aspects or to provide support on one aspect and set a boundary condition on another aspect. By selecting subtasks which require support, the robotic assistance can be adapted to the capabilities of a subject. However, also within a subtask, the amount of support needs to be adapted to fit the needs of the patient. The support should be such that large errors are prevented and safe walking is guaranteed and such that small errors and variation over steps are allowed.

To adapt the support within a subtask, we incorporated the error-driven adaptation algorithm of Emken and colleagues [41] in the selective control of step height [46]. The resulting algorithm modified the virtual spring stiffness at each percentage of the gait cycle based on the experienced error in the previous steps. We evaluated this algorithm in ambulatory chronic stroke survivors. These stroke survivors did not need the

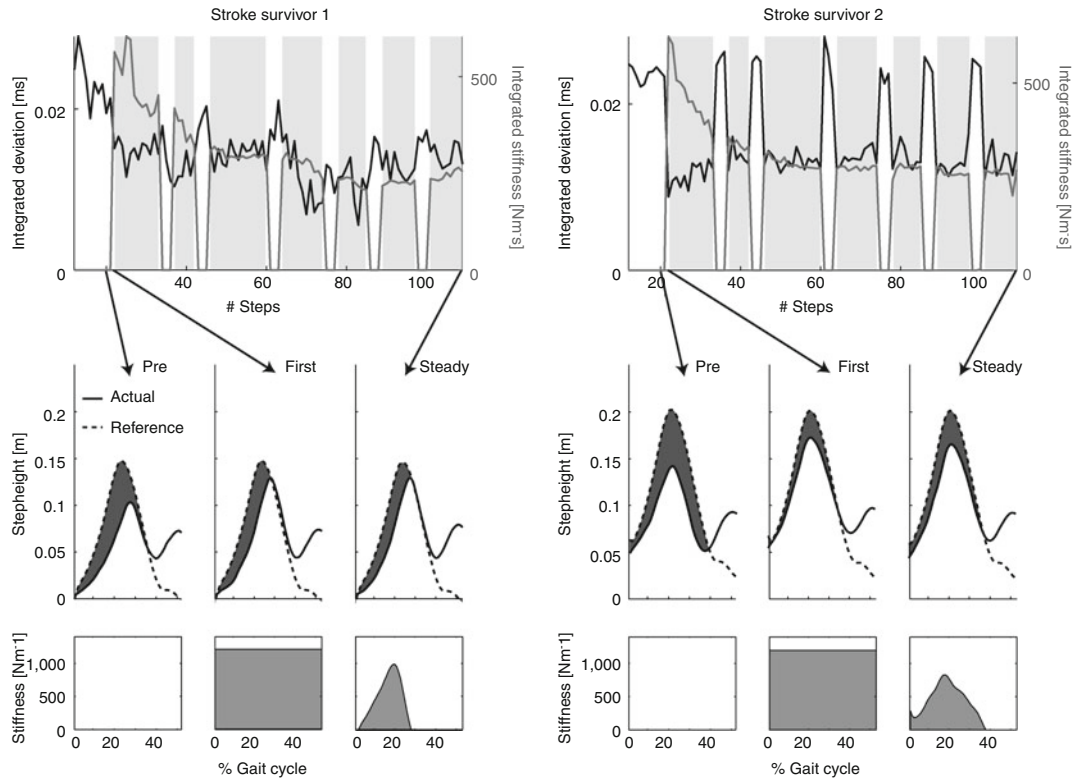

Fig. 21.6 Shaping of the virtual stiffness of the step height controller in two ambulatory chronic stroke survivors. The *left* and *right* set of graphs shows the responses for two different chronic stroke survivors. The *upper row* shows the course of the deviation from the reference (*light gray line* and *axis*) and the stiffness (*dark gray line* and *axis*) over multiple steps in a walking trial. The support is turned on after 20 steps and turned off for three steps after random intervals. The *shaded vertical bars* indicate the periods in which the support was turned on. The measures for the error and stiffness are obtained by integrating the *shaded area* indicated in the middle and lower row of graphs over time for each separate step. These graphs show the actual and reference ankle height (*middle row*) and virtual stiffness (*lower row*) as a function of the gait cycle for the step preceding the first exposure (stiffness is zero), for the first step of exposure (stiffness is constant, no shaping), and for a step when subjects walked for 70 steps with the support

robotic support to walk; the provided support was purely aimed at increasing their foot clearance. The results showed that the combined algorithm was effective in adapting the amount of support to each subject's capabilities (see Fig. 21.6). The profile of the virtual spring stiffness (stiffness versus percentage of the gait cycle) and the exerted robotic support were shaped to the initial deviation of the actual ankle trajectory from the reference trajectory.

Interestingly, subjects responded quite differently to the provided support, which stood out clearly by making use of "catch steps." In these steps, the subjects were not receiving any support, and these trials were randomly interspersed among the steps with support. Some subjects (see subject on the right in Fig. 21.6) did not take over the robotic support by improving their walking pattern. In these subjects, during the catch trials, the deviation of the step height from the reference increased to presupport values. Still, the subjects did not rely on the support, since the deviation did not increase above the presupport values. Other subjects utilized the robotic support (see subject on the left in Fig. 21.6) to improve their own performance. In these subjects, the integrated error during the catch trials decreased in comparison to the presupport errors (see for instance catch trial around step 73). In short, the adaptive algorithm automatically adjusts the amount of support to

the capabilities and the actual performance of the subject for the specific subtask; this reduces the need for the therapist to set the amount of the support on a trial and error basis. However, currently, the used parameters in the adaptive algorithm are not set specific to the subject, which would also decrease the chances of reliance on the support. The identification of the appropriate parameters is very cumbersome in neurological patients, and new methods need to be developed to make this identification possible.

The next step in the development of LOPES was to perform a first explorative training study in a small group of ambulatory chronic neurological patients. Five chronic stroke survivors whose gaits were characterized as stiff knee gait participated in a 6-week training program. During the training, the subjects received support using the previously described adaptive support of step height. The provided support was directed at facilitating recovery of function in the paretic leg. All subjects showed a marked increase in walking velocity during training. Yet, there was only limited transfer of this gain to overground walking (see Fig. 21.7). A larger gain in speed during training compared to overground walking has also been reported for body weight support training [35]. Still, the limited transfer might also indicate that walking in LOPES does not yet resemble overground walking enough. During training, subjects were stabilized as they were holding the side bars, and the dynamics of the device provides some stabilization, whereas during overground walking, this kind of stabilization is not provided. In two of the five subjects, the training resulted in a considerable increase in knee flexion during swing (5° or larger) in overground walking. Whether a subject showed an improvement in knee flexion or not was not clearly related to the walking ability at the start of the training or clinical measures of motor functioning like the leg portion of the Fugl-Meyer. The small number of patients included and the variation in effect between subjects do not allow drawing firm conclusion about the added value of the selective robotic support on promoting recovery of function. Still, as changes in overground walking velocity were rather small, and only two subjects showed an increase in knee flexion, we could argue that it might be more efficient in some chronic stroke survivors to direct the provided support on the use of compensatory strategies instead of on recovery of knee function to improve walking velocity.

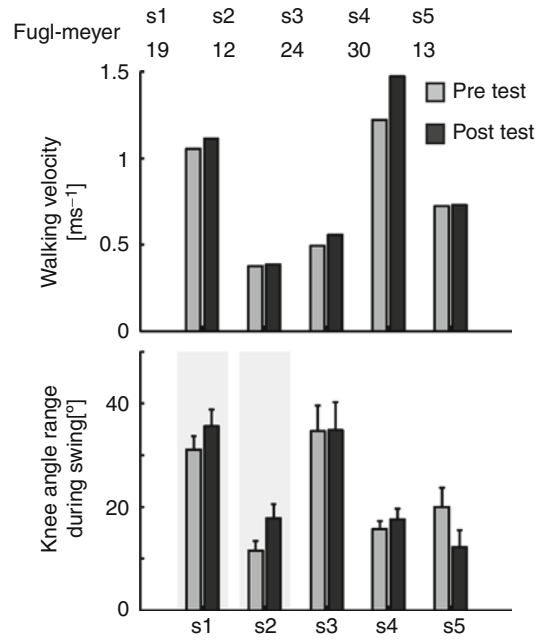

Fig. 21.7 Effect of training with selective support of step height on overground walking velocity and knee angular movement in chronic ambulatory stroke survivors. *Vertical bars* indicate the standard deviation. Subject s5 experienced a serious fall in a home situation during the training period but was able to complete the training

21.6 Current Developments and Ongoing Testing

From the results we obtained so far with LOPES, it can be concluded that the walking pattern while walking with LOPES in the transparent mode resembled overground walking, that patients utilize the redundant DOFs to make use of compensatory strategies, that the support on the level of subtasks is feasible, and that the amount of support can automatically be adapted to the specific needs of the patients.

These results are encouraging; however, LOPES is still under development, and different aspects need further improvement, and new features need

to be developed. First, the mechanical design and control of LOPES should be improved to provide less unwanted stabilization. The external stabilization provided by LOPES can largely explain the observed differences between overground walking and walking in LOPES and the limited transfer of the improvement in speed during training to overground walking as observed in the clinical trial. Second, we will extend, refine, and test the controllers to provide selective subtask control. We will pay special attention to controllers that provide support in balance. Third, we are developing feedforward controllers. Currently, the provided support is realized with feedback controllers, but these do not suffice for severely affected patients. Fourth, the observed difference in responses between patients to the currently implemented adaptive algorithm suggests that further optimization and individualization of these adaptive algorithms and their parameters is needed.

Effect studies in (sub)acute patients have to prove that selective support of intuitive subtasks according to the minimal robotic intervention principle indeed increases the active participation of patients and results in functional improvements that are at least as large as those obtained with conventional training. To perform these effect studies, LOPES is now being redesigned to make it suitable and available for rehabilitation clinics.

21.7 Perspectives

The application of robots in gait training is a relatively new development. Randomized clinical trials showed that conventional therapy outperforms the first generation of robotic devices. Recent insights and developments resulted in new devices and modifications of existing devices that overcome some of the limitations of the first generation of robotic gait trainers. In designing and controlling robotic devices, choices have to be made. We made these choices to improve on the task specificity, active participation, and facilitating different recovery process, whereas other researchers and companies might want to improve the training on other aspects. Clinical trials need to prove that the next generation of robotic gait training devices results in larger functional improvements and/or faster improvements. Comparison of the outcome of the clinical trials with the different devices should provide us with insight in which training aspects are the key elements in facilitating functional improvement.

In the end, robot-aided training should be tailored to each patient's specific impairments, capacities, and prognosis. This requires objective and quantitative measures of the impairments and capacities. The unique features of robotic gait training devices can be used to obtain (some of) the measures. So, robotic gait training devices can be used not only to apply the training but also to predict whether the training will be effective and what the content of the training should be.

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Robotic Devices for Overground Gait and Balance Training

22

Joseph M. Hidler and David A. Brown

Abstract

In recent years, we have seen the emergence of robotic technologies that focus on assisting individuals during overground gait and balance therapy following neurological injury and diseases. These devices range in complexity, depending on the type of assistance they provide. For example, at the single joint level, exoskeletons are now being used to supplement limb propulsion as a means of compensating for weakness and poor coordination. At the whole-body level, active body-weight support systems are being used to enhance postural stability as well as compensate for bilateral weakness during gait and balance training.

One of the key aspects of using robots that support overground gait and balance training is that they allow individuals the ability to practice the types of activities they will need to be competent in before returning to their home and into the community. The ability to walk overground, practice standing up and sitting down, and other functional tasks are critical components of achieving functional independence yet are often difficult to safely practice for patients with significant levels of impairment. Not only

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is the patient at risk for injury but so too is the therapist. The integration of robotic technologies into neurorehabilitation can play a critical role in the safe and effective delivery of gait and balance therapy.

The focus of this chapter is to present some of the newest robotic technologies that support overground gait and balance training, discuss the potential advantages and disadvantages of each, and provide a framework for how each may be useful in the clinical setting. Since the area of rehabilitation robotics is quickly expanding with many devices being developed in laboratories around the world, it is not possible for us to detail every technology. Instead, we will highlight a few of the devices and use them for providing a rationale for their usefulness in neurorehabilitation.

Keywords
Robotics • Rehabilitation • Gait • Waling • Stroke • Spinal cord injury

22.1 Lower Extremity Exoskeletons

22.1.1 Ankle Robotic Technologies

Following neurological injuries such as stroke and traumatic brain injury, individuals often experience significant weakness and the loss of coordination in their lower extremities which leads to compromised walking ability and increased risks for falls [1–3] (see [4] for a review). Of particular interest in the lower extremities is the ankle, since ankle moments make up nearly 40% of the total positive work generated in gait [5]. Compensating for ankle weakness could potentially increase limb propulsion and consequently improve walking ability.

One therapeutic approach to ameliorating ankle impairments is by using an ankle robot. For example, the AnkleBOT, developed by Krebs and colleagues at MIT [6], is a 2-degree-of-freedom robot that actuates the ankle in both flexion and extension as well as inversion–eversion. The device, as shown in Fig. 22.1, weighs 3.6 kg and is mounted to a knee brace connected to the distal thigh and proximal shank. Moving the weight of the device higher on the individual's leg helps to reduce the inertial effects of moving the device through swing. The AnkleBOT is capable of generating 23 Nm of torque in flexion–extension and 15 Nm of torque in inversion–eversion. The device is programmed to only provide active assistance to the individual if they deviate too far from a reference trajectory, often derived from individuals with no gait disorders. As long as the user remains near this trajectory, the robot provides no assistance. However, as the user moves further away from this trajectory, the magnitude of assistance the AnkleBOT provides will increase.

Preliminary studies with the AnkleBOT have sought to determine whether the added inertia and friction of the device would negatively influence gait parameters (e.g., step length, cadence), interlimb symmetry, and lower extremity joint kinematics in subjects with lower extremity impairments [7]. Ten chronic stroke survivors walked overground and on a treadmill without any assistive devices and with the AnkleBOT turned off. It was found that when subjects walked with the AnkleBOT, there were no significant changes in spatiotemporal gait parameters or interlimb symmetry; however, the presence of the robot did decrease the nonparetic knee peak flexion on the treadmill and paretic peak dorsiflexion overground. While the presence of the AnkleBOT did not appear to adversely influence the gait patterns of the subjects tested in this study, it should be noted that the authors did not report on the impairment level of the participants in their study. Further testing is necessary to determine if all subjects, including those with significant impairments, can tolerate the added inertia and friction of the device. To date, there are no clinical studies examining the effects of overground gait

Fig. 22.1 AnkleBOT robot provides subjects active assistance in flexion–extension and inversion–eversion as they walk overground or on a treadmill

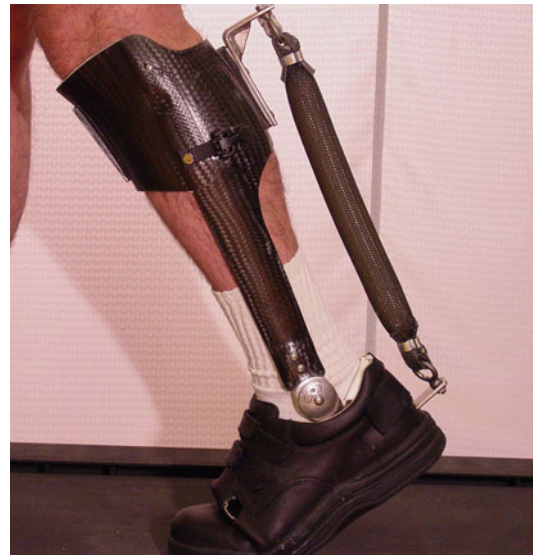

Fig. 22.2 Pneumatically actuated ankle device being tested to assist with limb propulsion [9]

training with the AnkleBOT, only in seated position [8]. There, a sample of convenience of eight chronic stroke patients trained for 6 weeks, three times per week, with a visually evoked and guided video game. This uncontrolled study demonstrated changes of 20% in self-selected gait speed and other spatiotemporal gait parameters, suggesting that there is potential to employ this kind of device even in a non-task-specific training, provided proper attention is paid to the concepts of motor leaning.

Ferris and colleagues are testing a similar ankle robot [9, 10], however with a few notable differences. Unlike the AnkleBOT, which uses electromechanical actuators, this device uses a pneumatic actuator to provide ankle flexion and extension torque during the gait cycle (Fig. 22.2) [11]. Pneumatic actuators are extremely lightweight, so the additional inertia felt by the subject is low compared to electromechanical actuators, particularly during the swing phase of the gait cycle. This could be extremely important in individuals who have significant weakness and poor postural control. The pneumatic actuators are mounted to a carbon fiber shell that pivots through a metal-hinged joint at the ankle. The device is capable of generating approximately 60–70% of the plantar flexor work done during normal walking [9].

The other key difference in the ankle robot being tested by Ferris and colleagues compared to the AnkleBOT is in the control strategy. As described above, the AnkleBOT utilizes a reference trajectory to establish the amount of assistance the subject receives. Ferris's device has been tested under myoelectric control (i.e., the magnitude of orthosis torque is nonlinearly related to the electromyography amplitude), foot-switch control, and push-button control. Each of these approaches puts the user in more control of the robot rather than relying on a predetermined control paradigm. Preliminary studies of these different control strategies indicate that myoelectric control was more successful in controlling the orthosis torque than using foot-switch control [12].

To date, no clinical studies have been reported on the effectiveness of using the pneumatically actuated ankle device in improving walking

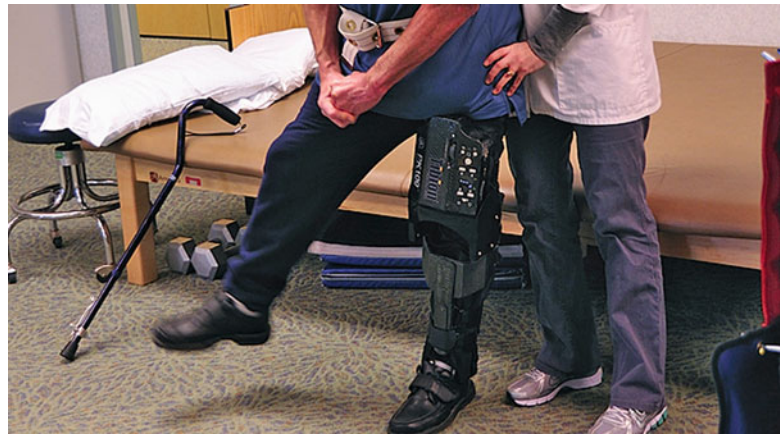

Fig. 22.3 Tibion robotic system applied to the knee of a patient with left leg hemiplegia

ability and lower extremity function in individuals with neurological injuries. While most studies with this device have taken place during treadmill ambulation, it is possible to extend training to overground with proposed management of the air supply to the pneumatic actuator.

22.1.1.1 Possible Limitations with Ankle Robotic Devices

There are a number of possible limitations with incorporating ankle robots into overground gait and balance training. The first and perhaps most obvious is the weight of these devices. Strapping a 5–10 lb weight onto the distal part of the leg of a patient with significant hemiparesis may limit the users of such devices to higher functioning patients who may not benefit from such technology. While these devices are capable of providing additional limb propulsion, this assistance may be negated by the weight of the units. Another possible limitation of ankle exoskeletons is that they are tethered to either a power supply or air supply, making them impractical for long-distance walking. Finally, the size of these units strapped onto the legs of patients may force them to walk with a slightly wider gait, which may not be advantageous in the long-term recovery of stable walking patterns. Ultimately, clinical testing will be necessary to examine the influences of ankle exoskeletons in helping to restore walking ability in individuals following neurological injuries.

22.1.2 Knee Robotic Technologies

Tibion's PK100 Bionic Leg Orthosis (Fig. 22.3) is a wearable, power-assist device for the leg, which actively supplements muscle strength in order to enhance rehabilitation therapy and provide mobility assistance for patients with loss of muscle function. The system is battery-powered and supplies knee extension assistance only. Utilizing sensors throughout the device, Tibion's PK100 detects the user's actions, such as sitting/standing, overground walking, and ascending/descending stairs. Microprocessors on the device analyze this information and then apply the force needed to augment the user's actions. Patients with neuromuscular impairment due to stroke or chronic disease, such as multiple sclerosis or Parkinson disease, and patients with muscle weakness due to osteoarthritis or knee surgery may benefit from this technology. To date, no clinical studies evaluating the effectiveness of the Tibion bionic leg have been published, only case reports on the company's web site.

22.1.2.1 Potential Limitations for Knee Devices

Similar to the ankle robotic technologies described above, one of the possible limitations with the Tibion bionic knee is that the added weight of the device may negate the potential benefits of knee assistance the system can provide. That is, the system can help the patient in knee extension; however, the subject will have to provide additional hip flexion propulsion to account for the exoskeleton,

Fig. 22.4 eLEGS by Berkeley Bionics (Berkeley, CA, USA). (**a**) eLEGS is an exoskeleton actuated at the hip and knee joints while the foot is passively supported. (**b**) A patient walking in eLEGS (**a** – Courtesy of Berkeley Bionics; used with permission)

particularly in the pre-swing phase of the gait cycle. Nevertheless, clinical testing will help determine whether patients can handle the additional weight of the system while, at the same time, benefit from the added knee extension assistance.

22.2 Whole-Leg Robotic Technologies

The first generation of whole-leg exoskeletons has been restricted to treadmill-based training so that the robot can be mounted to a gantry. Devices such as the Lokomat (Hocoma AG, Volketswil, Switzerland), the Autoambulator (Motorika, Israel), LOPES [13], and Active Leg Exoskeleton (ALEX) [14] attach to the subject's legs and provide them active assistance as they ambulate on the treadmill (see Chaps. 13 and 17). The problem with restricting patients to training on a treadmill is that this mode of therapy does not allow the patient to practice real-world gait scenarios, such as walking over nonsmooth surfaces, stepping over objects, practicing standing up and sitting down, and other activities of daily living. As such, there is a tremendous need to develop exoskeletons that support overground gait training. The difficulty with translating whole-leg exoskeletons to overground gait and balance training is that these systems are quite heavy. From a control perspective, it is therefore difficult to keep them stable when patients with gait impairments try to walk with them attached to their legs. In addition, these systems require large amounts of power so that they often need to be tethered to a power supply.

A number of new whole-leg exoskeletons are attempting to overcome these limitations so that individuals with neurological injuries can practice overground walking. Jointly developed by Berkeley Bionics (Berkeley, California, USA) and the University of California under the direction of Dr. Homayoon Kazerooni, eLEGS is a wearable exoskeleton that is battery-powered and straps to the outside of the individual's legs (Fig. 22.4). The

device weighs 45 lb and can be used by individuals who weigh up to 220 lb and range in height from 5′ 2″ to 6′ 4″. Both the knee and hip joints of eLEGS are actuated, allowing users to practice overground walking, standing from a sitting position, sitting from a standing position, and standing for an extended period of time. While details on the control strategy used by eLEGS are scarce, the device does not appear to utilize the impedance control strategy of its predecessor BLEEX [15]. Instead, eLEGS senses the movement intent of the patient from her/his crutches and the ground reaction forces measured by the device, then actively moves or assists the patient's legs throughout the step. Clinical testing of eLEGS is currently underway; however, no clinical or performance data has been reported on the device. It should be noted that eLEGS can be used as either a therapeutic device, in which patients can practice walking in the system, or as an assistive device, in which the device essentially moves the patient's legs through a kinematic pattern. Ultimately, the role of the system in the patient's rehabilitation program will be dictated by the return of function experienced by the patient.

Another whole-leg exoskeleton that allows individuals to practice overground walking is Rex (Rex Bionics, New Zealand) (Fig. 22.5). Similar to eLEGS, Rex is an exoskeleton that is worn by the user and can actively assist the patient in achieving a natural stepping pattern. However, unlike eLEGS, Rex is controlled using a joystick whereby the user can "drive" the system to walk over flat terrain, small slopes (up to 7.1°), and even steps. The system is battery-powered and, according to the manufacturer, can run for 3–4 h on a single charge. The system weights 84 lb and can accommodate users up to 220 lb with heights ranging from 4′8″ to 6′4″.

There are few technical details on Rex in terms of the control architecture, the degrees of freedom of the device, and the amount of assistance it can provide. In addition, there are no clinical reports discussing the usability and clinical results with the device. While it appears that the manufacturer's intent is for Rex to be utilized as a human transport system (akin to a wheelchair), it is conceivable that such a device could also be used for gait training in rehabilitation. Here, the subject could walk in Rex overground, up and down steps and slopes, and attempt to match the kinematic trajectory the system imposes. Such training may be highly effective in low-functioning patients, particularly in the early stages of injury.

Fig. 22.5 Rex exoskeleton by REX Bionics (New Zealand) (Courtesy of Rex Bionics; used with permission)

22.2.1 Potential Limitations with Whole-Leg Exoskeletons

Assuming batteries can supply sufficient power to these devices so that patients can use them for nontethered overground gait training, the most likely limitation with whole-leg exoskeletons is how effective they will be in improving walking ability in neurological patients. That is, from a

motor learning point of view, the question is whether patients will adapt and improve their walking yet be dependent on the device or whether they can use these devices to reestablish independent improvements in walking ability. If patients improve their walking ability but only when in the device, the ultimate role of these whole-leg exoskeletons may be as assistive devices rather than rehabilitation devices (i.e., devices patients use for a short time to improve their own function).

The other limitation with whole-leg exoskeletons will likely be cost. These devices require precision sensors, efficient actuators, lightweight materials, and other expensive components. This may make such devices cost-preventative to most patients and only allow the largest rehabilitation hospitals to adopt them. If production volumes increase and using these systems result in improvements in walking ability, perhaps costs will come down and healthcare providers will reimburse for these systems.

22.3 External Overground Gait Training Systems

While the devices described above are focused on supplementing lower extremity force-generating capacity, an alternative approach to providing assistance to patients during overground gait and balance therapy is through the use of a body-weight support system. Here, a harness is placed around the torso of the individual being trained which is then connected to the unloading system. As the subject walks, the system can relieve them of a percentage of their body weight, making it possible for patients with excessive weakness and poor coordination to get up and start walking early after their injuries. Due to limitations in available technologies, body-weight support systems were mainly restricted to treadmill-based systems throughout the 1990s and early 2000s.

Unfortunately, recent studies indicate that training individuals with neurological injuries using body-weight-supported treadmill training may only be as good and sometimes inferior to overground gait training. For example, a multi-center randomized clinical trial compared the effects of body-weight-supported treadmill training with comparable overground gait training in individuals with incomplete spinal cord injury [16]. One hundred forty-six participants completed the protocol, which consisted of 12 weeks of either body-weight-supported treadmill training or overground gait training. It was found that there were no significant differences between the groups in terms of the lower extremity Functional Independence Measure (FIM) [17] or overground walking speed. Another study compared four modes of gait training in incomplete spinal cord injury: (1) body-weight-supported treadmill training with manual assistance, (2) treadmill training with electrical stimulation, (3) overground gait training with electrical stimulation, and (4) robotic-assisted gait training [18]. Twenty-seven subjects were trained for 12 weeks, 5 days per week. It was found that the individuals in the overground gait training group had the best outcomes in terms of improvements in overground walking speed and walking distance. Similar results have been reported for robotic-assisted treadmill training studies in subacute stroke [19].

The lingering question is why do subjects who perform overground gait and balance training improve as much as or better than those individuals who are trained on a treadmill? While there are no definitive answers to this question, there are a few plausible reasons. The first potential reason is that there are key differences between walking on a treadmill and walking overground [20]. For example, when walking on a treadmill, there is no optic flow, muscle activation levels tend to be higher, and subjects often walk at a higher cadence. Another potential reason that training overground may be more advantageous than training on a treadmill is because it allows subjects to practice functional tasks other than simply walking. As mentioned above, in order for patients to regain functional independence and participate in society, it is important that they be able to safely stand up and sit down, walk overground, navigate a step or two, and have good postural control. Unfortunately, only a small subset of these traits can be practiced on a treadmill despite them being critical components of the patient's therapy.

