David J. Reinkensmeyer
Volker Dietz
Editors

Neurorehabilitation Technology

Second Edition

Springer

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Editors
David J. Reinkensmeyer
University of California at Irvine
Irvine
California
USA

Volker Dietz
Spinal Cord Injury Center
University Hospital Balgrist
Zürich
Switzerland

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Preface to the Second Edition

When I want to discover something, I begin by reading up everything that has been done along that line in the past – that's what all these books in the library are for. I see what has been accomplished at great labor and expense in the past. I gather data of many thousands of experiments as a starting point, and then I make thousands more.

Attributed to Thomas Edison

The aim of this book is to provide a current overview of the ongoing revolution in neurorehabilitation technology. This revolution began in the late 1980s when several research groups, apparently beginning with a group at MIT, made the observation that robotic technologies could enhance rehabilitation movement training by automating parts of it. Seminal work in neuroplasticity emerging at the same time observed for the first time that the nervous system retains a highly distributed capacity to alter its connectivity in response to repetitive sensory motor input even following severe damage and aging. Partially automating repetitive movement training was thus imagined as a way to increase movement therapy dose, improving recovery without increasing health care costs.

Thirty years later, tens and perhaps hundreds of companies worldwide now sell rehabilitation robotic technology. The most successful company is likely the Swiss company Hocoma. With the development of the gait orthosis 'Lokomat' in the early 1990s, Hocoma emerged as a spin-off from the Balgrist University Hospital in Zürich. It is now established well with over 1000 installations of its Lokomat gait orthosis, Armeo arm orthoses, and other technologies (its products and their evaluation are necessarily the focus of several chapters in the book). The number of papers published in rehabilitation robotics has increased from a few per year to over 1000 annually. Systematic reviews of tens of randomized controlled trials now affirm robotic training as a beneficial supplement to conventional training.

Yet the benefits provided by these devices are incremental for most patients and the cost high enough to limit their use mainly to flagship rehabilitation facilities. We are perhaps at a stage of invention similar to that of the light bulb in 1878. The best light bulbs in 1878 lasted only 13 h, despite the light bulb having been invented in 1802 by Humphry Davy. It would take Thomas Edison several more years of experimental and theoretical work to increase the average light bulb life to over 1000 h, thus producing one of the most impactful technologies of all time.

This second edition of *Neurorehabilitation Technology* details what might be described as the ongoing Edisonian process of improving neurorehabilitation technology. World leaders in their fields have taken the time to step back from their work, evaluate the state of the art in their field, and trace the development of their own work in creating this state of the art. In their chapters, they detail improved knowledge of motor impairment and neuroplasticity mechanisms; this knowledge is fundamental for a principled approach to neurorehabilitation technology design. They describe how they have not only incorporated robotic devices into their clinical practice, but then further refined these technologies based on their clinical experience. They highlight the potential of combination therapies with drugs, electrical stimulation, and brain-computer interfaces, to increase functional benefits achievable beyond hard limits set by neural destruction. And they describe the beginnings of the second wave of innovation in neurorehabilitation technology now occurring, this time driven by the worldwide emergence of wearable sensing, actuation, and computing for consumer health markets.

New chapters selected for the second edition include motor challenge in neurorehabilitation, neural coupling in neurorehabilitation after stroke, clinical application of robots for children, overground exoskeletons for locomotion recovery, virtual reality and computer gaming for rehabilitation, wearable sensors, and brain-computer interfaces for rehabilitation therapy. Chapters published in the first edition have also been updated and reorganized to reflect the ongoing revolution. Volker and I hope that this book will inspire the next generation of innovators—clinicians, neuroscientists, and engineers—to move neurorehabilitation technology forward, thus benefitting the next generation of people with a neurologic impairment.

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Irvine, USA — David Reinkensmeyer
Zurich, Switzerland — Volker Dietz

Contents

Contributors

Ana Maria Acosta, PhD Departments of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL, USA

Tabea Aurich (-Schuler), MSc Pediatric Rehab Research Group, Rehabilitation Center for Children and Adolescents, University Children's Hospital Zürich, Zurich, Switzerland

Sergi Bermúdez i Badia, Eng, PhD Madeira Interactive Technologies Institute and Centro de Competências das Ciências Exatas e da Engenharia, Universidade da Madeira, Funchal, Portugal

Amy J. Bastian, MD Department of Neuroscience, The Johns Hopkins School of Medicine and Kennedy Krieger Institute, Baltimore, MD, USA

Serafin M. Beer Department of Neurology and Neurorehabilitation, Rehabilitation Centre, Klinik Valens, Valens, Switzerland

Marc Bolliger, PhD Spinal Cord Injury Center, University of Zurich, Balgrist and University Clinic Balgrist, Zurich, Switzerland

Ingo Borggraefe Department of Pediatric Neurology and Developmental Medicine, University of Munich, Munich, Germany

David A. Brown, PT, PhD Departments of Physical Therapy and Occupational Therapy, University of Alabama at Birmingham, Birmingham, AL, USA

Sheila Burt, BS Center for Bionic Medicine, Rehabilitation Institute of Chicago, Chicago, IL, USA

Katrin Campen Quality Management arvato CRM Healthcare GmbH, Berlin, Germany

Grégoire Courtine, PhD Department of Neurology, Experimental Neurorehabilitation Laboratory, Zurich, Switzerland

Armin Curt, MD Spinal Cord Injury Research Lab, Spinal Cord Injury Centre, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

Judith E. Deutsch, PT, PhD Rivers Lab: Department of Rehabilitation and Movement Sciences, Rutgers – The State University of New Jersey, Newark, NJ, USA

Jules P.A. Dewald, PT, PhD Department Physical Therapy and Human Movement Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Volker Dietz, MD Spinal Cord Injury Center, University Hospital Balgrist, Zurich, Switzerland

An H. Do, MD Department of Neurology, University of California Irvine, Orange, CA, USA

Bruce H. Dobkin, MD Department of Neurology, Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Andrew K. Dorsch, MD Department of Neurology, UCLA Geffen School of Medicine, Los Angeles, CA, USA

Jaime E. Duarte, PhD Departments of Mechanical and Aerospace Engineering, University of California, Irvine, Irvine, CA, USA

V. Reggie Edgerton, PhD Departments of Integrative Biology and Physiology and Neurobiology and Brain Research Institute, University of California, Los Angeles, CA, USA

Dylan Edwards, PT, PhD Laboratory for Non-Invasive Brain Stimulation and Human Motor Control, Department of Neurology, Weill Cornell Medical College, Burk-Cornell Medical Research Institute, White Plains, NY, USA

Michael D. Ellis, PT, DPT Departments of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL, USA

Alberto Esquenazi, MD Department of Physical Medicine and Rehabilitation, MossRehab, Elkins Park, PA, USA

Gerard G. Fluet, DPT, PhD Departments of Rehabilitation and Movement Sciences, Rutgers – The State University of New Jersey, Newark, NJ, USA

Roger Gassert, PhD Rehabilitation Engineering Laboratory, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland

Joseph M. Hidler, PhD Aratech, LLC, Ashburn, VA, USA

Neville Hogan, PhD Department of Mechanical Engineering, Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA

Felix C. Huang, PhD Sensory Motor Performance Program, Rehabilitation Institute of Chicago, Chicago, IL, USA

Department of Physical Medicine and Rehabilitation, The Rehabilitation Institute of Chicago and Northwestern University, Chicago, IL, USA

Arun Jayaraman, PT, PhD Max Näder Lab for Rehabilitation Technologies and Outcomes Research, Departments of Physical Medicine and Rehabilitation, Medical Social Sciences, Physical Therapy and Human Movement Sciences, The Rehabilitation Institute of Chicago, Northwestern University, Chicago, IL, USA

Derek Kamper, PhD Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, USA

Urs Keller Sensory-Motor Systems Lab, Department of Health Sciences and Technology, Institute of Robotics and Intelligent Systems, Zurich, Switzerland

Rehabilitation Center, University Children's Hospital Zurich, Zurich, Switzerland

Christine E. King, PhD Department of Neurology, University of California Los Angeles, Los Angeles, CA, USA

Verena Klamroth-Marganska, MD Sensory-Motor Systems Lab, Department of Health Sciences and Technology, Institute of Robotics and Intelligent Systems, ETH Zurich, Zurich, Switzerland

Spinal Cord Injury Center, Balgrist Campus, Zurich, Switzerland

Alexander C. Koenig, PhD Sensory-Motor Systems Lab, Institute of Robotics and Intelligent Systems, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland

Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Zurich, Switzerland

Hermano Igo Krebs, PhD Department of Mechanical Engineering, MIT-Massachusetts Institute of Technology, Cambridge, MA, USA

Department of Neurology, University of Maryland, School of Medicine, Baltimore, MD, USA

Institute of Neuroscience, University of Newcastle, Newcastle Upon Tyne, UK

Department of Rehabilitation Medicine I, Fujita Health University, School of Medicine, Toyoake, Japan

Department of Mechanical Science and Bioengineering, Osaka University, Osaka, Japan

Olivier Lambercy, PhD Rehabilitation Engineering Laboratory, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland

Jill M. Landry, PT Sensor Motor Performance Program, Rehabilitation Institute of Chicago, Chicago, IL, USA

Timothy D. Lee, PhD Department of Kinesiology, McMaster University, Hamilton, ON, Canada

Hyunglae Lee, PhD School for Engineering of Matter, Transport, and Energy, Arizona State University, Tempe, AZ, USA

Roberto Lloréns, PhD Instituto de Investigación e Innovación en Bioingeniería, Universitat Politècnica de València, Valencia, Spain

Andreas R. Luft, MD Department of Neurology, University Hospital Zurich, Zurich, Switzerland

Lars Lünenburger, PhD Hocoma AG, Zurich, Switzerland

Serena Maggioni, MSc Biomedical Engineering Hocoma AG, Zurich, Switzerland

Sensory-Motor Systems (SMS) Lab, Department of Health Sciences and Technology, ETH Zürich, Zurich, Switzerland

Spinal Cord Injury Center, University of Zurich, Balgrist University Hospital, Zurich, Switzerland

Irin C. Maier Clinical Research and Clinical Application, Hocoma AG, Volketswil, Switzerland

Dimitrios Manoglou Department of Neurology and Neurorehabilitation, Rehabilitation Centre, Klinik Valens, Valens, Switzerland

Kei Masani, PhD Lyndhurst Centre, Toronto Rehabilitation Institute – University Health Network, Toronto, Ontario, Canada

Colin M. McCrimmon Department of Biomedical Engineering, University of California Irvine, Irvine, CA, USA

Jacob G. McPherson, PhD Department of Biomedical Engineering, Florida International University, Miami, FL, USA

Andreas Meyer-Heim Rehabilitation Center, Children's University Hospital Zurich, Zurich, Switzerland

Silvestro Micera, PhD Ecole Polytechnmique Federale de Lausanne, Lausanne, Switzerland

Scuola Superiore Sant'Anna, Pisa, Italy

Konstantinos Michmizos, MEng, PhD Department of Computer Science, Rutgers University, Piscataway, NJ, USA

Pratik K. Mutha, PhD Department of Biological Engineering and Centre for Cognitive Science, Indian Institute of Technology Gandhinagar, Ahmedabad, Gujarat, India

Tobias Nef, PhD Gerontechnologoy and Rehabilitation Group, ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland

Zoran Nenadic, DSc Department of Biomedical Engineering, University of California Irvine, Irvine, CA, USA

James L. Patton, PhD Sensory Motor Performance Program, Rehabilitation Institute of Chicago, Chicago, IL, USA

Department of Physical Medicine Rehabilitation, Northwestern University, Chicago, IL, USA

Department of Bioengineering, Universities of Illinois at Chicago, Chicago, IL, USA

Milos R. Popovic, PhD, Dipl El Eng Institute of Biomaterials and Biomedical Engineering, University of Toronto and Toronto Rehabilitation Institute – University Health Network, Toronto, ON, Canada

Arthur Prochazka, BEng, MSc, PhD Centre for Neuroscience, University of Alberta, Edmonton, AB, Canada

Department of Physiology, University of Alberta, Edmonton, AB, Canada

David J. Reinkensmeyer, PhD Department of Mechanical and Aerospace Engineering, University of California at Irvine, Irvine, CA, USA

Department of Anatomy and Neurobiology, University of California at Irvine, Irvine, CA, USA

Department of Biomedical Engineering, University of California at Irvine, Irvine, CA, USA

Department of Physical Medicine and Rehabilitation, University of California at Irvine, Irvine, CA, USA

Robert Riener, Dr.-Ing Sensory-Motor Systems Lab, Department of Health Sciences and Technology, Institute of Robotics and Intelligent Systems, ETH Zurich, Zurich, Switzerland

Spinal Cord Injury Center, Balgrist Campus, Zurich, Switzerland

Roland R. Roy, BS, MS, PhD Department of Integrative Biology and Physiology and Brain Research Institute, University of California, Los Angeles, CA, USA

Anindo Roy, PhD Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA

Rüdiger Rupp, PhD Spinal Cord Injury Center, Heidelberg University Hospital, Heidelberg, Germany

William Zev Rymer, MD, PhD Sensory Motor Performance Program, Department of Research, Rehabilitation Institute of Chicago, Chicago, IL, USA

Robert L. Sainburg, PhD Departments of Kinesiology and Neurology, The Pennsylvania State University and Penn State College of Medicine, University Park, PA, USA

Miriam Schrafl-Altermatt, PhD Spinal Cord Injury Center, Balgrist University Hospital, Zurich, Switzerland

Martina R. Spiess, PhD, PT Clinical Research and Clinical Application, Hocoma AG, Volketswil, Switzerland

Michelle Louise Starkey, MA, MSc, PhD Spinal Cord Injury Research Lab, Spinal Cord Injury Centre, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

Arno H.A. Stienen, BSc, MSc, PhD Department of Biomechanical Engineering, University of Twente, Enschede, The Netherlands

Tyler Susko, PhD Department of Mechanical Engineering, University of California Santa Barbara, Santa Barbara, CA, USA

Heike Vallery, Dr – Ing Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands

Edwin H.F. van Asseldonk, PhD Department of Biomechanical Engineering, University of Twente, Enschede, The Netherlands

Hubertus J.A. van Hedel, PhD, PT Pediatric Rehab Research Group, Rehabilitation Center for Children and Adolescents, University Children's Hospital Zürich, Zurich, Switzerland

Rubia van den Brand, MSc Department of Neurology, Experimental Neurorehabilitation Laboratory, Zurich, Switzerland

Herman van der Kooij, ir, PhD Department of Biomechanical Engineering, University of Twente, Enschede, The Netherlands

Po T. Wang, PhD Department of Biomedical Engineering, University of California Irvine, Irvine, CA, USA

Markus Wirz, PT, PhD Health Department, Institute of Physiotherapy, Zurich University of Applied Sciences, Winterthur, Switzerland

Ming Wu, PhD Sensor Motor Performance Program, Rehabilitation Institute of Chicago, Chicago, IL, USA

Burkhard Zimmermann Department of Quality Management, Hocoma AG, Zurich, Switzerland

IISART, Zurich, Switzerland

Daniel K. Zondervan, PhD Flint Rehabilitation Devices, LLC, Irvine, CA, USA

Introduction: Rationale for Machine Use

Neurorehabilitation technology, which includes robotics, wearable sensors, virtual reality, and functional electrical stimulation, is a rapidly expanding field in research and clinical applications. This second edition 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 machine use in neurorehabilitation?"

During the last 25 years, it has become evident that the efficacy of conventional physio- or occupational therapy applied during neurorehabilitation of stroke and spinal-cord-injured (SCI) patients can hardly be demonstrated in the context of evidence-based medicine. Conventional physio- or occupational therapy has usually been conducted on limited populations, with little objective and standardized assessments of its effects on outcomes over the course of rehabilitation and without a sound scientific basis. Different therapeutic "schools" (e.g., Bobath/Vojta) that emerged based on individual therapist experiences were not based on a rational approach driven by knowledge of the pathophysiological basis of impairment.

Relatively few, large 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, are difficult to implement rigorously, because of the confounding effects of spontaneous recovery of function. Furthermore, comparisons with "controls," i.e., patients without any treatment, are not feasible to perform. Thus, the quantitative effects of conventional physio- and occupational therapies still remain an open question. Some investigators have even argued that conventional therapy provides no real benefit for impairment reduction beyond that offered by spontaneous biological recovery alone, except in teaching patients compensatory strategies through motor learning [1, 2].

Key Developments Leading to the Emergence of Machines for Neurorehabilitation

From the late 1980s to the early 1990s, several key basic and clinical research developments led to profound changes in neurorehabilitation interventions and the emergence of machines for neurorehabilitation.

First, research performed in animal models showed the ability of rehabilitation training to alter both neural connectivity and movement function after injury. For example, experiments with cats with a transected spinal cord showed that a locomotor training approach, in which the cat walked on a treadmill with body weight support, was effective in promoting gait restoration [3]. This finding renewed interest in the notion of locomotion pattern generators in the mammalian spinal cord and indicated that they could potentially be harnessed for restoration of locomotion in the injured human as well [4, 5]. Recent studies using epidural spinal cord stimulation in animals and humans show that such stimulation heightens the responsivity of spinal networks, potentially further enhancing the gains possible with locomotor training [6].

For the upper extremity, seminal experiments conducted with monkeys that had received a focal ischemic infarct showed how rehabilitative training of skilled hand function prevented loss of cortical representation of the hand and was accompanied by functional behavioral gains [7]. Intense, skilled hand training formed a theoretical framework for constraint-induced therapy, which in turn was validated in one of the few large randomized clinical trials of neurorehabilitation that was successful [8]. Thus, one key change that began in the 1980s was that basic science studies began to verify that intense rehabilitation training applied in a physiologically appropriate way produced verifiable and beneficial changes even in the chronically injured nervous system.

Second, approaches to successfully induce axonal regeneration in animals with severe neural damage began to be introduced. For example, antibodies can be used to block the effects of myelin products on neuronal growth after spinal cord injury [9]. Neural stem cells engrafted into the damaged spinal cord promote new synapse formation and locomotor recovery [10]. 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 required [11]. These developments have forced rehabilitation centers in Europe [11] and in the United States to begin to build collaborative research networks, to introduce and establish standardized clinical and functional assessments, and to monitor therapeutic effects over the course of rehabilitation.

Third, we know today that elderly patients can also profit from rehabilitation procedures, a finding of key importance given the changing demographics of many industrialized nations. For example, it was demonstrated that the neurological deficit after an SCI recovers to a similar extent as in young subjects. However, elderly patients have difficulties to translate this gain in motor function into activities of daily living [12,13]. Therefore, age-specific rehabilitation approaches are required and should be applied as far as possible in a home environment of the patient.

Thus, in summary, three changes that have occurred are (1) increased scientific evidence for effectiveness of intensive neurorehabilitation therapy originating from studies in animal models; (2) new promise of neuroregenerative treatments, necessitating greater standardization and better outcome monitoring in rehabilitation practice; and (3) the opportunity and need to treat

the increasing number of elderly patients with neurologic injury, in the clinic as well as at home. All three of these changes contributed to the realization that appropriately designed robotic devices and other machines could be useful for rehabilitation therapy, both scientifically and clinically.

The First Robots for Rehabilitation 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 and only short training periods because of the need for multiple physiotherapists to assist the leg movements on both sides during the step cycle [14], as well as the need for additional therapists to substitute for the treating therapists, because the intervention is demanding on both therapist and patients. The cyclic nature of repetitive movements to be assisted over longer time periods led to the idea that a robotic device could take over the physically demanding training [15].

However, successful implementation of the first robotic device for providing locomotor training of SCI/stroke subjects—the Lokomat—still required that several other problems be solved, and in fact the development of the Lokomat has been an ongoing process of refinement. Safety constraints had to be established, mainly related to the forces that could be applied to the legs and prevention of skin ulcers. In the beginning, position-controlled fixed physiological stepping movements, which had been prerecorded from healthy subjects, were imposed on the legs of SCI subjects using an exoskeleton robot [15]. However, in subsequent years, it has become evident that merely imposing fixed movements on paretic limbs is not sufficient to achieve optimal training effects. Leg movements should only be assisted insofar as it is required by the severity of paresis of an individual subject. Therefore, ongoing developmental advances have focused on patient-cooperative and assist-as-needed controllers, as well as providing feedback information to both the patient and therapists about the patient's contribution to the locomotor movements [16], increased degrees of freedom for the pelvis, and quantitative assessments that assay the impairments contributing to locomotor dysfunction, as reviewed in chapters in this book and in [17].

For the upper extremity, the first robotic therapy device, MIT-MANUS, which was developed starting in the 1980s, targeted a simple functional arm movement—reaching to targets in the horizontal plane [18]. In this case, the device again provided a tool for therapists and patients to extend the number of practice movements the patient could make and also provided a consistent, standardized form of assistance during practice, which was useful for scientific studies of rehabilitation therapy. But MIT-MANUS also then has undergone a continual process of refinement and testing, including adding degrees of freedom to make the practice movements more functional, involving devices for the hand and wrist, and changing the way assistance is provided so that it progressively challenges the patient, as described in chapters in this

book. In addition, the most widely used upper extremity robotic technology now appears to be ArmeoSpring, in use in over 700 facilities. ArmeoSpring is based on the T-WREX arm exoskeleton [19] and is technically not even a robot, because it lacks programmable actuators.

The Rationale for Machine Use in Rehabilitation Therapy

In light of the above history, it is now reasonable to ask: What is the rationale for applying a robotic device or other machine for rehabilitation therapy in patients with a neurologic injury such as stroke or SCI? At present, the main potential advantages are:

- Machines allow standardized training sessions that simultaneously provide objective measures and feedback information to the patient/therapist about the physical aspects of the training performed (e.g., applied forces, velocity, duration of training, joint excursions) and about the training effects (i.e., the progress of recovery can be monitored). This is important both for improving decision-making in clinical practice and for improving clinical trial design and execution.
- Machines enable longer training times and, in some cases, more repetitions to be achieved per unit of time.
- Machines relieve therapists from physically demanding work, allowing them to optimize other aspects of the individual therapy and care.