Fig. 22.6 ZeroG gait and balance training system (Aretech, LLC, Ashburn, Virginia, USA). (**a**) An individual with chronic stroke practicing walking in ZeroG. (**b**) A stroke patient practicing walking up and down stairs in ZeroG

There are a number of important benefits of using a body-weight support system, such as the safety it provides, the ability to get patients training early and intensely after their injuries, and the ability to progress the intensity of their training by altering the amount of weight support provided to them. Until recent years, training patients during overground gait training with partial body-weight support was not possible; however, the development of two gait training systems now supports this type of gait and balance therapy.

22.3.1 ZeroG®

The ZeroG gait and balance training system has been under development since 2005 and is now commercially available through Aretech, LLC (Ashburn, Virgina, USA). The system (shown in Fig. 22.6), which can provide up to 300 lb of static body-weight support and 150 lb of dynamic body-weight support, rides along a track mounted to the ceiling. As the patient walks, a percentage of their body weight can be removed, which helps compensate for weakness, poor balance, and other impairments common to neurological injuries. This allows patients to begin practicing a wide variety of therapeutic exercises in a safe manner. A small motor drives the trolley along the track so that, as the patient walks, the system will automatically move with them so that they only feel the vertical unloading force.

One of the unique advantages of ZeroG is that, because the system rides on an overhead track, patients can practice walking overground, up and down steps, or perform sit-to-stand or other balance tasks. As mentioned previously, these activities of daily living are important since the patients will encounter such challenges everyday in their normal lives.

The performance of ZeroG has been evaluated using both bench-top testing and human trials. Example plots of ZeroG's ability to maintain constant levels of force are shown in Fig. 22.7. In the upper two traces, a subject walked approximately 25 ft in ZeroG at their self-selected speed, turned around, and returned to their starting position. During the trial, the level of body-weight support was set to 50 lb. The error in force was approximately ±2.5 lb, mainly due to the inertia of the movement plates within the system. The lower two traces show the unloading force during a large change in vertical motion. Here, the subject was asked to drop down to one knee from a standing position two consecutive times under 30 lb of body-weight support. It can be seen that the error in force is minimal despite a change in vertical motion of approximately 16 in.

To date, there are no published clinical trials on ZeroG. Currently, there is a 3-year randomized clinical trial comparing ZeroG gait and balance training to conventional gait training in acute and subacute stroke patients [21].

22.3.2 KineAssist®

Another system capable of providing body-weight support during overground gait training is the KineAssist Gait and Balance Training System (see [22] for a detailed description of the KineAssist). The system (Fig. 22.8), which has been under development since 2002 and is now being clinically tested in various clinical sites throughout the United States, consists of a mobile base system and smart brace system. The two systems are further broken down into subsystems described below. The sophisticated control system uses Cobot technology originally developed by Peshkin and Colgate at Northwestern University for assistive devices in materials handling [23]. The Cobotic algorithms form the basis of a new class of technology that senses human movement and allows devices to follow and take direction from this movement. This adds precision and safety to lifting, guiding, and positioning. This admittance control methodology renders a haptic display that compensates for the inertial effects of the robot, allowing easy forward, up-down, and turning motions while the machine moves in response to the motion of the patient. The mobile base of the KineAssist® is powered and is highly responsive to the patient's desires for motion so that the patient does not have to pull the base. The patient's intent for motion is detected by a combination of passive joints and force sensors incorporated into the pelvic part of the patient support structure. Control algorithms move the base in response to the patient's forces and motions so that the patient's walking and turning motions are unconstrained. A software-driven "safety zone" limits the patient's vertical range of motion and implements a compliant bottom stop that gently catches the patients when they lose balance.

In addition to simply acting as a fall-arresting device, this device can partially support the patient's weight at the level of the pelvis, and the system is also capable of comfortably applying forces to the body. The KineAssist® is able to produce unweighting of the patient (partial body-weight support training) up to 150 lb of vertical force. The vertical column is powered to provide this force continuously and at the same time to easily allow the vertical motions of the pelvis and torso, which are a part of normal gait. The unweighting feature is rated to 150 lb, but the KineAssist® is designed for patients up to 350 lb, and it can safely bring such a patient to a stop after only a few inches of fall. (The clinician selects the threshold distance for identifying and stopping a fall.) The therapist has the freedom to change parameters and assist or challenge the patient to the level that is necessary to gain the best clinical outcomes.

22.3.3 Limitations with Overground Body-Weight Support Systems

The potential limitations with the devices described above are device specific. For example, with ZeroG, patients are restricted to walk under the track and cannot deviate more than a couple of feet without feeling a large horizontal restoring force. With the KineAssist, the responsiveness of the system is necessarily slow for stability purposes so that the patient can feel the weight and inertia of

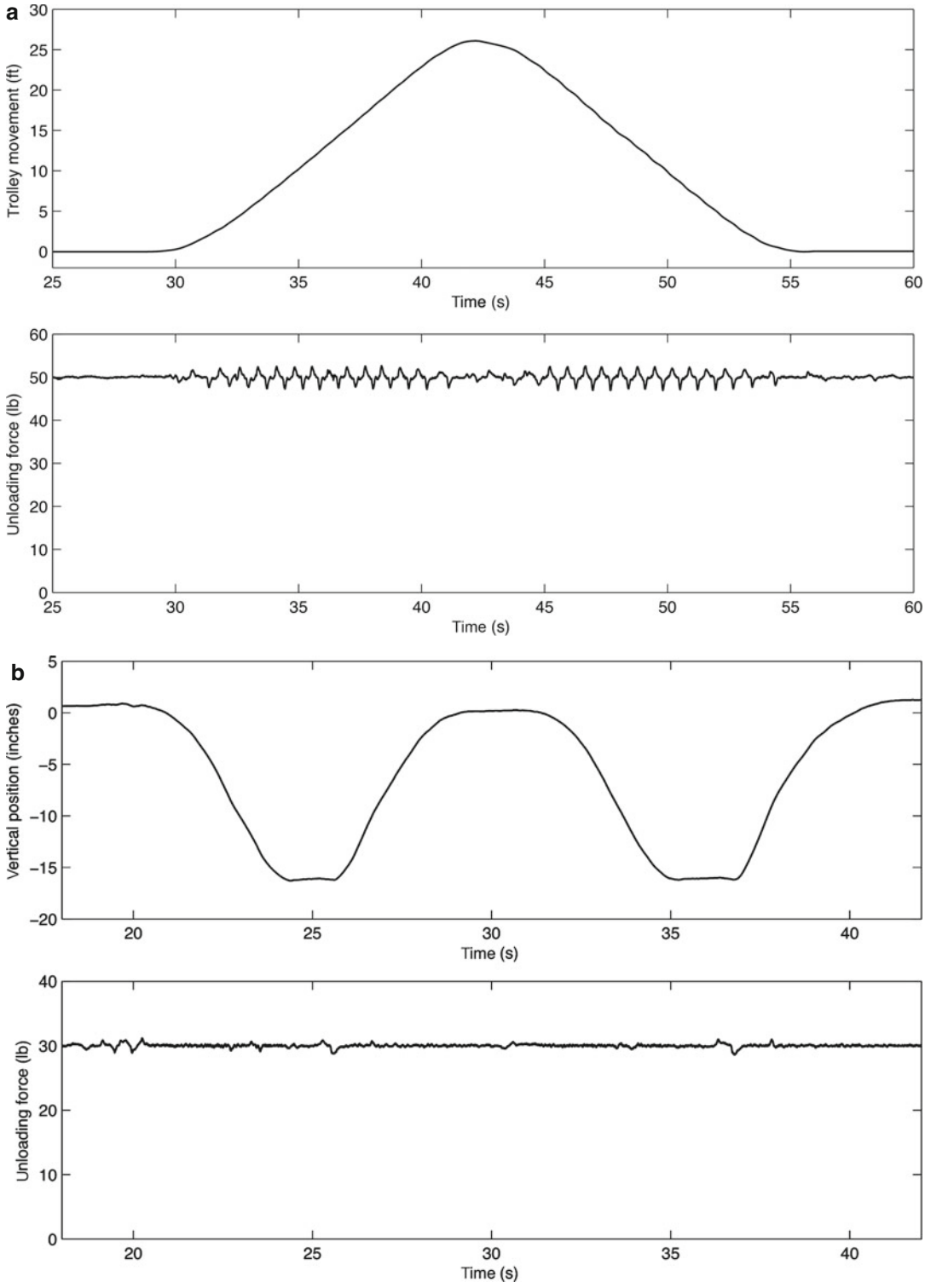

Fig. 22.7 ZeroG performance during an overground walking trial (**a**) and a balance task (**b**)

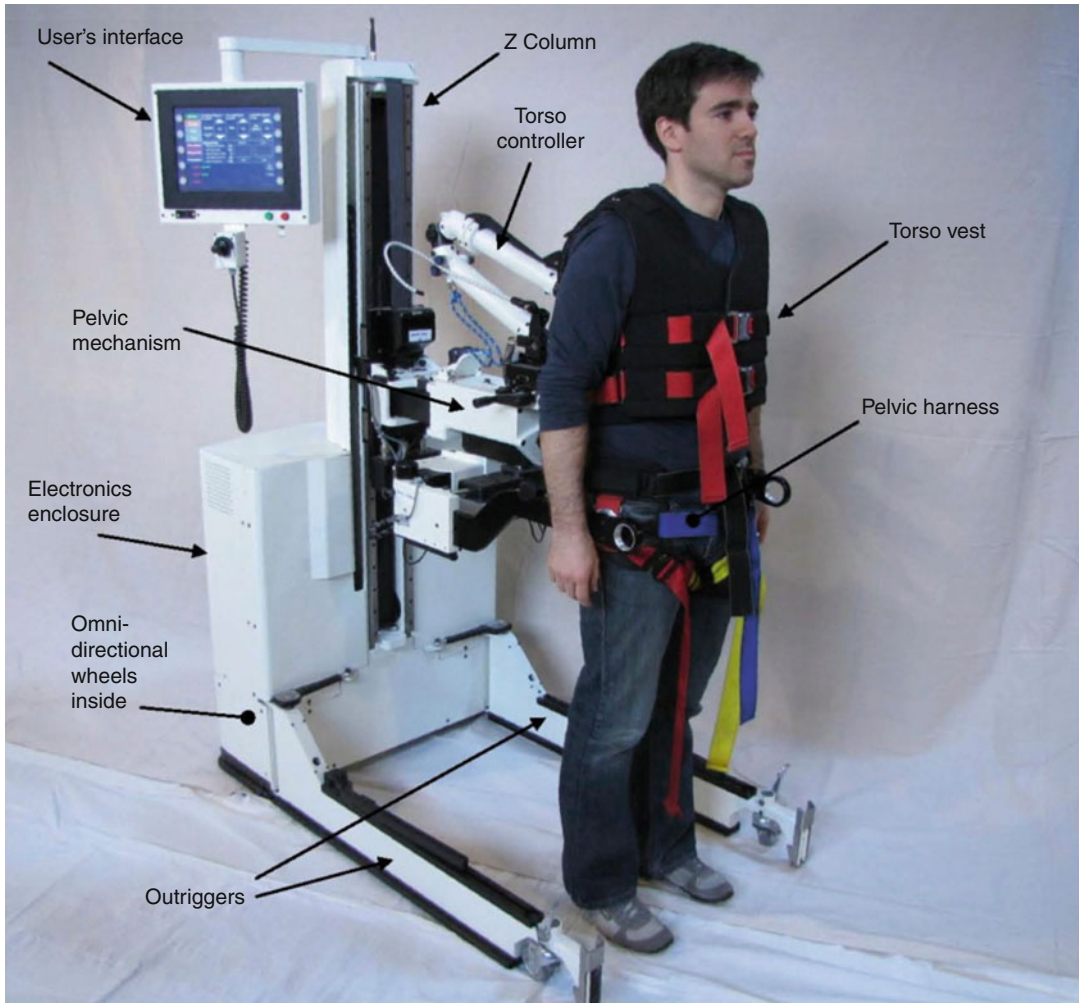

Fig. 22.8 KineAssist gait and balance training system (Courtesy of Kinea Design, LLC, Evanston, IL; used with permission)

the device as they walk, stand up, and perform other gait and balance activities. In addition, because KineAssist rolls on casters, patients are restricted to overground gait and balance training on smooth, flat surfaces.

Similar to whole-leg exoskeletons, another major disadvantage of these devices is cost. Because these systems contain numerous actuators, precisions sensors, and other custom components, the pricing for these systems only allow the largest rehabilitation centers to adopt the technology. Perhaps with increases in production volume, the costs will come down so that smaller outpatient clinics can also adopt these devices.

22.3.4 Future Directions

The field of rehabilitation robotic technology is at the very early stages, particularly as it relates to robots that promote overground gait training. In order for these devices to truly be integrated into the clinical setting, a number of factors will need to be explored and tested.

- Patient safety: The use of robotic technology that involves forces to control motion is inherently dangerous and unstable when interacting with patients who show a wide variety of movement variations. Safety standards need to be developed to assure that the robotic application does

not overstress the musculoskeletal system or induce high forces that cause tissue trauma.

- Optimized parameterization of exercise components: The success of any robotic technology will be limited by the effectiveness of the exercise regime with which it is used. As such, clinicians and scientists must be careful to avoid generalizing the effectiveness of a particular robotic technology within a particular patient care setting unless that application has been well tested and the effectiveness validated in a suitable, well-controlled clinical trial. The parameters for the exercise sessions that are designed for an exercise intervention must be scalable for each patient case, and future technologies will need to allow clinicians access to the controls of the devices so that they can alter these parameters appropriately.
- Clinical feasibility: Issues such as cost, weight, size, and flexibility of function will ultimately determine the clinical feasibility of any robotic system within a clinical or home-exercise environment. Future directions in robotic technology will need to take into account the patient's comfort, the ease of donning and doffing, and the tolerance for interacting with new technology during the design process.
- Problems with overground travel: A device that will accompany any patient as they move overground will need to assure safety in the case of loss of balance and falls, as well as collisions with objects and people, and moving through different flooring environments and negotiating around furniture. Future devices will need to occupy small spaces and catch and maintain the person's full body weight after a fall.

As the field moves forward, each of these factors needs to be strongly considered as new robotic technologies are developed and existing technologies refined.

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Part IX

Specific Aspects of Neurorehabilitation Technology: Restoration of Bladder Function After Stroke/Spinal Cord Injury

Technologies for the Rehabilitation of Neurogenic Lower Urinary Tract Dysfunction

23

Ulrich Mehnert

Abstract

The human lower urinary tract (LUT) function is dependent on a complex neuronal control involving spinal and supraspinal centers and different peripheral nerves. Thus, neurological disorders can often cause severe dysfunctions of the LUT, which is a daily burden for the affected patients and also an enormous economic burden for each health care system. Advantages in diagnostics and therapy of LUT dysfunction in neurogenic patients during the last four decades have contributed to a great extent of both a significant reduction of morbidity and mortality of those patients and in the improvement of health-related quality of life.

Basically, treatments and rehabilitation techniques for neurogenic LUT dysfunctions address three aims: (1) protection and maintenance of upper urinary tract function, (2) independency in the management of the LUT, and (3) improving the quality of life.

Important technology milestones that advanced treatment and rehabilitation of LUT dysfunction are, for example, intermittent self-catheterization, Finetech-Brindley sacral anterior root stimulator, augmentation cystoplasty with or without continent cutaneous urinary diversion, botulinum neurotoxin intradetrusor injections, artificial urinary sphincter, and different forms of neuromodulation.

This chapter provides a comprehensive overview of the pathophysiological background of neurogenic LUT dysfunction, the mechanisms and efficacy of currently used treatments and techniques in the rehabilitation of neurogenic LUT dysfunction, and upcoming techniques that will play a role in the management of LUT dysfunction in the near future.

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Neurogenic lower urinary tract dysfunction • Spinal lower urinary tract control • Lower urinary tract repair techniques • Botulinum toxin A • Artificial sphincter • Neuromodulation • Neurostimulation • Augmentation cystoplasty • Clean intermittent self-catheterization

23.1 State of the Art in Neuro-Urology

23.1.1 Relevant Biology/ Pathophysiology Background

The normal healthy human urinary tract can be divided anatomically and functionally into an upper urinary tract (UUT), consisting of two ureters and two kidneys, and a lower urinary tract (LUT), consisting of the urinary bladder, the bladder neck, the urethra, and the urethral sphincter.

Only the LUT relies on a direct neuronal input and control. The UUT is working more or less independently from any nervous system and is thus not or only indirectly affected by neurological disorders. Therefore, UUT function or dysfunction is not part of this chapter.

The human LUT has two functions: (1) low-pressure continent storage of urine; and (2) periodically, self-determined and more or less complete release of the stored urine.

For a proper execution of those functions, the LUT structures rely on an intact neuronal innervation that involves different neurons, nerves, and fiber types from different levels of the spinal cord (Fig. 23.1a, b) [1, 2]. In healthy individuals, the innervation and LUT reflexes from the spinal cord are under the control of a complex supraspinal network. This network is necessary to make appropriate and deliberate decisions regarding the coordination of the two LUT functions. Neurophysiological studies in animals and recent neuroimaging studies in humans revealed a certain network of brain stem and supraspinal areas including the pons, periaqueductal gray, thalamus, insula, anterior cingulated gyrus, cerebellum, and frontal and prefrontal cortical areas that seems to be involved in LUT control [2, 3]. The dependence of the LUT functions on complex central neuronal circuits makes it unique in comparison to other visceral functions (e.g., UUT, gastrointestinal tract, cardiovascular system) but also more vulnerable to neurological disorders.

Alterations of LUT function due to neurological disorders usually affect at least one of the following main functional areas: bladder sensibility, bladder contractility, and urinary sphincter function. Each of these areas can be either over-, normo-, or underactive and thus resulting in numerous different clinical findings and symptoms. The most relevant single findings are [4]:

- *Urinary incontinence*: complaint of any involuntary leakage of urine
- *Detrusor overactivity* (DO): urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked
- *Detrusor sphincter dyssynergia* (DSD): a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle; occasionally, flow may be prevented altogether
- *Detrusor hypo- or acontractility*: detrusor cannot or only insufficiently be demonstrated to contract during urodynamic studies
- *Overactive bladder syndrome* (OABS): urinary urgency, with or without urinary urgency incontinence, usually with frequency and nocturia
- *Incompetent urethral closure mechanism/ sphincter insufficiency*: leakage of urine in the absence of a detrusor contraction
- *Reduced/low bladder compliance*: relationship between change in bladder volume and change in detrusor pressure <25 mL/cmH_2O
- *Nonrelaxing urethral sphincter obstruction*: nonrelaxing, obstructing urethra resulting in reduced urine flow

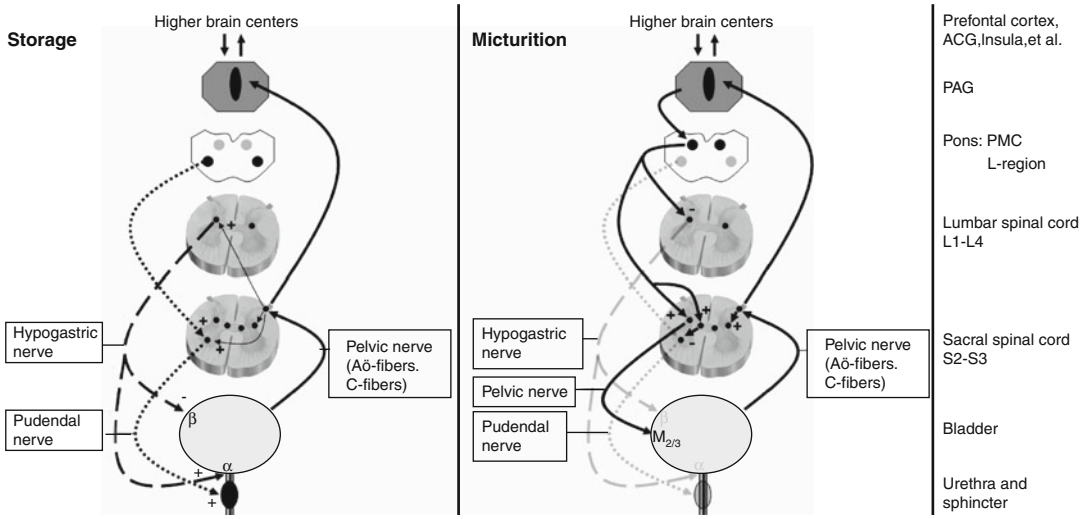

Fig. 23.1 Schematic illustration of spinal cord and brain stem regions involved in lower urinary tract (*LUT*) control and their most relevant neuronal connection to the LUT. The illustration summarizes the findings of neurophysiological animal studies and early functional neuroimaging studies in humans from De Groat, Holstege and Blok (Blok and Holstege 1999; [1, 5]). During the storage phase (**a**), which normally accounts for most of the daily time (98%), the detrusor is relaxed and the bladder neck closed due to a certain sympathetic tone on bladder body and bladder neck. Sympathetic fibers (thick dashed lines) travel along the hypogastric nerve from the sympathetic nuclei in the intermediolateral column of the lumbar spinal cord to the LUT and provide adrenergic input to beta-receptors on intramural ganglia of the bladder body (→ relaxation) and alpha-receptors at the bladder neck (→ contraction/closure). Bladder afferents traverse through the pelvic nerve (thick continuous line until S2-S3) and enter the dorsal horn of the sacral spinal cord. At low filling volumes, there might be only little afferent activity, and weak afferent signals might reach the PAG and diencephalic structures (e.g., thalamus), but bladder sensations do usually not reach consciousness during this state. With increasing bladder volumes, afferent activity might increase probably due to changes in intravesical pressure, and at some degree of filling, bladder sensations will reach consciousness in form of a first desire to void. From the sacral dorsal horn, excitatory collaterals (thin continuous lines) reach to the sympathetic nuclei in the lumbar intermediolateral column and to the sacral frontal horn, where the motor neurons of the external urethral sphincter (*EUS*) are located (Onuf's nucleus), to facilitate sympathetic input to the bladder and bladder neck and somatic input to the EUS, respectively. This supports continence during increasing bladder volumes, when voiding has to be postponed. Another region supposed to be responsible for continence is the pontine L-region (named L-region as it is lateral to the other relevant pontine structure named pontine micturition center or M-region or Barrington's nucleus), which has excitatory input (thick dotted lines) to the EUS motor neurons in Onuf's nucleus and thus facilitates the elevation of the EUS tone. If the decision to empty the bladder is made (in the higher brain centers), the periaqueductal gray (*PAG*) activates the pontine micturition center (*PMC*) (**b**). The switch between L-region and PMC activation is sometimes model-likely simplified as moving a lever from one program to the other. Only one region can be activated at a time. From the PMC, strong inhibitory inputs reach the sympathetic nuclei in the intermediolateral lumbar cord to suppress the sympathetic input to bladder body and bladder neck to enable a synergic micturition. Simultaneously, the PMC has strong excitatory projections to the parasympathetic nuclei in the sacral spinal cord that in turn activate the detrusor muscle via muscarinic receptors. The parasympathetic fibers travel along the pelvic nerve. In addition to the parasympathetic activation, the PMC has excitatory collaterals to inhibitory interneurons in the sacral cord that reduce the activity of EUS motor neurons and thus facilitate EUS relaxation and synergic micturition

The diagnostic tools to describe these dysfunctions are a 3-day voiding diary, a physical examination (including abdominal, pelvic, perineal, and a focused neurological examination), and a urodynamic examination that usually includes a filling cystometry (method by which the pressure/volume relationship of the bladder is measured during bladder filling) and a pressure flow study (method by which the relationship between pressure in the bladder and urine flow rate is measured during bladder emptying) or simple uroflowmetry (method to measure the urine flow rate).

These dysfunctions can occur solely and some usually in combination with each other.

DSD or detrusor hypocontractility usually results in incomplete emptying of the bladder or

even urinary retention, which in turn facilitates urinary tract infections and the formation of urolithiasis. DO and sphincter insufficiency result in severe urinary incontinence. DO in combination with DSD causes increased intravesical pressures during the storage phase, which in the long term can cause deformation of the bladder (e.g., diverticles, trabeculation, thickening of the bladder wall, and decreased capacity), a decreased bladder compliance, vesicoureteral reflux with damage of the kidneys, and/or urosepsis [6, 7]. Resting bladder pressures persistently greater than 40 cmH_2O are assumed to result in a high risk of inefficient ureteral urine expulsion into the bladder, vesicoureteral reflux, hydroureteronephrosis, complicated pyelonephritis, irreversible renal damage, and even irreversible renal failure [8]. However, the current evidence for using such an exact pressure threshold of 40 cmH_2O is rather poor, and although there is agreement that DO and high intravesical pressures have negative effects on the upper and lower urinary tract, the definition of what is "high" and which intravesical pressure might be "too high" is less clear, and the exact pressure threshold value of 40 cmH_2O is discussed critically.

OABS is a purely clinical entity of mainly sensory dysfunctions during the storage phase with urinary urgency and urinary frequency. OABS and DO can be associated.

Nearly every neurological disorder can affect the functions of the LUT. The most common neurological disorders frequently causing LUT dysfunction are: spinal cord injury (SCI) (e.g., traumatic or ischemic) or spinal cord malformations (SCM) (e.g., spina bifida, syringomyelia), multiple sclerosis (MS), cerebrovascular accident (CVA), and Parkinson disease (PD).

SCI and SCM often cause profound alterations of LUT function due to the interruption of efferent and afferent connection with supraspinal neuronal structures. Complete suprasacral SCI usually results in detrusor overactivity (DO) and detrusor sphincter dyssynergia (DSD) because the LUT is solely functioning on the level of sacral reflexes without the regulatory input from the pontine micturition center responsible for a synergic micturition (Fig. 23.1). Depending on lesion level and completeness of the SCI, different forms of bladder and sphincter dysfunctions can result (Fig. 23.2) [9].

Because symptoms and forms of LUT dysfunction could be relatively easy allocated to certain lesion levels in SCI, SCI has become a role model for describing the different forms of neurogenic LUT dysfunction (Fig. 23.2).

23.1.2 Rationale for Application of Current Technology

Although there are several health-related factors (e.g., respiratory dysfunction, cardiovascular dysfunction, and digestive dysfunction) that can affect the long-term survival of SCI patients depending on the age at SCI, type of lesion (traumatic vs. nontraumatic), lesion level, completeness of lesion, and time after SCI, LUT complications usually ranked among the top five mortality reasons [10, 11]. Just until the 1970s, LUT complications were reported to be the primary cause of death in SCI patients [12, 13].

Next to improvements in the medical care and rehabilitation during the acute and subacute phase following SCI, improvements in the diagnosis and treatment of LUT dysfunction in SCI and SCM patients in the last 30–40 years contributed largely to a significant increase in the life expectancy of those patients [10, 14]. However, life expectancy in SCI patients remains still below normal [14, 15].

If LUT dysfunction is left untreated, this can lead in the long term not only to an increase in morbidity and mortality of the patients [16–19], especially if kidney function is affected, but also to a severe reduction in the quality of life, body image, and sexuality of those patients due to urinary incontinence, urinary urgency, urinary frequency, and recurrent urinary tract infections [7, 20–25]. It is thus not surprising that SCI patients give the treatment and possible cure of their LUT dysfunction top priority during their rehabilitation, even before regaining walking function [26].

LUT dysfunction can interfere with nearly every area of daily life and can influence the suc-

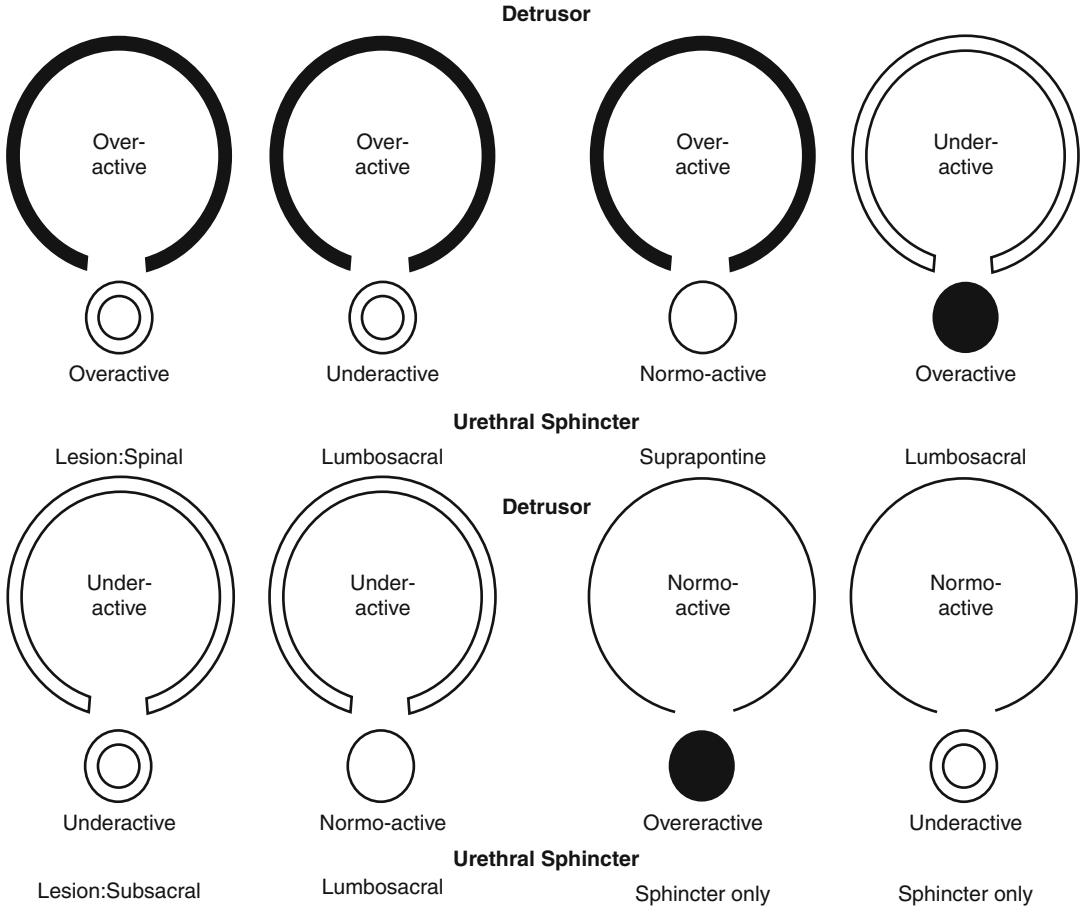

Fig. 23.2 Classification system according to Madersbacher, showing different lesion levels of spinal cord injury and the according lower urinary tract dysfunction that can result (Reprinted by permission from Macmillan Publishers Ltd: Madersbacher, Paraplegia 28, 217–229, copyright 1990)

cess of the whole rehabilitation process. Thus, rehabilitation of LUT function and treatment of LUT dysfunctions with current and future technologies are mandatory.

23.1.3 Overview on the Therapeutic Action/Mechanisms and Aims of Current Rehabilitation Techniques and Their Potential Value and Risks

The therapeutic action and mechanism of techniques for the rehabilitation of neurogenic LUT dysfunction is always aiming at three goals:

1. Maintenance or reconstruction of the LUT as a low-pressure urinary reservoir to protect and maintain upper urinary tract function and, if applicable, to prevent autonomic dysreflexia.
2. Independency in the management of LUT function.
3. Improvement of the quality of life.

23.1.3.1 Maintenance or Reconstruction of the LUT

To reach the first goal, most techniques for neurogenic LUT dysfunction are designed to reduce or keep intravesical storage pressures low to avoid vesicoureteral reflux and subsequent damage to the kidneys.

Low intravesical pressures can be either achieved (a) by inhibiting the detrusor or (b) by markedly reducing the outlet resistance.

Inhibiting the Detrusor

Detrusor inhibition can be either achieved pharmaceutically or using surgical techniques. Pharmaceutical therapy currently includes different formulations and applications of antimuscarinic drugs (not discussed in this chapter) or the intradetrusor injections of botulinum toxin A (BoNT/A). Detrusor contractions mainly result from acetylcholine release from parasympathetic nerve fibers (pelvic nerve) and, subsequently, activation of muscarinic M2 and M3 receptors on the detrusor [27]. BoNT/A is a 150 kDa molecule, consisting of a heavy and a light chain, of which the light chain destroys the docking molecules (SNAP-25) that are responsible for the release of the acetylcholine vesicles into the neuromuscular junction [28, 29]. Thereby, BoNT/A causes a chemodenervation of the detrusor which is presumably not 100% but sufficient enough to cause a significant reduction in detrusor tone and pressure. However, this therapy is not self-applicable, and patients have to return for reinjection as the average duration of efficacy is 8 months [30] due to resprouting of the axon terminals [28, 29]. Intradetrusor injections of BoNT/A are highly effective with only few adverse events and since August 2011 an FDA approved medical therapy for neurogenic detrusor overactivity (NDO).

Surgical techniques for the treatment of neurogenic DO include sacral deafferentation, sacral neuromodulation, augmentation cystoplasty, and complete cystectomy with the creation of a new continent or incontinent urinary diversion.

Sacral deafferentation: The efficacy of the sacral deafferentation, also known as posterior rhizotomy, results from the direct interruption of the afferent part of the sacral reflex arc that causes the DO [31]. When properly done and complete transection of the sacral roots S2–S5 can be achieved, this operation leads to an acontractile or flaccid bladder, which can be emptied via clean intermittent self-catheterization (CISC). In addition, sacral deafferentation can effectively abolish autonomic dysreflexia [31]. Disadvantage of this operation is that potentially preserved sensation of the pelvis and lower limbs and sexual function (e.g., reflex erections) will be lost [32]. In addition, the defecation reflex will be lost and secondary myoatrophy of buttock and lower limb musculature can occur, which in turn increases the risk of pressure ulcers.

Sacral neuromodulation (*SNM*): SNM is less invasive and does not rely on stimulation of nerves to produce a contraction. Rather, it relies on the influence of activity in one neural pathway that affects the preexisting activity in another neural pathway by synaptic interaction. The electrodes for neuromodulation are implanted (minimally invasive under local or general anesthesia) and are usually placed in the third sacral foramen (S3) in close proximity to the S3 nerve root. The stimulation applied reaches the S3 nerves and interferes with their neural activity, which seems to normalize LUT afferent and/or efferent signals, as OAB symptoms and DO can improve under neuromodulation. The exact therapeutic mechanism of neuromodulation in LUT dysfunction has yet not been completely understood and not all patients selected for this treatment do benefit from it [33].

Augmentation cystoplasty: With an augmentation cystoplasty, overactive detrusor will be removed (sparing the trigone) or cleaved at the dome and subsequently replaced or augmented by a pouch created from tissue of the gastrointestinal tract (usually ileum). This surgery is usually performed as open surgery and can be combined with a continent cutaneous urinary diversion to facilitate CISC via an abdominal site when CISC via the urethra is not possible. An augmentation cystoplasty increases the bladder capacity and restricts detrusor contractility [34]. However, it requires a long hospitalization (2–4 weeks), some time to regenerate and readapt after discharge, and comes with the risks of an open abdominal surgery including bowl dysfunction (e.g., diarrhea, obstruction), infection, and fistula formation [35]. Long-term complications can include changes in acid–base balance, urinary stone formation, and perforation of the augmentation [35]. Urinary incontinence via the urethra might still be possible in some cases and subsequent surgery

might be necessary. Augmentation cystoplasty with or without continent cutaneous diversion should be only performed in patients who are able and willing to perform CISC. Otherwise, the patient will gain nothing from this kind of surgery.

Cystectomy + urinary diversion: The complete bladder is removed and replaced by a newly created urinary reservoir. Operative and postoperative risks and complications are similar to those of the augmentation cystoplasty. However, complete cystectomy and creation of a new urinary reservoir might be more complex and time-consuming and require the reimplantation of the ureters, which implies the risk of ureteral stenosis. The new urinary diversion can be constructed to be continent or incontinent. There are several different forms of continent urinary diversions available using different forms of pouches and neobladders [36–38].

The construction of an incontinent urinary diversion is less complex and requires "only" the connection of the ureters to the abdominal skin via a short ileum segment [39]. As the urine is now directly draining outward, a urinary bag has to be placed on the stoma site to collect the draining urine. This latter operation, also known as ileum conduit, might appear radical, but is an excellent option for some patients with neurogenic LUT disorders. It requires usually less hospitalization than the augmentation cystoplasty or a continent urinary diversion, no CISC, no pads or diapers, no recurrent or daily drug treatment, and a urinary incontinence via the urethra is completely excluded. However, changes in kidney function and morphology, stenosis of the ureteroileal and ileocutaneous junction, and bowl dysfunctions are known postoperative complications [40, 41].

Reducing Outlet Resistance

The reduction of outlet resistance can be also done by pharmaceutical (not discussed in this chapter) or surgical therapy. Surgical techniques include urethral stents and endoscopic resection/transection.

Urethral stents: A very simple and also reversible technique to achieve a free urinary outflow and to keep the intravesical pressures low. A urethral stent distends the functionally or anatomically obstructive structure in the urethra (e.g., bladder neck, urethral sphincter, prostate) and keeps it open [42–44]. However, if the stent does not epithelialize well, dislocation and formation of urinary calculi can occur.

Endoscopic resection/transection: Under cystoscopic view, the functionally or anatomically obstructive structure (e.g., bladder neck, urethral sphincter, prostate) is either resected using an electrical resection sling or transected using a cold knife or an electrical knife. Very often, a reoperation becomes necessary at some time during follow-up to achieve a continuous good functional result.

All surgical therapies for the reduction of the outflow resistance in case of DO require the wearing of a urinary sheath thereafter as the patients are completely incontinent. Before considering this therapy, the ability of using a urinary sheath needs to be controlled. Consequently, these treatment options are mainly preserved for men as there is no adequate alternative for a urinary sheath in women.

23.1.3.2 Independency in the Management of LUT Function

To reach this goal, it is important to use techniques that are adapted to the patient's individual situation. Independency in LUT management is important for the patient's self-esteem, a simpler integration into a work activity, and the relief of involved caregivers.

Understandably, independency in LUT management strongly relies on the arm and hand function of the patient. Thus, it is often reasonable and necessary to involve rehabilitation specialists (e.g., ergo- and physiotherapists) into the discussion of relevant therapy options.

Techniques that advanced the independent management of LUT (dys-) function include CISC, continent catheterizable abdominal stoma, sacral anterior root stimulator (SARS), and ileum conduit.

Clean intermittent self-catheterization: CISC brought an enormous improvement for the autonomic care of LUT dysfunction. During CISC, the patient introduces a catheter transurethrally

into the bladder and drains the urine through the catheter into a urine bag or directly into the toilet. This technique is atraumatic and allows an efficient and timely evacuation of urine, although preparation might be a little time-consuming in some cases (e.g., women who are wheelchair-bound).

Continent catheterizable abdominal stoma: If CISC via the native urethra is not possible but would be possible if the bladder could be catheterized via the abdominal skin, a continent catheterizable abdominal stoma is a reasonable option. A continent catheterizable abdominal stoma is a construction of a catheterizable tube usually from the appendix (Mitrofanoff technique) [45, 46] or a small segment of ileum (Monti technique) [47]. This tube is then implanted into the bladder or cystoplasty where required and connected to the abdominal skin (usually at the umbilicus). To prevent urinary leakage through the catherizable tube, the implantation into the bladder or cystoplasty is performed through a submucous tunnel (=antirefluxive) to create a valve-like continence mechanism.

Sacral anterior root stimulator: The SARS introduced by Brindley also brought great advantages for the autonomy of impaired bladder control. Using an external controller to activate the implanted stimulator, the patients are able to empty their bladder on demand without performing CISC. However, this therapy is usually reserved to SCI patients as implantation of a SARS is, in most cases, combined with a sacral posterior rhizotomy to abolish DO. Posterior rhizotomy causes irreversible loss of pelvic and lower limb sensibility.

Ileum conduit: In regard to independency and mobility, an ileum conduit might be an interesting therapy option for some severely affected patients as the necessity to perform CISC can be omitted (= less additional material necessary), pads and diapers can be omitted as urinary incontinence via the urethra is excluded, and it does not require an artificial implant that needs to be regularly used and controlled and that can be subject to malfunction or interference with other electrical devices or medical diagnostic measures and therapies. However, this technique requires a major abdominal surgery, and patients need to comply with an external urinary bag that is continuously attached to their body.

23.1.3.3 Improvement of the Quality of Life

To reach the third goal, (a) achievement of continence, (b) low time consumption and high practicability of techniques, (c) the recovery of spontaneous self-controlled micturition, and (d) the reduction and/or abolishment of irritating and/or painful LUT sensations are factors of major importance.

Achievement of Continence

Continence can be achieved using the techniques mentioned under goal 1 in cases of DO, but also by applying therapies that improve sphincter function in cases of sphincter and bladder neck insufficiency. Insufficiency of the closing mechanisms at bladder neck or sphincter due to the lack or impairment of neurogenic innervation of these structures results in stress urinary incontinence (SUI).

Techniques to treat SUI aim to support or increase the closing function of sphincter or bladder neck. Three different types of surgical interventions can be distinguished: (1) injectables (e.g., bulking agents), (2) suspensions (e.g., Burch, suburethral tapes and slings), and (3) implants (e.g., artificial sphincter). To apply these therapies, it is absolutely mandatory that the patient has a normo- or hypotone detrusor and no or sufficiently treated DO. Otherwise, these therapies would be counterproductive to goal 1.

Injectables: Injectables can consist of different materials (e.g., autologous fat, collagen, silicon, carbon, Teflon®, polyacrylamide hydrogel), and they are injected transurethrally below the bladder neck to create a submucous cushion/bulking of the urethra that causes obstruction to withhold the urine. Despite some recent promising findings [48, 49], the current literature does not provide sufficient evidence for this kind of therapy [50].

Suspensions: Suspension therapies aim to restore or to improve urethral and/or bladder neck position and support thereby enhancing the

bladder neck or sphincteric closing mechanism. These are established treatment methods for female SUI [51, 52] and have been just recently introduced also for male SUI [53, 54]. Next to traditional techniques like a Burch colposuspension, there are several different forms and materials of slings and tapes available. However, there are currently not many studies reporting results of suspension therapies in neurogenic patients. Most of those studies describe the use of autologous rectus abdominis fascia slings in children or adolescents usually in combination with an augmentation cystoplasty, demonstrating excellent results and low complication rates [55–61]. Only one study reports on the use of a polypropylene tape in 14- to 20-year-old boys with good initial results regarding continence but high complication rates [62].

Implants: Implants for SUI treatment are implantable devices that cause adjustable mechanical obstruction or closure of the urethra and/or bladder neck. There are currently two devices available, the artificial sphincter (AMS 800) and the inflatable paraurethral balloons (ACT/ProACT). The artificial sphincter is an established, highly effective treatment for male and female SUI [63]. It is a completely implantable, easy-to-use hydraulic device that enables the patient to close the urethra and thus keep the urine within the bladder. An inflatable cuff is placed around the bulbar urethra (in men) or bladder neck (in men after prostatectomy and women, or in some neurogenic indications) and connected to a control pump that is placed in the scrotum (in men) or labium majus (in women). Pressing the pump opens the cuff, and the patient can empty the bladder, either by CISC or self-contained micturition. Closure of the cuff usually occurs spontaneously after 1–2 min.

The inflatable paraurethral balloons are a rather new technique that has not yet been investigated in neurogenic LUT dysfunction [64, 65]. The balloons are placed bilaterally of the urethra at the bladder neck (in women) or at the membranous urethra (in men) and can be inflated until the desired effect is achieved or the maximum capacity of the balloons is reached. Each balloon has a port that is placed into the ipsilateral scrotum or labium majus. The inflation is performed during follow-up visits with saline via the port of each balloon. Depending on the volume, the balloons cause a functional obstruction that should keep the urine within the bladder during situations of increased abdominal pressure.

Time Consumption and Practicability of Techniques

Despite these elaborated techniques and therapies, continence might not be the primary quality-of-life goal for all patients. For some patients, it is time and practicability. When considering that in a healthy person, only a maximum of 5% of 24 h is occupied for bladder emptying (including hand washing), it is a comprehensible wish to spend as little time as possible dealing with one's LUT disability, which includes not only daily time consumption when performing CISC and/or changing diapers and pads but also frequent medical consultations for retreatment (e.g., BoNT/A intradetrusor injections, refilling of the paraurethral balloons, control and readjustment of implanted devices, recurrent treatment failure of previous therapy). Hence, some patients might consider a treatment with an ileum conduit or a urethral stent/sphincterotomy (= transection of the urethral sphincter) in combination with a urinary sheath and urinary leg bag as a very practical and effective long-term treatment option.

Recovery of Spontaneous Self-controlled Micturition

Regaining the possibility to induce a controlled micturition to empty the bladder can be an improvement in the quality of life for many patients with neurogenic LUT dysfunction. In patients with suprasacral lesions, i.e., they have intact lower motor neurons, a SARS can be implanted on the efferent, sacral anterior roots S2–S4 to enable patients to empty their bladder using an implanted but externally controllable impulse generator that causes a detrusor contraction and subsequent micturition. However, this neurostimulator-driven micturition is not comparable with a healthy bladder contraction. The micturition remains dyssynergic, and the intermittent electrical stimulation bursts just

fatigue the fast-reacting urethral sphincter muscle before the slow reacting detrusor contraction occurs [66, 67]. Usually, repetitive stimulation over several minutes is necessary to empty the bladder. Theoretically, this technique omits the necessity to perform CISC, but some patients might still occasionally use CISC if bladder emptying with the stimulator is too incomplete or if no adequate possibility for micturition is given, i.e., no adequate accessible toilet is available. In general, this stimulator has its greatest advantage in patients who are able to independently transfer on a toilet. Male patients, however, can use a urinary sheath if toilet transfer or CISC are not possible. Depending on the stimulation parameters and the stimulated anterior root, this form of therapy can also have beneficial influence on defecation and sexual function [67]. However, implantation of the SARS usually requires a prior sacral deafferentation to adequately treat DO and to prevent or reduce stimulation-induced pain, spasms, and autonomic dysreflexia.

Reduction/Abolishment of Irritating /Painful LUT Sensations

Irritating LUT sensations like urgency, frequency, and/or dysuria can be extremely bothersome and severely reduce the quality of life [25]. Sacral neuromodulation seems to be an effective technology for selected patients to treat OAB symptoms by modulation of the irritating afferent neuronal activity [33] and thus improve quality of life.

BoNT/A intradetrusor injections have been also effectively used in the treatment of irritating symptoms like urgency and frequency [68–70]. Although very well tolerable, elevated postvoid residual volumes might be an undesired adverse effect in some patients [68, 70].

23.1.4 Review of Experience and Evidence for the Application of Specific Technologies

This section highlights the six currently most relevant techniques in the therapy and rehabilitation of neurogenic LUT dysfunction.

23.1.4.1 Clean Intermittent Self-catheterization

One of the simplest but most effective techniques in the treatment of neurogenic LUT dysfunction is CISC. Introduced in 1972 by Lapides [71], it is today's gold standard to regularly, efficiently, and autonomically empty the bladder in case of voiding dysfunction. Catheter models and characteristics significantly improved during the last decades, and today there is a wide selection of high-tech catheters available, covering the needs of nearly every patient. Atraumatic, hydrophilic catheters in different sizes with or without integrated urinary bag greatly improved the tolerance and comfort of self-catheterization (Figs. 23.3 and 23.4). Today's catheters are compact and occupy very little space. Intelligent integrated insertion aids reduce additional material (e.g., disinfection material, sterile compresses, gloves) to a minimum and enable even patients with mild to moderate impaired hand function to perform CISC. CISC is usually well accepted and improves the quality of life in patients with LUT dysfunction [72]. CISC can be applied from early infancy on (e.g., in children with spina bifida) and is well tolerated [73–76]. Good education and instruction in addition to an individually adapted catheter type and catheterization technique are important core elements for high compliance and patient satisfaction and a low rate of complications [77, 78].

Some patients might be apprehensive and biased toward CISC and might need further guidance and/or education. It also has to be considered that in some patients, needs in catheter material and technique can change over time.

Complications that can occur with CISC include urinary tract infections, urethral trauma, bleeding, urethral strictures, urethritis, prostatitis, and epididymitis/orchitis. Although the current literature is sparse and very heterogenic on this issue, complication rates of CISC are generally considered very low [74, 75, 78, 79]. Most complications, especially traumatic complications occur rarely (<5%). However, UTIs and epididymitis are recurrent problems in a relevant proportion of patients. In cases or recurrent infections,

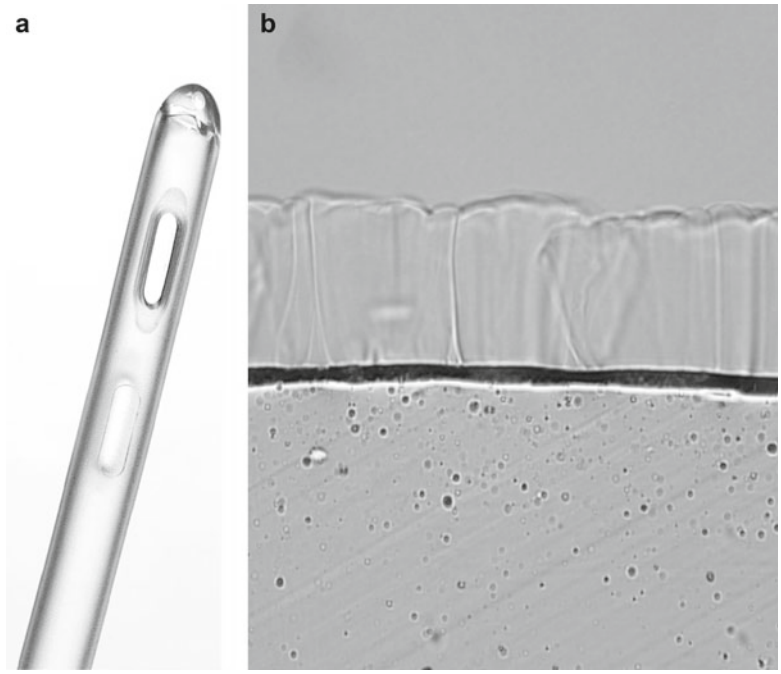

Fig. 23.3 Catheter with round, atraumatic tip and atraumatic large catheter eyes that enable comfortable, quick, and sufficient bladder emptying (**a**). Hydrophilic microfilm on catheter that enables comfortable, atraumatic self-catheterization (**b**) (Courtesy of Coloplast (Coloplast, Humlebaek, Denmark; www.coloplast.com))

catheter type, catheterization technique, and frequency as well as management of DO (if applicable) should be reevaluated and revised if necessary. Only symptomatic UTIs should be treated with the according antibiotic drug.

The most common misapprehension regarding CISC in adolescent and adult patients is that using a catheter with smaller diameter (<14 Fr) will facilitate catheterization and cause less urethral or bladder trauma. Quite in contrary, the smaller the diameter of the catheter, the softer it is and the more difficult it is to place the catheter correctly into the bladder. Smaller catheters more easily twist in the wrong direction, and with the elevated force necessary to push a softer catheter through the urethra into the bladder, trauma becomes more likely. Larger-diameter catheters facilitate rapid and complete elimination of urine and also of urinary sediments that can form calculi if left in the bladder.

Although CISC is an inherent part of LUT rehabilitation, there are still some important questions that are only insufficiently or unanswered [79]: (1) Is single use of a catheter better than multiple use? (2) Are coated (= hydrophilic) catheters better than uncoated catheters?

23.1.4.2 Finetech-Brindley Sacral Anterior Root Stimulator

In 1986, Brindley reported on the first implantation of a sacral anterior root stimulator (SARS) for the treatment of LUT dysfunction in SCI patients [80]. Improvements and refinements of this technique became known as Finetech-Brindley bladder stimulation system. Today this technique is an FDA-approved therapy that has been applied in several thousand SCI patients for neurogenic LUT dysfunction in specialized centers throughout the world [67].

The electrodes are implanted intra- or extradurally on the anterior sacral nerve roots S2–S4 bilaterally [67, 81]. The electrodes are connected to a receiver that is implanted subcutaneously in the lower left- or right-side abdomen (Fig. 23.5). For stimulation, the patient places a transmitter pad, which is connected to a programmable stimulation generator, directly above the implanted receiver. The stimulation signal is then transmitted transcutaneously to the receiver and subsequently to the electrodes. Different stimulation programs can be set up to allow the patient to use different stimulation parameters for different nerve roots. The stimulation of the anterior sacral nerve roots

Fig. 23.4 Catheter with integrated urinary bag and insertion aid to facilitate quick and straightforward self-catheterization, also for patients with impaired hand function (Courtesy of Coloplast (Coloplast, Humlebaek, Denmark; www.coloplast.com))

S3–S4 does not cause a single complete contraction of the bladder as during voiding in a healthy person. Rather, a stimulation and, hence contraction, of both detrusor and urethral sphincter results. However, due to the different characteristics of the muscle fibers in the detrusor and urethral sphincter (smooth vs. striated muscle), intermittent stimulation bursts result in fast sphincter contraction with subsequent fatigue and relaxation while the detrusor shows a slower but more sustained contraction, allowing the urine to be evacuated until sphincter tonus increases again and detrusor contraction ceases [67]. This results in intermitted micturitions, usually requiring the application of intermittent stimulation bursts for several minutes.

With the implantation of a Finetech-Brindley sacral anterior root stimulator only, DO or DSD is not treated, and patients probably will still be incontinent between stimulation sessions. To treat the DO, it is in addition necessary to interrupt the reflex arc causing DO, which means to perform a S2–S5 posterior rhizotomy. It is this procedure that effectively abolishes DO and autonomic dysreflexia triggered by the bladder or lower bowel. In addition, posterior rhizotomy prevents or reduces stimulation-induced pain and spasms. However, posterior rhizotomy will result in an irreversible loss of pelvic and lower limb sensibility and of sexual function (e.g., reflex erections). Also, secondary myoatrophy can occur, increasing the risk for pressure ulcers.

Although SARS have been implanted in patients with different forms of spinal cord lesions (e.g., SCI, MS, spina bifida, transverse myelitis) and also in neurologically normal patients, by far the most implantations have been performed in SCI patients [31, 82]. Essential prerequisites for the implantation of a SARS are: (1) an intact sacral motor neuron, i.e., intact neural pathways between the nuclei of the pelvic nerve in the sacral spinal cord and the bladder, enabling stimulation of the nerves, (2) a detrusor that is capable of contracting, and (3) a neurologically stable situation [32]. At least 1 and 2 years are usually waited after complete and incomplete SCI, respectively, before implanting a SARS and performing posterior rhizotomy, to exclude any relevant neurological improvements as far as possible [32]. However, some patients, especially those with incomplete SCI and preserved sensory function will understandably hesitate to undergo such an operation. Advantages and disadvantages must be weighed out well in every single case.