What Is Needed for a Successful Training?

Systematic reviews of clinical studies of both lower and upper extremity robotic therapy devices now support their effectiveness as adjuncts to conventional therapy, yet the therapeutic benefits these devices help deliver are still modest [20, 21]. Robotic devices can assist to exploit neuroplasticity after a damage of the CNS. However, restoration of function is limited depending on the individual condition [22]. There are many essential questions that have to be answered in order to optimize training effects and advance the field of rehabilitation technology. We conclude this Introduction by posing some of these questions (for more questions, see also [23]):

- What are the essential sensory cues [24] and appropriate forms of mechanical assistance/control laws [25] to optimize the training by a machine?
- What is the best type of feedback information for the patient during a machine training episode, and how should it best be delivered to reinforce training effects?
- With a machine, longer training sessions become feasible. How long should a training session last per day to achieve optimal effects? How do the individual's health condition, needs, and capabilities affect this determination?
- What types of movements and speeds of movements are appropriate to achieve the best effects? How should movement type and speed be varied

during a training session? How "physiological" must the training conditions be? When should compensatory movements be allowed?
- How early after a neurologic injury should a patient start machine training and how strongly should the patient be challenged by the training?
- How can technologies be developed that are appropriate and viable for home use?
- How does optimal technology design vary with patient subgroups, e.g., children or elderly patients?
- To what extent can other emerging interventions, such as virtual reality, brain-computer interfaces, and functional electrical stimulation, enhance the effectiveness of machine-based training?

References

1. Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. Curr Opin Neurol. 2006;19(1):84–90.
2. Prabhakaran S, Zarahn E, Riley C, Speizer A, Chong JY, Lazar RM, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. Neurorehabil Neural Repair. 2008;22(1):64–71.
3. Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in the adult cat. Brain Res. 1987;412:84–95.
4. Barbeau H, Fung J. The role of rehabilitation in the recovery of walking in the neurological population. Curr Opin Neurol. 2001;14:735–40.
5. Barbeau H, Rossignol S. Enhancement of locomotor recovery following spinal cord injury. Curr Opin Neurol. 1994;7:517–24.
6. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain. 2014; 137(Pt 5):1394–409.
7. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science. 1996; 272: 1791–4.
8. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, Nichols-Larsen D, EXCITE Investigators. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006;296(17):2095–104.
9. Schwab ME, Bartholdi D. Degeneration and regeneration of axons in the lesioned spinal cord. Physiol Rev. 1996;76:319–70.
10. Cummings BJ, Uchida N, Tamaki SJ, Salazar DL, Hooshmand M, Summers R, Gage FH, Anderson AJ. Human neural stem cells differentiate and promote locomotor recovery in spinal cord-injured mice. Proc Natl Acad Sci U S A. 2005;102(39):14069–74.
11. Curt A, Schwab ME, Dietz V. Providing the clinical basis for new interventional therapies: refined diagnosis and assessment of recovery after spinal cord injury. Spinal Cord. 2004;42:1–6.
12. Jakob W, Wirz M, van Hedel HJA, Dietz V. Difficulty of elderly spinal cord injured subjects to translate motor recovery—body function—into activity of daily living. J Neurotrauma. 2009;26:2037–44.
13. Wirz M, Dietz V, EMSCI network. Recovery of sensorimotor function and activities of daily living after cervical spinal cord injury: the influence of age. J Neurotrauma. 2015;32:194–9.
14. Dietz V, Harkema SJ. Locomotor activity in spinal cord-injured persons. J Appl Physiol. 2004;96:1954–60.
15. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37:693–700.
16. Riener R, Lunenburger L, Colombo G. Human-centered robotics applied to gait training and assessment. J Rehabil Res Dev. 2006;43:679–94.

17. Riener R, Lünenburger L, Maier IC, Colombo G, Dietz V. Locomotor training in subjects with sensori-motor deficits: an overview of the robotic gait orthosis lokomat. J Healthc Eng. 2010;1:197–216.
18. Aisen ML, Krebs HI, Hogan N, McDowell F, Volpe BT. The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. Arch Neurol. 1997;54:443–6.
19. Sanchez RJ, Liu J, Rao S, Shah P, Smith R, Rahman T, et al. Automating arm movement training following severe stroke: functional exercises with quantitative feedback in a gravity-reduced environment. IEEE Trans Neural Syst Rehabil Eng. 2006;14(3):378–89.
21. Prange GB, Jannink MJA, Groothuis CGM, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev. 2006;43(2):171–84.
21. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke: updated evidence. Stroke. 2013;44:e127–8.
22. Dietz V, Fouad K. Restoration of sensorimotor functions after spinal cord injury. Brain. 2014;137(Pt 3):654–67.
23. del-Ama AJ, Cuesta A, Rajasekaran V, Trincado F, In H, Reinkensmeyer DJ. Robotic rehabilitation: ten critical questions about current status and future prospects answered by emerging researchers. In Pons JL, Torricelli D, editors. Emerging therapies in neurorehabilitation series: volume 4 of the series biosystems & biorobotics. Springer Heidelberg, 2014, p. 189–205.
24. Dietz V, Muller R, Colombo G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. Brain. 2002;125:2626–34.
25. Marchal-Crespo L, Reinkensmeyer DJ. Review of control strategies for robotic movement training after neurologic injury. J Neuroeng Rehabil. 2009;6:20.

Part I

Basic Framework: Motor Recovery, Learning, and Neural Impairment

Learning in the Damaged Brain/ Spinal Cord: Neuroplasticity

1

Andreas Luft, Amy J. Bastian, and Volker Dietz

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

1.1 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 in the lesioned brain that mediates functional recovery is not identical to learning in the healthy state. Nevertheless, there are certain mechanisms on the cellular of systems level, termed as *neuroplasticity*, which are shared by healthy learning and recovery. Clearly, the main behavioral determinants of healthy learning of novel movements,

A. Luft, MD (✉)
Department of Neurology, University of Zurich, Frauenkliniksrasse 26, Zurich 8091, Switzerland
e-mail: andreas.luft@usz.ch

A.J. Bastian, PhD
Department of Neuroscience, The Johns Hopkins School of Medicine and Kennedy Krieger Institute, 707 N. Broadway, Baltimore, MD 21205, USA
e-mail: bastian@kennedykrieger.org

V. Dietz
Spinal Cord Injury Center, University Hospital Balgrist, Forchstr. 340, Zurich 8008, Switzerland
e-mail: vdietz@paralab.balgrist.ch

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activity, and repetition are also important in recovery.

Hence, movement recovery may depend in part on motor learning. 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 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 can be de-adapted when the predictable perturbation is reversed or removed. Discontinuation of training also leads to "forgetting" of the adaptations over relatively short periods of time [3].

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 links 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 [4]. 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 presented, 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 [5] or negative in the form of avoidance learning [6]. 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 reinforcement processes [7]. Small improvements after repeating a novel movement, e.g., when learning to play a piano piece, are often not obvious or consciously perceived. Unconscious rewarding feedback may play a role. The conscious reward of playing the piece well typically comes late and temporally unrelated to the movement (e.g., the audience applauds). Thus, implicit motor learning may be mediated through use-dependent or Hebbian-like plasticity rather than reinforcement 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 [8]. Classical conditioning can involve the cerebellum and hippocampus depending on the specific timing between stimuli [4]. Reward and avoidance learning are dependent on basal ganglia circuitry [9]. Use-dependent learning likely occurs at many levels of the nervous system, including the spinal cord, brain stem, and cerebral structures. Complex motor skill learning induces plasticity in the motor cortex especially during consolidation of the learned movement [10–12]. 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.

1.2 Mechanisms of Neuroplasticity in Learning and After Lesions

1.2.1 Gene Expression

Learning of a motor skill requires gene expression in the primary motor cortex (M1) [11, 12]. If this expression is pharmacologically blocked, learning is reduced. Gene and subsequent protein expression is a common requirement of various learning processes [13, 14] as well as for cellular equivalents of learning, i.e., the changes in neuronal structure [15] and synaptic strength in the form of long-term potentiation (LTP) and long-term depression (LTD) [16]. For motor skill

learning, proteins are not only expressed during training but also thereafter while the subject is resting [11]. This delayed synthesis can be regarded as reflecting intersession consolidation processes [17]. The genes induced by learning are manifold, including immediate early genes (IEG, transcription factors). Expression of the IEG Arc in M1 was shown to occur specifically during skill learning but not during movement without learning [18].

Gene expression is induced by ischemia, especially in the peri-infarct cortex [19]. Some of these genes could also promote cellular plasticity offering the potential for stroke-induced plasticity as self-healing mechanisms of the brain. Genes and proteins induced by ischemia include axonal growth stimulators, while growth inhibitors are suppressed [20, 21].

1.2.2 Cellular Plasticity

Long-term potentiation (LTP) and long-term depression (LTD) are commonly seen as cellular equivalents of the brain's learning abilities [22]. 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 [23]. LTD is induced by low-frequency stimulation and leads to a lasting reduction in synaptic strength [22]. Both LTP and LTD have been described in various brain regions including the primary motor cortex (M1) [24]. 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 the primary motor cortex LTP/LTD is involved in motor skill learning [25]. 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 LTP has recovered and is now expressed on a higher level of synaptic strength [24].

In addition to changes in synaptic strength, the structure of neuronal networks is reorganized in association with motor skill learning. Apical and basal dendrites expand in association with skill training [26, 27]. This expansion is specific to the neurons involved in the control of the muscles used in the trained movement but not in other musculature [28]. It remains open whether these changes are permanent or reflect a temporary expansion of M1 connectivity. Changes in dendritic spines, in contrast, were shown to be temporary and return to baseline 1 week after training has ended [29].

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 [30]. 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 the hippocampus, short-term ischemia leads to a disruption of LTP formation [31]. 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 [32]. 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 [33]. LTP-like phenomena are enhanced by serotonin [34] possibly explaining the beneficial effect of serotonin reuptake inhibitors in stroke recovery [35]. Hence, the ability of the lesioned cortex to undergo LTP may be a requisite for recovery.

1.2.3 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 [36, 37]. Longitudinal motor cortex-mapping experiments in rats show that this expansion is transient and is reversed after training ends although the skill is maintained [38]. In humans who continuously train new motor skills, e.g., professional pianists, task-related activation is smaller in area and more focused [39, 40]. Musicians also have enlarged gray matter volumes in various areas of the cortex including the motor cortices [41]. The M1 of musicians contains memory traces of practiced skills that can be probed by TMS [42].

Representations in the 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) [43, 44]. If M1 itself is lesioned, expanded activation is found in peri-infarct cortex [45] or in premotor cortex [46]. As subjects recover, this hyper-activation is reduced, and movement-related activity focuses in the ipsilesional hemisphere contralateral to the moving limb [47–49]. If recovery is unsuccessful, cortices remain hyper-activated in the lesioned as well as the non-lesioned hemisphere which has been interpreted as a sign of a continuous attempt to initiate recovery [50]. But recovery is not only accompanied by cortical activation changes. Larger activation in the cerebellum ipsilateral to the moving limb [47] and smaller activation in the contralateral cerebellum are associated with better recovery [48].

Connectivity between different cortical regions in the brain is impaired after stroke, not only in areas in vicinity to the lesion but also in the intact hemisphere [51]. There is reduced interhemispheric connectivity after stroke, especially between primary motor cortices [52].

While movement-related activation observed with functional imaging methods demonstrates the brain areas that are involved in the control of the movement performed during imaging, 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 [53, 54].

1.2.4 Plasticity in the 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 [55, 56]. When stepping is practiced in spinal cat, this task can be performed more successfully than when it is not practiced, but standing duration is not improved and vice versa, training of standing has only an effect on this task [57, 58]. The training effects of any motor task critically depend on the provision of sufficient and appropriate proprioceptive feedback information 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 is associated with the development of neuronal dysfunction below the level of lesion in humans [44], and rodents [45] following neural injury becomes enhanced when locomotor networks are no longer used, for example, following an SCI or stroke [55].

1.2.4.1 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 neuronal circuits within 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].

1.2.4.2 Task-Specific Plasticity Here

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 [55, 56, 59–61]). The detailed assessment of the modifiability of neuronal network function is reflected in the research on central pattern generators (CPGs) underlying stepping movements [62–65]. 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 similar task is subsequently trained, then the performance of the task previously trained is degraded [55]. 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 [66, 67]. The provision of an adequate sensory input to the spinal cord during training is of great importance to achieve an optimal output of the spinal neuronal circuitry with the consequence of an improved function. This essential aspect of training could meanwhile also be demonstrated for the locomotor training of subjects with an SCI [68]. Furthermore, in association with hind limb exercise, reflex activity becomes normalized in adult rats following spinal cord transection [69]. 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 mediation of plastic changes following repetitive task performance [55]. 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 [70–72]. However, application of dopamine in patients with an SCI has no effect on outcome of function [73]. Furthermore, serotonin seems to be involved in the production of locomotor rhythms [74].

Training paradigms of stepping and standing can modify the efficacy of the inhibitory neurotransmitter, glycine [55]. 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 [55, 61]. These findings suggest that the effect of glycine is insofar specific in its action as it enables spinal networks to integrate sensory input by reducing inhibition [71, 72].

1.2.5 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 [75]. This feedforward control requires stored knowledge (i.e., "models") of the body's dynamics, the environment, and any object to be manipulated. For example, recent work has demonstrated that cerebellar damage causes a bias in the brain's representation of limb inertia relative to actual inertia, which results in characteristic patterns of reaching dysmetria (i.e., over- or under-shooting targets) [76]. This specific deficit was confirmed in simulation and in behavioral studies of control subjects reaching with their limb inertia

unexpectedly changed via an exoskeleton robot. Perhaps most importantly, this work also demonstrated a way of correcting this mismatch using cerebellar patient-specific compensations rendered by an exoskeleton robot. This suggests that there may be ways to compensate for biases in internal model representations using robotics. Unfortunately, cerebellar patients cannot learn to correct their internal model biases due to a loss of a cerebellum-dependent learning process often referred to as 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 [77], walking [78], balance [79], and eye movements [80]. To date, there has been no systematic way to substitute or compensate for deficits in this form of learning.

The microcircuit involved in cerebellar adaptation was first proposed by Marr [81], Albus [82], and Ito [83]. 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 [84]. Hence, climbing fiber inputs onto Purkinje cells can be viewed as providing a unique type of teaching or error signal to the cerebellum. Recent work has shown that the climbing fiber may not simply be an all-or-none signal indicating error [85]. Instead, the duration of climbing fiber bursts is predictive of the magnitude of plasticity and learning, making it a graded instructive signal for adaptation. In addition to the climbing fiber-dependent LTD, there are many other sites of plasticity in the cerebellar cortex and deep nuclei that involve LTP and non-synaptic plasticity [for review, see [86]]. 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 [87] are specifically necessary for acquiring but not for performing a skill once acquired. Elimination of dopaminergic terminals in M1 [88] or destruction of dopaminergic neurons in VTA impairs the acquisition of a reaching skill in rat [89]. Dopamine modulates the excitability of M1 [90] and S1 [91] and, more importantly, is necessary for the formation of LTP in layer II/III synapses [88] 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 as compared to those that activate dopaminergic neurons from VTA to nucleus accumbens and prefrontal cortex. The latter encodes rewarding feedback to behavior [92] (Fig. 1.1).

1.3 Learning and Plasticity During Rehabilitation Therapy

1.3.1 Lesions of Cortex and Descending Pathways

Rehabilitative training is associated with neurophysiological alterations that are related to the improvement in motor function observed in individual stroke survivors [93]. Although

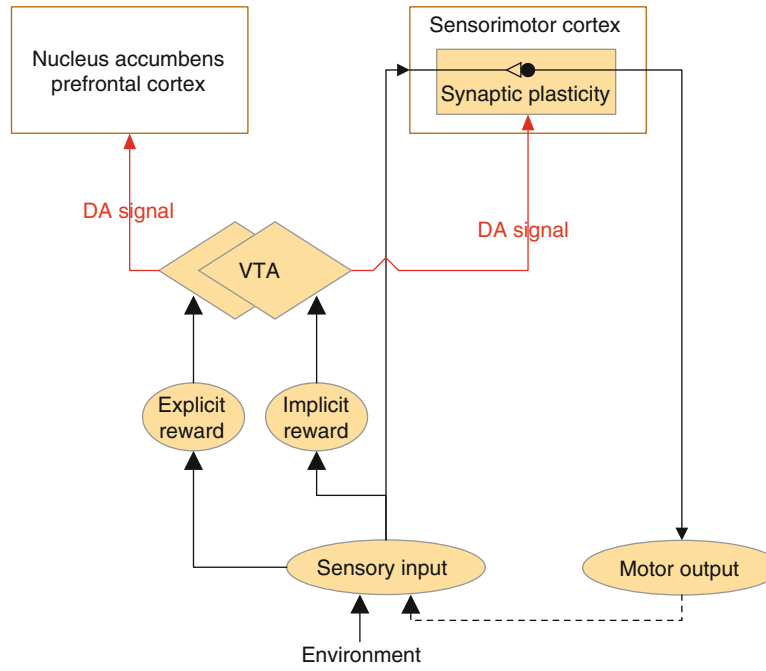

Fig. 1.1 Schematic representation of the integration of a postulated "implicit reward" into the simplified circuit that is required for motor learning. Via the dopamine (*DA*) signal, the reward could directly modulate synaptic plasticity in sensorimotor cortex synapses to store a new motor program

correlation is not proof for causation, these studies provide an argument for neuroplasticity being one possible mechanism by which rehabilitative training can operate effectively. 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 [94] and Wolf tests [95], conventional physical therapy (based on Bobath exercises) did not show altered brain activation despite being equally effective [95]. Conventional physical exercise may have utilized a mechanism other than those detectable by fMRI, e.g., by inducing changes in the 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 the cerebellum and brain stem as detected with fMRI of paretic knee movement [96]. Interestingly, the areas recruited in the cerebellum and brain stem 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 [97–99]. Repeated split-belt training over a 1-month time resulted in improvements in step length symmetry in chronic stroke survivors [99]. Importantly, the split-belt treadmill was used to augment the step asymmetry errors that the stroke survivors produced. This was done to drive a cerebellum-dependent learning process that would correct their error. Stated simply, making their error bigger drove the nervous system to learn how to correct it. After training, when they walked over ground, they had learned to correct their step length asymmetry. Training over 4 weeks led to improvements that lasted (and even improved further) at 3 months post training. 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 rehabilitation clinician with many tools 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.

1.3.2 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 [100–102]. On the other hand, individuals with degenerative cerebellar disorders tend to have persistent or progressively worsening clinical signs and symptoms [103]. 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 [104]. Thus, the etiology of the lesion and extent of damage are major indicators in recovery.

There is a growing body of literature on the effectiveness of rehabilitation interventions for individuals with primary cerebellar damage. To date, there have been no randomized controlled trials published. There are studies on the effects of rehabilitation interventions in this patient population, but all have been nonrandomized, noncontrolled small group [e.g., 105] or case study designs [e.g., 106]. 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 [105, 106]. Dynamic balance activities in sitting, kneeling, and quadruped have also been advocated [105]. Individuals with acute cerebellar stroke seem to recover similarly regardless of whether they participated in a 2-week treadmill training intervention [107]. Further, individuals with superior cerebellar artery infarcts tend to show more severe ataxia than those with posterior inferior cerebellar artery infarcts early on, but both groups tend to recover to the same extent after 3 months. People with degenerative disorders tend to benefit more from rehabilitation training. 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 has also been shown that a 6-week home balance exercise program can improve balance and walking measures in people with cerebellar degeneration [108]. In that study, it was shown that the difficulty of the balance exercise is what predicted the best outcomes, with more challenging balance activities resulting in the greatest improvement. It was also shown that the effects of home exercise lasted for a month after therapy. In all of these studies, 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 [109, 110]. 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 [111, 112].

1.3.3 Spinal Lesions

1.3.3.1 Plasticity of Spinal Neuronal Circuits: Rehabilitation Issues

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 spinal and supraspinal neuronal circuits and should less be directed to the correction of isolated clinical signs, such as the reflex excitability and muscle tone. For the monitoring of outcome and for the assessment of the effectiveness of any interventional therapy, standardized functional tests should be applied.

1.3.3.2 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 [113]. 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 80 %) the patients who are standing on a moving treadmill ([114, 115]; for review, see [68, 116]). 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 [117]. The timing of the pattern of leg muscle Electromyogram 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 [67, 118, 119]), and patients who undergo locomotor training have a greater mobility compared to a control group without training [120]. The neuronal networks below the level of an SCI can be activated to generate locomotor activity even in the absence of supraspinal input [71, 72, 121]. 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 [122]. In addition, recent observations indicate that locomotor movements induced by a robotic device in patients who are completely unloaded do not lead to a significant leg muscle activation [123]. This implies that the generation of the leg muscle EMG pattern in these patients is programmed at a spinal level and requires appropriate afferent input from load signaling receptors.

During the course of daily locomotor training, the amplitude of the EMG in the leg extensor muscles increases and becomes better modulated during the stance phase, and inappropriate leg flexor activity decreases. Such training effects are seen both in complete and incomplete paraplegic patients [114]. 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 [124–127]. However, only persons with incomplete paraplegia benefit from the training program insofar as they can learn to perform unsupported stepping movements on solid ground [114]. Neuroplastic changes also occur in elderly SCI subjects. This becomes reflected in an improvement of neurological deficit similar to that of young subjects. However, the translation of this improvement to function is significantly worse in elderly subjects [128]. Therefore, it is required to develop and apply specific rehabilitation procedures in elderly subjects.

In complete paraplegic patients, the training effects on leg muscle activation become lost after the training has been stopped [121]. Furthermore, after about 1 year after injury, complete paraplegic patients develop a neuronal dysfunction below the level of injury [129] which might have adverse consequences for future regeneration-inducing therapies. According to rodent experiments, this dysfunction is thought to be due to an undirected sprouting within neuronal circuits [45].

1.3.3.3 Prerequisites for a Successful Training

The spinal pattern generator has to be activated by the provision of an appropriate afferent input by proprioceptive feedback that leads to a meaningful muscle activation associated with plastic neuronal changes and consequently to an improvement of function [123].

Afferent input from receptors signaling contact forces during the stance phase of gait is essential for the activation of spinal locomotor centers [123, 127, 130–132] and is important to achieve training effects in paraplegic patients [114] (Fig. 1.2). Furthermore, hip joint-related afferent input seems to be required to generate a locomotor pattern [123]. In addition, for a

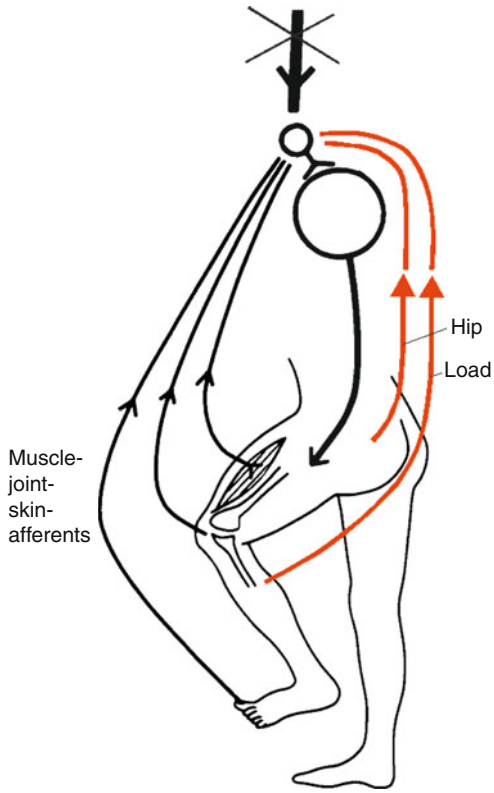

Fig. 1.2 Schematic demonstration of proprioceptive input during locomotor training in SCI subjects. The input from load and hip joint afferents was shown to be essential to achieve training effects

successful training program for stroke and SCI subjects, spastic muscle tone has to be present as a partial compensation for paresis [133].

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 [126, 134, 135]. In these cases, a relatively low voluntary force level in the leg muscles (reflected in the ASIA score) is required to achieve an automatic synergistic muscle activation with the ability to walk.

A considerable degree of locomotor recovery can be attributed to a reorganization of spared neural pathways ([136]; for review, see [137]). It has been estimated that if as little as 10–15 % of the descending spinal tracts are spared, some locomotor function can recover [138, 139]. In addition, by a training approach with the provision of appropriate afferent input, a directed, meaningful sprouting within neural circuits takes place below the level of lesion with the consequence of an improved recovery of function in the rat [45].

The improvement of locomotor activity might be attributed to a spontaneous recovery of spinal cord function that can occur over several months following a spinal cord injury [137, 140]. 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 [115, 125, 135, 137, 141]. Thus, functional training effects on spinal locomotor centers most likely contribute to an improvement of locomotor function in incomplete SCI subjects [115, 141]. However, part of the recovery in locomotion corresponding to observations in the rat [55] might also be attributed to changes in muscle properties that occur during the training period.

Conclusion

Neuroplasticity mechanisms and training methods can improve patients with cerebral, cerebellar, and spinal cord injury. However, patients with complete or almost complete hemi- or paraplegia do not, as yet, profit from training because they cannot actively train. In the future, in these patients a combination of regeneration-inducing therapy and exploitation of neuronal plasticity possibly by using novel training devices could have a beneficial effect on the recovery of function, as the research in spinal cord regeneration appears to be quite encouraging (for review, see [142]). Novel training devices (often referred to as rehabilitation robots) become increasingly important and popular in clinical and rehabilitation settings for functional training and standardized assessments (for review cf. [143]). Such devices allow a prolonged training duration, increased number of repetitions of movements, improved patient's safety, and less physical demands for the therapists. Supportive therapies that enhance the brain's potential to undergo plastic changes could supplement the training itself. For all these

developments, testing in clinical trials will be required to prove efficacy and optimize the treatment for various disease and lesion types.

References

1. Martin TA, Keating JG, Goodkin HP, Bastian AJ, Thach WT. Throwing while looking through prisms. II. Specificity and storage of multiple gaze-throw calibrations. Brain. 1996;119(Pt 4):1199–211.
2. Tseng Y-W, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ. Sensory prediction errors drive cerebellum-dependent adaptation of reaching. J Neurophysiol. 2007;98(1):54–62. United States.
3. Shmuelof L, Huang VS, Haith AM, Delnicki RJ, Mazzoni P, Krakauer JW. Overcoming motor "forgetting" through reinforcement of learned actions. J Neurosci. 2012;32(42):14617–21. United States.
4. Christian KM, Thompson RF. Neural substrates of eyeblink conditioning: acquisition and retention. Learn Mem. 2003;10(6):427–55.
5. Schultz W, Apicella P, Ljungberg T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J Neurosci. 1993;13(3):900–13.
6. Iordanova MD. Dopaminergic modulation of appetitive and aversive predictive learning. Rev Neurosci. 2009;20(5–6):383–404. England.
7. Tranel D, Damasio AR, Damasio H, Brandt JP. Sensorimotor skill learning in amnesia: additional evidence for the neural basis of nondeclarative memory. Learn Mem. 1994;1(3):165–79.
8. Galea JM, Vazquez A, Pasricha N, de Xivry J-JO, Celnik P. Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. Cereb Cortex. 2011;21(8):1761–70. United States: Oxford University Press.
9. O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science. 2004;304(5669):452–4.
10. Hosp JA, Luft AR. Dopaminergic meso-cortical projections to m1: role in motor learning and motor cortex plasticity. Front Neurol Front. 2013;4:145.
11. Luft AR, Buitrago MM, Ringer T, Dichgans J, Schulz JB. Motor skill learning depends on protein synthesis in motor cortex after training. J Neurosci. 2004;24(29):6515–20.
12. Luft AR, Buitrago MM, Kaelin-Lang A, Dichgans J, Schulz JB. Protein synthesis inhibition blocks consolidation of an acrobatic motor skill. Learn Mem. 2004;11(4):379–82.
13. D'Agata V, Cavallaro S. Gene expression profiles – a new dynamic and functional dimension to the exploration of learning and memory. Rev Neurosci. 2002;13(3):209–19. 2002nd ed.
14. D'Agata V, Cavallaro S. Hippocampal gene expression profiles in passive avoidance conditioning. Eur J Neurosci. 2003;18(10):2835–41.
15. Steward O, Schuman EM. Protein synthesis at synaptic sites on dendrites. Annu Rev Neurosci. 2001;24(1):299–325.
16. Miyamoto E. Molecular mechanism of neuronal plasticity: induction and maintenance of long-term potentiation in the hippocampus. J Pharmacol Sci. 2006;100(5):433–42.
17. Davis HP, Squire LR. Protein synthesis and memory: a review. Psychol Bull. 1984;96(3):518–59.
18. Hosp JA, Mann S, Wegenast-Braun BM, Calhoun ME, Luft AR. Region and task-specific activation of arc in primary motor cortex of rats following motor skill learning. Neuroscience. 2013;250:557–64. United States.
19. Carmichael ST. Plasticity of cortical projections after stroke. Neuroscientist. 2003;9(1):64–75.
20. Li S, Carmichael ST. Growth-associated gene and protein expression in the region of axonal sprouting in the aged brain after stroke. Neurobiol Dis. 2006;23(2):362–73.
21. Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: making waves. Ann Neurol. 2006;59(5):735–42.
22. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron. 2004;44(1):5–21.
23. Kandel ER. Cellular mechanisms of learning and the biological basis of individuality. 4th ed. Princ Neural Sci. 1991;1247–79.
24. Rioult-Pedotti MS, Donoghue JP, Dunaevsky A. Plasticity of the synaptic modification range. J Neurophysiol. 2007;98(6):3688–95.
25. Rioult-Pedotti MS, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. Science. 2000;290(5491):533–6.
26. Greenough WT, Larson JR, Withers GS. Effects of unilateral and bilateral training in a reaching task on dendritic branching of neurons in the rat motor-sensory forelimb cortex. Behav Neural Biol. 1985;44(2):301–14.
27. Kolb B, Cioe J, Comeau W. Contrasting effects of motor and visual spatial learning tasks on dendritic arborization and spine density in rats. Neurobiol Learn Mem. 2008;90(2):295–300. United States.
28. Wang L, Conner JM, Rickert J, Tuszynski MH. Structural plasticity within highly specific neuronal populations identifies a unique parcellation of motor learning in the adult brain. Proc Natl Acad Sci U S A. 2011;108(6):2545–50. United States.
29. Xu T, Yu X, Perlik AJ, Tobin WF, Zweig JA, Tennant K, et al. Rapid formation and selective stabilization of synapses for enduring motor memories. Nature. 2009;462(7275):915–9. England.
30. Hagemann G, Redecker C, Neumann-Haefelin T, Freund HJ, Witte OW. Increased long-term potentiation in the surround of experimentally induced focal cortical infarction. Ann Neurol. 1998;44(2):255–8. Available from: http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd

=Retrieve&list_uids=9708549&dopt=abstractplus, [Internet].
31. Gasparova Z, Jariabka P, Stolc S. Effect of transient ischemia on long-term potentiation of synaptic transmission in rat hippocampal slices. Neurol Endocrinol Lett. 2008;29(5):702–5.
32. Di Lazzaro V, Profice P, Pilato F, Capone F, Ranieri F, Pasqualetti P, et al. Motor cortex plasticity predicts recovery in acute stroke. Cereb Cortex. 2010;20(7):1523–8. United States.
33. Castel-Lacanal E, Marque P, Tardy J, de Boissezon X, Guiraud V, Chollet F, et al. Induction of cortical plastic changes in wrist muscles by paired associative stimulation in the recovery phase of stroke patients. Neurorehabil Neural Repair. 2009;23(4):366–72.
34. Batsikadze G, Paulus W, Kuo M-F, Nitsche MA. Effect of serotonin on paired associative stimulation-induced plasticity in the human motor cortex. Neuropsychopharmacology. 2013;38(11):2260–7.
35. Chollet F, Tardy J, Albucher J-F, Thalamas C, Berard E, Lamy C, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123–30.
36. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. J Neurosci. 1996;16(2):785–807.
37. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. J Neurophysiol. 1998;80(6):3321–5. United States.
38. Molina-Luna K, Hertler B, Buitrago MM, Luft AR. Motor learning transiently changes cortical somatotopy. Neuroimage. 2008;40(4):1748–54.
39. Jancke L, Shah NJ, Peters M. Cortical activations in primary and secondary motor areas for complex bimanual movements in professional pianists. Brain Res Cogn Brain Res. 2000;10(1–2):177–83.
40. Lotze M, Scheler G, Tan H-RM, Braun C, Birbaumer N. The musician's brain: functional imaging of amateurs and professionals during performance and imagery. Neuroimage. 2003;20(3):1817–29.
41. Gaser C, Schlaug G. Brain structures differ between musicians and non-musicians. J Neurosci. 2003;23(27):9240–5. United States.
42. Gentner R, Gorges S, Weise D, aufm Kampe K, Buttmann M, Classen J. Encoding of motor skill in the corticomuscular system of musicians. Curr Biol CB. 2010;20(20):1869–74.
43. Marshall RS, Perera GM, Lazar RM, Krakauer JW, Constantine RC, DeLaPaz RL. Evolution of cortical activation during recovery from corticospinal tract infarction. Stroke. 2000;31(3):656–61.
44. Dietz V, et al. Neural coupling of cooperative hand movements: a reflex and FMRI study. Cereb Cortex. 2015;25(4):948–58.
45. Beauparlant J, et al. Undirected compensatory plasticity contributes to neuronal dysfunction after severe spinal cord injury. Brain J Neurol. 2013;136(Pt 11):3347–61.
46. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of outcome after stroke: a cross-sectional fMRI study. Brain. 2003;126(Pt 6):1430–48. England.
47. Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, et al. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke. 1997;28(12):2518–27.
48. Seitz RJ, Höflich P, Binkofski F, Tellmann L, Herzog H, Freund HJ. Role of the premotor cortex in recovery from middle cerebral artery infarction. Arch Neurol. 1998;55(8):1081–8. United States.
49. Small SL, Hlustik P, Noll DC, Genovese C, Solodkin A. Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke. Brain. 2002;125(Pt 7):1544–57.
50. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain. 2003;126(Pt 11):2476–96. England.
51. Calautti C, Leroy F, Guincestre JY, Marié RM, Baron JC. Sequential activation brain mapping after subcortical stroke: changes in hemispheric balance and recovery. Neuroreport. 2001;12(18):3883–6. Rehme AK, Grefkes C. Cerebral network disorders after stroke: evidence from imaging-based connectivity analyses of active and resting brain states in humans. J Physiol (Lond). 2013;591(Pt 1):17–31. England: Blackwell Publishing Ltd.
52. Calautti C, Baron J-C. Functional neuroimaging studies of motor recovery after stroke in adults: a review. Stroke. 2003;34(6):1553–66. Lippincott Williams & Wilkins. Carter AR, Astafiev SV, Lang CE, Connor LT, Rengachary J, Strube MJ, et al. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann Neurol. 2010;67(3):365–75. Wiley Subscription Services, Inc., A Wiley Company.
53. Turton A, Wroe S, Trepte N, Fraser C, Lemon RN. Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. Electroencephalogr Clin Neurophysiol. 1996;101(4):316–28.
54. Escudero JV, Sancho J, Bautista D, Escudero M, Lopez-Trigo J. Prognostic value of motor evoked potential obtained by transcranial magnetic brain stimulation in motor function recovery in patients with acute ischemic stroke. Stroke. 1998;29(9):1854–9.
55. Edgerton VR, de Leon RD, Tillakaratne N, Recktenwald MR, Hodgson JA, Roy RR. Use-dependent plasticity in spinal stepping and standing. Adv Neurol. 1997;72:233–47.
56. Pearson KG. Plasticity of neuronal networks in the spinal cord: modifications in response to altered sensory input. Prog Brain Res. 2000;12:861–70.

57. Lovely RG, Gregor RJ, Roy RR, Edgerton VR. Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. Exp Neurol. 1986;92(2):421–35.
58. Lovely RS, Falls LA, Al-Mondhiry HA, Chambers CE, Sexton GJ, Ni H, et al. Association of gammaA/gamma' fibrinogen levels and coronary artery disease. Thromb Haemost. 2002;88(1):26–31.
59. Wolpaw JR, Seegal RF, O'Keefe JA. Adaptive plasticity in primate spinal stretch reflex: behavior of synergist and antagonist muscles. J Neurophysiol. 1983;50(6):1312–9.
60. Wolpaw JR. Operant conditioning of primate spinal reflexes: the H-reflex. J Neurophysiol. 1987;57(2):443–59.
61. Edgerton VR, Roy RR, Hodgson JA, Prober RJ, de Guzman CP, de Leon R. Potential of adult mammalian lumbosacral spinal cord to execute and acquire improved locomotion in the absence of supraspinal input. J Neurotrauma. 1992;9 Suppl 1:S119–28.
62. Harris-Warrick RM, Marder E. Modulation of neural networks for behavior. Annu Rev Neurosci. 1991;14:39–57.
63. Dickinson PS. Interactions among neural networks for behavior. Curr Opin Neurobiol. 1995;5(6):792–8.
64. Katz PS. Intrinsic and extrinsic neuromodulation of motor circuits. Curr Opin Neurobiol. 1995;5(6):799–808.
65. Pearson KG, Misiaszek JE. Use-dependent gain change in the reflex contribution to extensor activity in walking cats. Brain Res. 2000;883(1):131–4.
66. Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in the adult cat. Brain Res. 1987;412(1):84–95.
67. Barbeau H, Rossignol S. Enhancement of locomotor recovery following spinal cord injury. Curr Opin Neurol. 1994;7(6):517–24.
68. Dietz V, Fouad K. Restoration of sensorimotor functions after spinal cord injury. Brain. 2014;137:654–67.
69. Skinner RD, Houle JD, Reese NB, Berry CL, Garcia-Rill E. Effects of exercise and fetal spinal cord implants on the H-reflex in chronically spinalized adult rats. Brain Res. 1996;729(1):127–31.
70. Chau C, Barbeau H, Rossignol S. Effects of intrathecal alpha1-and alpha2-noradrenergic agonists and norepinephrine on locomotion in chronic spinal cats. J Neurophysiol. 1998;79(6):2941–63.
71. de Leon RD, Hodgson JA, Roy RR, Edgerton VR. Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats. J Neurophysiol. 1998;79(3):1329–40.
72. De Leon RD, Hodgson JA, Roy RR, Edgerton VR. Full weight-bearing hind limb standing following stand training in the adult spinal cat. J Neurophysiol. 1998;80(1):83–91.
73. Maric O, Zorner B, Dietz V. Levodopa therapy in incomplete spinal cord injury. J Neurotrauma. 2008;25(11):1303–7.
74. Schmidt BJ, Jordan LM. The role of serotonin in reflex modulation and locomotor rhythm production in the mammalian spinal cord. Brain Res Bull. 2000;53(5):689–710.
75. Shadmehr R, Krakauer JW. A computational neuroanatomy for motor control. Exp Brain Res. 2008;185(3):359–81.
76. Bhanpuri NH, Okamura AM, Bastian AJ. Predicting and correcting ataxia using a model of cerebellar function. Brain J Neurol. 2014;137(Pt 7):1931–44.
77. Smith MA, Shadmehr R. Intact ability to learn internal models of arm dynamics in Huntington's disease but not cerebellar degeneration. J Neurophysiol. 2005;93(5):2809–21.
78. Morton SM, Bastian AJ. Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. J Neurosci. 2006;26(36):9107–16.
79. Horak FB, Diener HC. Cerebellar control of postural scaling and central set in stance. J Neurophysiol. 1994;72(2):479–93.
80. Yagi T, Shimizu M, Sekine S, Kamio T, Suzuki JI. A new neurotological test for detecting cerebellar dysfunction. Ann N Y Acad Sci. 1981;374:526–31.
81. Marr D. A theory of cerebellar cortex. J Physiol. 1969;202(2):437–70.
82. Albus JS. A theory of cerebellar function. Math Biosci. 1971;10(1–2):25–61.
83. Ito M. Long-term depression. Annu Rev Neurosci. 1989;12:85–102.
84. Ito M, Kano M. Long-lasting depression of parallel fiber-Purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex. Neurosci Lett. 1982;33(3):253–8.
85. Yang Y, Lisberger SG. Purkinje-cell plasticity and cerebellar motor learning are graded by complex-spike duration. Nature. 2014;510(7506):529–32.
86. Hansel C, Linden DJ, D'Angelo E. Beyond parallel fiber LTD: the diversity of synaptic and non-synaptic plasticity in the cerebellum. Nat Neurosci. 2001;4(5):467–75.
87. Luft AR, Schwarz S. Dopaminergic signals in primary motor cortex. Int J Dev Neurosci. 2009;27(5):415–21.
88. Molina-Luna K, Pekanovic A, Rohrich S, Hertler B, Schubring-Giese M, Rioult-Pedotti MS, et al. Dopamine in motor cortex is necessary for skill learning and synaptic plasticity. PLoS ONE. 2009;4(9):e7082.
89. Hosp JA, Pekanovic A, Rioult-Pedotti MS, Luft AR. Dopaminergic projections from midbrain to primary motor cortex mediate motor skill learning. J Neurosci. 2011;31(7):2481–7.
90. Hosp JA, Molina-Luna K, Hertler B, Atiemo CO, Luft AR. Dopaminergic modulation of motor maps in rat motor cortex: an in vivo study. Neuroscience. 2009;159(2):692–700.
91. Hosp JA, Hertler B, Atiemo CO, Luft AR. Dopaminergic modulation of receptive fields in rat