With SARS + posterior rhizotomy, normal bladder capacities of 400–500 mL can be achieved, and 80–90% of patients are able to sufficiently empty the bladder (post void residual volume < 50 mL) with repetitive stimulation; 73–85% of patients are continent [31, 83, 84]. UTIs, episodes of autonomic dysreflexia, antimuscarinic medication, and catheter use are significantly reduced [31, 83, 84]. Thereby, SARS + posterior rhizotomy seems to reduce the economic burden in regard to the health care management of NDO [85, 86].

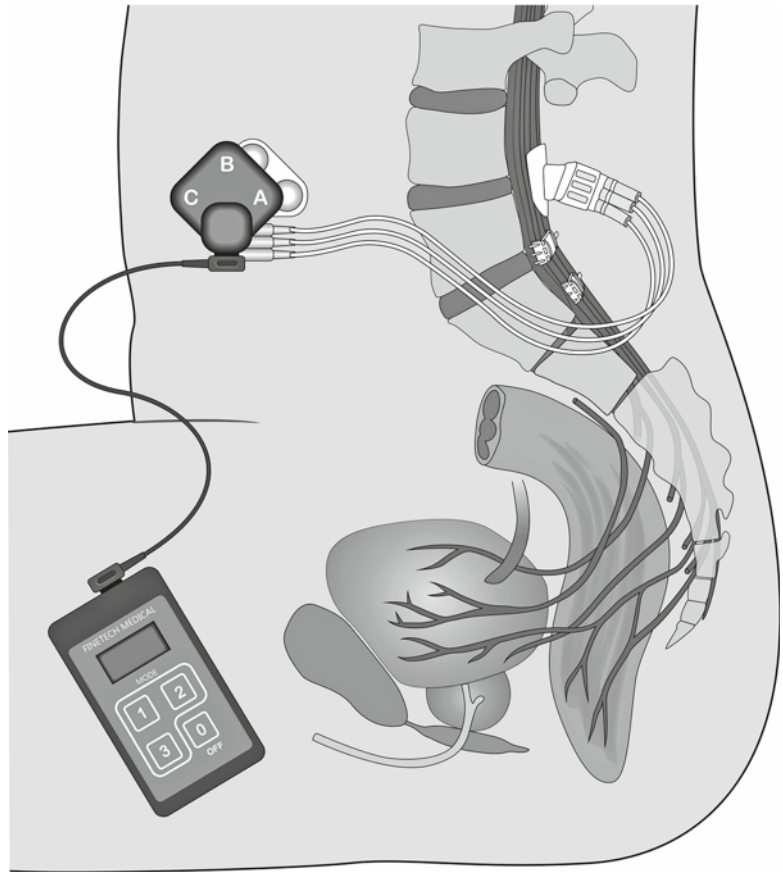

Fig. 23.5 Schematic illustration of the Finetech-Brindley neurostimulator and its position in the human body after implantation (Reprinted by permission from RBM, Germany)

Moreover, the implantation of a SARS can in part recompense for the disadvantages that might be experienced following posterior rhizotomy. While bladder contraction is mainly elicited by stimulation of S3 and S4, specific stimulation of S2 has been demonstrated to elicit a penile erection for the time of stimulation [87]. However, stimulation-triggered erections cannot be guaranteed, and only 26–55% of patients report about erections sufficient for coitus [66]. Prolongation of intervals between the stimulation bursts on S2 has been demonstrated to facilitate colorectal motility and thereby reducing constipation and improving defecation [67, 88]; 55–70% of patients use their SARS to assist in defecation [66]. Even muscle training of the gluteus medius muscle using S2 stimulation is possible [89]. This and the above-mentioned beneficial effects on the LUT contribute to the improvement in quality of life of patients with neurogenic LUT dysfunction treated with SARS + posterior rhizotomy [66].

Known but usually rare peri- and postoperative adverse events are stress urinary incontinence, leak of cerebrospinal fluid, implant infection, transmitter defect, surgical revision due to implant failure, incomplete deafferentation that requires reoperation, myogenic damage of the detrusor, and neurogenic damage of bladder afferents [31, 83, 90].

With the propagation of intradetrusor injections of BoNT/A, the SARS became less important during the last years. Nevertheless, it is still a relevant and effective treatment option for several patients and has inspired new, less invasive, and posterior root preserving forms of neurostimulation and modulation for LUT treatment in

SCI patients. Unfortunately, there are currently only very few centers worldwide that are experienced in the implantation of a SARS with or without posterior rhizotomy and the according follow-up.

23.1.4.3 Augmentation Cystoplasty With or Without Continent Cutaneous Urinary Diversion

Augmentation cystoplasty is an established surgical treatment of intractable NDO and also of other LUT dysfunctions that cannot be sufficiently treated with less invasive methods [34]. Especially, patients who already present with low bladder compliance are candidates for this kind of therapy. In general, an augmentation cystoplasty allows to transform the overactive bladder into a low-pressure continent urinary reservoir to provide a highly effective long-term treatment of DO that addresses all three above-mentioned treatment goals. Especially the combination with a continent urinary diversion enables independent management of the bladder function also for patients that are not able to catheterize via the urethra, i.e., wheelchair-bound female patients with impaired mobility of legs and pelvis (e.g., spina bifida), patients with significant urethral stenoses or strictures, or patients with insufficient hand function.

Augmentation cystoplasty is usually performed using a segment of the digestive tract that is placed on top of the transversally or sagittally dissected bladder or on the trigone in case of supratrigonal cystectomy. For the success of this operation, it is of utmost importance that the intestinal segment chosen for bladder reconstruction/augmentation retains its original blood supply. Otherwise, the intestinal segment will inevitably become necrotic, causing major complications. The use of nearly all different digestive tissues has been described: colon, sigmoid, ileum, or stomach [35]. Thus, any bowel disease (e.g., ulcerative colitis, Crohn's disease) or abnormality (e.g., radiation colitis) is a contraindication for an enterocystoplasty. In those cases, autoaugmentation or ureterocystoplasty (applicable in dilated ureters) are possible but often less effective alternatives [35].

Although not the most ideal augmentation tissue, the most frequently used tissue for augmentation cystoplasty is the ileum, which seems to be slightly more advantageous than other bowel tissues in regard to intraoperative handling, postoperative complications, and effectiveness. The overall efficacy of augmentation cystoplasty is excellent with continence rates of 69–88%, increase in MCC from mean 166–500 mL, and reduction of MDP from 60 to 15 cmH_2O [91–95]. Augmentation cystoplasty even seems to resolve preexisting reflux [96]. Patient satisfaction is usually high [97], as most patients already suffered for some time under severe DO and usually had several failed treatment attempts before being considered for augmentation cystoplasty. In patients with neurogenic sphincter insufficiency, it can be necessary to additionally perform a SUI operation (e.g., aponeurotic sling, artificial sphincter) to achieve continence.

Overall mortality of augmentation cystoplasty is low with 0–3.2% [35]. However, there are several moderate to severe complications that can occur in the short and long term [91–93, 95, 97]: urinary stones (6–21%), recurrent symptomatic urinary tract infections (20%) including recurrent pyelonephritis (1.5–11%), ileus (1.9–11.7%), chronic diarrhea (7–18.6%), perforation (0.75–4%), and fistulas (0.4–1.3%). In addition, metabolic complications can occur due to altered absorption/reabsorption of metabolic products in the augmented bladder and in the shortened gastrointestinal tract. Thus, type and severity of metabolic complications largely depend on type and length of the resected gastrointestinal tissue. Metabolic complications include: hypochloremic acidosis, lipid malabsorption, vitamin B12 deficiency, and bile acid deficiency [98].

Patients with a catheterizable cutaneous derivation might experience additional complications regarding the urinary stoma [99–101]: stomal stenosis (6–15%), channel leakage (9%), false passage (6%), and stomal prolapse (5%).

The complication rates can be extremely variable between different studies. Most complications can be effectively managed within one reoperation or using medications.

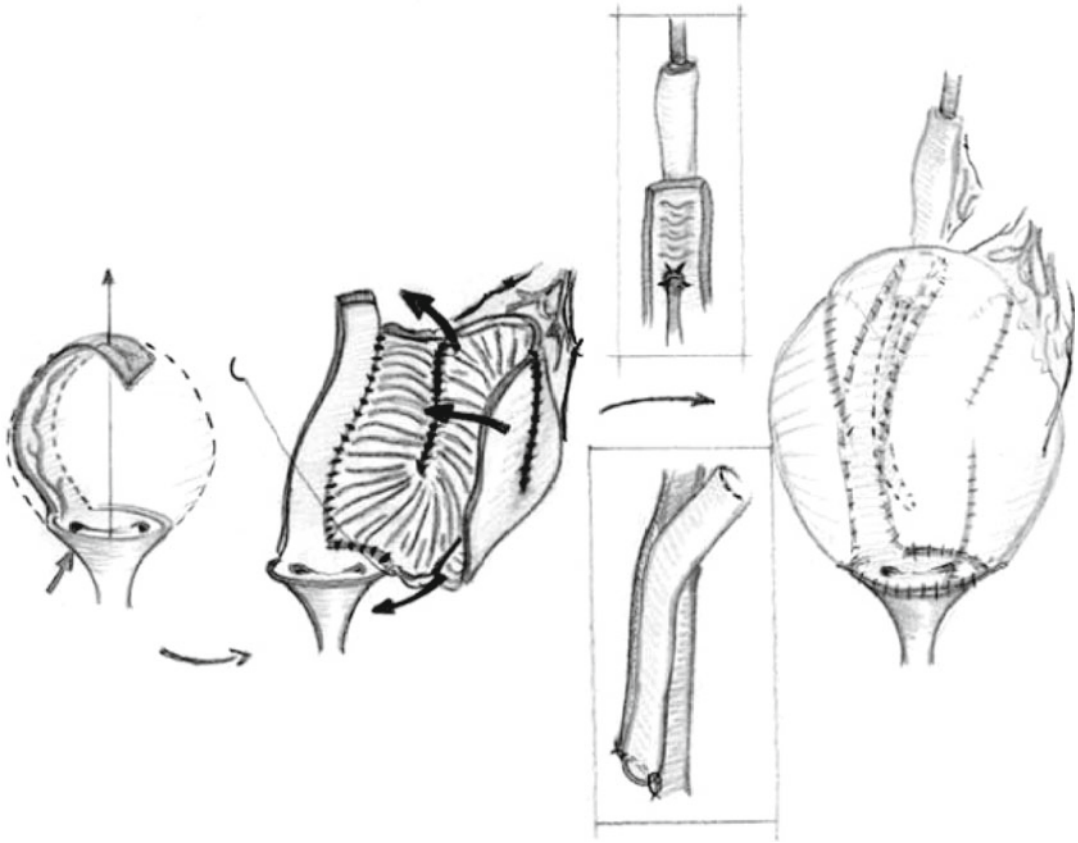

Fig. 23.6 Schematic illustration of a supratrigonal cystectomy, leaving a posterolateral detrusor flap that is used for antirefluxive, i.e., submucosal, reimplantation of a catheterizable tube. The created ileum pouch is then attached to the trigone and detrusor flap (Reprinted by permission from Macmillan Publishers Ltd: Karsenty et al., Spinal Cord 46:305–310, copyright 2008)

To reduce the risk of recurrent UTIs and stone formation, which is strongly promoted by the mucus secretion of the gastrointestinal tissue, attempts with demucosalized/de-epithelialized intestinal segments have been performed, showing promising results also in the long term [94].

A recently published study describes a modified operation technique in a pure neurogenic patient population [102]. In the selected patients, a supratrigonal cystectomy was performed to remove the overactive and pathological detrusor tissue. Only the trigone and a 2.5–3.0-cm-wide and 10–16-cm-long dorsolateral detrusor flap remained (Fig. 23.6). The detrusor flap was used to implant the newly created catheterizable tube. The catheterizable tube was constructed either from a short ileum segment (Monti technique) (Fig. 23.7a) or, if available, from the appendix (Mitrofanoff technique) (Fig. 23.7b). The implantation of the catheterizable tube into the detrusor flap was performed antirefluxive in a submucosal tunnel to prevent urine leakage (Fig. 23.6). The enterocystoplasty to create the new urinary reservoir was formed from a 50–55-cm ileum segment according to the technique described by Hautmann et al. (Figs. 23.6 and 23.7). Subsequently, the enterocystoplasty was attached to the remaining trigone and the detrusor flap (Fig. 23.6). Finally, the distal end of the catheterizable tube was attached to the desired skin site, usually at the umbilicus.

In cases of a severe SUI component due to sphincter insufficiency, suitable surgical options (e.g., autologous fascia sling, artificial sphincter,

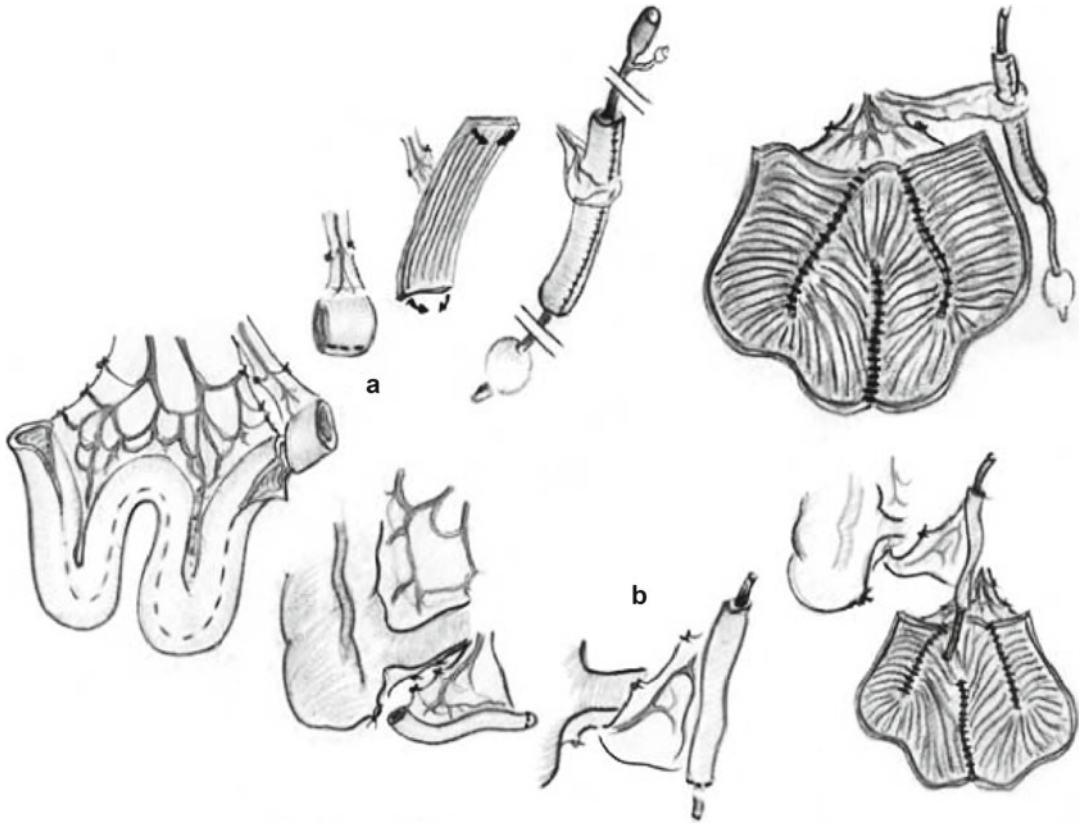

Fig. 23.7 Schematic illustration of the creation of a Hautmann ileum pouch for bladder augmentation, and the creation of a catheterizable tube using either the Monti (**a**) or Mitrofanoff technique (**b**) (Reprinted by permission from Macmillan Publishers Ltd: Karsenty et al., Spinal Cord 46:305–310, copyright 2008)

paraurethral balloons, tapes) were performed directly within the same surgical session or in a separate operation.

The first report on this specific technique in NDO is very promising, showing a continent stoma in all 12 patients. All patients performed four to six times CISC per 24 h via the stoma. Three women with SUI were treated additionally with a bulking agent or bladder neck closure. The functional bladder capacity increased from median 180 mL (70–445 mL) preoperatively to median 540 mL (380–800 mL) postoperatively. Two patients had to be surgically revised, the one due to bowel obstruction and the other due to a pelvic abscess. Seven patients developed postoperative infections that could be managed with antibiotic treatment. Long-term results of this specific technique are still pending.

Although reports on development of malignancies following enterocystoplasty vary [103, 104], regular follow-up should also be performed to control for urinary stones, renal function, urodynamic function, and integrity of the cystoplasty, and possible metabolic problems.

23.1.4.4 Botulinum Neurotoxin A Intradetrusor Injections

BoNT/A intradetrusor injections have revolutionized the treatment and understanding of LUT dysfunctions. First applied in men by Brigitte Schurch and Manfred Stöhrer in 1998 as treatment for DO due to SCI [105], this technique rapidly spread around the world and inspired a whole new field of basic and clinical research [68]. Today, BoNT/A injections are not only used for the treatment of NDO but also in patients with

different kinds of neurogenic and non-neurogenic lower urinary tract symptoms (LUTS) like urgency, frequency, pain, and benign prostatic hyperplasia–related LUTS [68]. Already the first noncontrolled and the first placebo-controlled study by Schurch et al. showed that BoNT/A intradetrusor injections are a highly effective treatment [106]. Schurch et al. reported that 53–74% of patients becoming completely continent and that the maximum detrusor pressure could be significantly reduced from 65–92 to 36–55 cmH_2O [106]. Furthermore, quality of life could be significantly increased for 56–61%. Up today, there are many studies confirming the initial results and just recently, in August 2011, the FDA approved the use of Botox(R) intradetrusor injections as treatment for NDO.

Most authors use the initially described procedure, injecting a total dose of 300 units Botox(R) (for NDO) with a dilution of 10 units/mL saline, and 30 injections of 1 mL each, sparing the trigone [30]. Following the latest studies for FDA approval, it is now recommended in cases of NDO to use a total dose of 200 units Botox(R), as 1 mL (~6.7 units) injections across 30 sites into the detrusor. The injections can be performed using a rigid or flexible cystoscope under local or general anesthesia. General anesthesia is usually chosen if the patient has intact bladder sensibility or if the patient is prone to develop autonomic dysreflexia. Known adverse events of BoNT/A intradetrusor injections are urinary retention, hematuria, injection site pain, procedure-related urinary tract infection, and generalized muscle weakness [30]. Urinary retention has to be considered and explained to the patient. Usually, it is necessary that the patient learns how to perform CISC before treatment with BoNT/A [107]. In SCI patients, urinary retention is not relevant in most cases as urinary retention existed before and was already treated with CISC. Hematuria (2–21%) is usually very mild and self-limited, however, clotting parameters and concomitant medication (e.g., Plavix, coumarin) should be checked to avoid a hemorrhagic vesical tamponade. Injection site pain is usually mild and can be avoided with adequate local, spinal, or general anesthesia. Procedure-related UTI (2–32%) can be treated with adequate antibiotic drugs following urine culture. Systematic antibiotic prophylaxis is not necessary and advisable but might be considered in risk patients with recurrent pyelonephritis and vesicoureteral reflux.

A relative disadvantage of this therapy is the duration of action that lasts for a maximum of 8–9 months [30]. Thereafter, patients require reinjection. However, reinjections are equally safe and effective and do not cause any structural changes of the detrusor tissue [108–110].

Currently, there are three BoNT/A formulations commercially available, namely, Botox® (Allergan, Irvine, California, USA), Dysport® (Ipsen, Paris, France), and Xeomin® (Merz, Frankfurt am Main, Germany). They mainly differ in their envelope proteins covering the BoNT/A molecule and in the application dosage.

23.1.4.5 Artificial Urinary Sphincter

The first experiences with an implantable artificial sphincter have been published 1974 by Scott et al. [111]. Following continuous improvements and refinements, today almost exclusively, the newest model AMS 800® (American Medical Systems, Minnetonka, Minnesota, USA) is in use. The AMS 800® consists of three major components: the inflatable cuff, the pump, and the balloon (Fig. 23.8). All three components are implanted and connected via special flexible but noncolliding tubes, allowing hydraulic functioning of the sphincter. With the pump, the cuff is deflated by pumping the water from the cuff into the balloon, from where it flows back into the cuff due to the hydraulic gradient between balloon and cuff. The reclosing of the cuff takes 2–4 min during which the patients can empty the bladder via spontaneous voiding or CISC.

The artificial sphincter is suitable for both men and women. Due to its high efficacy, the artificial sphincter is today's gold standard in the therapy of SUI [54]. Also patients with neurogenic SUI, in whom the natural sphincter is insufficiently working due to damage of its neuronal control, have greatly benefited from this therapy [63]. The success rate (proportion of continent patients) in patients with neurogenic SUI lies between 23%

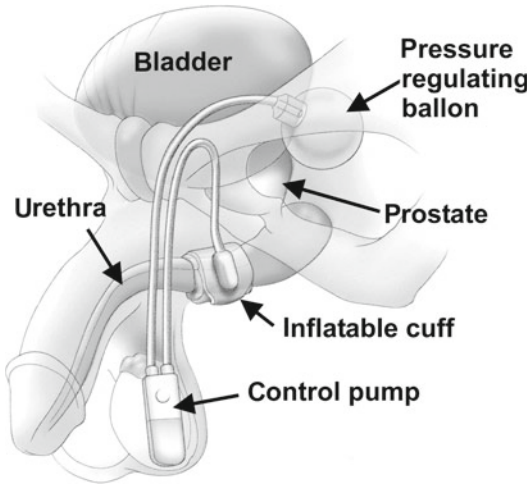

Fig. 23.8 Schematic illustration of the AMS 800® and its position in a male body after implantation. The AMS 800 consists of three components: the inflatable cuff, the balloon, and the pump. The cuff is placed around the bulbar urethra (in men) or bladder neck (in women and in men after prostatectomy or in some neurogenic indications). The balloon is placed extraperitoneally into the lower abdomen. The pump is usually placed in the scrotum (in men) or labium majus (in women) for manual control of the sphincter (Courtesy of American Medical Systems (American Medical Systems, Minnetonka, Minnesota, USA; www.AmericanMedicalSystems.com))

and 91% (mean 73%) [112–118]. However, Fulford et al. and Venn et al. investigated a mixed population (neurogenic and nonneurogenic SUI) [112, 118].

Frequent complications are erosion, infection, and mechanical/device-related failure that cause a reoperation rate for revisions and/or explantations of 16–80% [112, 113, 115–118].

Murphy et al. compared the treatment outcomes between patients with neurogenic SUI and patients with nonneurogenic SUI [114]. According to this study, patients with neurogenic SUI tend to have more frequent complications that were not related to mechanical- or device-related failure [114].

A recently published study by Bersch et al. reported the very promising long-term results of a modified AMS800 system in patients with neurogenic SUI [119]. This modified system has the advantage that it works without the pump and is thus less susceptible to device-related defects and less costly [119]. Instead of the pump, a subcutaneous port is implanted that enables postoperative adjustments of the cuff pressure. This system also seems to have some advantage in regard to the risk of pump erosion in wheelchair-bound female patients [119]. In addition, cuff pressure can be adjusted at any later time point via the subcutaneous port.

23.1.4.6 Neuromodulation

In contrast to the SARS, techniques for neuromodulation do not stimulate a certain efferent nerve to cause a muscle contraction; rather, they cause modulation of afferent and efferent signals traveling in the nerve next to the source of stimulation. Thus, neuromodulation has effects on the periphery and the central nervous system [120–122]. However, the exact mechanism of action of neuromodulation for LUT dysfunction remains unknown. It is hypothesized that in the dorsal horn of the sacral spinal cord, bladder afferent activity may be inhibited through interneurons activated by somatic sensory pathways originating in the external genitalia, perineum, and some muscles of the pelvic floor via the pudendal nerves [123]. This inhibitory interaction between larger somatic sensory fibers and small bladder afferents (thinnly myelinated A delta or unmyelinated C fibers) could operate in a similar way to the "gate control" theory of pain [124]. Animal studies suggest that pudendal nerve stimulation can elicit two effects [125]: (1) suppression of pelvic nerve activity to the detrusor by inhibition of the sacral micturition reflex at either the afferent input or the parasympathetic preganglionic motoneurons and (2) activation of sympathetic neurons which run in the hypogastric nerves and cause inhibition of the parasympathetic efferent motoneurons at the level of the pelvic ganglia.

There are several techniques available to perform neuromodulation of pelvic nerves to treat LUT dysfunction, including transcutaneous electric stimulation, magnetic induction stimulation, percutaneous electric stimulation, and continuous stimulation via implanted electrodes [33]. To make it even more complex, application of electrical and/or magnetic stimulation to

treat LUT dysfunction can be performed on different sites: sacral, pudendal, penile/clitoral, transvaginal, transrectal, perineal, suprapubic, and tibial [33].

Two of the most commonly investigated approaches of neuromodulation in regard to neurogenic LUT dysfunction are (1) transcutaneous stimulation of the pudendal nerve either using penile or clitoral surface electrodes or vaginal or rectal plug electrodes and (2) continuous stimulation using implanted electrodes at the S3 nerve root.

Many small single-center studies demonstrated the proof of principle and somehow favorable short-term results of transcutaneous stimulation of the pudendal nerve [126–131]. However, there is a lack on long-term results and larger randomized controlled trials, which might be, in addition to the handling and necessity for regular appliance of an external device, a reason that this kind of therapy is still not very commonly used despite that commercially, devices are available and adverse events are almost nonexistent.

With the development of a small implantable stimulation device named BION® (Advanced Bionics Corporation, Valencia, California, USA), an attempt of comfortable and continuous stimulation of the pudendal nerve was possible [132, 133]. After initially promising but not overwhelming results [134, 135], this therapy largely disappeared mainly due to complications based on the migration of the device.

Sacral neuromodulation introduced by Thanago and Schmidt 1989 [136] became a popular second-line treatment for OAB, DO, and urinary retention [33]. Next to LUT dysfunction, sacral neuromodulation has been demonstrated to be effective also in bowel dysfunction, i.e., fecal incontinence and constipation [137], which will be not discussed in this chapter.

The currently used devices for sacral neuromodulation are the InterStim® or the new InterStim-II® device and the according electrodes (Medtronic, Minneapolis, Minnesota, USA). The implantation usually consists of two steps: (1) Electrodes (tined lead) are implanted unilateral under general or local anesthesia minimally invasively by needle puncture of the S3 foramen using fluoroscopic imaging. During the procedure, repetitive test stimulations can be performed to find the optimal position for definitive electrode placement. Following the placement of the electrode, the electrode lead is passed subcutaneously and connected to an intermediate lead that passes subcutaneously to the contralateral body side and exits the skin to be connected with an external temporary stimulator. (2) If the neuromodulation shows efficient treatment of symptoms during 1–3 weeks after implantation (controlled with voiding diaries), the implantation of a permanent stimulator (InterStim® or InterStim-II®) can be performed. The permanent stimulator is usually placed subcutaneously in the buttock. The exact implantation technique might vary between centers.

Although there are much more case series than randomized controlled trials investigating efficacy and safety of sacral neuromodulation, both study types present similar outcomes in efficacy [33, 138]; 67–80% of treated patients achieved continence or indicated an improvement of incontinence symptoms of more than 50% [138, 139]. These beneficial effects seem to last for at least 5 years [140]. The overall operative revision rate was indicated as 33% due to pain at stimulator or lead site (25%), lead related problems (e.g., migration, broken lead) (16%), replacement/reposition of stimulator (15%), wound complications (7%), adverse effects on bowel function (6%), and infections (5%) [138]. Complication rates in more recent studies vary strongly, indicating operative revision rates ranging from 7–53% [139–141].

Most studies did not distinguish between neurogenic and nonneurogenic LUT dysfunction, and commonly nonneurogenic patients were investigated. However, sacral neuromodulation is well suited to be used also in patients with neurogenic LUT dysfunction as demonstrated in some newer studies [142, 143].