sensorimotor cortex. Neuroimage. 2010;54: 154–60.
92. Schultz W. Behavioral dopamine signals. Trends Neurosci. 2007;30(5):203–10.
93. Schaechter JD. Motor rehabilitation and brain plasticity after hemiparetic stroke. Prog Neurobiol. 2004;73(1):61–72.
94. Luft AR, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. JAMA. 2004;292(15):1853–61.
95. Whitall J, Waller McCombe S, Sorkin JD, Forrester LW, Macko RF, Hanley DF, et al. Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms: a single-blinded randomized controlled trial. Neurorehabil Neural Repair. 2011;25(2):118–29.
96. Luft AR, Macko RF, Forrester LW, Villagra F, Ivey F, Sorkin JD, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. Stroke. 2008; 39(12):3341–50.
97. Reisman DS, Wityk R, Silver K, Bastian AJ. Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke. Brain. 2007;130(Pt 7):1861–72.
98. Reisman DS, McLean H, Bastian AJ. Split-belt treadmill training poststroke: a case study. J Neurol Phys Ther. 2010;34(4):202–7.
99. Reisman DS, et al. Repeated split-belt treadmill training improves poststroke step length asymmetry. Neurorehabil Neural Repair. 2013;27(5):460–8.
100. Jauss M, Krieger D, Hornig C, Schramm J, Busse O. Surgical and medical management of patients with massive cerebellar infarctions: results of the German-Austrian Cerebellar Infarction Study. J Neurol. 1999; 246(4):257–64.
101. Tohgi H, Takahashi S, Chiba K, Hirata Y. Cerebellar infarction. Clinical and neuroimaging analysis in 293 patients. The Tohoku Cerebellar Infarction Study Group. Stroke. 1993;24(11):1697–701.
102. Kelly PJ, Stein J, Shafqat S, Eskey C, Doherty D, Chang Y, et al. Functional recovery after rehabilitation for cerebellar stroke. Stroke. 2001;32(2): 530–4.
103. Morton SM, Tseng YW, Zackowski KM, Daline JR, Bastian AJ. Longitudinal tracking of gait and balance impairments in cerebellar disease. Mov Disord. 2010;25(12):1944–52.
104. Schoch B, Dimitrova A, Gizewski ER, Timmann D. Functional localization in the human cerebellum based on voxelwise statistical analysis: a study of 90 patients. Neuroimage. 2006;30(1):36–51.
105. Ilg W, Synofzik M, Brötz D, Burkard S, Giese MA, Schöls L. Intensive coordinative training improves motor performance in degenerative cerebellar disease. Neurology. 2009;73(22):1823–30.
106. Gill-Body KM, Popat RA, Parker SW, Krebs DE. Rehabilitation of balance in two patients with cerebellar dysfunction. Phys Ther. 1997;77(5): 534–52.
107. Bultmann U, et al. Functional recovery and rehabilitation of postural impairment and gait ataxia in patients with acute cerebellar stroke. Gait Posture. 2014;39(1):563–9.
108. Keller JL, Bastian AJ. A home balance exercise program improves walking in people with cerebellar ataxia. Neurorehabil Neural Repair. 2014;28(8): 770–8.
109. Vaz DV, Schettino Rde C, de Castro TR R, Teixeira VR, Cavalcanti Furtado SR, de Mello Figueiredo E. Treadmill training for ataxic patients: a single-subject experimental design. Clin Rehabil. 2008; 22(3):234–41.
110. Cernak K, Stevens V, Price R, Shumway-Cook A. Locomotor training using body-weight support on a treadmill in conjunction with ongoing physical therapy in a child with severe cerebellar ataxia. Phys Ther. 2008;88(1):88–97.
111. Kleim JA, Swain RA, Armstrong KA, Napper RM, Jones TA, Greenough WT. Selective synaptic plasticity within the cerebellar cortex following complex motor skill learning. Neurobiol Learn Mem. 1998; 69(3):274–89.
112. Kleim JA, Pipitone MA, Czerlanis C, Greenough WT. Structural stability within the lateral cerebellar nucleus of the rat following complex motor learning. Neurobiol Learn Mem. 1998;69(3):290–306.
113. Dietz V. Proprioception and locomotor disorders. Nat Rev Neurosci. 2002;3(10):781–90.
114. Dietz V, Colombo G, Jensen L. Locomotor activity in spinal man. Lancet. 1994;344(8932):1260–3.
115. Dietz V, Wirz M, Colombo G, Curt A. Locomotor capacity and recovery of spinal cord function in paraplegic patients: a clinical and electrophysiological evaluation. Electroencephalogr Clin Neurophysiol. 1998;109(2):140–53.
116. Dietz V. Neurophysiology of gait disorders: present and future applications. Electroencephalogr Clin Neurophysiol. 1997;103(3):333–55.
117. Popovic MR, Curt A, Keller T, Dietz V. Functional electrical stimulation for grasping and walking: indications and limitations. Spinal Cord. 2001;39(8): 403–12.
118. Fung J, Stewart JE, Barbeau H. The combined effects of clonidine and cyproheptadine with interactive training on the modulation of locomotion in spinal cord injured subjects. J Neurol Sci. 1990;100(1–2): 85–93.
119. Wernig A, Müller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia. 1992;30(4):229–38.
120. Wernig A, Müller S, Nanassy A, Cagol E. Laufband therapy based on ‘rules of spinal locomotion’ is

effective in spinal cord injured persons. Eur J Neurosci. 1995;7(4):823–9.
121. Wirz M, Colombo G, Dietz V. Long term effects of locomotor training in spinal humans. J Neurol Neurosurg Psychiatry. 2001;71(1):93–6.
122. Dietz V, Colombo G, Jensen L, Baumgartner L. Locomotor capacity of spinal cord in paraplegic patients. Ann Neurol. 1995;37(5):574–82.
123. Dietz V, Müller R, Colombo G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. Brain. 2002;125(Pt 12): 2626–34.
124. Cramer SC, Riley JD. Neuroplasticity and brain repair after stroke. Curr Opin Neurol. 2008;21(1): 76–82.
125. Dietz V, Harkema SJ. Locomotor activity in spinal cord-injured persons. J Appl Physiol. 2004;96(5): 1954–60.
126. Martino G. How the brain repairs itself: new therapeutic strategies in inflammatory and degenerative CNS disorders. Lancet Neurol. 2004;3(6):372–8.
127. Dietz V. Body weight supported gait training: from laboratory to clinical setting. Brain Res Bull. 2009;78(1):I–VI.
128. Wirz M, Dietz V. Recovery of sensorimotor function and activities of daily living after cervical spinal cord injury: the influence of age. J Neurotrauma. 2015;32(3):194–9.
129. Dietz V, et al. Changes in spinal reflex and locomotor activity after a complete spinal cord injury: a common mechanism? Brain. 2009;132(Pt 8):2196–205.
130. Dietz V, Müller R. Degradation of neuronal function following a spinal cord injury: mechanisms and countermeasures. Brain. 2004;127(Pt 10):2221–31.
131. Dobkin BH, Harkema S, Requejo P, Edgerton VR. Modulation of locomotor-like EMG activity in subjects with complete and incomplete spinal cord injury. J Neurol Rehabil. 1995;9(4):183–90.
132. Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR. Human lumbosacral spinal cord interprets loading during stepping. J Neurophysiol. 1997;77(2):797–811.
133. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6(8):725–33.
134. Moseley AM, Stark A, Cameron ID, Pollock A. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev. 2003;(3):CD002840.
135. Wirz M, Zemon DH, Rupp R, Scheel A, Colombo G, Dietz V, et al. Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil. 2005;86(4):672–80.
136. Curt A, Dietz V. Ambulatory capacity in spinal cord injury: significance of somatosensory evoked potentials and ASIA protocol in predicting outcome. Arch Phys Med Rehabil. 1997;78(1):39–43.
137. Curt A, Keck ME, Dietz V. Functional outcome following spinal cord injury: significance of motor-evoked potentials and ASIA scores. Arch Phys Med Rehabil. 1998;79(1):81–6.
138. Basso DM. Neuroanatomical substrates of functional recovery after experimental spinal cord injury: implications of basic science research for human spinal cord injury. Phys Ther. 2000;80(8):808–17.
139. Metz GA, Curt A, van de Meent H, Klusman I, Schwab ME, Dietz V. Validation of the weight-drop contusion model in rats: a comparative study of human spinal cord injury. J Neurotrauma. 2000; 17(1):1–17.
140. Katoh S, el Masry WS. Neurological recovery after conservative treatment of cervical cord injuries. J Bone Joint Surg (Br). 1994;76(2):225–8.
141. Dietz V, Wirz M, Curt A, Colombo G. Locomotor pattern in paraplegic patients: training effects and recovery of spinal cord function. Spinal Cord. 1998;36(6):380–90.
142. Schwab ME, Bartholdi D. Degeneration and regeneration of axons in the lesioned spinal cord. Physiol Rev. 1996;76(2):319–70.
143. Reinkensmeyer DJ, Dietz V, editors. Neurorehabilitation technology. 2nd ed. London: Springer; 2012.

Movement Neuroscience Foundations of Neurorehabilitation

2

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 principles that have been derived from research on neural control of movement, including optimal control, impedance control, motor lateralization, and principles of motor learning. 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 motor lateralization has indicated that different aspects of motor control have been specialized to the two cerebral hemispheres. This organization leads to hemisphere-specific motor deficits in both the ipsilesional and contralesional arms of stroke patients. Ipsilesional deficits increase with severity of contralesional impairment level and have a substantial effect on functional independence. Finally, motor learning research has indicated that different neural mechanisms underlie different aspects of motor learning, such as adaptation vs skill learning, and that learning different aspects of tasks can generalize across different coordinates. In this chapter, we discuss the neurobiological basis of these principles and elaborate the implications for designing and implementing occupational and physical therapy treatment for movement deficits in stroke patients.

Keywords

Rehabilitation • Motor control • Motor learning • Motor lateralization

R.L. Sainburg, PhD (✉)
Departments of Kinesiology and Neurology,
Penn State University, Penn State College
of Medicine, University Park, PA 16801, USA
e-mail: RLS45@PSU.EDU

P.K. Mutha, PhD
Department of Biological Engineering and Centre
for Cognitive Science, Indian Institute of Technology
Gandhinagar, Ahmedabad 382424, Gujarat, India
e-mail: pm@iitgn.ac.in

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2.1 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. Occupational and physical therapy interventions often focus on reducing motor impairment, following stroke, by exposing patients to a range of movement activities, with a major focus on repetitive experience or practice. In general, the amount of practice corresponds 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 carry over to the home environment.

Over the past decade, rehabilitation approaches have incorporated technological innovations that can provide more cost-effective means of achieving higher intensity practice over longer periods of time. These computer-based and robotic technologies [2–5] have been shown to match or even exceed the efficacy of traditional therapy in promoting improvements in motor performance [6]. 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 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 best utilize them to accelerate recovery of function. In this chapter, we will discuss principles that have been derived from research in motor control and learning that could be applied to training strategies using computer-based movement interventions.

2.2 Principle 1: Optimal Control

While most therapists recognize that practice and repetition of motor activities lead 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 non-impaired 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 [7]. 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 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. 2.1). 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

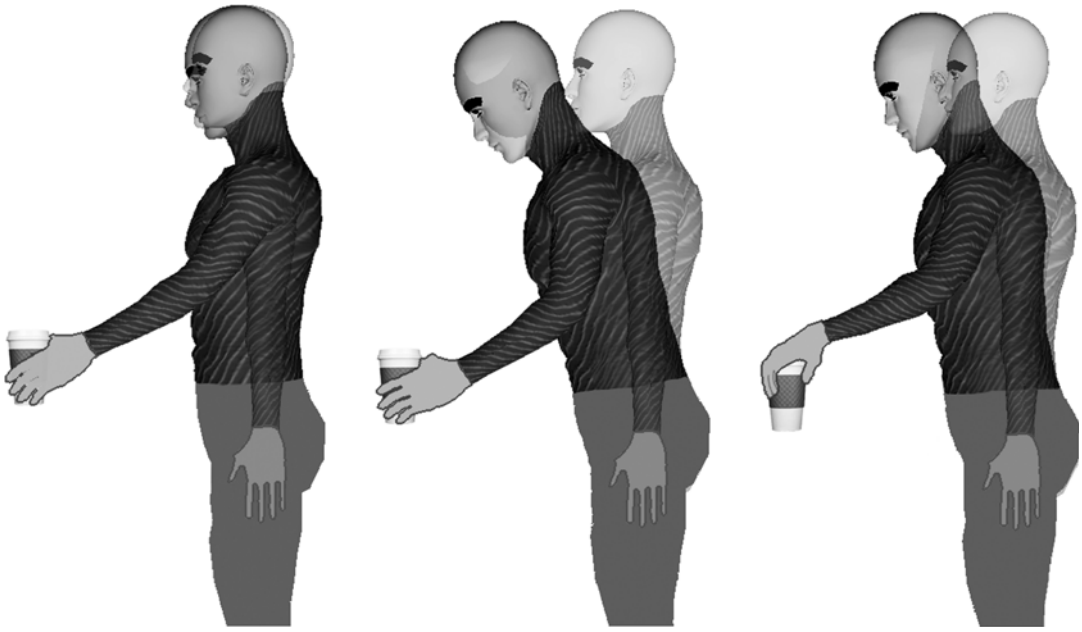

Fig. 2.1 Different ways of picking up a coffee cup starting from the same initial posture. The left pose involves shoulder flexion and elbow extension. The middle pose involves flexion of the trunk, slightly less shoulder flexion, and more elbow extension. The right pose shows some trunk flexion, shoulder abduction, elbow flexion, and forearm pronation

characteristics include approximate straightness of the hand trajectory and smooth bell-shaped velocity profiles (see Fig. 2.2) [7–11]. 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 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 [9] tested the idea that the smoothness of hand trajectories might reflect an important cost in the planning of reaching movements and proposed a model that minimized the jerkiness of the hand trajectory (mathematically defined as the 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 [10], peak work [12], or muscle energy [13, 14], among others. These models accounted for some experimental observations

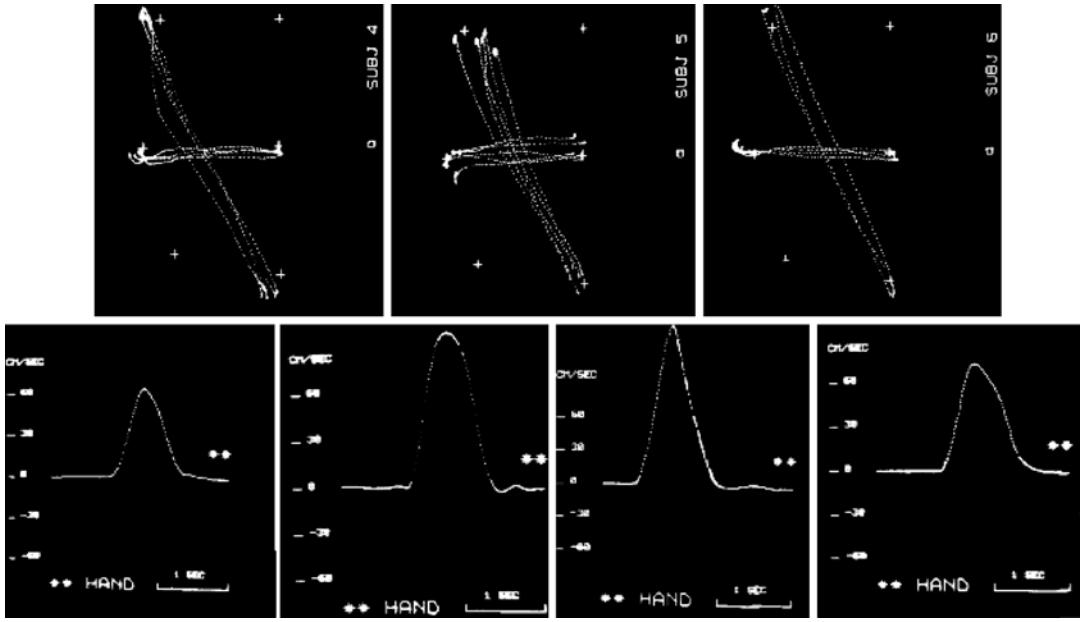

Fig. 2.2 Some "invariant characteristics" of point-to-point movements. The *top panel* shows fairly straight trajectories for multiple movements starting from and ending at varying locations for three different subjects. The *bottom panel* shows fairly similar bell-shaped velocity profiles for four different movements (Adapted from Morasso [7])

that could not be accounted for by optimizations based on kinematic parameters [11]. While minimization of cost functions such as smoothness or torque change accurately predicted average behavior, Wolpert and colleagues [8] 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 end point variability 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 don't 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 and mechanisms that predict sensory consequences of motor commands, has gained prominence. According to this idea, the optimal solution is the best possible transformation from the current state to the motor com-

mands that aid in achieving the task goal [15]. 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 [16] showed that subjects' performance could be best described using a composite cost function that optimized for movement duration, accuracy, end point 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.

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 physiological and biomechanical pathologies [17]. 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 [18, 19]) or the ability to perform simulated ADL tasks in particular times (Jebsen-Taylor Hand Function Test [20]), we suggest that direct analysis of biomechanical costs may provide an important supplement to these tests, as an indicator of energetic efficiency. It may also be important to assess one's subjective sense of effort, which does not always accurately reflect measures of biomechanical cost [21]. 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 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 don't. In fact, Ballester et al. [22] recently reported exactly this manipulation, using a virtual reality environment to train reaching in hemiparetic stroke patients. The movements of a virtual representation of the patients' paretic limb were amplified in only the dimension parallel to the target direction. Following virtual reality training, the authors reported that the probability of using the paretic limb during a subsequent real-world task was increased by the reinforcing experience of seeing the virtual limb reach the

target during training. These types of capabilities are now becoming available in the clinic, due to the increasing availability of computer-based robotic and virtual reality technologies.

2.3 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. 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 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 [23, 24], measured in the electromyogram (EMG) as shown in Fig. 2.3: 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

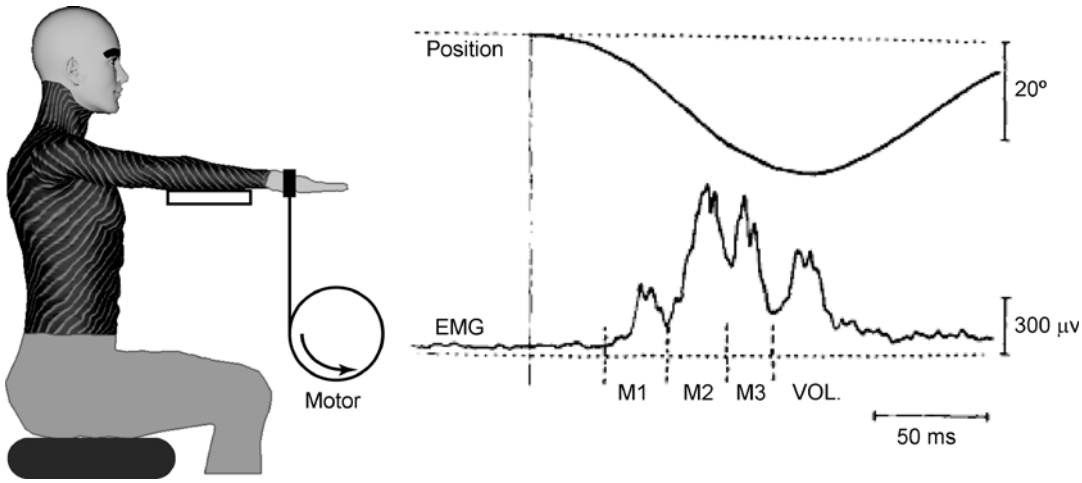

Fig. 2.3 Typical reflex response to muscle stretch. An example of the wrist extensor being stretched using a motor is shown on the *left*. The *right panel* shows the typical components of the electromyographic response to muscle stretch: the short-latency component M1 and the longer-latency components M2 and M3 (Adapted from Matthews [24])

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 [25]. 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 [18]. 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 [26]. 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 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, many environmental perturbations cannot 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 breaking 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 [27] and colleagues directly tested how subjects might selectively modify impedance without interfering with coordination of the intended movement. 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. 2.4a). 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. 2.4b). Remarkably, at the joint level, this impedance modification was achieved without changing baseline force and torque profiles (see Fig. 2.4c): 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 [28]. 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 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.

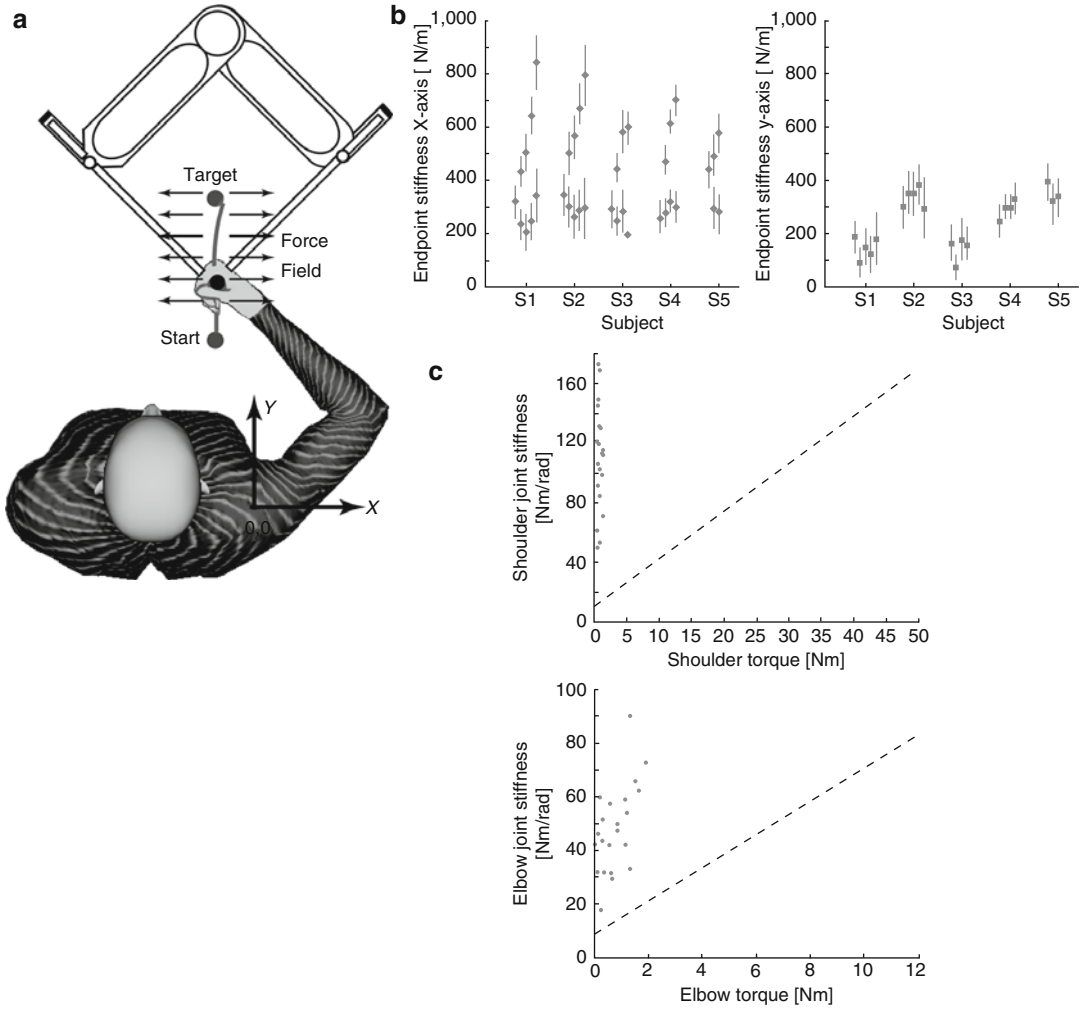

Fig. 2.4 Modulation of limb impedance. (**a**) The typical setup and the perturbing force field. The field acts to push the arm perpendicular (along *X-axis*) to the direction of motion (*Y-axis*). (**b**) An increase in limb stiffness along the *X*- but not *Y*-axis for all subjects. (**c**) Shoulder and elbow joint stiffnesses were independent of the respective joint torques (Adapted from Franklin et al. [27])

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.