Many questions regarding sacral neuromodulation remain still largely unanswered. This does not only concern the mechanism of action but also surgical technique, patient selection, stimulation parameters, and cost-effectiveness.

23.2 Current Developments and Ongoing Testing

23.2.1 Neuromodulation

Recent and ongoing investigations are trying to develop automated systems that can identify a beginning DO and immediately trigger pudendal stimulation to suppress DO [144–147]. Such a device in an implantable format would be a highly interesting treatment option for patients with DO.

Just recently, Sievert et al. published the results of an interesting approach using bilateral sacral neuromodulation in ten patients with complete SCI and urodynamically proven DO [148]. The time after injury was on average 3 months and in regard to this, the technique was named early sacral neuromodulation. The underlying hypothesis was that sacral neuromodulation might be able to positively influence the neural plasticity of LUT-relevant nerves below the lesion and thus can contribute in the reduction of DO [148]. The results were extraordinary, as all patients were continent, the DO abolished, and UTIs significantly reduced during a mean follow-up of 26 months [148]. In addition, bilateral SNM facilitated bowel and erectile function in some patients. Lead displacement and/or rupture in five of ten patients caused DO, which could be treated with replacement of the electrode [148]. Although these results are very preliminary in a small group, they might be a milestone in the treatment of LUT dysfunction in SCI and deserves further investigations.

A different approach has been described by Possover et al., with laparoscopic bilateral implantation of octapolar electrodes directly across the pudendal and sciatic nerves in complete SCI patients with DO [149]. Pudendal stimulation with 15–20 Hz caused an inhibition of DO up to 550 mL during filling cystometry [149]. Subsequently, the pudendal stimulation was switched off to unleash a detrusor reflex contraction. In patients with no or insignificant DSD, this resulted in efficient bladder emptying [149]. However, DSD could get in the way of that outcome. Thus, Possover et al. tried not to switch off pudendal stimulation completely, but rather switch to high-frequency pudendal stimulation with 1,200 Hz, resulting in a reduction of DSD and nearly complete bladder emptying [149]. However, it has to be admitted that Possover et al. still used Finetech-Brindley electrodes in addition to the octapolar pudendal electrode to promote sufficient bladder emptying [149].

In addition to the promising effects on bladder control, this therapy seems to be also beneficial for erectile function, reduction of lower limb spasticity, and even to enable short-term assisted standing by a sustained contraction of the quadriceps muscles via sciatic nerve stimulation [149].

However, this approach is still experimental, and the results presented are very preliminary (only three patients with 3 months maximum follow-up). Nevertheless, this is the first therapy addressing multiple pelvic dysfunctions at the same time without destroying or remodeling any nerves or organs. Further refinement of the system and technique without additional implantation of a Finetech-Brindley electrode in a larger series of patients is in planning.

Recent and ongoing studies investigate the effect of chronic pudendal nerve stimulation in patients with nonneurogenic and neurogenic DO using the InterStim® device with placement of the tined lead electrodes directly next to the pudendal nerve. This approach seems feasible, with first promising short-term results [150, 151]. Randomized controlled trials are in progress [152].

23.2.2 Nerve Rerouting

Rerouting of LUT nerves after SCI has been investigated in animals and recently also in a quite large population of complete SCI patients. This technique is based on a microsurgical anastomosis between the L5 and S2/3 ventral root, leaving the dorsal roots intact (Fig. 23.9) [153, 154]. The idea is that impulses delivered from the efferent neurons of a somatic reflex arc can be

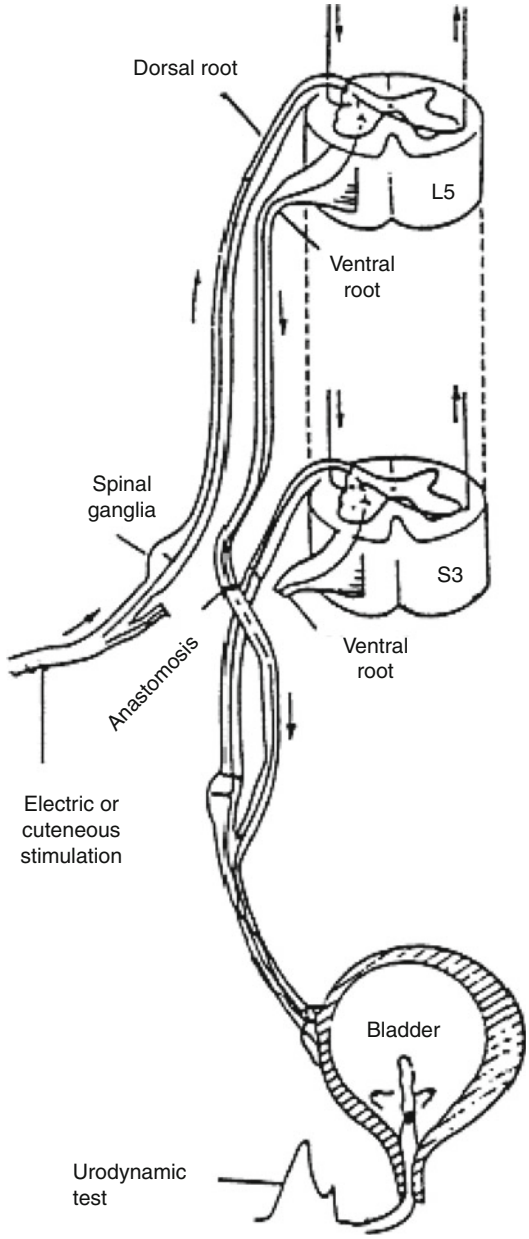

Fig. 23.9 Schematic illustration of the skin-spinal cord reflex pathway after re-rerouting the ventral roots of L5 with S3 (Reprinted by permission from Elsevier: Xiao et al., J Urol 170:1237–41, Copyright 2003)

transferred to initiate responses of an autonomic effector [153, 154]. To elicit a bladder contraction, patients have to scratch or squeeze on the L5 dermatome [153, 154].

Xiao et al. reported a success rate of 67–88% in SCI and 85% in spina bifida patients after unilateral rerouting of the ventral nerve roots L5 with S3 [153, 154]. However, the therapy success was poorly defined. Postvoid residual significantly decreased from 332 to 31 mL, and maximum urinary flow increased from 2.4 to 14.3 mL/s. But maximum detrusor pressure decreased, although significantly, only from 82 to 62 cmH_2O, and bladder capacity remained nearly unchanged (364 mL preop vs. 387 mL postop) [153, 154]. Moreover, patients had to wait for approximately 1 year until improvements occur [153, 154]. Although this approach seems to be an interesting alternative with only few reported adverse events, it appears inferior in efficacy to previously described techniques like botulinum toxin intradetrusor injections, augmentation cystoplasty, and SARS + posterior rhizotomy. Other groups currently do not confirm the initial results of Xiao et al. [155].

23.2.3 Tissue Engineering

Tissue engineering is the umbrella term for a rapidly advancing and highly complex medical research field that aims to improve tissue and organ reconstruction using autologous cells and stem cells. Especially, augmentation cystoplasty could be largely improved by using grown autologous bladder tissue instead of bowel segments.

However, the major difficulty in tissue engineering is to find the most suitable scaffold to develop a biodegradable three-dimensional construct that can accommodate adequate amounts of cells for functional tissue formation [156, 157]. Another challenge is to provide sufficient blood supply to the engineered tissue once it is implanted [156, 157].

First successful results have been reported in a small group of young patients with meningomyelocele requiring cystoplasty for the treatment of their LUT dysfunction [156].

To be able to advance further, to enhance product development, and to make tissue engineering products widely available, current and upcoming research in this field need to be focused

on the clinical applicability and capability to fulfill the ethical and legal regulations and to master the boundaries of licensing [157].

23.3 Perspectives and Conclusions

The largest problem in regard to the treatment of neurogenic LUT dysfunction function is still the coordination of efficient micturition on the one hand and uninterrupted, i.e., without irritative symptoms and incontinence, storage of urine on the other hand. Although some therapeutic gold standards could be established, there is still a lot to discover, to understand, to confirm, and to develop. As there are already many therapy options available with a lot more to come, proper therapy selection for the individual patient is extremely important for the successful treatment of LUT dysfunction. Further studies especially in the field of neuromodulation will hopefully enhance our knowledge in this regard.

The next future improvements and technical developments can be expected especially in regard to artificial sphincter systems, tissue engineering, and neuromodulation/neurostimulation of LUT afferent and efferent nerves.

However, those techniques need to be accessible for other groups. It does not add to the overall advancement in patient health care, if a specific technique is performed only in one or two centers worldwide. That is for two reasons: (1) Studies from those centers are usually small and not randomized controlled as patient recruitment is limited. Thus, the scientific validity of a potentially excellent technique will remain poor. (2) The treatment is not accessible for the majority of patients.

As LUT control is highly complex and a large variety of different etiologies, types, and stages of LUT dysfunction exist, there is a high possibility that there will never be one, two, or three most effective therapies suitable for all patients. Rather, there will be several therapies among which the treating physician can choose a single therapy or a combination for the individual patient and his specific LUT dysfunction and symptoms.

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Part X

Specific Aspects of Neurorehabilitation Technology: Assessment and Safety Issues

Robots for Measurement/ Clinical Assessment

24

Olivier Lambercy, Lars Lünenburger, Roger Gassert, and Marc Bolliger

Abstract

Neurological disorders such as stroke, traumatic brain injury, cerebral palsy, or spinal cord injury result in partial or complete sensorimotor impairments in the affected limbs. To provide an optimal rehabilitation, a detailed assessment of the nature and degree of the sensorimotor deficits is crucial. Valid, reliable, and standardized assessments are essential to define the therapy setting. Many clinical assessments suffer from limitations such as poor validity, low reliability, and low sensitivity. However, as often no alternative exists, they are widely used in clinical settings. Rehabilitation robotics is a promising technology that can provide objective measurements, which could help overcome the common drawbacks of clinical assessments. This chapter focuses on the new possibilities robotic devices offer in the field of neurorehabilitation. Different strategies to evaluate sensorimotor impairments using robotic platforms are presented. We discuss how a link between conventional scales and robotic assessments could be established, and how this could result in more objective, clinically accepted assessment scales.

Keywords

Neurorehabilitation • Sensorimotor impairment • Clinical assessment • Medical robotics • Rehabilitation robotics • Robot-assisted assessment

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24.1 Introduction/Motivation

Neurological damage following a stroke, spinal cord injury, or other neurological disorder can result in severe impairment of sensorimotor function. A detailed assessment and understanding of the nature and level of sensorimotor deficits is crucial for neurorehabilitation in several ways. In an early phase after the neurological injury, assessments are used to diagnose the extent of the injury. This diagnosis then serves as a basis to identify the most suitable therapy, i.e., to establish appropriate protocols tailored to the patient's needs and goals. In a subsequent phase, therapy is progressively adapted based on assessments, by tuning training parameters, e.g., type and complexity of a task, to maximally challenge patients during rehabilitation. Finally, due to rising healthcare costs, assessments have an important socioeconomic role, as hospitals and insurance companies offer their services based on clinically meaningful thresholds on standardized assessment scales.

A *clinical assessment* can be defined as the evaluation of a patient's physical condition and prognosis based on a physical inspection by a physician or therapist. Several studies have shown that the long-term evolution in motor function can be well predicted by clinical scales early after a stroke [1, 2] or spinal cord injury [3]. Throughout the course of a rehabilitation therapy, clinical assessments are usually repeated only at a few stages during the therapy to monitor the patient's status and progress. Despite being widely used in clinical routine, many clinical assessments suffer from limitations such as low inter- or intra-rater reliability, low sensitivity, or poor validity, and are often time-consuming to administer, limiting the number of assessments that can be performed at a time.

The field of rehabilitation robotics has seen increasing interest over the last decades [4, 5]. Robotic devices are a promising solution to complement conventional therapy and provide a unique platform for more objective and sensitive assessment [6]. By *robotic assessment*, we understand the evaluation of the physical condition (in terms of sensorimotor function) of a patient by interpreting kinematic and kinetic data recorded by the sensors integrated into a robot. Robotic devices offer the possibility to precisely record movement trajectories, completion time, task precision, etc., and measure interaction forces during well-controlled interactions. This then allows extracting task-related features descriptive of sensorimotor function of the patient [7]. Additional to this observational approach, robotic devices can actively excite or perturb the patients' movement in order to investigate neuromuscular control and related dysfunctions, and even be used concurrently with neuroimaging to gain deeper insights into the impaired neural mechanisms [8].

Clinical and robotic assessments are fundamentally different, but both aim at providing patients and therapists with a precise evaluation of sensorimotor functions or their effect on activities or participation. The specific characteristics of each assessment pose additional challenges with regard to comparability between assessments. With the International Classification of Functioning, Disability and Health (ICF), a common reference framework for functioning has been established. The goal of the ICF is to serve as a scientific basis to describe the health status of an individual with a common language. This common language allows comparison of results between clinics all over the world. In the context of the ICF, the health condition of an individual can be described by three main components: (1) body functions and structures, (2) activities, and (3) participation. There is a dynamic interaction between these three entities: changes or intervention in one may have influence on one of the other components or both [9]. However, in order to allow a comparison of clinical and robotic assessments, we propose here to group them according to the measurement domain they characterize, namely, temporal, performance, and impairment (Fig. 24.1). Whereas the *temporal* domain includes the measurement of the time required to complete a task (e.g., the 10-meter-timed walking test or the Nine Hole Peg Test), the *performance* is defined here as how well (in terms of movement quality) a specific task is executed (e.g., Fugl-Meyer). In the *impairment* domain,

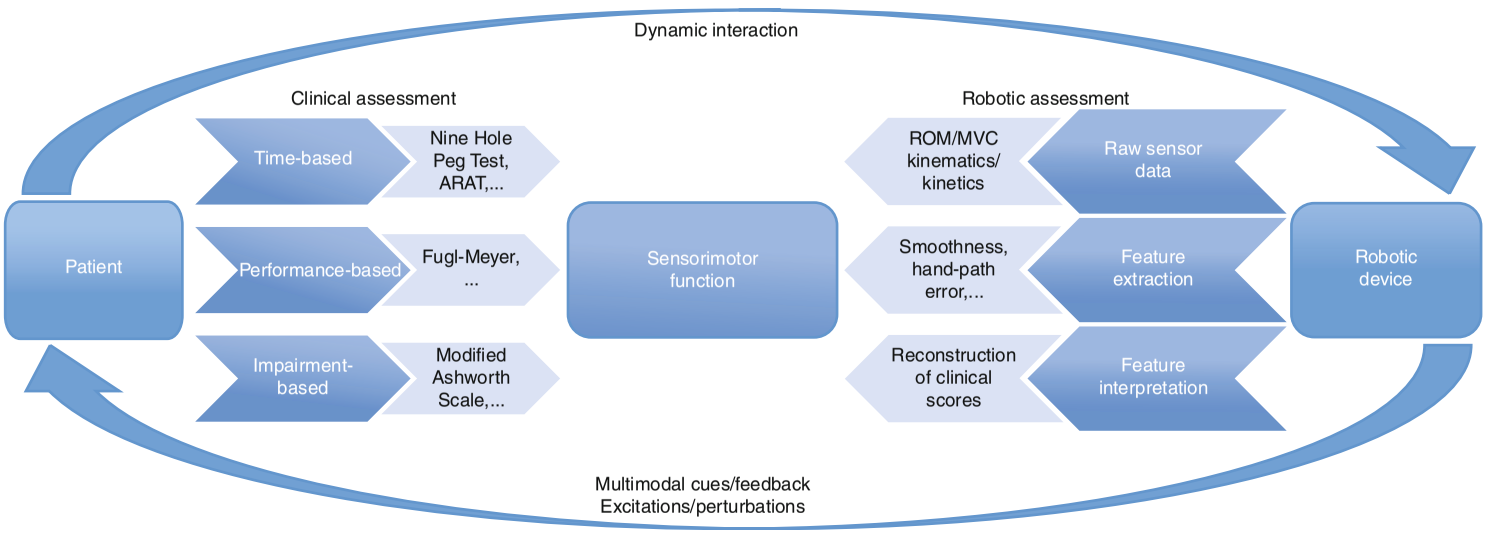

Fig. 24.1 Schematic representation of approaches for clinical and robotic assessments used to evaluate sensorimotor impairment resulting from neurological injuries. *ARAT* Action Research Arm Test, *ROM* range of motion, *MVC* maximal voluntary contraction

the measurement focuses on the direct physiological consequence of a disability (e.g., increased muscle tone in spasticity). It is essential to distinguish impairment and performance, as poor performance does not necessarily provide information on a specific disability, but usually reflects a combination of impairments.

A key challenge in robotic assessment is to translate raw measurements of physical parameters collected by the robotic system into clinically meaningful scales representative of sensorimotor deficits. Depending on the nature of these deficits, the scale values can either be deduced from the physical parameters directly or may require sophisticated algorithms to analyze motor performance.

This chapter will briefly describe the types of neurological impairments, which should be captured by assessments of sensorimotor function, and review clinical scales commonly employed after neurological injuries. It will then provide an overview of the current state of the art in robotic assessments for the upper and lower extremities. We first present different strategies used to evaluate sensorimotor impairments using commercial and research robotic platforms and then discuss how a link can be established between robotic assessments and conventional scales used in clinical routine. The chapter will conclude with an outlook on the main challenges toward realizing generally accepted robotic assessment scales and making them independent of the robotic platform. This independence will help these robotic assessments gain a wider usage and acceptance.

24.2 Impairments of the Upper and Lower Extremity Following Neurologic Injury

Good function of the lower and upper limbs is crucial for mobility and most activities of daily living (ADL). Neurological disorders such as stroke, traumatic brain injury, cerebral palsy, or spinal cord injury result in partial limitation or complete abolishment of sensorimotor function in the affected limbs. As a consequence, affected individuals become restricted in their activities and participation in society. Regaining motor abilities is therefore one major focus in neurorehabilitation. Lesions to the central nervous system affecting the control of the lower extremity often result in gait impairments. The resulting impairments range from asymmetrical gait – frequently observed after stroke – to the permanent need for a wheelchair for mobility. The physiological causes for gait impairments can be muscle weakness, spasticity, rigidity, sensory deficits, etc.

While impairment of the lower limb impacts mobility, impairment of the upper limb greatly defines the level at which one can interact with the environment and perform activities of daily living. Therapy and assessment of the upper limb focuses both on proximal arm function (shoulder and elbow), which is crucial for gross movements, and distal arm function (wrist and hand), which is important for grasping, manipulating, and orienting objects. Impaired sensorimotor function of the proximal upper limb following neurological accident includes abnormal muscle synergies (e.g., strong coupling between the arm flexor muscles), muscle weakness, or dystonia, resulting in poor interjoint coordination or the inability to position the hand in space. Distal arm function is particularly complex and is typically one of the last functions to recover after stroke.

At the level of the hand, damage to the sensorimotor system can lead to specific impairments that include (1) the limited ability to open the hand or position the thumb in opposition to the other fingers [10–12], (2) the loss of interjoint coordination and control, limiting the ability to move the fingers independently or generate force with individual fingers [13–15], (3) the inability to control endpoint force, and (4) the inability to explore the environment due to insufficient tactile sensation. These impairments result in difficulties in reaching, grasping, and manipulating objects, possibly leading to slow and uncoordinated movements or to the inability to perform these movements.

Because of the high complexity of the upper limb and the large set of actions we can perform therewith, conventional assessments for the upper extremity tend to focus on the evaluation of a specific task or impairment. Therefore, a battery of clinical tests is required to properly evaluate

arm and hand function, thus leading to time-consuming assessment sessions. One motivation for the use of robotic devices to assess upper extremity sensorimotor function lies in the possibility to quantitatively measure and record several parameters concurrently from multiple joints during a well-controlled, highly repeatable task.

24.3 Clinical Assessments

The outcomes of rehabilitation interventions show large variability in recovery between individuals. As a result, valid, reliable, and standardized assessments are needed in order to evaluate the effect of intervention therapies. These assessments can also be used to document the natural course after a neurological lesion. Good assessment tools allow investigating new intervention therapies and can identify their efficacy distinguishing between the therapeutic effect and the natural course of the neurological disease.

The quality of an assessment method is described by its sensitivity, validity, reliability, and responsiveness. Validity describes how precisely a measure assesses what it intends to measure. Hence, validity cannot be described by an all-or-nothing metric, but rather gradually. Reliability is given if an assessment produces equal results if repeated under equal conditions. This means that a reliable assessment must provide consistent measurement results [16]. Different aspects might influence the reliability of assessments of sensorimotor functions such as a learning effect between or during the tests, repeated administration of an assessment by the same or different raters (intra- or inter-rater reliability), or performing the test at two different points in time (test-retest reliability). Responsiveness of an assessment is defined as its sensitivity to detect real changes. For use in a clinical setting, it is essential that an assessment can detect changes over time that might reflect therapeutic effects [17].

Many clinical outcome measures to assess upper or lower limb function have been developed for use in different neurological pathologies. Unfortunately, some challenges remain with regard to the application of these clinical assessments. In the following section, examples of clinical assessments of the lower and upper limbs are given. The assessments are grouped into time-based, performance-based, and impairment-based assessments.

Time-based assessments rate the individual abilities based on the time required to complete the assessment task. The measurements are done on an interval or ratio scale (time). After neurological diseases that affect the lower limbs, walking tests with time measurements are widely used assessments. The time required to accomplish the test can also be used to calculate the walking speed. A typical time-based clinical assessment is the 10-m walking test (10 mWT), in which the patient is asked to walk 10 m along a defined direction. The test can be conducted at preferred or maximum walking speed. The 10 mWT has shown high inter-rater reliability in subjects with hemiparesis due to stroke [18] and with incomplete spinal cord injury patients [19]. Good validity for the 10 mWT could be shown in different neurological gait disorders [20]. However, walking speed in elderly is affected by body height, body weight, age, sex, and cardiovascular disease [21], and therefore, validity in this population is reduced.

An example for a time-based assessment for upper extremity is the Nine Hole Peg Test (NHPT). The NHPT was developed to measure finger dexterity and can be applied to patients with low to moderate impairment of hand function due to a variety of neurological diseases. The task consists in taking nine pegs from a container (one by one) and placing them into nine holes on a square board as fast as possible. In stroke subjects, a good construct validity compared to the Barthel Index has been shown [22]. In multiple sclerosis patients, a strong correlation between the NHPT and the expanded disability status scale, upper extremity scale, and quality of life has been shown [23]. Inter-rater reliability of the NHPT is higher than intra-rater reliability [24]. Reliability of the measurement degrades for longer completion times – a result of larger deficits.

Performance-based assessments describe how well a patient can achieve a specific task. These assessments are usually scored on ordinal scales.

An example for a performance-based assessment is the spinal cord independence measure (SCIM). The SCIM evaluates how good patients with a spinal cord injury can manage activities of daily living (ADL). ADL which are estimated to be most relevant to the well-being of the patients are scored and weighted in proportion to the rated importance of the function. Two revised versions of the SCIM (SCIM II & III) have already been proposed. Good validity of the SCIM has been found in several studies [25–27]. Test-retest reliability as well as inter-rater reliability have been shown to be high [26–28]. Responsiveness has been shown to be good [26, 28].

A typical performance-based clinical assessment in stroke is the Fugl-Meyer Assessment (FMA). The FMA is an established and widely used clinical as well as scientific assessment. Voluntary movement of the upper and lower limbs, balance, sensation, passive range of motion, and pain are assessed, each being scored on a three-point ordinal scale. The FMA has shown to have a good validity and reliability [16]. A good responsiveness could be found for patients with severe impairments [29]. A limitation has been shown in the ceiling effect in the motor domain of the FMA [29], resulting in patients achieving the maximum score on the FMA despite residual impairment.

Impairment-based assessments measure the direct physiological consequence of a disability. A common impairment after a neurological lesion is spasticity, which is characterized by involuntary muscle activity after damage of the upper motor neuron. A clinical assessment method of spasticity is the Modified Ashworth Scale (MAS) [30]. The test can be applied to the lower as well as the upper limbs. The rater flexes and extends the patient's limb from maximal extension to maximal flexion or vice versa and rates the perceived resistance on a six-point scale (ordinal scale). The MAS is the most commonly used assessment method in clinical as well as scientific research to measure spasticity. However, the validity of the MAS has been questioned [31]. Additionally, research on the reliability of the MAS revealed ambiguous results [30, 32]. Overall, the reliability is regarded as insufficient. Responsiveness has never been examined, as reliability is not given.

Whereas clinical assessments are widely used to diagnose individuals after a neurological accident, their assessment scores often constitute ordinal scales. The responsiveness of these tools and consequently their usability in clinical trials to investigate new intervention therapies is limited. This gap could be filled by robotic assessments.

24.4 Robotic Assessments

Over the last decades, many robotic devices have been developed to provide therapy to the lower and upper extremity, with the main goal of increasing the intensity and quality of rehabilitation therapy. Exoskeleton robotic devices such as the Lokomat [33] or the LOPES [34] have been developed for gait rehabilitation. Further, robotic systems such as the MIT-Manus [35], the MIME [36], the ARM Guide [7], or the ARMin [37] allowed training of proximal joints of the upper limb. More recently, devices such as the Rutgers Master II [38], the BiManuTrack [39], Hand Wrist Assistive Rehabilitation Device (HWARD) [40], the HapticKnob [41], or the HandCARE [42] were proposed to also target rehabilitation of hand function.

Robotic systems can provide therapy under well-controlled and repeatable conditions while assisting the patient in an optimal way (assist-as-needed [43]). A further advantage of robotic systems is that they can reduce the burden on the therapist, especially in gait therapy. While classical therapy forms require therapists to assist specific movements of the patients during walking, e.g., during body weight–supported treadmill training, or to completely support the weight of the patient during therapy, robotics and computer technology allowed the development of devices that provide this assistance by mechanical means.

The desire to quantify the effect of a specific therapy and the resulting improvements, along with the (financial) pressure on the health system to restrict reimbursement to quantifiably increased therapy outcomes, have motivated the extension of such devices to also allow performing assessments.

This is especially interesting as robotic systems are per se equipped with sensors required for the control of their multiple degrees of freedom. This can provide detailed information about the movement kinematics and kinetics (e.g., muscle force, active range of motion, movement smoothness, movement accuracy, movement velocity, motor coordination, and amount of robotic assistance), thus promising more objective assessments with higher sensitivity.

24.4.1 Assessments Based on Raw Sensor Data and Parameters

The assessment of upper and lower extremity functions with robotic devices can be based on a large variety of parameters collected by the robot during interaction with a patient, and the main challenge is to properly interpret these parameters and extract information in a meaningful way. A straightforward way to objectively evaluate sensorimotor function is to record the number of successful trials in a specific task the patient has to perform with the robotic system. For example, the number of successful reaching movements to a target position represented in a virtual environment during a specific amount of time can be a good general indicator of overall upper limb (shoulder, elbow, and wrist) motor function. Similarly, the time required to perform a specific task, for example, moving a virtual object from one point to another, with or without assistance from a robotic device is a commonly used measure to estimate motor function [44, 45]. While easily implementable on any robotic platform, this type of measurement does not provide any information on how well the task is performed by the subject and does not take full advantage of the measurement capabilities of a robotic system.

Training parameters can also be used to assess performance, for example, for the evaluation of gait performance of the patients and their improvement, as in the case of the walking speed [e.g., 46] or the required amount of body weight support. Although, these parameters can be set relatively arbitrarily by the therapist during the training, the therapists usually select the most challenging or difficult settings according to the capabilities of the individual patient. The therapists' concept is based on the assumption that "assist-as-needed" will lead to good therapy outcomes [47–49]. The settings used therefore represent the maximum challenge or minimal assistance respectively, and thus reflect the sensorimotor ability of the patient.

Raw sensor data can be advantageously collected by most robotic devices for therapy and assessment of upper extremity function equipped with position and force/torque sensors during specific movements with the device. This allows for objective measurement of parameters such as the range of motion (ROM) and maximum voluntary muscle contraction. As example, several commercial devices can passively flex and extend fingers and effectively measure finger ROM. More sophisticated robotic systems such as the ACT3D robot have been used to assess the arm-reaching workspace of stroke subjects on a virtual table, and how it is influenced by shoulder abduction loading [50]. Exoskeleton devices provide a simple mean to assess the range of motion. The therapist moves the corresponding joint manually through the patient's range of motion while the device records the maximal and minimal angles as measured by the integrated position sensors. This procedure was reported for the driven gait orthosis Lokomat [51]. Assumed the joints of the patient and the device are reasonably well aligned, this method provides a quick and easy quantification. This method is generally applicable to all devices with backdrivable joints (i.e., those that can be moved by an external force). In another example, here for a measurement method for maximum voluntary muscle force [52], the exoskeleton system is controlled to maintain predefined joint positions while the patient is instructed to generate maximum voluntary force in one joint (e.g., left knee) in one movement direction (extension or flexion) for 5 s. The computer instructs the movement on the screen and uses audio cues according to a predefined fixed sequence of joints and movement directions. The key outcome variable is the maximum torque using a time window of 1 s. The study showed good inter- and intra-rater reliability for this

outcome value in subjects with and without neuromuscular disorder. The intra-class correlation coefficients (ICC) ranged from 0.72 to 0.97 for inter-rater reliability in subjects without neuromuscular disorder, while intra-rater reliability ranged from 0.71 to 0.90. In subjects with neuromuscular disorder, ICCs ranged from 0.66 to 0.97 for inter-rater and from 0.50 to 0.96 for intra-rater reliability.

Even though devices for lower extremity rehabilitation are mainly designed to support gait movements, they usually allow generating other tasks such as single joint flexion and extension patterns. The most frequently targeted physiological property is spasticity. Lance [53] defined spasticity as a velocity-dependent increase in muscle tone when the muscle is passively stretched. More recent reviews of spasticity [54, 55] propose a wider definition. Based on these definitions, passive movements of a single joint were applied by isokinetic machines in many studies [56, 57]. In most studies, the torque during repetitive movements with constant velocity was recorded and analyzed [for review, see 58]. Many studies added electromyography to determine the muscle activity, thereby increasing the complexity of the measurement. One very interesting direction is the use of pseudorandom binary perturbations as proposed by Mibagheri and colleagues [59] based on system identification as described by Mirbagheri et al. [60]. Stiffness measurement in multi-joint robots has been described for the Lokomat [51]. Joint position and torque are measured while the device performs a smooth movement trajectory. Each of the four joints (hip and knee, left and right) is moved individually with two repetitions and different angular velocities. The elastic mechanical stiffness is calculated off-line taking into account the passive effects of the orthosis and the patient's legs using mathematical models. Counterintuitively to Lance's definition, these stiffness values show a reasonable relation to spasticity that was clinically measured using the Modified Ashworth Scale (MAS) [30]. Estimated values of viscosity – that would much closer correspond to the "velocity dependent increase" – has inconsistent relation to the MAS [61]. Schmartz et al. [62] report good test-retest reliability of the method extended to children with cerebral palsy.

While raw parameters can be easily interpreted and provide a clear idea of a patient's impairment level, they offer only little information on the source of the impairment and the relation to impaired sensorimotor function.

24.4.2 Assessment Based on Feature Extraction

More advanced robotic assessment techniques have been proposed with the aim of extracting more information from the data collected by robotic platforms. Performance metrics are parameters that are extracted from the raw data using dedicated algorithms, with the aim of better evaluating motor function and typical impairments.

As example in the case of robots for lower extremity rehabilitation that enable deviation from a prescribed trajectory, such as the LOPES [34], the actual foot trajectory can be analyzed similar to motion capture data in gait analysis. Using this exoskeleton device and footswitches, Van Asseldonk et al. [63] determined stride length, duration of stride, stance, and swing, as well as double-stance ratio kinematic parameters, to assess the subjects' performance. When no deviation from the prescribed trajectory is possible – e.g., for a high-impedance setting in an impedance controller– the trajectory does not provide information. Instead, the drive torques required to keep the patient's movement along the predefined trajectory are indicative of the patient's actions. One approach is to use torques measured by the device and multiplied by a weighting function for each instant of the gait cycle [64–66]. Averaging for stance and swing phases provides two values per leg and joint that can be displayed to the patient and therapist, as well as stored for later analysis [66].

In upper extremity rehabilitation, where movements with a robot are less stereotyped than in the case of gait rehabilitation, other performance metrics have to be used to assess sensorimotor function. Movement smoothness is a typical performance metric that has been extensively studied

using robotic devices training arm-reaching movements. In the literature, smoothness can be evaluated based on the jerk as the third derivative of position [67], the ratio of mean speed over peak speed [68], the number of zero crossings of the acceleration reflecting the number of putative submovements the movement is composed of [69], or the number peaks in speed [70]. Several studies with stroke patients have shown that movement smoothness improves over the course of rehabilitation [71–73], suggesting that smoothness indicators are valid measures of motor recovery [74]. During point-to-point reaching movements, the error with respect to a straight trajectory, or equivalent measures such as hand path ratio, e.g., ratio of trajectory length over straight-line length, is also used to evaluate motor control. It has been shown that neurologically impaired patients tend to deviate more from the ideal straight line, reflecting impaired inter joint coordination in the upper limb [44, 75]. Abnormal muscle synergies can be evaluated from simultaneous force recordings at different joints of the upper limb while asking subjects to produce isolated isometric force, e.g., shoulder flexion/extension or elbow flexion/extension in different position [76, 77]. Miller et al. [78] proposed a similar approach with a robotic platform recording isometric flexion and extension forces generated by the fingers, wrist, and thumb during robot-mediated 3D dynamic movements of the upper limb.

Performance metrics have also been developed in an attempt to assess hand function using haptic interfaces where neurologically impaired patients perform object manipulation in a virtual environment. Bardorfer et al. [79] used a PHANToM haptic device to create a virtual labyrinth in which subjects have to navigate. Hand function was evaluated using performance metrics such as motion speed, number of collisions with the labyrinth walls, impact duration, and impact force and allowed to distinguish between patients suffering from different types of neurodegenerative diseases. Using a similar approach, Emery et al. developed a virtual reality assessment inspired by the conventional Nine Hole Peg Test, where subjects have to insert nine virtual pegs into nine virtual holes by controlling the manipulandum of a PHANToM device [80]. Performance metrics based on the time required to perform meaningful movement segments, movement smoothness, and precision allowed to differentiate between various simulated hand impairments.

24.4.3 Reconstruction of Clinical Scores

The major challenge to solve before robotic assessments could be accepted for application in clinical routine is thus to validate performance metrics, for example, by relating them to established and standardized clinical assessments (concurrent validity) or by demonstrating that their assessment method corresponds to the underlying construct of the motor function, e.g., spasticity (construct validity). In lower extremity rehabilitation, only few studies have directly compared scores of robotic assessments with results of clinical scales. Robotic measurements of single-joint mechanical stiffness [51] were compared to the most widely used, yet controversially discussed, clinical measurement of the MAS. Despite large interindividual scatter, more severe spasticity (as measured by the MAS) related to higher stiffness in the same joint. However, there was little sensitivity in the robotic method to discriminate between MAS level 1, 1+, and 2 due to the stiffness calculation over the full range of movement, thus neglecting transient resistance at movement onset.

In studies of robot-assisted rehabilitation of the upper extremity, several groups have recently tried to directly correlate robotic parameters to clinical scales using simple regression analysis. Colombo et al. compared upper limb FMA scores of nine chronic stroke patients undergoing robot-assisted therapy focusing on shoulder, elbow, and wrist movements with robotic metrics based on an exercise score reflecting the amount of voluntary activity of the subject during the movement, the mean movement velocity, and an active movement index quantifying patients' ability in executing the motor task without assistance from the robot [81]. A moderate correlation ($r = 0.53$–0.55)

was observed between robotic measurements and the FMA scores. In a similar way, Celik et al. analyzed correlations between FMA, Motor Activity Log, Action Research Arm Test (ARAT), and Jebsen-Taylor Hand Function Test scores and robotic measures during 2D point-to-point target reaching movements with a robotic joystick [82]. Movement smoothness, trajectory error, average number of target hits, and mean velocity were selected as parameters representative of motor function. For the nine chronic stroke patients involved in this study, movement smoothness (defined in this study as a correlation coefficient between the actual trajectory and a minimal jerk trajectory profile) and trajectory error (defined as the normalized error with respect to the straight line) were found to have significant, moderate to strong correlations with all four of the clinical measures ($r = 0.49$–0.83). Regarding assessment of hand function, Feys et al. [45] developed a test with a PHANToM device where 21 multiple sclerosis patients performed tasks in a virtual environment, such as navigating a cursor following a predefined path or pick up and manipulate virtual objects. Performance metrics based on the total time to perform a task and the total distance traveled during the task were correlated with the NHPT, the ARAT, and the Purdue Pegboard. While correlations with the NHPT were not significant, good direct correlation was found between the performance metrics and the ARAT and Purdue Pegboard ($r = 0.48$–0.69). In summary, these results suggest that movement smoothness and deviations from a reference trajectory during point-to-point reaching, which can be implemented on most robotic platforms, could be valuable indicators characteristic of upper limb motor function.

Bosecker et al. investigated more complex linear regression models to compare the FMA, the Motor Status Score, Motor Power, and MAS to robot-based metrics collected during point-to-point arm-reaching movements for a population of 111 chronic stroke patients who received robot-assisted rehabilitation with the InMotion2 robot [83]. Multiple linear regression models were developed to reconstruct the scores of clinical scales based on an optimal linear combination of meaningful parameters collected by the robot. Results showed a good reconstruction of FMA scores ($r = 0.80$) and the Motor Status Score ($r = 0.79$) for the group with which the models were trained. Motion smoothness (calculated here as the ratio of mean to peak speed) was found to be the most important parameter for the reconstruction of clinical scores, together with maximal speed, movement duration, and joint independency (correlation during elbow and shoulder angles measured during circle drawing with the robot). In a recent study on hand rehabilitation with the HapticKnob, a two-degrees-of-freedom device to train grasping and forearm pronation/supination, a stepwise linear regression analysis was performed in an attempt to reconstruct clinical assessment scores from the kinematic data collected during a 6-week rehabilitation therapy involving 15 chronic stroke patients [84]. Hand and arm impairment was clinically assessed before and after robot-assisted therapy with the FMA, Motricity Index (MI), Motor Assessment Scale (MS), and MAS. In addition, robotic assessments were performed on the first and last days of therapy by asking patients to perform a succession of grasping movements against a resistive load and precise target-aligning movements in forearm pronation/supination. Results of the stepwise linear regression analysis showed that clinical scores could be well explained by only one or a combination of two of the extracted parameters representative of movement control, smoothness (n_0), and precision (t_{adj}) (Fig. 24.2). Good correlation was observed between clinical scores of the upper extremity and their respective reconstructed scores ($r = 0.669$ for FMA, $r = 0.689$ for MI, $r = 0.599$ for MS, and $r = 0.792$ for MAS). The principal parameter used to reconstruct clinical scores was the time to precisely adjust the forearm angle during pronation/supination exercises (t_{adj}). This parameter may describe both hand and arm function, as the task required the patient to coordinate hand and arm in order to accurately reach and maintain a specific orientation, while maintaining a grasping force to hold the robot. The promising possibility to reduce the robotic assessment to only a few significant metrics typically decreases the number of exercises

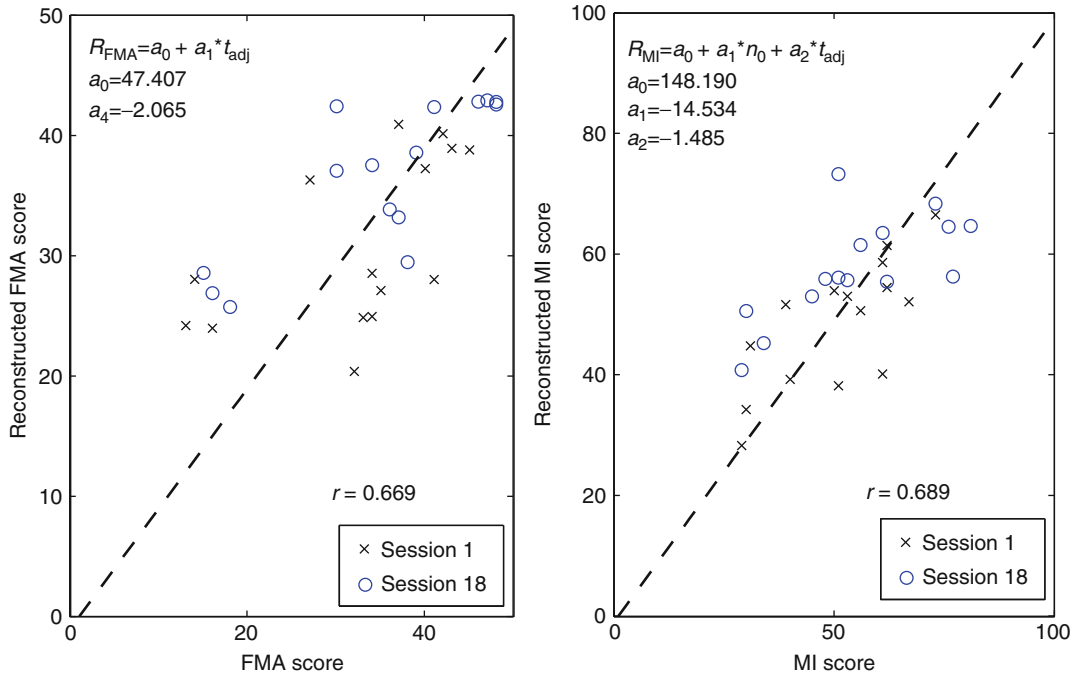

Fig. 24.2 Correlations between Fugl-Meyer (*left*) and Motricity Index (*right*) clinical assessment scores, and reconstructed scores based on performance metrics of hand opening/closing and pronation/supination movements with the HapticKnob. Linear models for the reconstruction were computed using stepwise linear regression on data collected 15 chronic stroke patients at beginning (session 1) and end (session 18) of robot-assisted therapy [84]

to be performed and evaluated, with the potential of simplifying and shortening assessment sessions [83].

24.5 Conclusions

The promising results of recent robot-assisted rehabilitation studies demonstrate the potential of using robotic platforms not only to complement conventional therapy but also to assess sensorimotor function in a more objective and reliable way. Performance metrics obtained from such systems offer new possibilities to objectively investigate sensorimotor impairment under repeatable conditions. These metrics can provide unique information on the quality of patient's performance in a defined task, which cannot be captured with conventional clinical scales. Because of the quantifiable assistance that the robots can provide, robotic assessments can be administered even if the patient is not able to perform the movement without support. This can enlarge the measureable range of impairment and improve sensitivity. Nevertheless, while it is clear that these metrics have a promising potential to assess function of the lower and upper extremities, they remain abstract values that are difficult to interpret for therapists and patients relative to the well-established and standardized clinical measures. Also, validity and sensitivity of a novel performance metric can only be evaluated through comparison with established clinical assessments.

Robotic assessments will only find wider application and reach their full potential once the community agrees on assessment metrics that can be implemented on various robotic platforms with adequate instrumentation. This could lead to platform-independent assessments that can be used for quality assurance and to allow comparison of treatment outcomes across rehabilitation centers worldwide. While such a goal seems achievable in the near future for isometric and passive measurements, the transparency

(apparent dynamics) of any given device will need to be considered in assessments involving active, dynamic movements.

In the future, robotic assessments based on feature extraction and the reconstruction of clinical scores could be performed online, during therapy, allowing continuous monitoring of the improvement in sensorimotor function. It is likely that they would also offer the possibility to continuously adapt type and complexity of a therapy to the current state and principal impairment of the patient, with the aim of maximizing engagement and therapeutic effect. However, the reconstruction and estimation of a clinical scale should not be seen as the final goal of robotic assessment. Even if studies showed good correlations between clinical and reconstructed scores, these remain only estimations based on models, which would need to be refined with more patient data. Robotic assessments should rather be seen as independent scales that could become new standards offering the advantage of increased sensitivity, reliability, and objectivity.

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Standards and Safety Aspects for Medical Electrical Devices in the Field of Neurorehabilitation

25

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Abstract

An overview of standards and safety aspects for medical electrical devices in the field of neurorehabilitation is given as a snapshot in time. Common basic safety principles for medical devices, specific aspects from the Machinery and Medical Device Directive and their harmonized standards, and new standardization efforts about "medical robots" are summarized.

Keywords

First fault • Medical devices • Predictable hazards • Risk management • Safety aspects • Software requirements • Standards

25.1 Introduction

The requirements for technical appliances within rehabilitation in its various phases are as varied as the individual patterns of disease of patients affected in the still-young medical discipline of neurorehabilitation.

The focus of this chapter is the consideration of necessary and reasonable safety aspects and standards that must be maintained when using technical appliances in the area of neurorehabilitation. Here we will concentrate on such appliances, whose objective is the ability to relearn the functions of extremities that have been completely or partially lost.

At present, it does not matter whether these technical appliances are simple or complex in structure, or whether they offer active or passive support. The essential common ground – expressed very simply – is the support for relearning the movements of the individual body extremities. Thus, it will already be clear that these products do not contain any life-supporting functions, which is an important aspect for further safety considerations. However, the technical appliances being considered here are always in very close contact with patients who differ from one another in so many ways. A few aspects are listed here, but these are not exhaustive:

- Age of the patients (from child to advanced old age)
- Mild/medium serious impairment by, for example, the limited freedom of movement of

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an arm following a stroke up to quadriplegia in the cervical region after an accident
- From no cognitive disorders to severe impairment
- From absence of spasticity to severe spasticity
- From no autonomic disorders to severe impairment
- From self-administration by the patient up to specially trained (para-) medical users specifically schooled in the use of the devices
- From the application in special clinical situations such as intensive care and monitoring rooms to application in the patient's residence
- From early rehabilitation immediately following the occurrence of the neurological losses to late or long-term rehabilitation

All these aspects should be noted at the conception and design phase of the technical devices. Since the therapy of the patient is at the forefront when utilizing technical appliances, we are dealing with medical devices that must be safe and effective. Only after it has been verified that:
- The construction of such products is safe and effective, taking into consideration the purpose and intended use
- The patient population
- The surroundings of the application
- The usability for the user
- The product risk management

can the product be called a "medical device." All of these considerations must meet the cost demands of today's nationally very varying health system. Thus, not only investment and maintenance costs and space and infrastructure costs but also personnel costs will have a decisive influence on the reimbursement of expenses by the service providers in the health system.

Further requirements on medical devices are regulated in national laws and regulations and are to be noted prior to putting them on the market. They must often be verified, and placement on the market has to be approved. But the scope and form are subject to a certain spectrum. Basically, these rules follow the purpose of patient safety by making the risk–benefit analysis efficient as well as sufficiently protecting both user and third parties. Newer systems classify "medical devices" on the basis of their risk potential.

At the same time, the concept of "medical devices" is defined in different ways on a national regulative level. One international organization, the Global Harmonization Task Force (GHTF), which is aiming at a national legislative body, is becoming increasingly important when it is a question of "medical devices" and their regulations. The GHTP (http://www.ghtf.org/) defines "medical device" as follows:

Medical device means any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material, or other similar or related article:

(a) Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:
   - Diagnosis, prevention, monitoring, treatment, or alleviation of disease
   - Diagnosis, monitoring, treatment, alleviation of, or compensation for an injury
   - Investigation, replacement, modification, or support of the anatomy or of a physiological process
   - Supporting or sustaining life
   - Control of conception
   - Disinfection of medical devices
   - Providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body

(b) Which does not achieve its primary intended action in or on the human body by pharmacological, immunological, or metabolic means but which may be assisted in its intended function by such means

Note 1: The definition of a device for in vitro examination includes, for example, reagents, calibrators, sample collection and storage devices, control materials, and related instruments or apparatus. The information provided by such an in vitro diagnostic device may be for diagnostic, monitoring, or compatibility purposes. In some jurisdictions, some in vitro diagnostic devices, including reagents and the like, may be covered by separate regulations.

Note 2: Products that may be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach are:

- Aids for disabled/handicapped people
- Devices for the treatment/diagnosis of diseases and injuries in animals
- Accessories for medical devices (see Note 3)
- Disinfection substances
- Devices incorporating animal and human tissues which may meet the requirements of the above definition but are subject to different controls

Note 3: Accessories intended specifically by manufacturers to be used together with a "parent" medical device to enable that medical device to achieve its intended purpose should be subject to the same GHTF procedures as applied to the medical device itself. For example, an accessory will be classified as though it is a medical device in its own right. This may result in the accessory having a different classification than the "parent" device.

Note 4: Components to medical devices are generally controlled through the manufacturer's quality management system and the conformity assessment procedures for the device. In some jurisdictions, components are included in the definition of a "medical device."

The manufacturer plays an important role by specifying among other things the intended use of the medical device for which he has to verify safe and effective utilization.

New technologies today support the patient to such an extent that the medical devices can be individually adapted or are adaptable to the performance and the necessary degree of support that the patient requires. For this purpose, sensory and associated control systems that can control the essential ability to detect and adapt in a given situation are necessary. Such systems are also used outside medical devices technology. Under the catchword "robots," there are very diverse products on the market, which on the one hand have been in industrial use for a long time, but recently are also becoming established in the "service sector." Both application sectors have their own standards and safety mechanisms, which will be briefly addressed in the following sections and considered with regard as to whether they can be adapted to the "medical device sector."

High research and development costs in the new field of neurorehabilitation technology must be able to be covered, as, too, the capital expenditure arising from the use of the newest "medical devices." At the same time, the focus must remain on the safety of the patient, user, and third parties, together with the effectiveness of treatment.

Technical standards and safety packages do not or insufficiently take into consideration some of the above-listed basic conditions in the conflicting priorities of cost-effective, highly effective, and safe "medical devices."

25.2 Standard and Safety Aspects for Medical Electrical Devices

When it comes to the conception and realization of medical devices, different international, national, or regional standards are brought to bear. To some extent, compliance with these is directly or indirectly demanded by national/regional legislation, as for example, is valid in the European Union. The Medical Device Directive [1] uses the term "harmonized standards," and this list of harmonized standards is regularly published in the "Official Journal of the European Union" (http://ec.europa.eu/enterprise/policies/european-standards/documents/harmonised-standards-legislation/list-references/medical-devices/index_en.htm).

The applicable standards are often given indirectly, by frequently having to substantiate their contents for approval or registration procedures. In particular, the product standards contain details for safety aspects that can be either of a general or highly specific nature. These interrelations will be outlined roughly subsequently.

25.2.1 Standards for Medical Electrical Devices

International standards for medical devices can be classified into the following listed groups.

25.2.1.1 Product Standards

These standards are related to a specific product or group of products. These include:

(a) Safety standards that include the safety specifications necessary for and applicable to the intended use of the product (e.g., IEC 60601-1 and the associated supplementary standards and special specifications for medical electrical devices).
(b) Standards for the essential performance with specifications necessary for the effective performance of the product.
(c) Standards with nonsafety relevant specifications that are not included under (a) or (b). These standards contain requirements for the performance or testing procedures that help the manufacturer or operator to determine the usability of the device.

25.2.1.2 Procedural Standards

A series of types of standard falls in this category, including:

- Quality assurance standards (e.g., standards for "good manufacturing practice (GMP)" and "quality control (QC)")
- Other standards that require the assessment of the "process verification" (e.g., standards for programmable electronic systems, sterility, biocompatibility [2], or ergonomics)

25.2.1.3 Construction and Environmental Standards

These standards include:

- Construction and installation standards (e.g., radiation protection, rules for electrical installation)
- System standards (e.g., the essential specifications for correct interfaces and interaction), such as standards for a medical information bus (MIB)
- Commissioning standards, if the safety can be increased by evaluating the design or testing of the installation and settings of the medical devices immediately prior to commissioning
- Environmental standards, which limit the probable influence of the medical device and its surroundings or the effect of external influences on the medical device (e.g., standards related to electromagnetic compatibility)

25.2.1.4 Rules Governing Application

These include:

- Specifications about regular checking during operation, if the safety could be endangered by wear and tear or aging of the medical device or installation
- Specification for constancy and calibration, if the safety of the medical device is dependent on a proven function and precision
- Explanatory guides that inform about any hazards associated with the special medical devices types and their applications and which offer appropriate safety recommendations
- Guidelines for the operator for information about the classification systems for the safety in the associated product standards

25.2.2 Standards for Medical Electrical Devices for Neurorehabilitation

If medical devices are involved in this application, electrically operated medical devices will not be able to avoid the IEC 60601 Standards series as product standard, and this is supplemented by the ISO 80601 standards.

The IEC 60601 Standards series essentially defines safety requirements for medical electrical devices and medical systems. IEC 60601-1 is valid for the basic safety and the essential performance characteristics of medical electrical devices and medical electrical systems. The latest revision of IEC 60601-1 [3], which is supplemented to some extent with national variations and supplements, although already published in 2005, will only become applicable after an appropriate transitory period in the most important sales markets and in following years will become obligatory. This standard is accompanied by a series of further requirements of a general nature (coded as IEC 60601-1-x) as well as by requirements for certain types of medical devices (coded as IEC 60601-2-x and ISO 80601-2-x).

Standards from the IEC 60601-2 series, which could relate directly and completely to the subject of medical devices in neurorehabilitation, based on current knowledge, are not known to the author. Standards that could be used in part are, for example:

- TC/SC 62D
- Medical electrical equipment – Parts 2–5: Particular requirements for the basic safety and essential performance of ultrasonic physiotherapy equipment
- TC/SC 62D
- Medical electrical equipment – Part 2: Particular requirements for the safety of nerve and muscle stimulators
- Amendment 1, Medical electrical equipment – Part 2: Particular requirements for the safety of nerve and muscle stimulators

Appendix 25.1 to this chapter offers an overview of the currently published IEC 60601-1-x standards that contain basic requirements from all medical devices, provided they are electrically operated and are used for all cases described.

Product standards that can be partially or totally used are not found exclusively in the sector of medical devices. They are found, for example, in the sport and leisure sector. International standards that make comments about treadmills or stationary training equipment can, for example, be drawn upon on the basis of recognized rules for better evaluating certain risks with standardized tests. In addition, it must be mentioned that apart from the ISO 60601-x // ISO 80601-x Standards series, further individual standards or standard series exist that refer to medical devices. Regular standards research should be carried out in order to ensure the respective current status of information. In this respect, service providers offering an appropriate service can also be called upon.

Quality management system standards are ranked among the procedural standards. ISO 13485 [4] Medical Devices Quality Management System for International Applications must here be fulfilled, and for the American market, the Food and Drug Administration (FDA) regulations according to 21 CFR § 820. Here, it should be noted that the requirements from the American market are not standards but regulations having a legislative character.

For medical devices that are categorized as PEMS (programmable electrical medical systems), apart from the requirements which IEC 60601-1: 2005 sets, those of IEC 62304 [5] concerning the life-cycle requirements for medical device software must also be complied with.

IEC 60601-1: 2005 already requires that for medical devices intended to have direct or indirect contact with biological tissues, cells, or body fluids, one should proceed according to the instructions and principles of ISO 10993, in order to verify the biocompatibility of the materials utilized, where this is necessary. Similarly, for usability, requirements are made that refer to IEC 60601-1-6 standard for electrical medical devices. For nonelectrical medical devices, the IEC 62366 [6] standard Application of Usability Engineering to Medical Devices should be consulted.