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 asso-

ciated 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. [29] 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 activities of daily living. 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.

2.4 Principle 3: Motor Lateralization

As discussed thus far, both optimal control and impedance control are component mechanisms underlying control of voluntary movements. 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 [30] 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 was a natural consequence of developing complex functions during the course of evolution. 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, with little attention to the motor systems. We introduced the dynamic-dominance hypothesis of motor lateralization [31], based on left- and right-arm advantages in reaching performance in healthy adults, and expanded this hypothesis based on computational modeling studies [32, 33] and studies in patients with unilateral brain lesions [34–39]. The dynamic-dominance model proposes that the left hemisphere, in right-handers, is specialized for predictive processes that specify smooth and efficient movement trajectories under mechanically stable environmental circumstances, while the right hemisphere is specialized for impedance control mechanisms that confer robustness to movements performed under unpredictable and mechanically unstable environmental conditions. In fact, this type of division of labor between the two sides of the brain appears to predate humans by half a billion years [40]. Rogers and colleagues have proposed a single-organizing principle that might account for the large array of emotional, language, perceptual, and cognitive asymmetries that have been described across the evolutionary spectrum of vertebrates. While the left hemisphere appears "specialized for control of well-established patterns of behavior, under ordinary and familiar circumstances," the right hemisphere is specialized for "detecting and responding to unexpected stimuli in the environment" [41]. The dynamic-dominance model provides the movement analogue to Roger's model and thus places handedness in the context of a

larger array of neurobehavioral asymmetries across the animal kingdom [42].

An important feature of these models is that both hemispheres are recruited for their complimentary contributions to integrated functional activities. Thus, during the movement of a single arm, both hemispheres contribute their specific aspects of control [43]. Because each hemisphere contributes specialized processes to control of each arm, unilateral brain damage actually produces hemisphere-specific movement deficits in the non-paretic, ipsilesional arm, as well as the contralesional arm. Remarkably, this is the arm that is usually considered unaffected by unilateral brain damage. The idea that each hemisphere contributes to motor coordination of both arms is an important implication of ipsilesional, non-paretic arm motor deficits. While the role of contralateral motor areas in controlling limb movements is well understood [44], the role of the ipsilateral hemisphere has more recently been implicated by the robust occurrence of ipsilesional motor deficits in both animal models of unilateral brain damage [45–47] as well as human stroke survivors [34, 36, 39, 48–58]. In addition, both electrophysiological and neural imaging studies have shown that unilateral arm and hand movements recruit motor-related areas in both cerebral hemispheres [43, 59–61]. Thus, it is the loss of the contributions of the ipsilateral hemisphere to movement control that gives rise to motor deficits in the non-paretic arm of stroke patients. Most importantly, these deficits can substantially limit functional performance [51, 54], a particularly concerning phenomenon, given that patients with severe contralesional paresis depend on the ipsilesional arm for the majority of their activities of daily living.

Our recent studies have examined the specific nature of the ipsilesional movement deficits that result from left or right brain damage, shedding light on motor lateralization. These studies have confirmed that right and left sensorimotor strokes produce predictable deficits in impedance control or optimal control, respectively [51, 62]. 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. 2.5a. While control subjects made relatively straight and accurate movements, patients with left-hemisphere damage made movements that were very curved, but nevertheless were accurate in final position. In contrast, patients with right-hemisphere damage 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. 2.5b, 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) is 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 be emphasized that these errors were associated with functional impairments in the ipsilesional arm, as measured by the Jebsen-Taylor Hand Function Test (JTHFT). Thus, motor lateralization leads to deficits that depend on the side of the stroke and can lead to significant deficits, as tested with clinical assessments, such as the JTHFT.

Figure 2.6 shows data from 72 age- and gender-matched control subjects, 22 left-hemisphere-damaged stroke survivors, and 29 right-hemisphere-damaged stroke survivors. The *Y*-axis represents the JTHFT score, taken as a percentage of right dominant arm function in our control group. Thus, 100 % is the mean for the right hand of 36 of the control subjects (those who

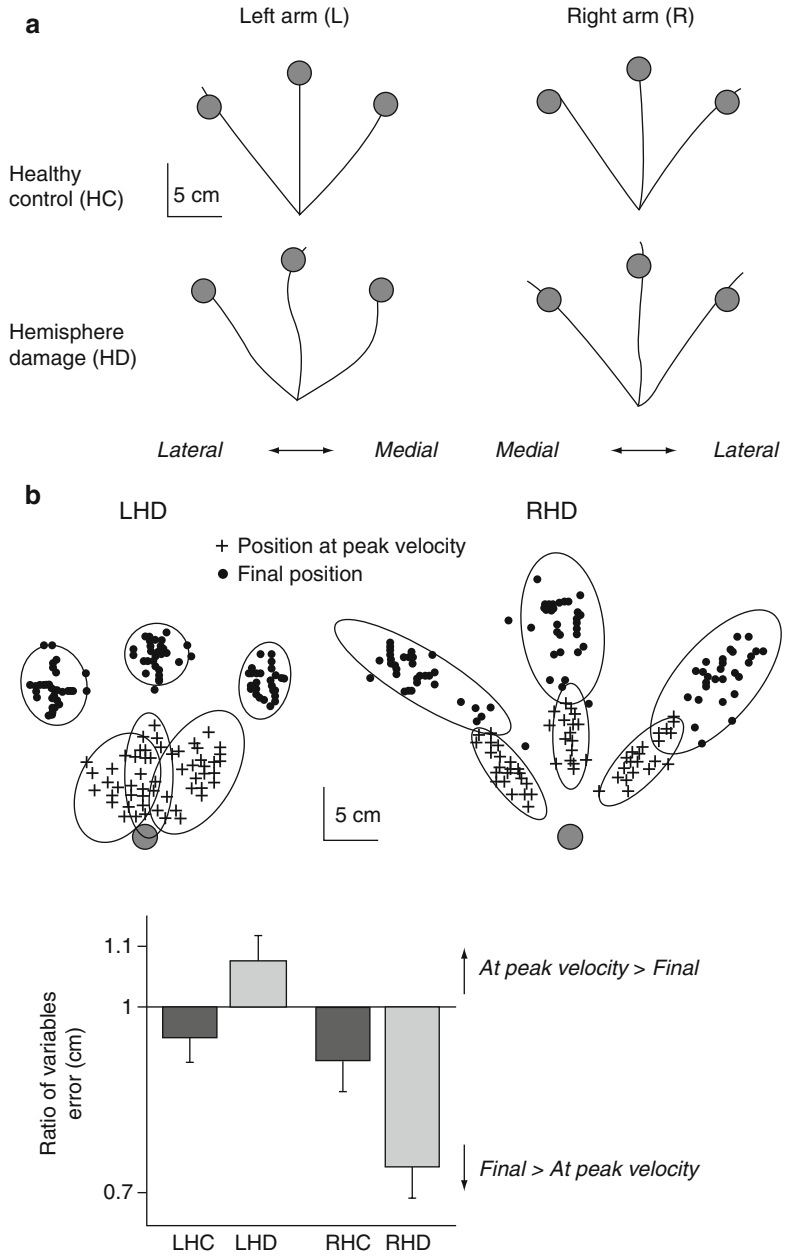

Fig. 2.5 Lateralization of motor deficits after stroke. (**a**) Shows typical hand paths for healthy control subjects performing with their right or left arm (*top panel*) and left- and right-hemisphere-damaged stroke patients performing with their ipsilesional arm (*bottom panel*). (**b**) Shows hand 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])

used their right hand). The JTHFT is a rather thorough assessment of unilateral arm function that includes a large range of tasks that elicit the coordination requirements of functional daily activities, such as writing, turning pages, placing large and small objects on a table, stacking checkers, and feeding. The left column (control) shows the difference between healthy subjects performing with the left arm and right arm.

The data are stratified on the *X*-axis by both hand (right/left; in the case of stroke survivors, this is only the ipsilesional arm) and severity of contralesional paresis, as measured by the upper limb component of the Fugl-Meyer et al. [63] assessment of motor impairment (mild $\geq$ 55, moderate >35, severe $\leq$ 35). In healthy subjects, the left nondominant arm takes, on average, 33 % longer than the right arm to carry out these tasks. For

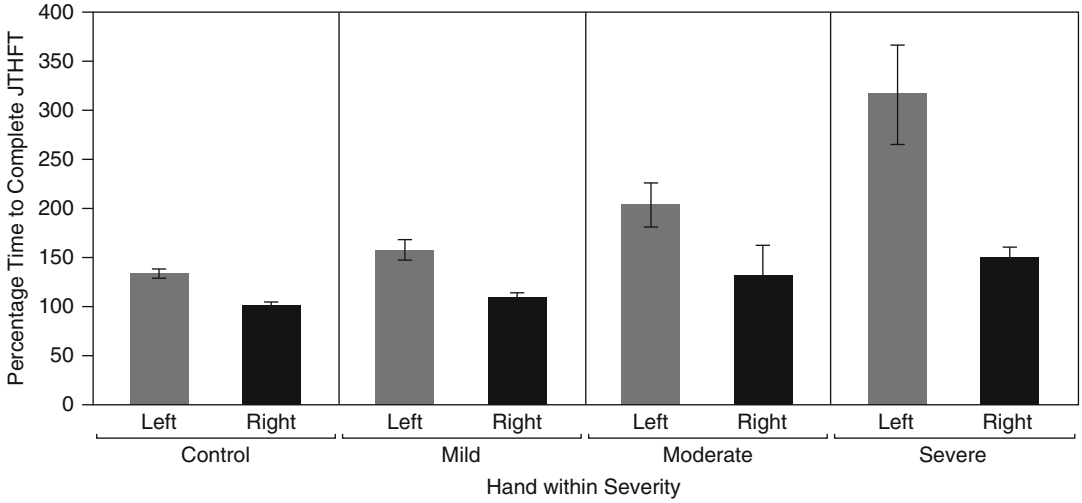

Fig. 2.6 JTHFT score, normalized to control group right-hand score. Scores for non-paretic arm of stroke survivors. Control subjects were matched to gender and age distribution of each stroke survivor group. The two control groups were comprised of those that used their left or right hands and included 18 participants each. The left-hemisphere-damaged group comprised 22 stroke survivors, whereas the right-hemisphere-damaged group comprised 29 stroke survivors. On the *X*-axis, these groups are stratified by severity of contralesional arm paresis

reference, this reflects the frustration a typical adult would experience when trying to get through their day with only the nondominant arm, for example, due to a broken dominant arm. In our stroke survivors, there is a substantial effect of both severity of impairment in the paretic arm and side of the brain lesion on JTHFT performance with the non-paretic arm. First, the more severe the contralesional paresis, the greater the impairment in the non-paretic arm. This effect is potentiated by the side of lesion, such that left-hemisphere-damaged survivors who have severe paresis in their contralesional arm take 216 % longer to complete the JTHFT than the dominant arm of control subjects, whereas right-hemisphere-damaged survivors with severe contralesional paresis take 51 % longer than do control subjects. Functionally, this effect is concerning for two reasons: First, the finding that the extent of ipsilesional deficit varies with the extent of contralesional paresis indicates that the survivors who must depend most on the ipsilesional arm for function have the greatest impairments in that arm. Second, these stroke survivors were tested, on average 1.8 years following their stroke, suggesting that these deficits do not spontaneously change over time. Even right-hemisphere-damaged patients with severe paresis take nearly 52 % longer than age-matched control subjects to complete the JTHFT, regardless of the "forced use" of the ipsilesional arm imposed by severe contralesional paresis. This introduces the questions of whether focused remedial therapy might improve function by increasing the speed and dexterity of the non-paretic arm in patients with moderate to severe contralesional paresis (Fig. 2.6).

Implications for Rehabilitation While most robotic rehabilitation devices have been focused on training 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 activities of daily living [64].

It is, thus likely that intensive training of the ipsilesional, non-paretic arm could substantially improve functional independence in patients with hemiparesis. However, it should be noted that *remediation of the non-paretic arm is so novel that little empirical evidence exists as to whether*

such intervention might lead to positive effects on motor performance and functional independence. One recent pilot intervention study compared a group of patients who received therapy that included training of the non-paretic arm to another group who only received traditional therapy, without non-paretic arm training [65]. The results indicated that when traditional therapy was combined with non-paretic arm training, the speed and accuracy of non-paretic arm movements improved, as did the impairment level of the paretic arm, when compared to patients who received traditional therapy alone. This suggests that focused non-paretic arm training might produce both improvements in non-paretic arm motor performance and modest improvements in paretic arm function, both of which should facilitate improvements in functional independence. However, some caution is indicated because of the phenomenon of learned nonuse of the paretic arm, an effect that has been successfully addressed by constraining the non-paretic arm in patients with moderate to mild paresis [66–69]. While the pilot results cited above suggest positive effects of non-paretic arm training on paretic arm function, there currently is no conclusive evidence to predict whether non-paretic arm training will influence paretic arm function, either positively or negatively. *This is an important area for future research in rehabilitation intervention for stroke patients*.

In contrast to focused non-paretic arm training, bilateral training has a long history in rehabilitation research and practice and should represent a critical component to therapeutic intervention in unilateral stroke. In fact, most activities of daily living are performed with both hands contributing to different aspects of the activity [54, 64]. For example, when buttoning a shirt, the nondominant arm tends to stabilize the buttonhole, while the dominant arm manipulates 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 [70, 71]. 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 [72], 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.

More importantly is the question of whether remediation focused on the non-paretic arm might improve stroke survivor's participation in daily activities, for those patients who rely on this arm as their sole or primary manipulator and have substantial ipsilesional motor deficits. Currently, the usual standard of care in rehabilitation for patients with *low moderate to severe paresis* tends to focus on task training in essential ADL activities rather than on intensive remediation. We suggest that the combination of moderate to severe paresis with persistent motor deficits in the non-paretic arm limits performance of and participation in activities of daily living. We, thus, predict that intense rehabilitation, sequentially focused on each arm, should provide a durable and substantial improvement in functional performance. However, this approach must be addressed with some caution because while sequential arm training has never been studied in human stroke survivors, Jones et al. [73] showed, in an acute model of stroke in rats, that initial training of ipsilesional forelimb reaches can limit the subsequent response to training in the contralesional forelimb (2010). On the other hand, interlimb transfer of motor learning often shows a positive effect in healthy individuals [74–77], and mirror training has shown positive transfer between the arms in stroke patients [78–80]. It is critical to carry out studies of ipsilesional arm intervention in survivors with moderate to severe contralesional paresis to determine whether such training can positively affect functional outcomes and participation in human stroke survivors.

2.5 Principle 4: Motor Learning

The discussion so far noted that rehabilitation should focus on improving both optimal control and impedance control while bearing in mind that these control mechanisms are likely lateralized to different brain hemispheres. However, rehabilitation itself rests on the assumption that patients can relearn such control with repeated practice. As such, knowledge of how motor learning occurs, how it is retained, and how it generalizes to other conditions that haven't been practiced is central to the development of effective rehabilitation strategies.

Motor learning is used as an umbrella term to incorporate any practice-related improvement in motor performance. 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 task conditions such as when a cursor, representing the location of the hand on a screen, deviates from the actual hand location or when the hand is pushed from its intended trajectory using force perturbations. Under such conditions, subjects readily adapt to the new environment, a process that appears to occur, at least in part, through changes in predictive control or, in other words, movement planning [81, 82]. The 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 movement patterns seen on early exposure to the imposed perturbation and are based on the subject's expectation that they will continue to experience the novel environment. In other words, the effects of the perturbation are predicted and accounted for, and the motor output is appropriately modified [83, 84]. Computationally, such adaptation can be modeled as an iterative update of a forward model, defined as a transformation from movement commands to their desired sensory consequences. In this scheme, sensory prediction errors or the difference between the intended and actual sensory feedback should drive the process of improving the accuracy of the forward model, so that the predicted sensory consequences of motor commands coincide with the actual sensory feedback. This process has been shown to occur implicitly [83], although new research suggests that adaptation may also involve explicit or declarative strategies [85] as well as reinforcement mechanisms that are driven by task success [86].

In order to examine how motor learning might be represented in the nervous system, many studies have examined conditions to which the learning generalizes. Interestingly, these studies have generally suggested that generalization of visuomotor adaption is different from generalization of adaptation to novel dynamic conditions such as force fields. For example, Krakauer et al. [87] examined generalization of visuomotor adaptation and found that 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 [31]. 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 [88, 89]. Generalization of adaptation to dynamic conditions such as novel force fields in contrast has been shown to occur along intrinsic or joint coordinates [77, 90]. Malfait et al. [91] showed that learning of novel force fields transferred to movements made in different regions of the workspace, if similar joint excursions were required, 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 [92] 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 nondominant arm along intrinsic coordinates [77, 90]. Thus, while learning of novel visuomotor conditions appears to generalize in extrinsic coordinates, learning of novel dynamic conditions appears to transfer along intrinsic coordinates.

To explore the neural basis of adaptation, which has important implications for rehabilitation post-stroke, we recently examined the impact of different brain lesions on the ability to adapt to novel visuomotor conditions. In general, we have found that left-hemisphere damage, particularly to posterior parietal regions, impairs visuomotor adaptation [39]. Our results significantly expanded on prior studies that focused on the cerebellum as the neural substrate critical for adaptation [93–96]. Our results also agreed with Tanaka et al. [97] who showed that experimentally observed visuomotor adaptation and generalization patterns could be reproduced using a population-coding model in which adaptation induced changes in the synaptic weights between narrowly tuned, parietal like neurons and units in the motor cortex. Importantly, models that utilized tuning properties of motor cortical or cerebellar neurons could not reproduce behavioral data. Thus, more recent findings have strongly implicated posterior parietal regions for adaptation, particularly under conditions in which visuomotor errors are imposed. The neural substrates critical for dynamic adaptation are less clear.

In contrast to adaptation, which requires improvement in performance in response to environmentally induced errors, learning in the absence of such errors has not been as extensively studied. Newer studies term such learning in the absence of sensory prediction errors as "skill learning," and it is thought that mechanisms that drive learning of new skills are different from those that drive adaptation [98]. Behaviorally, adaptation only focuses on return to baseline level of performance in the presence of error-inducing perturbations, progresses rapidly, is short-lived, and shows limited generalization. In contrast, skill learning occurs over much slower time scales, and learned skills are rarely forgotten [86]. Research suggests that learning of skills may recruit reinforcement-like processes, where a successful action is found through trial and error, and is then repeated since it leads to a rewarding outcome. However, this needs to be explored further. Neurophysiologically, skill learning has been mapped on to substrates that appear to be different from adaptation. For instance, primary motor cortex and basal ganglia are believed to be crucial for learning of new skills, but not for adaptation. For example, transcranial magnetic stimulation applied over M1 does not appear to impair adaptation [99], but facilitation of M1 via anodal direct current stimulation enhances skill learning [99], suggesting that M1 might play a different role in these two processes.

Despite these differences, however, there is good reason to believe that adaptation and skill learning processes interact during the learning of real-life tasks. For instance, recent results suggest that even in what would otherwise be classified as a pure adaptation task, reinforcement mechanisms are recruited [86]. Under certain conditions, adaptation to errors can in fact be driven completely by reward-based reinforcement mechanisms [100]. Other mechanisms, including the use of explicit strategies [101, 102] and declarative memory [85], have also been suggested to contribute significantly during motor learning.

Implications for Rehabilitation The array of findings on motor learning and its underlying neural substrates has several potential implications for rehabilitation. First, it is critical to recognize that multiple mechanisms, presumably dependent on distinct neural substrates, contribute to an improvement in motor performance with practice. Loss of a particular component process because of focal lesions in different regions of the brain therefore does not automatically imply a complete loss of learning capacity. Different processes and alternate "routes" can be exploited for improvement in motor function. For instance, for a patient with injury to parietal regions, which might affect his/her capacity to adapt to a novel environment, reinforcement mechanisms could be exploited for learning in the same environment. Second, given that adaptation and skill might recruit different neural resources, rehabilitation approaches must focus on training or facilitating both these processes, possibly along with other mechanisms such as use of explicit strategies and declarative memory processes. Third, the fact that learning might occur and generalize in different coordinate systems must be taken into account. While learning

in environments that perturb performance in the extrinsic, task space allows adaptation to task constraints, such as improving accuracy and precision, learning in dynamic environments allows the central nervous system to optimize intrinsic coordination and mechanical energy. It is therefore 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 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, particularly as patients become proficient at a given set of movement patterns. Robotic- and technology-aided rehabilitation, which have the capacity to provide a large range of interactive visual and dynamic environments along with the capacity for high-intensity and high-dose practice, hold great promise in this regard.