Concerning construction and environmental standards, the standards IEC 62353 [7] for periodic tests and IEC 60601-1-2 [8] concerning electromagnetic compatibility, in particular, are to be included, which are to be taken into account for the case under consideration.

25.2.3 Standards for Medical Electrical Devices for Neurorehabilitation: Medical Robots

It should be mentioned that, recently, the ISO (International Organization for Standardization) has addressed the subject of "medical care robots" within TC 184/SC 2 "robots and robotic devices" and started deliberations about creating a standard for robots in medical use, such as medical devices. Such "robots" are already in operation in neurorehabilitation and thus will also be affected by such a standard.

The industrial robots utilized today fundamentally differ most of the time with respect to the safety concept of medical devices. Such robots are today predominantly shielded from their

surroundings and do not come into contact with humans, apart from maintenance and repair. The exceptions here are those robots that can be grouped together as "service robots."

Robots in the neurorehabilitation sector are in direct contact with humans, directly with patients and indirectly with a user. Consequently, safety concepts from industrial applications cannot be directly transferred to our medical devices under consideration here.

Table 25.1 offers an overview of the current status (June 2010) and the perspective of the ISO TC 184/SC 2 subcommittee work.

25.2.4 Safety Aspects for Medical Electrical Devices

If safety concepts are being considered for medical devices, it is not possible to avoid getting involved with certain definitions. What is safety, what is danger, and what degree of what safety must be realized? How does one attain safety, with what measures, and under what acceptable residual risks?

Colloquially, safety is probably mostly equated with expressions such as "freedom from danger" or "freedom from risk." IEC/TR3 [9] explains that *"safety generally refers to acceptable freedom from risk."* IEC 60601-1:2005 firstly defines basic safety as "freedom from unjustifiable risk directly caused by physical hazards, if the medical device is used in the normal state and at the occurrence of the first fault." It becomes clear that safety is linked to a combination of boundary conditions or expressed in another way, absolute safety cannot be realized.

Besides the (fundamental) requirements for safety of a medical device, identical requirements are made for the performance and effectiveness, or so to speak, on the efficacy of the medical device. From the medical-therapeutic viewpoint, this is understood to mean the medical efficacy so that the medical device should deliver the results expected for treatment or diagnosis. Similarly, the medical device should render the specified services in the form of defined physical properties, such as, for example, speeds or forces.

The requirements for safety and medical effectiveness and technical efficiency cannot be considered apart from each other. The success of a treatment or even life and limb of the patient or user could be endangered by a medical device, if it possesses hazardous capabilities, or if it does not function or is not used as intended by the manufacturer.

An example often quoted in the standardization literature about a medical device makes this impressively clear. A defibrillator can save a patient's life if used correctly and can counteract a ventricular fibrillation. At the same time, if such a defibrillator is improperly used, there is a certain risk for both user and third parties that can lead to a life-threatening situation or even death for the patient in case of the wrong indication.

It is becoming clear that there must be a middle course between "freedom from risk" and other requirements for a medical device, and thus an acceptable degree of risk or the freedom from unjustifiable hazards must be aimed for. In order to successfully progress along this middle course, it is necessary to draw up a product-specific risk analysis, from which measures to control risk can be implemented.

Apart from ascertaining the hazards associated with a certain type of medical device, risk analysis also includes the specification of the essential performance characteristics, i.e., those particular characteristics of a medical device that also ensure that no unacceptable risk arises under faulty situations. This is probably most clear for life-supporting medical devices such as a breathing apparatus, which can still provide sufficient ventilation to a patient even in faulty conditions so that his life is not immediately threatened.

Acceptable risk is partly based on the realization that complete absence of risk is unattainable and partly that the degree of risk must be sufficiently low. Risk is a combination of frequency of occurrence and the resulting hazard for patients, user, third party, and, if need be, objects.

Table 25.1 ISO TC 184/SC 2 Subcommittee current status (June 2010) and the perspective of standard works

Standard	Name	WG	Status	Task	Task date
ISO 8373	Vocabulary	WG1	CD	Publication	2013
ISO 10218-1	Robot	WG3	DIS	Publication	2010/2011
ISO 10218-2	Robot system and integration	WG3	FDIS	Publication	2010
ISO/TS 15066	Collaborative work space	WG3	NWIP	Publication	2011
ISO 13482	Non-medical personal care safety	WG7	CD	Publication	2012
ISO xxxxx	Medical personal care robot	WG7	Study Group	NWIP	2011
ISO 9409	Mechanical interface – plates/shafts	–	DIS	Part 1 revised	2011
ISO 9283	Performance criteria and testing	–	–	NWIP	2011
ISO/TR 13309	Guide for robot performance evaluation	–	–	Follows ISO 9283	–
ISO 9787	Coordinate system and motion nomenclature	–	–	Systematic review	2014
ISO 9946	Presentation of characteristics	–	–	Systematic review	2014
ISO 11593	Automatic end effector exchange systems	–	–	Systematic review	2011
ISO 14539	Object handling with grasp-type grippers [12]	–	–	Systematic review	2010

Adapted from ISO TC 184/SC2

Table 25.2 Risk classification of accidents: fundamental aspects of safety standards for medical electrical equipment

Occurrence	Consequence			
	Catastrophic	Critical	Marginal	Negligible
Frequent	I	I	I	II
Probable	I	I	II	III
Occasional	I	II	III	III
Remote	II	III	III	IV
Improbable	III	III	IV	IV
Incredible	IV	IV	IV	IV

Adapted from IEC/TR 3 60513ble 2

The tests that are usually applied according to IEC/TR3 60513 [10], in order to decide whether a risk is acceptable or not, also determine whether:

(a) The risk is so high or the consequences are so unacceptable that it must be rejected as a whole.
(b) The risk is so low or made so low that it is negligible.
(c) The risk lies between (a) and (b), after it has been reduced to the lowest practical amount, being conscious of the benefits that result, taking the costs of any further reduction of risk into account.

Risks must be reduced to as low a level as reasonably practical (the ALARP principle: *As Low As Reasonably Practicable*). If, e.g., a risk falls between the two extremes "not acceptable" and "insignificant" and the ALARP principle is applied, the resulting risk is an acceptable risk for the application being considered. Although the main considerations for determining the acceptable degree of risk are the extent of damage and the probability, other factors also have to be taken into consideration, e.g.,:

- How often the prerequisites for the hazard occurrence can be expected (e.g., frequency of the device usage or number of patients treated)
- The feasibility of further improvements
- The costs of further improvements
- Clinical constraints and boundary conditions
- The benefits that arise by the application of the medical device
- Public acceptance/customer acceptance

Assessment according to Tables 25.2 and 25.3 has also proven to be useful.

Table 25.3 Interpretation of risk level

Risk level	Interpretation
I	Intolerable risk
II	Undesirable risk, tolerable only if reduction is impractical or if the costs are grossly disproportionate to the improvement gained
III	Tolerable risk if the costs of risk reduction would exceed the improvement gained
IV	Negligible risk

Adapted from IEC/TR 3 60513

Avoiding and controlling faults is implied from the necessity, listed in Table 25.3, of reducing risks to an acceptable level. Avoiding faults means preventing faults from occurring. Controlling faults means taking additional measures in the case of a fault occurring so that dangerous effects can be prevented. Since complex systems cannot be exhaustively assessed by tests, their correctness (functionality) and reliability must be assessed in other ways. Certainty about this is attained by applying suitable procedures during the design process, which have to be transparent and universally consequently applied. The growing realization that unlimited safety cannot be reached has led to the development of risk management concepts. More detailed information on the subject of risk management for medical devices can be found in IS014971 [10, 11].

IEC 60601-1 and IEC 60601-2-xx already specify most of the general hazards for a wide variety of medical devices. A large number of hazards have already been listed:

- Acceptable configurations of safety-relevant systems (e.g., systems that contribute to safety,

such as basic insulation plus a protective earth connection as a reliable configuration for avoiding electric shock)
- The exclusion of certain events in the normal state or in case of a single fault

A requirement formulated according to one of these two types states that a risk is acceptable.

Fault conditions that have to be taken into consideration can be categorized as follows:
- Some faults can be recognized by the user (e.g., external physical damage can be noticed by the careful operator; a broken wire will cause an obvious malfunction in several types of medical electrical devices).
- Some faults cannot be observed, not even by the careful user, but they can be detected by regular maintenance (e.g., partial breakdown of the insulation between the main connection and the protective earth connection in medical electrical devices).
- Some fault conditions can be neither detected by the user nor discovered by regular maintenance (e.g., breakdown of an insulation layer in double insulation).

Only in the fewest cases are there investigations about the actual probabilities of different hazards; instead trust is widely placed on the "philosophy of the first fault," which can be set out as follows:
- No hazards may result in any of the listed "conditions of the first fault."
- All instrument parts that are there to provide safety must be "appropriately reliable" so that the probability of an "initial fault" is low.
- Then the probability of two "initial faults" is very low, and thus the hazard risk caused by a multi-fault condition is acceptable.
- If an initial fault immediately causes others, the probability of these faults is the same as those of the initial fault, and the medical device must remain safe (direct aftereffect on another component caused by the breakdown of an initial component).
- If under certain circumstances two faults arise from a common cause (e.g., bridging of both insulation layers in a double insulation by a conducting liquid or metal objects), the probability of these two faults is the same as the common cause.
- If a fault cannot be discovered at reasonable cost with workable maintenance procedures and it is not likely that it will be noticed by the user because it does not influence the device function, the high probability that the fault will remain unnoticed for a long period of time must be taken into account when developing the safety requirements.

Indeed the probability of simultaneous occurrence of two "initial faults" is not zero. According to IEC/TR3, for medical devices, it is presently considered to be sufficient to guarantee that hazards cannot occur with a "single fault." In the case of a double fault, a hazard can occur, but the risk is considered to be slight. The first fault philosophy implies that in general, it is expected that a medical device will have two measures as a protection against each and every hazard. Then it will be assumed that the risk is negligible, provided that the probabilities of faults in the individual systems are low.

This implied demand for "two measures of defense" cannot be covered by redundancy of the same safety systems in every case. The specific circumstances should be taken into consideration, along with the components, their life cycles, and their typical signs of aging. The use of differently designed safety systems that utilize different technologies has proven useful.

Medical electrical devices should remain within acceptable risk limits when faults occur, which:
- Can be recognized by the user (e.g., by a signal or a function that is missing)
- Can be discovered by regular inspection or maintenance, which is carried out in compliance with the accompanying documents
- Cannot be observed by the user or during a systematic maintenance, but can be discovered or controlled by safety measures that have been installed

They also have to remain within acceptable risk limits in the case of non-detectable faults.

The safety of medical electrical devices often demands an integral approach, in which the

manufacturer and operator implement a combination of measures, including the following:

- Prerequisites fulfilled by the design of the medical device
- Additional measures such as installation requirements, formal commissioning, regular maintenance, and safety checks
- Measures that make the operator aware of the necessity of special precautions when using certain types of medical electrical devices or with certain applications

The safe use of medical electrical devices depends on a series of influences, including:

- The construction of the medical device, which must allow and contain the facilities for avoiding hazards
- Appropriate validation of design of hardware and software prior to the start of production
- Application of "good manufacturing practice (GMP)" during the production of the medical device
- Selection of the correct medical device for the respective medical application
- User's familiarity of the medical device and its application, which can be dependent on training or labels on the medical device and manufacturer's instructions
- Use of accessories that are suitable for the medical device
- Connection of the medical device to suitable supply network (e.g., electrical power supply, central gas supply)
- Preventive maintenance of the medical device
- Utilization of specified replacement parts when repairing medical devices

25.2.5 Safety Aspects for Medical Electrical Devices for Neurorehabilitation

To the special safety aspects that medical devices in the neurorehabilitation sector have to take into consideration are the issues that accompany the particular impairments of the patients, who, due to their neurological changes, are lined up for therapy. Nevertheless, the way in which the appropriate medical device is designed and the manufacturer's intended purpose also have to be taken into consideration.

As explained in the introduction, the severity of shock of the patient and the cognitive and functional limitations must be taken into consideration so that sufficient attention has already been paid to appropriate reflections in the design and risk management process. It may be assumed that for the majority of the patients, there is a limited reaction and perception capacity. Risk assessments in this respect and options for reducing risk are therefore to be designed appropriately. In addition, many of the patients in therapy often suffer from a series of secondary impairments or aftereffects, which are direct or indirect results of the illnesses or injuries. Risk analyses must therefore be accompanied by clinically experienced persons, familiar with handling the patient population in question.

The guarantee of usability of medical devices for neurorehabilitation should also be considered from this perspective. Patients who will be possibly rehabilitated with the medical devices being considered here are often cognitively and functionally severely impaired, which again demands a high level of care and concentration from the user of the medical devices and distracts from the actual operation of the corresponding medical devices. This must also be taken into account in the design and risk management process and verified by adequate usability tests.

As a result of the above-given patient population, the benefits and drawbacks that a patient could experience in a therapy using a medical device must be very carefully assessed. For this, the user, who is often not familiar with the application of modern medical technology, should be given enough information in the form of indication, contraindication, and possible side effects, which enable him to provide the correct and optimal form of therapy. The user must be able to make the correct risk–benefit assessment for the well-being of his patient, taking into account, on the one hand, the desired therapy progress for his

patient and on the other hand a possible risk of deterioration of the patient's state of health. For this, there must be sufficient information and descriptions of the existing risks, which should be available to him in the user's instructions.

There is sometimes a considerable fear of contact on the part of potential users with modern medical devices, along with inexperience with the utilization of technological processes compared to the conventional manual therapies in the neurorehabilitation, and this, too, should be taken into consideration in the design of medical devices. Furthermore, the correct measures should be provided in order to introduce the user to the new technology and adequately bring him closer to the application of the medical device. This should already be taken into consideration at the conception and risk assessment stage and must be systematically implemented. The medical device user is an important factor not to be neglected when it comes to ensuring safety and effectiveness of a medical device in neurorehabilitation. This can be taken into account by adequate training of the future user at the time when the medical device is being commissioned. It is recommended to adapt the duration of training to the prior medical knowledge of the user and to the complexity of the medical device. Regular further training courses and exchange-of-experience workshops reinforce a deeper understanding about the effective application of this type of medical device.

25.2.6 Safety Aspects for Medical Electrical Devices for Neurorehabilitation Robots

Robots are defined as follows in ISO TC 184/SC 2 (version not yet published at the current time [September 2010]):

Robot: actuated mechanism programmable in more than one axis with a degree of autonomy, moving within its environment, to perform intended tasks. Note: it includes the control system and communication interface. Example: examples of robot include industrial robot and service robot.

Autonomy: ability to control movement and communication to perform intended tasks without human intervention.

Robotic device: actuated mechanism fulfilling the characteristics of industrial robot or service robot but lacking either number of programmable axes (4.3) or the degree of autonomy. Example: examples include power-assist device, teleoperated device, and two-axes industrial manipulator.

This autonomy is implemented by the use of detectors, sensors, control loops, software controls, and algorithms, just to mention a few aspects of this complex interplay, and mostly without the influence of human interactions. The latter is the prerequisite for the given autonomy. Of course, there are certain pre-settings to be effected, which are essential for the patient, his particular neurological and general medical situation, and to establish his capability. In addition, a corrective intervention by the users is possible at any time and should also be guaranteed. This inherent autonomy of a robot constituting a medical device (medical robot), however, requires additional consideration in the design and risk management process.

Special importance is, therefore, attached to software in this type of medical device. Here again, the software architecture, in particular, must be mentioned. If this can be transparently and exactly built up and displayed coherently in itself and within the whole medical device, it will facilitate the verification and validation effort to concentrate on the right, safety-relevant modules (Fig. 25.1).

Figure 25.2 provides a good overview about the subject of software verification and validation.

Chapter 14 of the cited standard describes the requirements of such a PEMS and gives guidelines for a corresponding development life cycle in which, among other things, again draws upon ISO 14971.

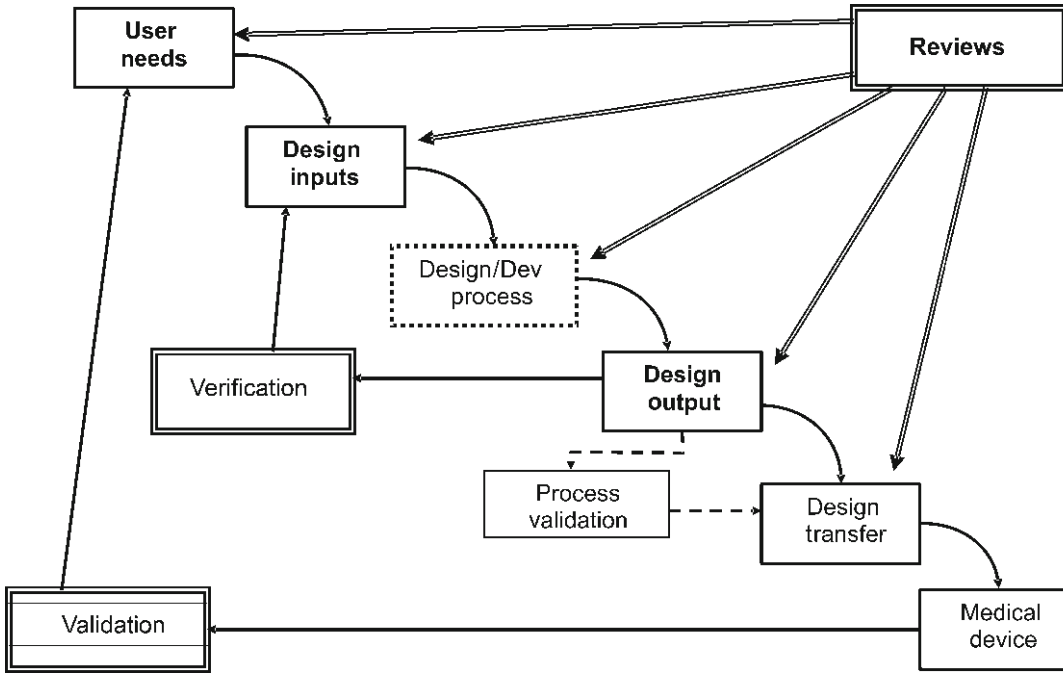

Fig. 25.1 Validation/verification plan (Adapted from Medical Device Bureau, Health Canada)

Software architecture is mandatorily prescribed by this standard and must cover the following:

- Components with characteristics of high reliability
- Fail-safe functions
- Redundancy
- Diversity
- Separation of functionality
- Defensive design, e.g., limitation of possible hazardous effect by limiting the available output capacity or by installation of resources that limit the movement of actuators

The architecture specifications must take the following into consideration:

- Allocation of measures and risk control to PEMS subsystems and components
- (subsystems and components include sensors, actuators, PESS, and interfaces)
- Modes of failure of components and their repercussions
- Malfunctions with a common cause
- Systematic malfunctions
- Length of inspection intervals and the degree of coverage of the function diagnosis
- Maintainability
- Protection against reasonably predictable misuse
- Specification of the network/data sharing if applicable

IEC 62304 describes processes that have to be included in the software development cycle for the development of safe software for medical devices.

In order to determine which functions create or control risk, it is necessary to completely identify the PEMS/PESS requirements. It is not possible to carry out an appropriate risk assessment without a complete specification of the requirements and an architecture design that satisfies this specification. The requirements should include the following, if applicable to the PEMS software:

- Functional performance requirements including essential performance characteristics in compliance with IEC 60601-1

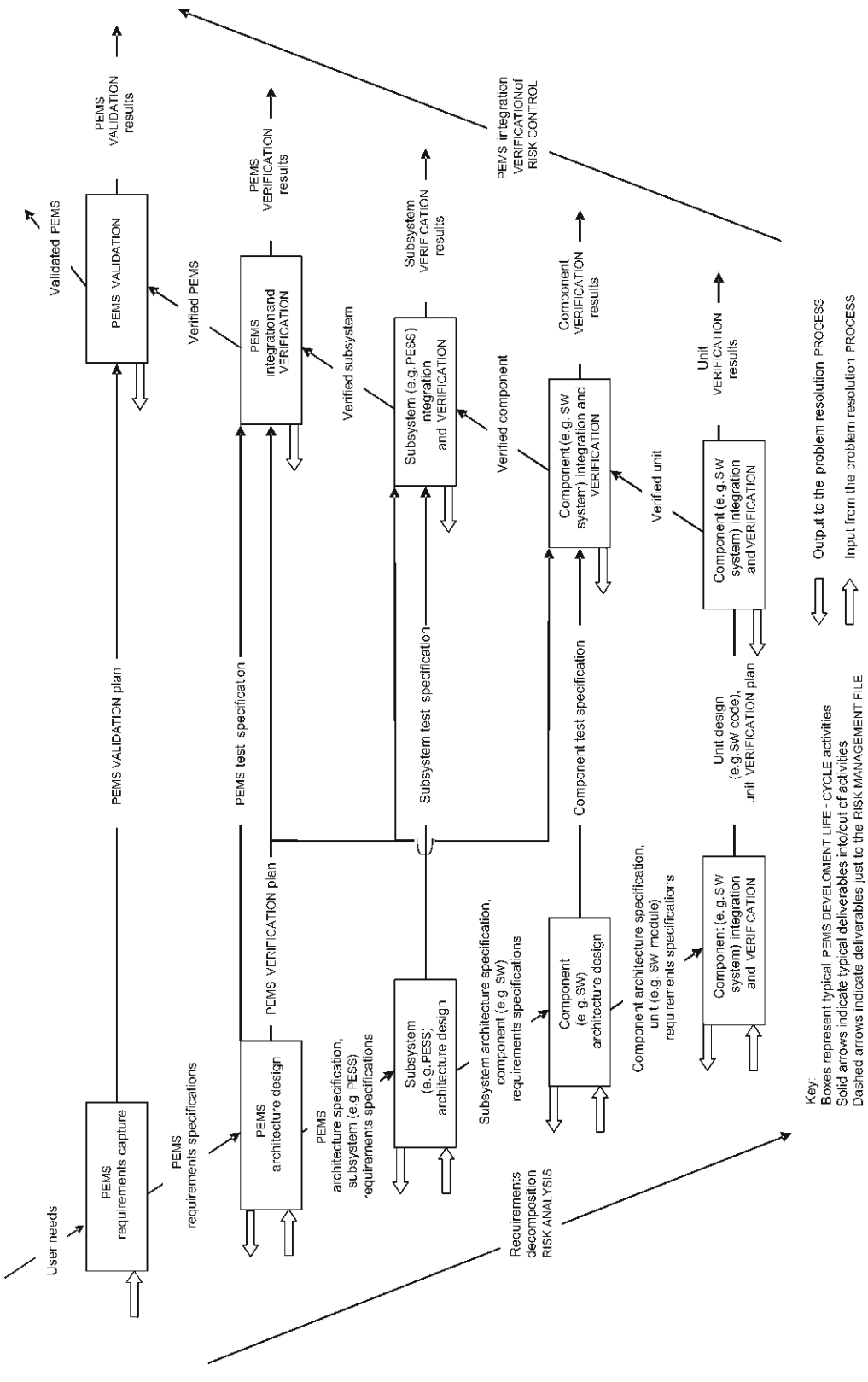

Fig. 25.2 A PEMS development life-cycle model. *PEMS* programmable electrical medical system, *PESS* programmable electronic subsystem (Adapted from IEC 60601-1[3])

- Physical characteristics and the conditions of their surroundings under which the software should run
- External interfaces with the software
- Safety requirements, including risk-control measures for hardware breakdowns and possible software defects and specifications regarding the method of operation and maintenance, environmental influences, and risk control
- Software-controlled alarm signals, warnings, and operator messages
- Safety requirements, where any gaps in safety could affect overall safety
- Ergonomic requirements regarding the use of PEMS, including those that refer to the following elements: support when operating manually, human–machine interactions, limitations of personnel, and areas where intense human attention is required and are susceptible to human error and training
- Data definitions and requirements for the database
- Installation and acceptance requirements for the PEMS software
- The documentation that has to be drawn up
- Operation and design requirements
- Maintenance requirements

A risk assessment should be carried out to ascertain to what extent the architecture design can be used to reduce risk.

In order to be able to identify known or predictable hazards, it is necessary to characterize all software from external companies or OTS (off-the-shelf) software used in PEMS.

The developer should specify requirements of software from external companies or OTS software. These requirements should include the following:

- Title and manufacturer, version, release date, patch number, and upgrade identification
- System hardware and software that is necessary for a proper operation (e.g., processor type and speed, storage type and size and system, communication and display software requirements)
- Interfaces with the software components
- Critical safety functions and risk-control functions dependant on software components

25.2.6.1 Integration

The developer should specify an integration plan to integrate components of each PESS and each PEMS. The plan should include the methods, responsibilities, sequences, and all software components. If the PESS software is developed using incremental integration methods, a sufficient number of regression tests must be carried out to ensure that the previous verification is still adequate. Integration tests should include test cases that not only check the software behavior in the normal case but also in exceptional, stress, or worst-case conditions.

25.2.6.2 Configuration Management

Since the risk analysis is based on the software requirements, configuration management and change control are necessary to ensure that additional software functionality is not added during development without passing through the risk management process. A configuration management plan should be specified that describes the following:

- The elements to be controlled
- The configuration management activities
- Procedure and schedules for the execution of these activities
- Responsibilities for the execution of these activities
- Procedures to monitor the reception, installation, and acceptance of each software component

A plan should be fixed for the unambiguous identification of elements of the software configuration and for the version check. This plan must include software components from external companies or OTS software components.

25.2.6.3 Modification/Change Control

For the modification/change control, the following should be carried out:

- Identification and documentation of the change requirements
- Analysis and assessment of the changes
- Acceptance or rejection of the change
- Implementation, verification, and release of the changed software

A monitoring record should be kept in which every change, the reason for the change, and authorization of the change can be traced. Records

of the history of the monitored parts should be retrievable.

25.2.6.4 Design and Implementation

When applying the PEMS development life-cycle model, the design and implementation include the following specifications:

- The development environment, for example
  - Software development methods
  - Computer-assisted software development tools (case)
  - Program language
  - Hardware and software development platforms
  - Simulation tools
  - Design and coding standards
- Electronic components
- Redundant hardware
- Interface between human and PEMS
- Energy sources
- Environmental conditions
- Software from external companies
- Network options

These elements of the development environment can be displayed in the design and implementation process both generally and in the particular manner in which they are used.

25.2.6.5 Documentation

Figure 25.3 includes the complete documentation that is required from section 14 and ISO 14971. It is only intended to show an example of a structure. Special documentary references can be merged or distributed over several documents. The section numbers starting with "#" refer to the section numbers of ISO 14971. The other numbers refer to the subsections of ISO 60601-1.

The interplay of the various standard requirements that are applied to PEMS is reflected in Fig. 25.4.

Apart from the international standards listed in Fig. 25.5, there are other helpful guidelines mentioned in Appendices 25.2 and 25.3. Examples for constructing and maintaining a software development cycle are given in Appendix 25.4.

25.3 Summary

(Robotically supported) neurorehabilitation is a new, innovative field of activity and is in a continuous state of change. Thus, an overview of standards and safety aspects for medical electrical devices for this field can only represent a snapshot in time. As stated above, new standardization efforts are in progress for "medical robots." Attempts to generally portray the "state of the art" or the standards are subject to constant change. National regulations tend to drift apart, instead of moving together toward a uniform global procedure. Only a permanent systematic observation and adaptation to the various constraints can ensure that products from the sector of neurorehabilitation comply with the constraints from the regulated medical device sector. The field of view of neurorehabilitation has shown how multifarious these constraints are.

Society in general and the health sector in particular expect highly efficient products that have a greater and better functionality. As stated above, the efforts are being placed increasingly on extending the provision of proof for safety and effectiveness here and on more detailed documentation, safeguarding in all directions. The more complex medical devices become, the costlier the whole process will be. The world of neurorehabilitation will have to grapple with this development, and medical device manufacturers, in particular, will have to adjust to the increasing constraints from various sources. Environmental, hazardous materials and recycling requirements, which also have to be met by all of the electronics sector, have been intentionally omitted from this chapter.

Some national health systems have so inflated their sets of rules that innovations and new technologies will only be available for the circle of patients affected after considerable delays.

In the future, the art will consist of achieving a balance between increasing safety demands, expressed in increasing constraints, with the ability to promptly introduce innovative treatment alternatives.

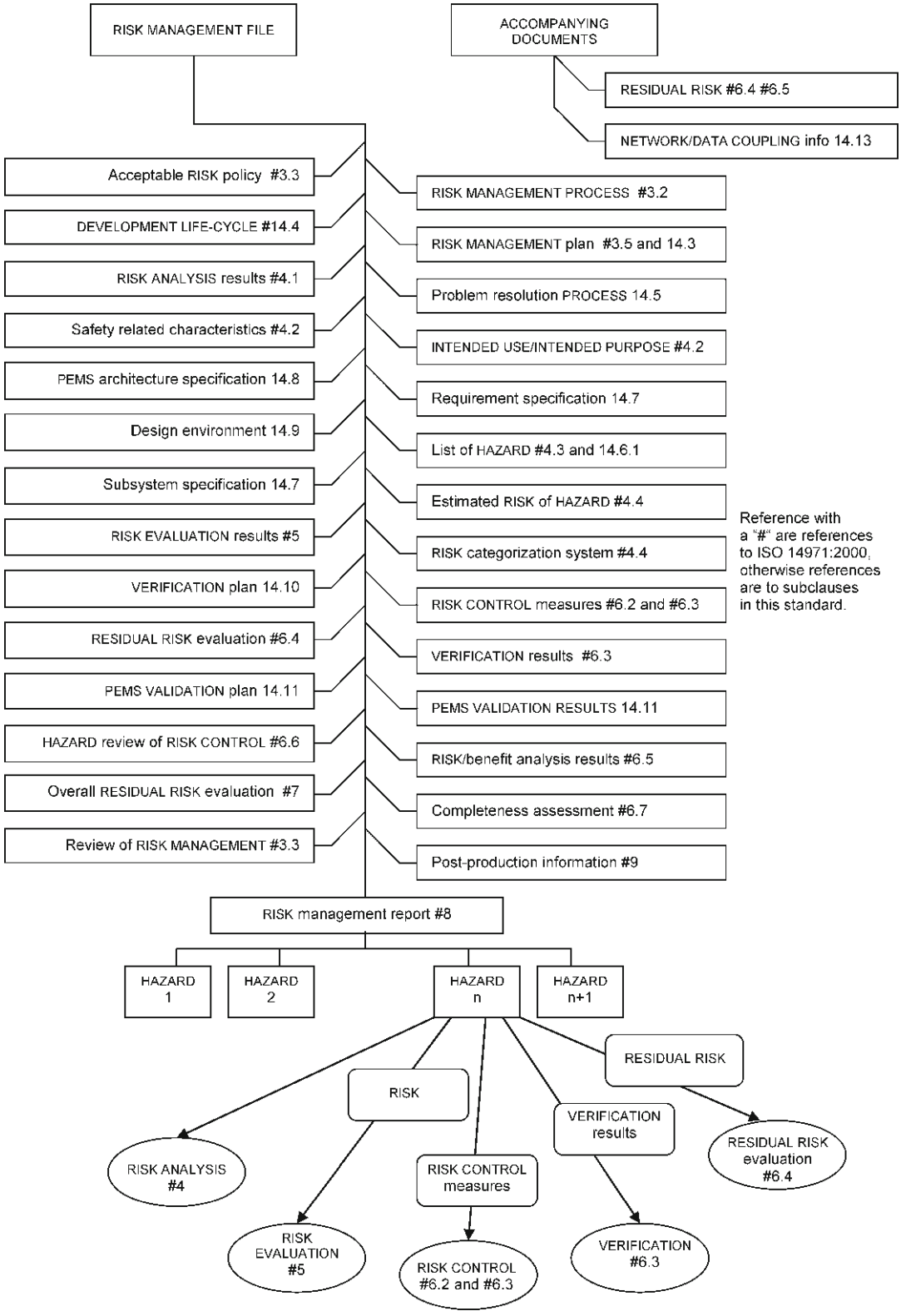

Fig. 25.3 PEMS document requirements from section 14 of IEC 60601-1 and ISO 14971

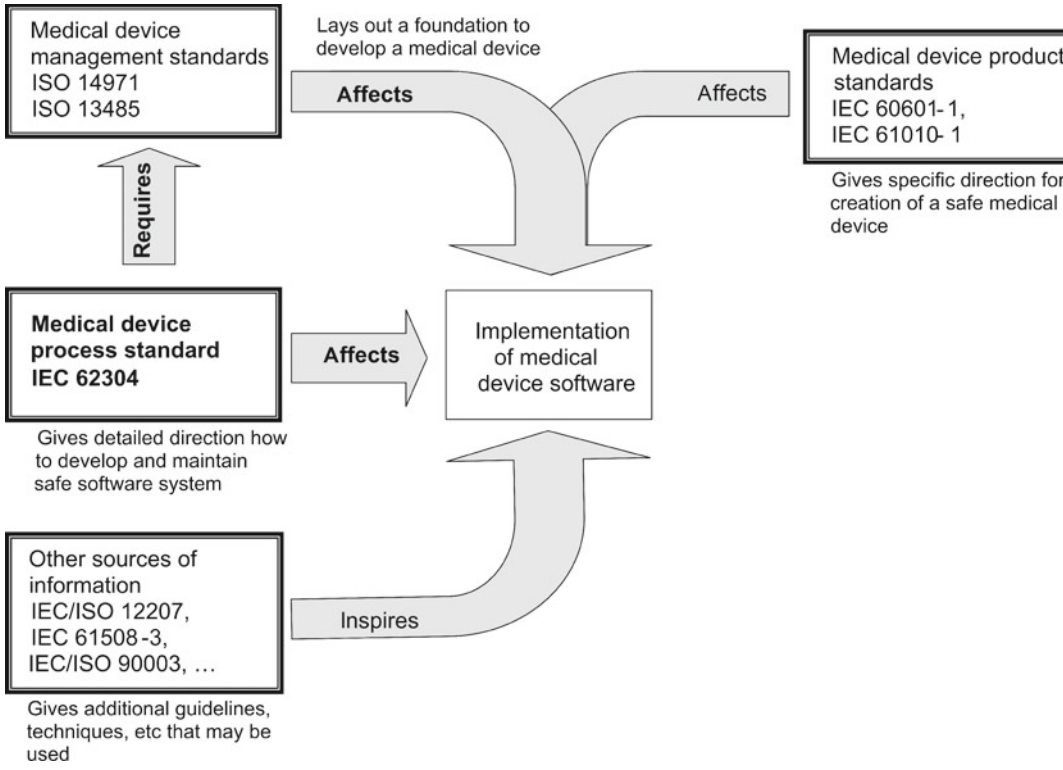

Fig. 25.4 Relationship of medical device standards to IEC 62304 (Adapted from IEC 62304 [5])

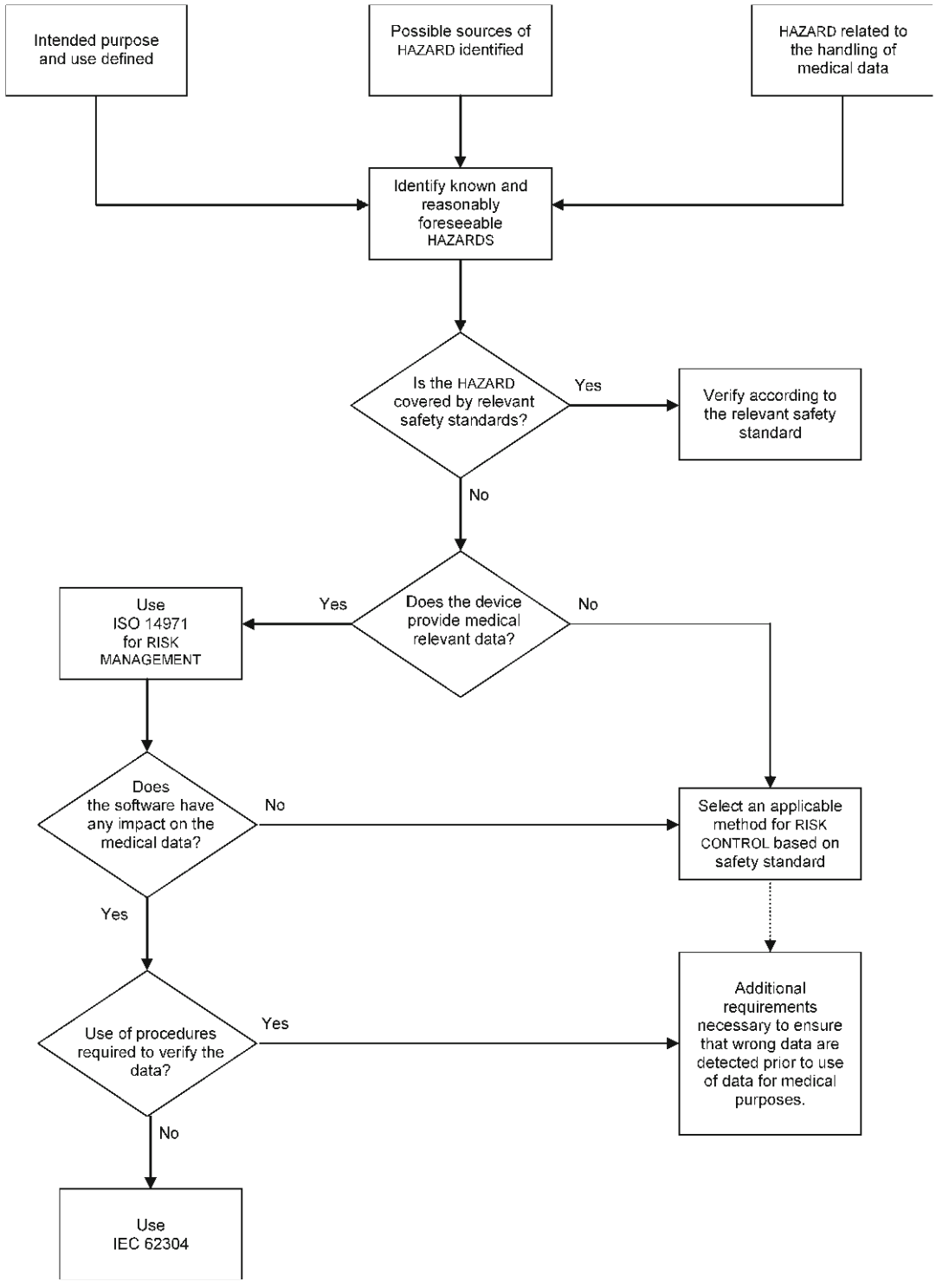

Fig. 25.5 Application of IEC 62304 with IEC 61010-1. Medical device software: software life-cycle processes (Adapted from IEC 62304 [5])

25.4 Appendix 25.1: Overview of the Currently Published IEC 60601-1-X Standards [Sept. 2010]

- Medical electrical equipment – Parts 1–1: General requirements for safety – Collateral Standard: Safety requirements for medical electrical systems (IEC 60601-1-1:2000)
- Medical electrical equipment – Parts 1–2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic compatibility – Requirements and tests (IEC 60601-1-2:2007, modified)
- Medical electrical equipment – Parts 1–3: General requirements for basic safety and essential performance – Collateral Standard: Radiation protection in diagnostic X-ray equipment (IEC 60601-1-3:2008)
- Medical electrical equipment – Parts 1–4: General requirements for safety – Collateral standard: Programmable electrical medical systems (IEC 60601-1-4:1996 + A1:1999)
- Medical electrical equipment – Parts 1–6: General requirements for basic safety and essential performance – Collateral Standard: Usability (IEC 60601-1-6:2006)
- Medical electrical equipment – Parts 1–8: General requirements for basic safety and essential performance – Collateral Standard: General requirements, tests, and guidance for alarm systems in medical electrical equipment and medical electrical systems (IEC 60601-1-8:2006)
- Medical electrical equipment – Parts 1–9: General requirements for basic safety and essential performance – Collateral Standard: Requirements for environmentally conscious design (IEC 60601-1-9:2007)
- Medical electrical equipment – Parts 1–10: General requirements for basic safety and essential performance – Collateral Standard: Requirements for the development of physiologic closed-loop controllers (IEC 60601-1-10:2007)
- Medical electrical equipment – Parts 1–11: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment (IEC 62A/590/CD:2007)
- Medical electrical equipment – Parts 1–12: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in *"emergency situations/surroundings"* (starting phase)

25.5 Appendix 25.2: Overview of the Currently Published GHTF Documents [Sept. 2010]

Title	Description	Posted date
SG1-N55:2009	Definition of the Terms Manufacturer, Authorised Representative, Distributor and Importer	7 July 2009
SG1-N46:2008	Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices	26 August 2008
SG1-N45:2008	Principles of In Vitro Diagnostic (IVD) Medical Devices Classification	23 June 2008
SG1-N11:2008	Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) Note: Discrepancy Between GHTF/SG1/ N040:2006 and GHTF/SG1/ N011:2008	29 May 2008
SG1-N44:2008	Role of Standards in the Assessment of Medical Devices	16 April 2008
SG1-N15:2006	Principles of Medical Devices Classification	31 August 2006

Title	Description	Posted date
SG1-N40:2006	Principles of Conformity Assessment for Medical Devices Note: Discrepancy Between GHTF/SG1/ N040:2006 and GHTF/SG1/ N011:2008	31 August 2006
SG1-N43:2005	Labelling for Medical Devices	29 August 2005
SG1-N29R16:2005	Information Document Concerning the Definition of the Term "Medical Device"	21 July 2005
SG1-N41R9:2005	Essential Principles of Safety and Performance of Medical Devices	21 July 2005
SG2/N38R19	Application Requirements for Participation in the GHTF National Competent Authority Report Exchange Program	16 September 2009
SG2-N79R11:2009	Medical Devices: Post Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form	17 July 2009
SG2-N54R8:2006	Medical Devices: Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices	18 December 2006
SG2-N57R8:2006	Medical Devices: Post Market Surveillance: Content of Field Safety Notices	31 August 2006
SG2/N47R4: 2005	Review of Current Requirements on Post Market Surveillance	01 February 2006
SG2-N8R4	Guidance on How to Handle Information Concerning Vigilance Reporting Related to Medical Devices	16 February 2000 *Reposted: 25 October 2000
SG2-N16R5	Charge and Mission Statement	16 February 2000 *Reposted: 25 October 2000
SG3/N17/2008	Quality Management System – Medical Devices – Guidance on the Control of Products and Services Obtained from Suppliers	5 February 2009
SG3/N15R8/2005	Implementation of Risk Management Principles and Activities Within a Quality Management System	21 July 2005
SG3/N99-10 (Edition 2)	Quality Management Systems – Process Validation Guidance	22 January 2004
SG4/N28R4:2008	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 1: General Requirements	24 October 2008
SG4/ N33R16:2007	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 3: Regulatory Audit Reports	19 November 2007
SG4/ N30R20:2006	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy	31 August 2006
SG4 (00) 3	Training Requirements for Auditors (Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 1: General Requirements – Supplement 2)	15 March 2000 *Reposted: 30 October 2000
SG5/N4:2010	Post Market Clinical Follow-Up Studies	26 April 2010
SG5/N3:2010	Clinical Investigations	26 April 2010
SG5/N2R8:2007	Clinical Evaluation	29 June 2007
SG5/N1R8:2007	Clinical Evidence – Key Definitions and Concepts	29 June 2007

25.6 Appendix 25.3: Overview of the Currently Published MEDDEV Documents [Sept. 2010]

	Title	Date
2.1 Scope, field of application, definition	MEDDEV 2.1/1 Definitions of "medical devices", "accessory" and "manufacturer"	April 1994
	MEDDEV 2.1/2 rev.2 Field of application of directive "active implantable medical devices"	April 1994
	MEDDEV 2.1/2.1 Interface with other directives – Medical devices/medicinal products – February 1998	February 1998
	MEDDEV 2.1/3 rev.2 interface with other directives – Medical devices/medicinal products	July 2001
	MEDDEV 2.1/3 rev.3 Borderline products, drug-delivery products and medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative – December 2009	December 2009
	MEDDEV 2.1/4 Interface with other directives – Medical devices/directive89/336/EEC relating to electromagnetic compatibility and directive 89/686/EEC relating to personal protective equipment	March 1994
	For the relation between the MDD and directive 89/686/EEC concerning personal protective equipment, please see the Commission services interpretative document of 21 August 2009	
	MEDDEV 2.1/5 Medical devices with a measuring function	June 1998
2.2 Essential requirements	MEDDEV 2.2/1 rev.1 EMC requirements	February 1998
	MEDDEV 2.2/3 rev.3 "Use by" – date	June 1998
2.4 Classification of MD	MEDDEV 2.4/1 rev.9	June 2010
2.5 Conformity assessment procedure	Content of mandatory certificates	2.5/1 (n.a.)
	Quality assurance.	
2.6 General rules	Regulatory auditing of quality systems of medical device manufacturers	
Conformity assessment for particular groups of products	(See document in the GHTF-Global Harmonization Task Force website)	
	MEDDEV 2.5/3 rev.2 Subcontracting quality systems related	June 1998
	Reporting of design changes and of changes of the quality system	(n.a.)
	MEDDEV 2.5/5 rev.3 Translation procedure	February 1998
	MEDDEV 2.5/6 rev.1 Homogenous batches (verification of manufacturers' products)	February 1998
	MEDDEV 2.5/7 rev.1 Conformity assessment of breast implants	July 1998
	Evaluation of medical devices incorporating products of animal origin.	
	(See MEDDEV 2.11/1 rev.2)	
	MEDDEV 2.5/9 rev.1 Evaluation of medical devices incorporating products containing natural rubber latex	February 2004
2.7 Clinical investigation, clinical evaluation	MEDDEV 2.7/1 rev.3 Clinical evaluation: Guide for manufacturers and notified bodies	December 2009
	Appendix 1: Clinical evaluation on coronary stents	December 2008
	MEDDEV 2.7/2 Guide for Competent Authorities in making an assessment of clinical investigation; notification	December 2008

	Title	Date
2.10 Notified bodies	MEDDEV 2.10/2 rev.1 Designation and monitoring of Notified Bodies within the framework of EC Directives on Medical devices	April 2001
	Annex 1	
	Annex 2	
	Annex 3	
	Annex 4	
2.11 Products using materials of biological origin	MEDDEV 2.11/1 rev.2 Application of Council Directive 93/42/EEC taking into account the Commission Directive 2003/32/EC for Medical Devices utilising tissues or derivatives originating from animals for which a TSE risk is suspected	January 2008
	Annex 1	
2.12 Market surveillance	MEDDEV 2.12/1 rev.6 Medical devices vigilance system	December 2009
	Manufacturer Incident Report – Field Safety Corrective Action	
	List of contact points	
	MEDDEV 2.12/2 Clinical Evaluation – Post Market Clinical Follow-up	May 2004
2.13 Transitional period	MEDDEV 2.13 rev.1 Commission communication on the application of transitional provision of Directive 93/42/EEC relating to medical devices (OJ 98/C 242/05)	August 1998
	As regards the transitional regime of Directive 2007/47/EC see the Interpretative Document of the Commission's [services of 5 June 2009]	August 1998
2.14 IVD	MEDDEV 2.14/1 rev.1 Borderline issues	January 2004
	MEDDEV 2.14/2 rev.1 Research Use Only products	February 2004
	MEDDEV 2.14/3 rev.1 Supply of Instructions For Use (IFU) and other information for In-vitro Diagnostic (IVD) Medical Devices	January 2007
	Form for the registration of manufacturers and devices In Vitro Diagnostic Medical Device Directive, Article 10	January 2007
2.15 Other guidances	MEDDEV 2.15 rev.3 Committees/Working Groups contributing to the implementation of the Medical Device Directives	December 2008

25.7 Appendix 25.4: Guidelines About Software and Software Development Cycle

- Design Control Guidance for Medical Device Manufacturers; FDA Center for Devices and Radiological Health. http://www.fda.gov/downloads/Medical/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf
- General Principles of Software Validation, Final Guidance for Industry and FDA Staff; FDA Center for Devices and Radiological Health. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf
- Title 21 – Food and Drugs; Chapter I – Food and Drug Administration; Department of Health and Human Services; Subchapter A – General Part 11 Electronic Records; Electronic Signatures. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

- Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application
- U.S. Department of Health and Human Services; Food and Drug Administration. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf
- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices; U.S. Department of Health and Human Services; Food and Drug Administration; Center for Devices and Radiological Health; Office of Device Evaluation. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf
- IEEE Recommended Practice for Software Requirements Specifications; Software Engineering Standard Committee of the IEEE Computer Society
- IEEE Recommended Practice for Software Design Descriptions; Software Engineering Standard Committee of the IEEE Computer Society
- IEEE Standard for Software Project Management Plans; Software Engineering Standard Committee of the IEEE Computer Society
- IEEE Standard for Software Quality Assurance Plans; IEEE Computer Society; Software Engineering Standard Committee

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1. Commission communication in the framework of the implementation of the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices; Publication of titles and references of harmonised standards under the directive 2010/C 183/03.
2. ISO 10993:2009 Biological evaluation of medical devices – Part 1: evaluation and testing within a risk management system and additional parts.
3. IEC 60601-1:2005; Medical electrical equipment – Part 1: General requirement for basic safety and essential performance.
4. ISO 13485:2003 + Cor. 1:2009; Medical devices – Quality management systems – Requirements for regulatory purposes.
5. IEC 62304:2006; Medical device software – Software life cycle processes.
6. IEC 62366:2007; Medical devices – Application of usability engineering to medical devices.
7. IEC 62353:2007; Medical electrical equipment – Recurrent test and test after repair of medical electrical equipment.
8. IEC 60601-1-2:2007, modified; Medical electrical equipment – Part 1–2: General requirements for basic safety and essential performance – Collateral standard: electromagnetic compatibility- Requirements and tests.
9. IEC/TR3 60513:1994; Fundamental aspects of safety standards for medical electrical equipment.
10. ISO 14971:2007; Medical devices – Application of risk management to medical devices.
11. IEC/TR 80002-1: 2009; Medical device software – Part 1: Guidance on the application of ISO 14971 to medical device software.
12. Internal ISO TC 184 working documents.

Epilogue: What Lies Ahead?

We are still in the early stages of regular use of robotic-assisted therapies in the neurorehabilitation of stroke, SCI and brain-injured subjects. The relative superiority, or at least equivalence, of these devices compared to conventional therapies still remains to be demonstrated. Furthermore, these robotic devices must still be technologically optimized in order to meet essential requirements discussed in this book, such as the provision of targeted inputs and of appropriate task challenges tailored to the needs of the individual patient.

However, once these basic requirements are met and the technology is further advanced, and likely supplemented by enhanced feedback and sensing tools, robotic devices will almost certainly emerge as a standard feature of neurorehabilitation for the following reasons:

- Therapy can be standardized for specific illnesses yet adapted to individual patient needs.
- Training times can be extended to fit the individual capacity of a patient and are less likely to be constrained by reimbursement schemes for clinical caregivers.
- The effects and the intensity of training can be enhanced and made more challenging, such as by the implementation of virtual reality, engaging both visual and haptic communication channels.
- Standardized assessments of motor and sensory function can be implemented to objectively monitor the effects of training over time.

Clinical Application Outlook

Looking forward, although there are strong grounds for optimism about the beneficial roles of rehabilitation technologies in the future, there remain compelling needs to compare different rehabilitation approaches to determine their relative superiority. There also remain critical needs to establish a strong cost benefit analysis of neurotechnology devices, to validate the potential economic benefits of widespread use of robotic devices for consumers and health care providers alike.

For example, VR approaches might generally be less effective as an independent therapy, yet specific forms of VR presentations might still prove to be highly effective in improving the subject's performance when combined with suitable robotic training. VR systems allow rapid experiential transitions in both visual and haptic environment, including exposure to physically non-realizable yet beneficial experiences. For example, the use of novel viscous force fields during training to enforce motor adaptation seems promising as a tool to expedite the speed and degree of motor functional improvement. Multicenter studies are clearly required to evaluate the most effective treatments. VR might also not prove to be equally effective in all subject groups and might depend e.g. on the age and cognitive function of the individual patient.

In addition, in the future robotic devices should become more adaptive in their design so

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that they can be tailored to fit the training program of the individual subject, including his/her neurological deficits, age, physical condition, intent to learn and residual (e.g. cognitive) functions. Examples will include wheelchairs that can learn the degree of impairment of their users and adapt the chair controllers to fit changing motor and sensory capacities as recovery proceeds.

Unresolved Issues

In light of the above, we yet have to address several unresolved issues to optimize rehabilitation approaches.

The Role of Feedback

The effects and the optimal form of feedback information to the training subjects have to be explored. In particular, we also need to know the relative impact of visual versus haptic feedback and whether error correcting or error augmenting schemes will prove to be most effective.

Gait Parameters

The influence of gait velocity on the improvement of locomotor ability of stroke and SCI subjects is still a matter of debate. In addition, the effect of hip joint excursions, in which afferent input was shown to be essential for the activation of locomotor centers, on locomotor recovery is not yet solved.

Training Parameters

We need more information on the optimal duration of a training session and the number of training sessions per day as well as the optimal number of training sessions overall. We also need to know whether training of different tasks within a day can adversely affect motor learning and whether patients should be allowed to sleep between sessions to solidify training effects on motor performance.

The Role of the Therapist

Physiotherapists are needed to help determine which therapies are best suited initially to the patient, to analyse data provided by the devices and to compose an appropriate training program which continuously adapts to the actual condition of the individual stroke/SCI subject. The program has to be always updated to be sufficiently challenging but physically appropriate for the individual patient.

Therapists are also important to help design the optimal training schemes. Currently there is considerable debate about the role of learning theories in relation to choosing stereotypic tasks versus varying tasks and in terms of establishing the degree of their difficulty.

Several investigators are even proposing that robots help train patients to the point where failure in task performance is a consistent feature, allowing clinicians to calibrate optimal therapy designs.

Combination Therapies

The best timing for the combination of regeneration-inducing treatment and functional training has yet to be determined, as in spinalized rats a too-early onset of training also can be deleterious [1].

Technology Outlook

Future robotic devices might be designed in a way that they combine different applications during the rehabilitation process, such as:

- Basic clinical assessments such as motor output, muscle tone and fatigability.
- Monitoring of function over the time of rehabilitation, i.e. provide objective measures about the course of rehabilitation.
- Home use: Simple robotic devices will be designed which allow training at home and some basic assessments.
- Interactions with assistive devices: For many stroke/SCI subjects assistive devices would improve life quality, which support physiological movements during daily life activities.

They should be modifiable for the individual requirements and eventually should be powered as far as needed.

A clear example is the role of robotics in restoring upper extremity function, where robotic training is routinely helpful in promoting accurate movements of proximal joints, yet appear unable to induce significant functional recovery of hand movements. The combination of robot devices for training coupled with assistive devices for promoting improvement in hand and finger function is likely to constitute an important integrative strategy. In addition, most robotics are designed to train only the upper limb function of the affected side. However, most everyday movements require the cooperation of both hands. Therefore, robot devices should allow a training with a combination of unimanual and bimanual cooperative movements.

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