2.6 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 tenets derived from research in movement neuroscience that have an impact on this question and that have been derived from literature on the neural control of movement. These tenets are optimal control, impedance control, motor lateralization, and motor learning. 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 system 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 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.

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, or often the sole, manipulator for activities of daily living. Thus, efficient performance of ADL will require well-coordinated movements of this arm. This is particularly important for patients who have severe contralesional paresis, which tends to be associated with substantial ipsilesional motor deficits. Intensive training focused on the ipsilesional arm can improve coordination, but research is needed to determine whether this will impact function, either positively or negatively, of the contralesional arm. Because most ADL tasks require some degree of bilateral coordination, we recommend that following sequential unilateral training with each 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.

Motor learning research has shown that multiple brain regions represent distinct motor learning processes. These processes include skill learning, in which one develops new sensorimotor patterns that were not previously learned, and adaptation, in which one learns to compensate for an environmental or sensory disturbance in order to perform a previously well-practiced task, such as reaching in a force field, or under the influence of altered visuomotor feedback. It should be stressed that as stroke survivors learn to adapt to their new sensory and motor conditions, both of these forms of learning should be required. Even well-learned tasks, such as brushing one's teeth, may require substantially new skill development, given altered motor capacities. Similarly, distortions in sensory feedback including visual field deficits and proprioceptive and tactile deficits can require adaptation to recover old skills. Generalization is also an aspect of motor learning with particular application to neurorehabilitation. It should be stressed that one cannot assume a particular pattern of motor generalization, following training. This is because some aspects of learning transfer along different coordinates than others. For example, task dynamics seem to be learned and transferred in intrinsic coordinates, whereas visuomotor distortions are transferred across extrinsic coordinates. Since it is not simple, or even possible, to segregate these aspects of learning in a clinical environment, it is important to provide a range of training experiences that can ensure generalization across a range of tasks. Task-specific training, of course, should be done for key activities of daily living, but limiting training to specific tasks severely limits the potential of physical rehabilitation. We therefore strongly recommend providing a range of dynamic and kinematic training experiences that include the requirement for variability and response to unpredictable perturbations.

References

1. Teasell R, Meyer MJ, McClure A, et al. Stroke rehabilitation: an international perspective. Top Stroke Rehabil. 2009;16(1):44–56.
2. Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neurorehabilitation. IEEE Trans Rehabil Eng. 1998;6(1):75–87.
3. Krebs HI, Hogan N, Volpe BT, Aisen ML, Edelstein L, Diels C. Overview of clinical trials with MIT-MANUS: a robot-aided neuro-rehabilitation facility. Technol Health Care: Off J Eur Soc Eng Med. 1999;7(6):419–23.

4. Volpe BT, Krebs HI, Hogan N, Edelsteinn L, Diels CM, Aisen ML. Robot training enhanced motor outcome in patients with stroke maintained over 3 years. Neurology. 1999;53(8):1874–6.
5. Krebs HI, Volpe BT, Aisen ML, Hogan N. Increasing productivity and quality of care: robot-aided neurorehabilitation. J Rehabil Res Dev. 2000;37(6): 639–52.
6. Fazekas G, Horvath M, Troznai T, Toth A. Robot-mediated upper limb physiotherapy for patients with spastic hemiparesis: a preliminary study. J Rehabil Med. 2007;39(7):580–2.
7. Morasso P. Spatial control of arm movements. Exp Brain Res. 1981;42(2):223–7.
8. Harris CM, Wolpert DM. Signal-dependent noise determines motor planning. Nature. 1998;394(6695): 780–4.
9. Flash T, Hogan N. The coordination of arm movements: an experimentally confirmed mathematical model. J Neurosci. 1985;5(7):1688–703.
10. Uno Y, Kawato M, Suzuki R. Formation and control of optimal trajectory in human multijoint arm movement. Minimum torque-change model. Biol Cybern. 1989;61(2):89–101.
11. Atkeson CG, Hollerbach JM. Kinematic features of unrestrained vertical arm movements. J Neurosci. 1985;5(9):2318–30.
12. Soechting JF, Buneo CA, Herrmann U, Flanders M. Moving effortlessly in three dimensions: does Donders' law apply to arm movement? J Neurosci. 1995;15(9):6271–80.
13. Goble DJ, Brown SH. Task-dependent asymmetries in the utilization of proprioceptive feedback for goal-directed movement. Exp Brain Res. 2007; 180(4):693–704.
14. Goble DJ, Brown SH. The biological and behavioral basis of upper limb asymmetries in sensorimotor performance. Neurosci Biobehav Rev. 2008;32(3):598–610.
15. Todorov E, Jordan MI. Optimal feedback control as a theory of motor coordination. Nat Neurosci. 2002;5(11):1226–35.
16. Liu D, Todorov E. Evidence for the flexible sensorimotor strategies predicted by optimal feedback control. J Neurosci. 2007;27(35):9354–68.
17. Latash ML. What are "normal movements" in atypical populations? Behav Brain Sci. 1996;19:55–68.
18. Pruszynski JA, Kurtzer I, Scott SH. Rapid motor responses are appropriately tuned to the metrics of a visuospatial task. J Neurophysiol. 2008;100(1):224–38.
19. Wright PJ, Fortinsky RH, Covinsky KE, Anderson PA, Landefeld CS. Delivery of preventive services to older black patients using neighborhood health centers. J Am Geriatr Soc. 2000;48(2):124–30.
20. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. Arch Phys Med Rehabil. 1969;50(6):311–9.
21. Burgess PR, Cooper TA, Gottlieb GL, Latash ML. The sense of effort and two models of single-joint motor control. Somatosens Mot Res. 1995;12(3–4):343–58.
22. Ballester BR, Nirme J, Duarte E, et al. The visual amplification of goal-oriented movements counteracts acquired non-use in hemiparetic stroke patients. J Neuroeng Rehabil. 2015;12:50.
23. Tatton WG, Forner SD, Gerstein GL, Chambers WW, Liu CN. The effect of postcentral cortical lesions on motor responses to sudden upper limb displacements in monkeys. Brain Res. 1975;96(1):108–13.
24. Matthews PB. The human stretch reflex and the motor cortex. Trends Neurosci. 1991;14(3):87–91.
25. Hammond PH. The influence of prior instruction to the subject on an apparently involuntary neuromuscular response. J Physiol. 1956;132(1):17–8P.
26. Lacquaniti F, Borghese NA, Carrozzo M. Transient reversal of the stretch reflex in human arm muscles. J Neurophysiol. 1991;66(3):939–54.
27. Franklin DW, So U, Kawato M, Milner TE. Impedance control balances stability with metabolically costly muscle activation. J Neurophysiol. 2004;92(5):3097–105.
28. Mutha PK, Boulinguez P, Sainburg RL. Visual modulation of proprioceptive reflexes during movement. Brain Res. 2008;1246:54–69.
29. Beer RF, Dewald JP, Rymer WZ. Deficits in the coordination of multijoint arm movements in patients with hemiparesis: evidence for disturbed control of limb dynamics. Exp Brain Res. 2000;131(3):305–19.
30. Gazzaniga MS. The split brain revisited. Sci Am. 1998;279(1):50–5.
31. Sainburg RL. Evidence for a dynamic-dominance hypothesis of handedness. Exp Brain Res. 2002; 142(2):241–58.
32. Yadav V, Sainburg RL. Motor lateralization is characterized by a serial hybrid control scheme. Neuroscience. 2011;196:153–67.
33. Yadav V, Sainburg RL. Handedness can be explained by a serial hybrid control scheme. Neuroscience. 2014;278:385–96.
34. Schaefer SY, Haaland KY, Sainburg RL. Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. Brain. 2007;130(Pt 8):2146–58.
35. Mutha PK, Haaland KY, Sainburg RL. Rethinking motor lateralization: specialized but complementary mechanisms for motor control of each arm. PLoS One. 2013;8(3):e58582.
36. Mutha PK, Haaland KY, Sainburg RL. The effects of brain lateralization on motor control and adaptation. J Mot Behav. 2012;44(6):455–69.
37. Mutha PK, Stapp LH, Sainburg RL, Haaland KY. Frontal and parietal cortex contributions to action modification. Cortex. 2014;57:38–50.
38. Mutha PK, Sainburg RL. Shared bimanual tasks elicit bimanual reflexes during movement. J Neurophysiol. 2009;102(6):3142–55.
39. Schaefer SY, Mutha PK, Haaland KY, Sainburg RL. Hemispheric specialization for movement control produces dissociable differences in online corrections after stroke. Cereb Cortex. 2012;22(6):1407–19.
40. Bisazza A, Rogers LJ, Vallortigara G. The origins of cerebral asymmetry: a review of evidence of behavioural and brain lateralization in fishes, reptiles and amphibians. Neurosci Biobehav Rev. 1998;22(3):411–26.

41. MacNeilage PF, Rogers LJ, Vallortigara G. Origins of the left & right brain. Sci Am. 2009;301(1): 60–7.
42. Sainburg RL. Convergent models of handedness and brain lateralization. Front Psychol. 2014;5:1092.
43. Kawashima R, Roland PE, O'Sullivan BT. Activity in the human primary motor cortex related to ipsilateral hand movements. Brain Res. 1994;663(2):251–6.
44. Kuypers HG. A new look at the organization of the motor system. Prog Brain Res. 1982;57:381–403.
45. Gonzalez CL, Gharbawie OA, Williams PT, Kleim JA, Kolb B, Whishaw IQ. Evidence for bilateral control of skilled movements: ipsilateral skilled forelimb reaching deficits and functional recovery in rats follow motor cortex and lateral frontal cortex lesions. Eur J Neurosci. 2004;20(12):3442–52.
46. Grabowski M, Brundin P, Johansson BB. Paw-reaching, sensorimotor, and rotational behavior after brain infarction in rats. Stroke. 1993;24(6):889–95.
47. Grabowski M, Nordborg C, Johansson BB. Sensorimotor performance and rotation correlate to lesion size in right but not left hemisphere brain infarcts in the spontaneously hypertensive rat. Brain Res. 1991;547(2):249–57.
48. Mutha PK, Sainburg RL, Haaland KY. Left parietal regions are critical for adaptive visuomotor control. J Neurosci. 2011;31(19):6972–81.
49. Mutha PK, Sainburg RL, Haaland KY. Critical neural substrates for correcting unexpected trajectory errors and learning from them. Brain. 2011;134(Pt 12):3647–61.
50. Haaland KY, Schaefer SY, Knight RT, et al. Ipsilesional trajectory control is related to contralesional arm paralysis after left hemisphere damage. Exp Brain Res. 2009;196(2):195–204.
51. Schaefer SY, Haaland KY, Sainburg RL. Hemispheric specialization and functional impact of ipsilesional deficits in movement coordination and accuracy. Neuropsychologia. 2009;47(13):2953–66.
52. Chestnut C, Haaland KY. Functional significance of ipsilesional motor deficits after unilateral stroke. Arch Phys Med Rehabil. 2008;89(1):62–8.
53. Haaland KY. Left hemisphere dominance for movement. Clin Neuropsychol. 2006;20(4):609–22.
54. Wetter S, Poole JL, Haaland KY. Functional implications of ipsilesional motor deficits after unilateral stroke. Arch Phys Med Rehabil. 2005;86(4): 776–81.
55. Haaland KY, Prestopnik JL, Knight RT, Lee RR. Hemispheric asymmetries for kinematic and positional aspects of reaching. 2004. Brain May; 127(Pt 5):1145–58.
56. Prestopnik J, Haaland K, Knight R, Lee R. Hemispheric dominance for open and closed loop movements. Soc Neurosci Abstr. 2003;30(1).
57. Winstein CJ, Pohl PS. Effects of unilateral brain damage on the control of goal-directed hand movements. Exp Brain Res. 1995;105(1):163–74.
58. Wyke M. The effect of brain lesions in the performance of an arm-hand task. Neuropsychologia. 1967;6:125–34.
59. Kawashima R, Yamada K, Kinomura S, et al. Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movement. Brain Res. 1993;623(1):33–40.
60. Kim SG, Ashe J, Hendrich K, et al. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science. 1993;261(5121):615–7.
61. Tanji J, Okano K, Sato KC. Neuronal activity in cortical motor areas related to ipsilateral, contralateral, and bilateral digit movements of the monkey. J Neurophysiol. 1988;60(1):325–43.
62. Schaefer SY, Haaland KY, Sainburg RL. Dissociation of initial trajectory and final position errors during visuomotor adaptation following unilateral stroke. Brain Res. 2009;1298:78–91.
63. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13–31.
64. Haaland KY, Mutha PK, Rinehart JK, Daniels M, Cushnyr B, Adair JC. Relationship between arm usage and instrumental activities of daily living after unilateral stroke. Arch Phys Med Rehabil. 2012; 93(11):1957–62.
65. Pandian S, Arya KN, Kumar D. Effect of motor training involving the less-affected side (MTLA) in post-stroke subjects: a pilot randomized controlled trial. Top Stroke Rehabil. 2015;22(5):357–67.
66. Wolf SL, Blanton S, Baer H, Breshears J, Butler AJ. Repetitive task practice: a critical review of constraint-induced movement therapy in stroke. Neurologist. 2002;8(6):325–38.
67. Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. Exp Neurol. 1989;104(2):125–32.
68. Wolf SL, Thompson PA, Morris DM, et al. The EXCITE trial: attributes of the Wolf Motor Function Test in patients with subacute stroke. Neurorehabil Neural Repair. 2005;19(3):194–205.
69. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006; 296(17):2095–104.
70. Nozaki D, Kurtzer I, Scott S. Limited transfer of learning between unimanual and bimanual skills within the same limb. Nat Neurosci. 2006;9:3.
71. Wang J, Sainburg RL. Generalization of visuomotor learning between bilateral and unilateral conditions. J Neurophysiol. 2009;102(5):2790–9.
72. Lum PS, Burgar CG, Van der Loos M, Shor PC, Majmundar M, Yap R. MIME robotic device for upper-limb neurorehabilitation in subacute stroke subjects: a follow-up study. J Rehabil Res Dev. 2006;43(5):631–42.
73. Jones RD, Donaldson IM, Parkin PJ. Impairment and recovery of ipsilateral sensory-motor function following unilateral cerebral infarction. Brain. 1989;112(Pt 1):113–32.

74. Wang J, Sainburg RL. Interlimb transfer of visuomotor rotations depends on handedness. Exp Brain Res. 2006;175(2):223–30.
75. Wang J, Sainburg RL. The symmetry of interlimb transfer depends on workspace locations. Exp Brain Res. 2006;170(4):464–71.
76. Wang J, Sainburg RL. Limitations in interlimb transfer of visuomotor rotations. Exp Brain Res. 2004;155(1):1–8.
77. Wang J, Sainburg RL. Interlimb transfer of novel inertial dynamics is asymmetrical. J Neurophysiol. 2004;92(1):349–60.
78. Oujamaa L, Relave I, Froger J, Mottet D, Pelissier JY. Rehabilitation of arm function after stroke. Literature review. Ann Phys Rehabil Med. 2009;52(3):269–93.
79. Selles RW, Michielsen ME, Bussmann JB, et al. Effects of a mirror-induced visual illusion on a reaching task in stroke patients: implications for mirror therapy training. Neurorehabil Neural Repair. 2014;28(7):652–9.
80. Stevens JA, Stoykov ME. Simulation of bilateral movement training through mirror reflection: a case report demonstrating an occupational therapy technique for hemiparesis. Top Stroke Rehabil. 2004;11(1):59–66.
81. Shadmehr R, Mussa-Ivaldi FA. Adaptive representation of dynamics during learning of a motor task. J Neurosci. 1994;14(5 Pt 2):3208–24.
82. Krakauer JW, Mazzoni P, Ghazizadeh A, Ravindran R, Shadmehr R. Generalization of motor learning depends on the history of prior action. PLoS Biol. 2006;4(10):e316.
83. Mazzoni P, Krakauer JW. An implicit plan overrides an explicit strategy during visuomotor adaptation. J Neurosci. 2006;26(14):3642–5.
84. Sainburg RL, Ghez C, Kalakanis D. Intersegmental dynamics are controlled by sequential anticipatory, error correction, and postural mechanisms. J Neurophysiol. 1999;81(3):1045–56.
85. Keisler A, Shadmehr R. A shared resource between declarative memory and motor memory. J Neurosci. 2010;30(44):14817–23.
86. Huang VS, Haith A, Mazzoni P, Krakauer JW. Rethinking motor learning and savings in adaptation paradigms: model-free memory for successful actions combines with internal models. Neuron. 2011;70(4):787–801.
87. Krakauer JW, Pine ZM, Ghilardi MF, Ghez C. Learning of visuomotor transformations for vectorial planning of reaching trajectories. J Neurosci. 2000;20(23):8916–24.
88. Krakauer JW, Ghilardi MF, Ghez C. Independent learning of internal models for kinematic and dynamic control of reaching. Nat Neurosci. 1999;2(11):1026–31.
89. Wolpert DH, Wolf DR. Estimating functions of probability distributions from a finite set of samples. Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Top. 1995;52(6):6841–54.
90. Criscimagna-Hemminger SE, Donchin O, Gazzaniga MS, Shadmehr R. Learned dynamics of reaching movements generalize from dominant to nondominant arm. J Neurophysiol. 2003;89(1):168–76.
91. Malfait N, Shiller DM, Ostry DJ. Transfer of motor learning across arm configurations. J Neurosci. 2002;22(22):9656–60.
92. Conditt MA, Gandolfo F, Mussa-Ivaldi FA. The motor system does not learn the dynamics of the arm by rote memorization of past experience. J Neurophysiol. 1997;78(1):554–60.
93. Bastian AJ. Learning to predict the future: the cerebellum adapts feedforward movement control. Curr Opin Neurobiol. 2006;16(6):645–9.
94. Bastian AJ, Thach WT. Cerebellar outflow lesions: a comparison of movement deficits resulting from lesions at the levels of the cerebellum and thalamus. Ann Neurol. 1995;38(6):881–92.
95. Thach WT, Bastian AJ. Role of the cerebellum in the control and adaptation of gait in health and disease. Prog Brain Res. 2004;143:353–66.
96. Tseng YW, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ. Sensory prediction errors drive cerebellum-dependent adaptation of reaching. J Neurophysiol. 2007;98(1):54–62.
97. Tanaka H, Sejnowski TJ, Krakauer JW. Adaptation to visuomotor rotation through interaction between posterior parietal and motor cortical areas. J Neurophysiol. 2009;102(5):2921–32.
98. Krakauer JW, Mazzoni P. Human sensorimotor learning: adaptation, skill, and beyond. Curr Opin Neurobiol. 2011;21(4):636–44.
99. Reis J, Schambra HM, Cohen LG, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A. 2009;106(5):1590–5.
100. Izawa J, Shadmehr R. Learning from sensory and reward prediction errors during motor adaptation. PLoS Comput Biol. 2011;7(3):e1002012.
101. Taylor JA, Klemfuss NM, Ivry RB. An explicit strategy prevails when the cerebellum fails to compute movement errors. Cerebellum. 2010;9(4):580–6.
102. Taylor JA, Krakauer JW, Ivry RB. Explicit and implicit contributions to learning in a sensorimotor adaptation task. J Neurosci. 2014;34(8):3023–32.

Designing Robots That Challenge to Optimize Motor Learning

3

David A. Brown, Timothy D. Lee,
David J. Reinkensmeyer, and Jaime E. Duarte

Abstract

The purpose of this chapter is to provide the reader with a better understanding of the theory and practice of providing effective levels of challenge for people with motor disability, using rehabilitation robotics to provide the safety and assurance that is necessary to prevent physical harm and mental frustration. First, we describe the therapeutic context with which clinicians encounter the need to design challenge into the motor learning sessions that are typical for individuals who are recovering from impaired movement. Second, we explore the challenge point framework as a major breakthrough in our understanding of the nature of challenge in motor performance and how this challenge contributes to efficacious motor learning. Next, we describe ways in which rehabilitation robotics can be designed and implemented to explore the ways in which people

D.A. Brown, PT, PhD (✉)
Departments of Physical Therapy and Occupational Therapy, University of Alabama at Birmingham, 1720 2nd Ave So, Birmingham, AL 35294-1212, USA
e-mail: dbrownpt@uab.edu

T.D. Lee, PhD
Department of Kinesiology, McMaster University, Hamilton, ON, Canada

D.J. Reinkensmeyer, PhD
Department of Mechanical and Aerospace Engineering, University of California at Irvine, Irvine, CA, USA

Department of Anatomy and Neurobiology, University of California at Irvine, Irvine, CA, USA

Department of Biomedical Engineering, University of California at Irvine, Irvine, CA, USA

Department of Physical Medicine and Rehabilitation, University of California at Irvine, Irvine, CA, USA

J.E. Duarte, PhD
Department of Mechanical and Aerospace Engineering, University of California at Irvine, Irvine, CA, USA

D.J. Reinkensmeyer, V. Dietz (eds.), *Neurorehabilitation Technology*,
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with motor disability can learn to move again and how results with these devices suggest extending the challenge point framework to take into account self-efficacy and willingness to practice. Finally, we provide a detailed example of a robotic system that works collaboratively with the clinician to provide physical challenge during walking and balance training in people with poststroke hemiparesis using a library of novel techniques. We conclude by providing further thoughts to engineers and clinicians who collaborate to develop a next generation of rehabilitation robotics that build on the concepts of optimal challenge into the engineering design.

Keywords

Movement rehabilitation • Motor learning • Rehabilitation technology • Challenge • Practice psychology • Self-efficacy • Stroke • Psychomotor performance

3.1 Therapeutic Context of Physical Challenge During the Rehabilitation Process

Impaired motor performance results in disability that becomes a major obstacle to community function in persons with movement disorders such as poststroke hemiplegia, spinal cord injury, Parkinson's disease, multiple sclerosis, head injury, osteoarthritis, postamputation loss of limb, etc. This disability is characterized by functional deficits, such as slow walking, inability to grasp objects, moving in a manner so as to avoid pain, and avoiding situations in life that may result in falls. Often these functional deficits are due to a combination of motor impairments such as reduced muscle strength, slow movement speed, poor balance and coordination, poor aerobic endurance and muscle fatigue, and an inability to move under conditions of environmental distractions due to fear of falling or lack of attention to movement. The inability to move functionally in a complex environment can result in some dire consequences. For example, in the case of persons with gait and balance impairments, there can be a high risk for falls at the home and in the community.

One of the promises of robotic rehabilitation applications is in providing persons with disability the opportunity to be physically challenged in a safe and efficacious manner. While clinicians are very effective at matching the capabilities of a person with disability with the challenge of the exercise, physical limitations in a clinician's strength and endurance can reduce the potential for providing consistently challenging and ever-progressing environments for continued performance improvement. In addition, there are some domains of challenge, such as with balance, strength training, and speed training, where smart machines, such as robots, can provide tireless and adaptable challenging exercise and motor learning environments.

It also may be argued that, unless the person is challenged to perform beyond their current capability, acquisition of new and improved functional movement behaviors will be limited. In fact, in such wide-ranging fields as athletic performance, musical instrument expertise, and chess mastery, the evidence shows that mastery in a task is best achieved with deliberate and persistent practice sessions that push a person to move beyond their current performance limitations. Of course, the physical risks of harm and mental frustration that come along with attempts to move against high-level challenges should cause concern. However, rehabilitation robotics, if designed appropriately, can allow individuals who are learning to move more functionally, to

attempt increasingly challenging tasks without fear of harm and with the knowledge that, if they make mistakes during the training, they can learn from the mistakes.

Further, in the case of neurological injury or disease, the concept of challenge must be applied intelligently when used as an adjunct to disorders that may limit ability to recover movement capability. Factors such as impaired sensory input (i.e., proprioceptive, cutaneous, visual, vestibular, etc.), inappropriate coupling of muscle activations, muscle hyper- or hypotonicity, poorly prepared and planned movement sequences, difficulty with starting and stopping movements, and psychological factors (i.e., cognitive status, memory, motivation, etc.). The sections that follow describe the concept of challenge; however, one must always remember that the nervous system can be overstimulated; therefore, a sensitive clinician will always monitor physiologic and behavioral responses when providing challenging learning environments. Optimal challenge conditions in the case of recovery of walking and balance poststroke will be discussed in Sect. 3.4.

3.2 The Challenge Point Framework

Motor performance and motor learning share a fluctuating relationship. A *performance* is usually defined as the outcome of an action. It can be measured at any one time or over a series of short-term intervals. In contrast, the term *learning* refers to performance improvements that "stick"; improvements that are relatively permanent over a longer term. One might assume that good short-term performances naturally lead to good longer-term improvements. But, that assumption does not hold, and in fact, many times the reverse is true—better learning often results from poor performances. Guadagnoli and Lee [1] introduced the "challenge point framework" (CPF) in an attempt to define how the relationship between performance and learning could be optimized.

Motor performance is critically dependent on the difficulty of the task. All other issues being equal, more difficult tasks generally result in less successful performances. However, learning can sometimes benefit from difficulties. Bjork [2] termed these as "desirable difficulties." Clearly, though, not all difficulties are desirable. Guadagnoli and Lee [1] hypothesized that difficulties could be optimized in order to promote the desirable and minimize the undesirable effects.

The CPF hypothesized a systematic attempt to introduce challenges to the learning environment. The critical factors that combined to define a challenge point included the task, the individual, and the practice-related constraints. Some tasks are more difficult to perform than other tasks, and optimal learning conditions are predicted to be associated with levels of task difficulty that are appropriate for the skill level of the learner. The CPF predicted that there are levels of task difficulty that are too easy for some individuals and levels that are too difficult for others. And, although there may exist a level of task difficulty that optimizes learning for each individual at some point in time, the level must be adaptable to changes in the performer that occur with learning (see also [3–5]).

The CPF considered adapted task difficulty as a key component for setting appropriate conditions of practice for learning. For example, an easy task, practiced under random practice conditions, makes performance on the task more difficult in a *functional* sense. Conversely, a difficult task, subjected to physically restricted guidance, makes performance on the task *functionally* less difficult. There are many other practice-related conditions that change the functional difficulty of practice too (such as rote repetition, the provision of feedback, and so on).

The CPF therefore considered the effects of functional task difficulty from a perspective of both performance in practice and the potential for learning that might result. Figure 3.1 illustrates a predicted optimal point at which increasing the functional task difficulty would maximum learning at the least cost to immediate performance. The goal of optimizing the functional task difficulty was to maximize the positive boost to learning combined with the negative detriments to immediate performance. Beyond the optimal

point, the framework predicts that performance will deteriorate rapidly at a cost to learning as well. Figure 3.1 illustrates the prediction from the framework that an optimal challenge point would occur at a level of functional task difficulty that was considerably lower for a novice than for a skilled performer.

Let's use golf practice as an example of how the CPF might be useful. For the beginner, striking a golf ball to result in an airborne trajectory is a very difficult task. Repeated failures do not optimize learning—at the beginner stage, learning is facilitated by successful performance. For the novice, physically restricted guidance devices, for example, make the task functionally, less difficult, which should positively influence both performance and learning. The use of physically restricted guidance devices, however, might have the opposite effect for the more advanced golfer. In this case, the learner needs to be challenged by more functionally difficult practice conditions, because the task itself does not bring about the same level of challenge as it did for the novice. Changing golf clubs on each practice attempt, or playing shots out of imperfect lies in the grass, adds a desirable challenge for the more advanced golfer that would optimize the benefits of practice that would "stick" for the longer term (see [6] for more examples).

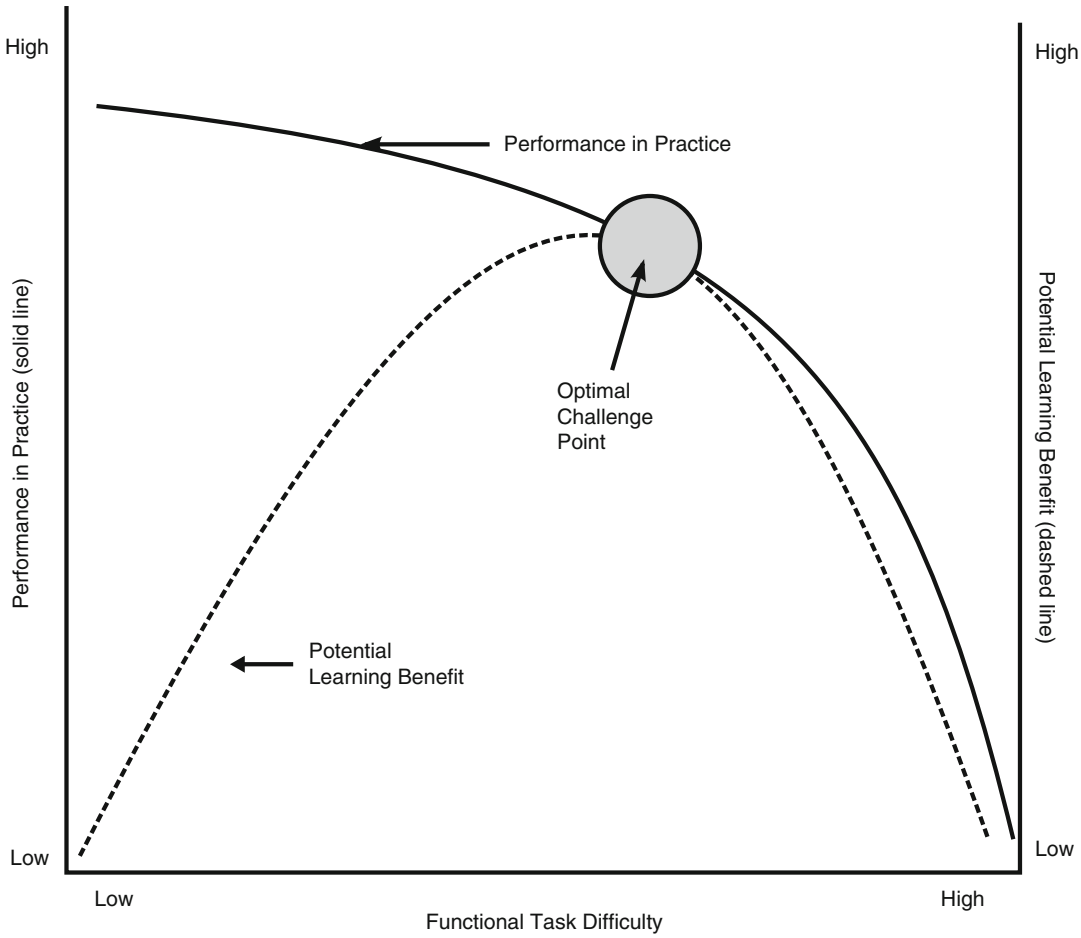

Fig. 3.1 The optimal challenge point predicts the level of functional task difficulty that maximizes learning at the least cost to performance during practice. This optimal challenge point is relative to the individual's abilities and thus changes in relation to the individual's level of expertise

3.2.1 Application of the CPF to Stroke Rehabilitation: A Pilot Study

Some predictions made in the CPF were examined in a randomized controlled pilot trial by Griffiths [7], involving patients in an inpatient stroke rehabilitation program. A small sample of participants, 2–12 weeks poststroke, was assigned to one of three training groups. A control group ($n=3$) received a usual-care, strength training protocol. A second group of participants ($n=3$) were assigned to a condition in which they were encouraged to select a set of specific tasks to be used in therapy with the goal to challenge their current capabilities as much as possible. As performance improved participants were taught how to change the tasks to make them more challenging. The third group of individuals poststroke ($n=5$) also practiced challenging tasks, but these were assigned by the therapist, rather than self-selected. Physical therapy was administered for 15 sessions over a 3- or 4-week period, which was followed by 4 weeks of self-managed physical therapy that usually occurred in the home post-discharge. A number of primary and secondary recovery-of-function assessments were taken at three time periods: pre-intervention (T1), post-intervention (T2, following the 15 sessions of physical therapy), and after the 4 weeks of self-managed therapy (T3). The general goal in selecting the tasks to be performed in the therapy session was that they were to be neither too difficult nor too easy to perform. Note that the difference between the two experimental groups was that in the self-selected group, the participants were taught to determine the tasks that optimally challenged their current skill capability, and in the therapist-selected group, the therapist chose the tasks to optimally challenge the participants' current capability.

The effect of the therapy conditions on the (CAHAI) Chedoke Arm and Hand Activity Inventory, a measure of functional activity performance, illustrated in Fig. 3.2, represents just one of the primary assessments. Many of these other outcomes showed similar effects, although not all were significant due to the small sample and low statistical power. The results for the CAHAI revealed that the self-selected group produced the best recovery-of-function result at T3 (after the self-management period), even though

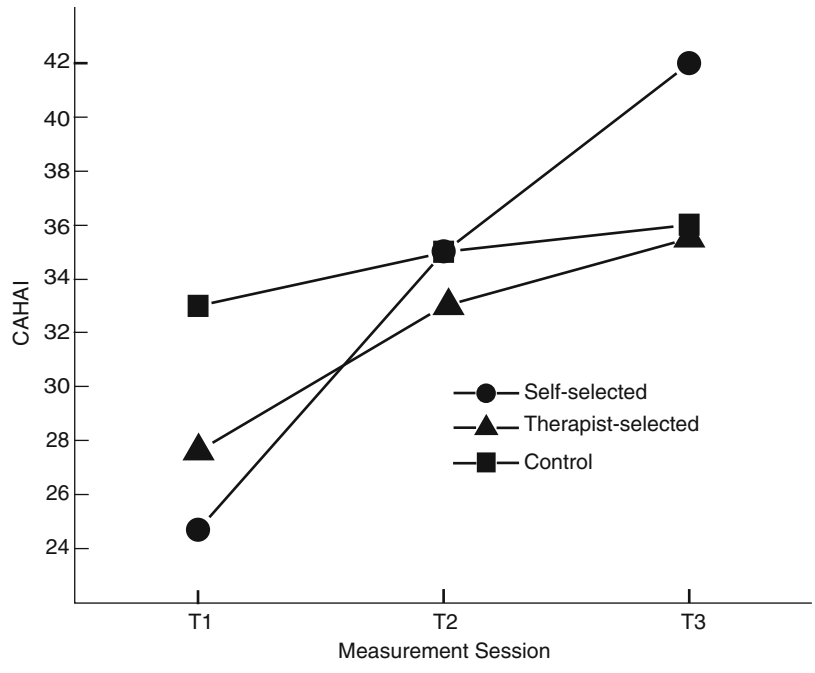

Fig. 3.2 Performance of three poststroke treatment conditions on the Chedoke Arm and Hand Activity Inventory (CAHAI) at T1 (prior to treatment), T2 (after a 15-session inpatient treatment), and T3 (after 4 weeks of at-home self-administered treatment) (From Griffiths [7]; used with permission)

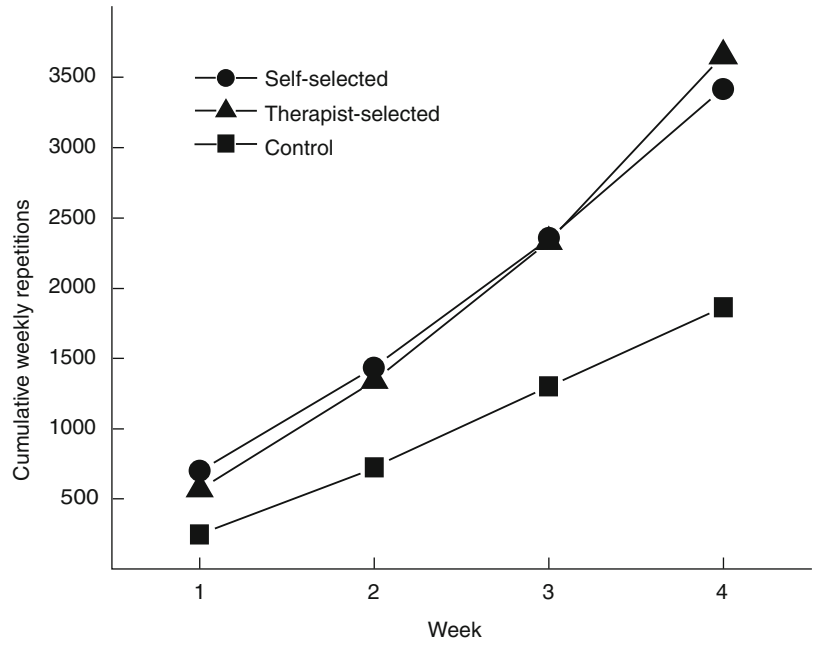

Fig. 3.3 Cumulative number of at-home task repetitions that were recorded (by diary) over a 4-week period treatment period (From Griffiths [7]; used with permission)

the participants in control group were much better at T1. In terms of proportional recovery of function, the self-select group improved by 41.7 % from T1 (pretest) to T2 (after the inpatient therapy) and by 70.0 % when considered from T1 to T3. The patients receiving therapist-selected tasks improved by 19.6 and 28.6 % over these same periods. Both of these proportional improvements were higher than the improvements seen in the control groups (3.0 % and 9.1 % in T1–T2 and T1–T3, respectively).

Perhaps of equal, if not more important, however, were the task repetition records that were observed in the patients' diaries over the 4-week period of self-managed treatment. These findings, illustrated as the cumulative number of task repetitions in Fig. 3.3, revealed that both the self-selected and therapist-selected groups continued the self-managed treatment with a significantly higher dose of training than the control group. This finding was unexpected, and Griffiths suggested that the finding indicated that the increasingly challenging aspects of the therapies resulted in higher, sustained motivation to continue self-managed treatment at home.

Minimally, the findings of this pilot study suggest that a larger trial is warranted. The data support the potential role of providing task appropriate challenges to individuals poststroke during physical rehabilitation, both in terms of recovery of function and in terms of enhanced motivation to continue treatment. The latter finding supports the long-held view in motor learning that *amount and intensity* of practice are the most important determinants of skill improvement. If that statement is true also for recovery of function following stroke (as many believe it to be), then therapy treatment conditions that facilitate recovery of function *and* motivate the individual to continue therapy serve as dual-purpose advantages. The CPF is one possible mechanism that could inform therapy (see also [8]).

3.3 Using Robotic Technologies to Provide Challenge in Rehabilitation Therapy

Based on the prior discussion, it is clear that a key issue in the design of neurorehabilitation therapy technology is to provide appropriate challenge during training. This section describes the evolution of robotic therapy device design to meet this requirement. Two initial strategies have been to provide

mechanical assistance for movement and, more recently, to automatically adjust therapeutic parameters using sensors and software algorithms.

3.3.1 Providing Appropriate Challenge by Providing Mechanical Assistance

The first robotic therapy devices were designed to provide mechanical assistance to help individuals complete training tasks (for reviews, see [9, 10]). This strategy mimicked the strategy of active assistance sometimes used by rehabilitation therapists, in which the therapist physically assists the active patient in completing movements. Therapists use active assistance for both the upper extremity, for example, for reach practicing, or for the lower extremity, for example, by providing balance support during overground walking training. Likewise, initial robotic therapy devices for the upper extremity, like MIT-MANUS [10], MIME [11], and the ARM Guide [12], assisted patients in completing reaching movements, while initial devices for the lower extremity, like the Lokomat [13] and the Gait Trainer [14], assisted patients in maintaining balance and achieving a stepping-like pattern of leg motions. These machines physically attached to the patient and essentially tried to work in harmony to achieve desired movements, specified by video games for the upper extremity or using a normative gait trajectory for the lower extremity.

Within the challenge point framework, this strategy of providing assistance can be viewed as a way to make rehabilitation tasks that are overly difficult practicable by individuals with severe impairment. As explained above, making a task practicable may make it more learnable. In addition, making tasks practicable may play a role in motivation. In the words of one participant with a stroke in a study with the arm training exoskeleton T-WREX, "If I can't do something once, why would I do it a hundred times?" [15].

The motivational significance of robotic assistance was recently confirmed in a study of the FINGER robotic finger training exoskeleton. In this study [16], 30 individuals with a moderate to severe finger movement impairment after chronic stroke were randomized to either a high success or low success group, where success was defined as the percentage of musical notes they successfully hit as they played a computer game similar to Guitar Hero. The FINGER robot adaptively assisted the participants to achieve either an 85 % success rate (high success) or a 60 % success rate (low success). Participants were asked to rate how motivating the rehabilitation training was after each of nine training sessions using a validated scale, the Intrinsic Motivation Inventory [17]. Figure 3.4 illustrates that the participants who received more assistance from the robot, and thus achieved higher success levels, consistently rated the robotic training as more motivating.

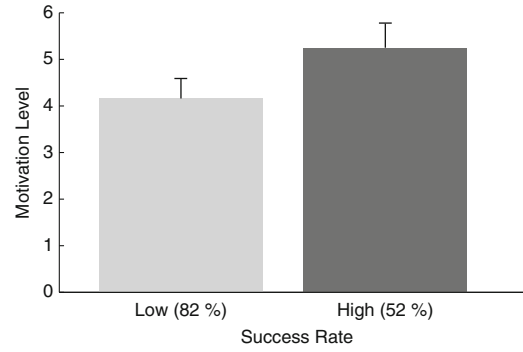

Fig. 3.4 Participants who received more assistance from the robot and thus achieved high success levels (high), consistently rated the robotic training as more motivating

Despite positive motivational effects of active assist robotic therapy, what became increasingly clear with ongoing clinical studies was that there was a danger of over assisting a patient and thereby decrementing the amount of learning that could happen during training. As outlined above, the challenge point theory states that there is an optimal challenge point that is patient specific, which will change with practice. Thus, using the golf example above, physical assisting of the golf swing may be appropriate early in learning but less appropriate as learning proceeds. In two key robotic therapy studies [18, 19], the Lokomat was used for gait training by patients with stroke who were already ambulatory and compared two control groups that trained with conventional gait

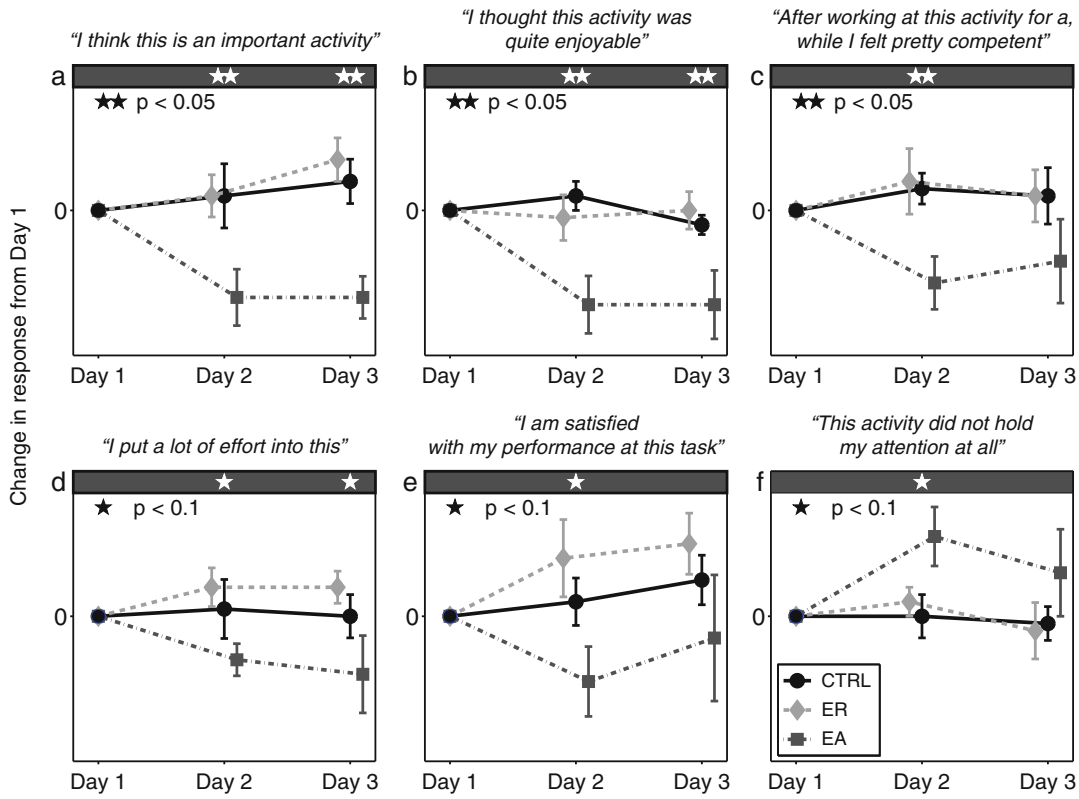

Fig. 3.5 Participants who trained in a virtual golf putting task reported decreased motivation after training with error augmentation and these feelings persisted even days later when errors where no longer augmented. (From Duarte and Reinkensmeyer [28])

training techniques. While patients improved their gait speed through training with the Lokomat, they improved less than via conventional training. One interpretation is that the Lokomat created a training environment with too low of challenge by over assisting the trainee.

Around the same time, research in human-robot interaction with upper extremity robotic training devices showed the intrinsic and automatic capacity of the human motor system to "slack." That is, when interacting with an assistive robotic device, the human motor system will automatically reduce its effort unless precautions are taken [20, 21]. Slacking was shown to be a consequence of the fact that the motor system acts as if it were trying to minimize a cost function with both error and effort terms [22]. When error is small, because, for example, a robotic device is assisting, then the motor system essentially minimizes a cost function with just an effort term. A reduction of effort in the presence of robotic assistance was also shown in a metabolic study with the Lokomat [23]. Reduced effort during rehabilitation training correlates with worse outcomes [24].

In part as a reaction to these findings, other robotic movement training studies began examining the use of error augmentation in training [25, 26]. Error augmentation can be seen as essentially the inverse of active assistance. Instead of a machine that reduces error, the trainee interacts with a machine that amplifies sensed movement errors. Studies of error augmentation with individuals with stroke showed that the technique could correct chronic reaching trajectory abnormalities that persisted throughout normal reaching practice [25], and, importantly, training with error augmentation produced better upper extremity outcomes for individuals with a chronic stroke than a matched amount of reach training without error augmentation [27]. On the other hand, a recent study that used a temporary bout of error augmentation to try

to enhance learning of golf putting found that increasing errors decreased trainee motivation, in a way that persisted days after the use of the error augmentation (Fig. 3.5 [28]). Thus error augmentation may have negative motivational effects, an important consideration for training techniques that are to be implemented in real-world clinical and home environments.

What is suggested by these results is that robotic therapy devices should be designed to provide gradable amounts of mechanical intervention. The key question is not whether active assistance, no mechanical intervention, or error augmentation should be used but where, on a continuum of levels of mechanical intervention, each patient should practice. Providing less active assistance to a severely impaired patient can be viewed as a form of error augmentation. Likewise, providing less error augmentation to a less severely impaired patient can be viewed as a form of active assistance. Several studies of robotic training with unimpaired participants already suggest that the effectiveness of active assistance or error augmentation may depend on the initial skill level of the trainee [28–32]. What is needed are ways to adjust the training environment to the challenge point of the trainee.

3.3.2 Adapting Challenge

What is promising for meeting this goal is the fact that adjustability is a fundamental property of robotic therapy technology. And not only are robotic therapy devices adjustable, but they are adjustable in real time based on automated readings from their sensors. Almost from the beginning of robotic therapy, developers began implementing ad hoc algorithms to provide varying amounts of assistance (see review [33]). It cannot be claimed that these algorithms have achieved the goal of automated challenge point selection, but they are first steps, as we survey now.

One of the first strategies tried was to provide assistance for movement only when a threshold of movement was not met within a specified time frame (see [33] for review of strategies to provide assistance). Soon, other algorithms were developed to adapt the forces applied to the trainee or the mechanical impedance of the training environment. These adjustments could be based on the ongoing performance of the trainee, analogous to the way the human motor system adjusts its own arm forces and impedance during interaction with dynamic environments.

For the Pneu-WREX arm exoskeleton, a model-based assist-as-needed paradigm was implemented, in which a sliding adaptive controller was used to build a real-time model of the patient's weakness using a radial basis function representation [20]. In a study of this algorithm, it was shown to be necessary for the robot to include a slacking term itself, to ensure that the patient did not slack [20]. With a robot slacking term, the assistance-as-needed strategy provided a level of mechanical support proportional to the patient's clinical impairment level. Recently, with the FINGER robot, an algorithm was implemented to transition the robot from active assistance to error augmentation based on the game success rate of the patient during training [34].

Besides adapting the forces, it is also possible to adapt game parameters. For example, using the BONES arm exoskeleton, the speed at which a virtual baseball was pitched was varied based on the success of catching the previous ball. In other words, this simple adaptive challenge algorithm altered a task difficulty parameter following each task attempt based on a binary measure of performance (success or failure). Spencer [35] showed that the average success rate can be controlled by adjusting the ratio of up-steps to down-steps, and the rate and variance of convergence can be adjusted by setting the overall step size.

Choi et al. [36] developed a novel upper extremity robotic training system that can automatically switch out objects for the patient to attempt to manipulate. A high-level task scheduler selects the task to practice and adjusts the task difficulty based on the previous performance at the task. Caurin et al. [37] used an adaptive algorithm to select the level of difficulty of a pong game based on measures of the user's motivation and performance during training. Metzger et al. [38] automatically adjusted the difficulty level from one session to the next in a hand rehabilitation program so that patients trained at a target level of 70 % found reductions in both motor and sensory impairments. As a final example of exercise adaptation, Zimmerli et al. [39] matched

the difficulty of a reaching task to the capabilities of the patients by controlling the time available for patients to reach a given target.

The algorithms developed so far are primarily based on the premise that task difficulty should be adjusted based on a performance measure. However, as shown in Fig. 3.5, performance levels may not be the same for different individuals at their optimal challenge point. A key question is whether performance, or possibly some other measure, should be the basis for task difficulty adaptation.

3.3.3 Implication of Challenge on Motivation and Self-Efficacy

As implicated in the discussion above, another factor that may be important for determining the optimal challenge level of a motor task is the level of motivation of the trainee. Specifically, the challenge level must be selected so that it maximizes the degree of engagement during practice and, in the case of neurological rehabilitation, motivates patients to use their impaired limbs in unsupervised practice beyond the clinic as seen in Griffiths' pilot study above [7]; this is especially important because of strong evidence that the current doses of rehabilitation training in areas such as stroke are insufficient to drive clinically meaningful improvements [40].

It may be possible to extend the challenge point framework [1] to incorporate the effect of motivation on a trainee's ongoing willingness to engage in motor training. As demonstrated recently in the FINGER study, using an adaptive challenge algorithm to regulate the rate of success during rehabilitation training led those stroke patients that trained with a higher success rate to self-report higher motivation about the task. In a similar implementation of this algorithm, this time tested with a rat model of rehabilitation following spinal cord injury, rats that trained at a lower challenge level and thus reached a higher success rate were more willing to engage in the training task, performing more repetitions in a fixed amount of time [41]. Thus, incorporating measures of motivation and engagement to determine the optimal challenge point may lead to therapies that are more motivating and ultimately increase the willingness to practice both during supervised and unsupervised practice.

This idea is illustrated in Fig. 3.6 where, following the convention of the CPF and including plausible curves for different levels of expertise, the functional difficulty of the task determines the willingness to engage in practice. For a novice, or for someone who has just started rehabilitation training, a lower difficulty level is accompanied by a high level of performance in practice (consistent with the CPF), and the willingness to practice is expected to increase as shown in the rat study above. However, as the trainee—or patient in the case of rehabilitation—gains mastery of the motor skill and transitions to higher skill levels, the engagement in the task and willingness to practice is expected to decrease for lower difficulty levels. On the other hand, as the difficulty is increased, the performance in practice may worsen to a point that leads to frustration and a decreased willingness to practice; this was evident in the recent FINGER study. There is therefore a point where the functional difficulty of the task maximizes the trainee's willingness to practice the task. This point must be combined with the optimal challenge point predicted by the CPF in order to strike a balance between motor performance, motor learning, and motivation.

Considering that for many patients the bulk of rehabilitation occurs away from direct supervision and that in many cases motor capacity exceeds actual performance [42, 43], an important goal of rehabilitation training is then to provide patients not only with the motor capacity but also the motivation to use their impaired limbs during activities of daily living and in unsupervised practice. An important concept to consider in this context is self-efficacy. Self-efficacy relates to a person's belief that he has the capacity to execute a specific action or achieve a specific goal [44]. Self-efficacy has been found to influence people's motivational, cognitive, and affective states [44], and increased self-efficacy has been shown to have positive effects on motor learning [45, 46]. Importantly for rehabilitation, self-efficacy has been shown to influence a person's level of effort,

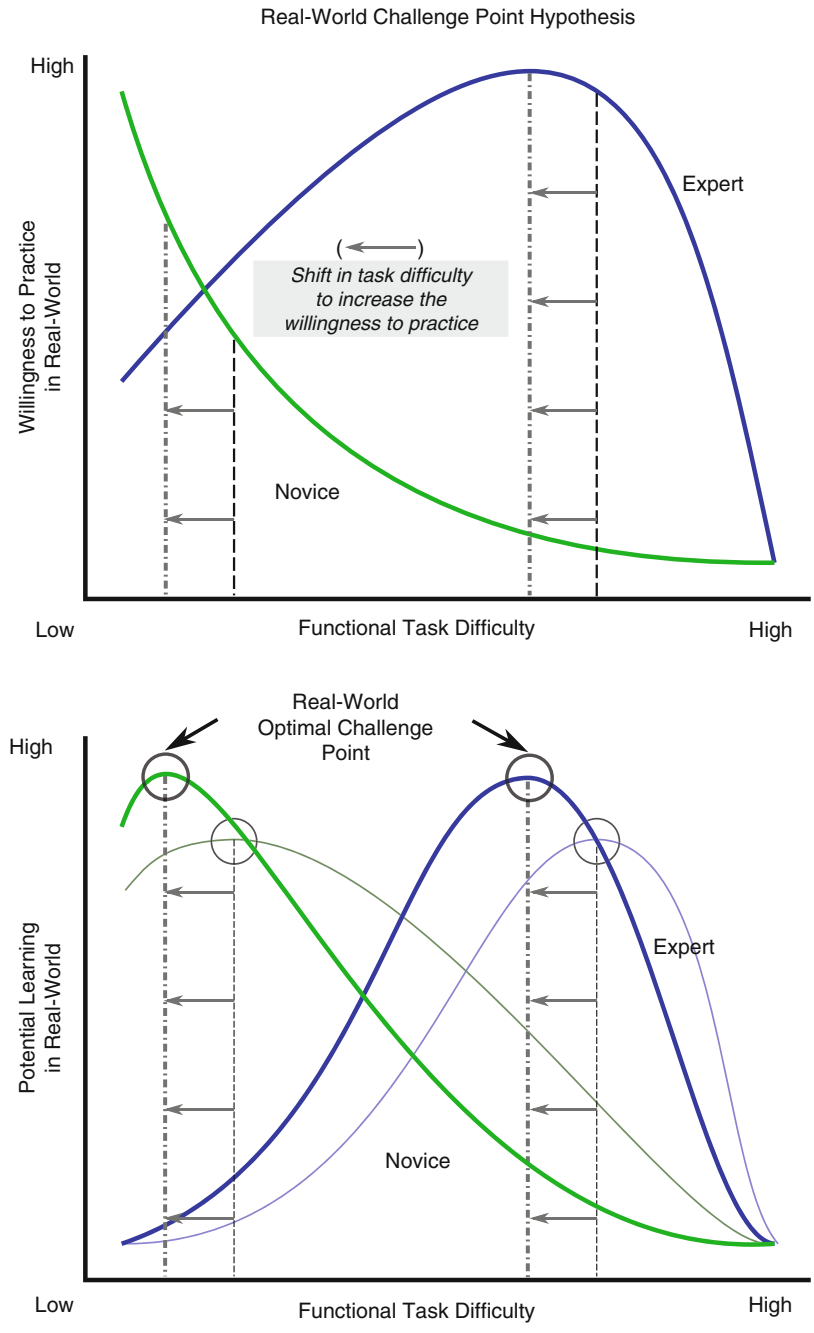

Fig. 3.6 [*Top*] Willingness to practice curves. The functional task difficulty determines the willingness to practice for trainees of different skill levels. For a novice, or someone who has recently begun rehabilitation training, a lower difficulty level means the task is doable and the trainee is likely to have a high willingness to practice. However, as the trainee gains mastery of the motor skill and transitions to higher skill levels, the engagement and willingness to practice is expected to decrease for lower difficulty levels. On the other hand, as the difficulty increases past the abilities of the trainee, then the performance in practice may worsen to a point that the willingness to practice will decrease. [*Bottom*] Based on the challenge point framework by Guadagnoli and Lee [1], the optimal challenge point may need to be shifted toward lower levels of functional task difficulty in order to promote higher self-efficacy levels

persistence, adherence to therapy, and resilience when confronted with failure [47, 48]. Studies of self-efficacy with populations of stroke and spinal cord injury patients have shown strong relations to measures of quality of life and well-being [49–51]. In another study, focused on self-efficacy as it relates to balance and falling, self-efficacy was found to be a strong predictor of ADL performance 10 months poststroke [52]. As a result of these findings, researchers have recommended the development of rehabilitation programs that, in addition to the development of patients' motor capacities, also take into account their level of self-efficacy [47, 49, 53].

In the context of robotic rehabilitation and challenge, it is important to know that the main source of efficacy information about a given task is based on a person's experience of success in performing the task [54]. These beliefs are not based on the person's motor capacity but rather on his beliefs of what he can accomplish with that capacity [55]; this is of special importance when translating motor capacities from therapy to the real world. For example, a patient who may display the motor capacity to reach out for and grab a glass of water in a therapy setting may be limited by fear to perform this same task in unsupervised practice if her level of self-efficacy is low. However, if self-efficacy is increased during therapy, for example, by providing increased assistance from a robotic device to decrease the functional difficulty of the task, then it may increase patient's willingness to use their impaired limbs in their activities of daily living and in unsupervised practice. This idea is consistent with the existence of a threshold of hand and arm function that predicts long-term use of a patient's impaired arm in activities of daily life [56]. Specifically, patients with function above the threshold are more likely to use their impaired arm than those below the threshold. As a result, these patients used their impaired arm outside of training and showed increased recovery. This functional threshold highlights the importance of developing therapies that give patients not only the motor capacity but also the motivation, to use their impaired limbs throughout their daily lives and beyond the rehabilitation clinic alone.

One approach may be to use measures of self-efficacy as feedback to adjust the functional task difficulty during training. Expanding again on the challenge point framework, this may require adjustments of the optimal challenge point—as defined by performance in training and the potential learning benefit—to account for patients' self-efficacy. These adjustments may come at the expense of lower potential learning benefits per unit of practice (as shown in Fig. 3.6) but with the benefit of increasing self-efficacy, motivation, and ultimately patient's willingness to engage in supervised and unsupervised practice, thereby ultimately resulting in greater amounts of learning.

3.4 Expanding Options for Patient Challenge with Rehabilitation Robotics: The KineAssist™-Mobility eXtreme as a Case Study

Robotic rehabilitation systems continue to evolve to be more capable of providing optimal challenge. In this section, we provide a detailed case study of a new rehabilitation robotic system, the KineAssist Mobility eXtreme, which works collaboratively with the patient and provides an extensive library of features for providing physical challenge during walking and balance training in people with poststroke hemiparesis.

Collaboration is an emerging emphasis in robotics that refers to devices that sense human movement and take direction from this movement. In rehabilitation robotics, the term is used to describe mechanized systems that sense the intent of the user and work with the user to accomplish some movement goal. This type of system can be a useful tool for clinicians who are working with clients who are at risk for harm during challenging movements and/or who will likely experience frustration if presented with tasks that are too difficult to achieve. In addition, since the "intent to move" feature of these robots require the person to desire movement, the person is able to develop their autonomy and independence during the rehabilitation process.

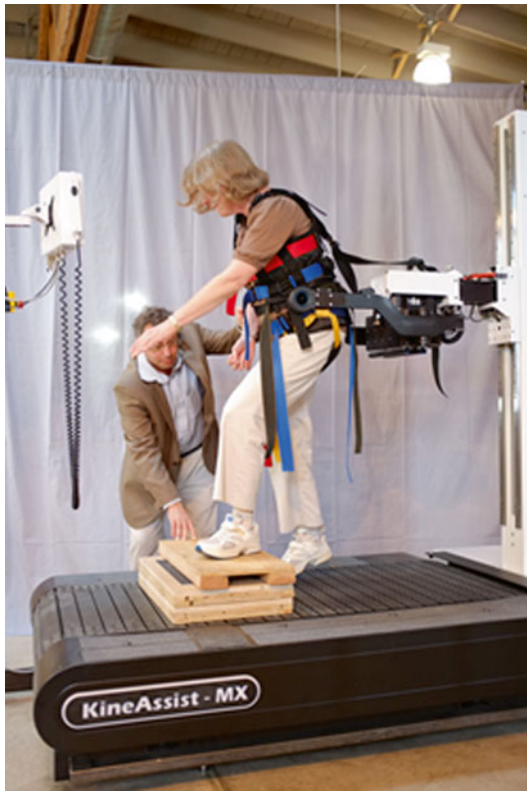

Fig. 3.7 Example of robotic device (KineAssist MX, HDT Robotics) that was used to enable to stroke survivors to practice highly challenging balance and walking tasks while also providing safety and stability against falls. (Photo courtesy of HDT Robotics)

The KineAssist™-Mobility eXtreme (MX) is an example of a collaborative device that senses intentional forces at a specialized pelvis interface and drives a treadmill surface to move in the user's intended direction and at an intended speed. The device is used by clinicians to challenge individuals, recovering from mobility disorders, to recover from perturbations, and to improve dynamic balance function during treadmill training that is performed within a locomotor control context (Fig. 3.7). This device addresses the fact that standard Body-weight supported treadmill or BWSTT exercise fails to incorporate progressive resistive gait training, high speed training, perturbation recovery training, and functional balance task training. Also, it is innovative because it enables fully expressed stumbling corrective responses, and it will drive the treadmill belt at speeds that are appropriate for each given specific dynamic task (solid, slippery, and foam surface stepping, front and backward perturbations, step length and step height hurdles, isotonic and isokinetic resistance walking). The implementation of these types of exercises during body -weight supported treadmill training represents a further progression in providing different forms and amounts of robotic challenge in rehabilitation practice that we expect to help generate advancements in the science of balance and walking control in neurologically impaired individuals.

3.4.1 Introducing Challenge During Balance and Walking Training Poststroke

Robotics allows for an exploration of a wide variety of challenging motor learning environments in a safe manner. With respect to poststroke recovery of balance and walking, the major issues to overcome are slow walking speeds and increased risk for falls that people experience when trying to regain function during the rehabilitation process. With slow movement and high fall risk, low propulsive ground reaction forces are generated, balance and stepping reactions are delayed, appropriate target levels of heart rate cannot be reached or sustained, and environmental distractions arrest movement. With the benefit of collaborative robotics, we have focused on developing methods for providing the highest level of challenge to three key areas of balance and walking recovery in stroke survivors—force generation, speed generation, and dynamic balance.

To introduce challenge in each of these three areas, certain key ideas were explored. First, the challenge should involve a motor task with some ecological validity. That is, the task should be meaningful to the person and represent some real-world problem that a person will encounter. Second, the challenge should be gradable, from very low levels of task difficulty to very high levels of task difficulty, so that the level of challenge that is introduced can be scaled up or down depending on the client's abilities. Finally, the

intervention challenge should be preceded by an assessment of each individual's highest capacity to perform the particular movement task so that the appropriate level of challenge can be introduced during the training session. This last requirement allows individuals with very different capacities (e.g., age, neurologic deficit, premorbid status, etc.) to be trained at a level that is appropriate for their particular situation.

Force challenge: *Individuals poststroke generate reduced muscle power during walking*. Impairment in muscle strength is an important limiting factor in determining walking speed after stroke. There is a positive correlation between muscle strength and maximum gait speed [57–62]. Specific muscle groups that demonstrate the strongest relationship with walking speed vary greatly among studies, depending on the number of muscles investigated, the parameter used to quantify strength, and the method of documenting gait speed [57–62].

To assess the highest level of force capability, individuals are tested, while walking against various levels of resistance provided to the pelvis by the robotic interface. During the force challenge (FG) walking mode, participants walk on a treadmill belt while attached to the same KineAssist MX. The horizontal forces exerted by the participant, against the pelvic harness, are used by the KineAssist MX to specify the speed of the treadmill belt. In this mode the participant is asked to walk at a comfortable speed while the amount of force required to generate that particular treadmill belt speed is progressively increased. As the participant encounters higher and higher resistive forces, their walking speed begins to slow until they can barely move the treadmill belt with their attempted horizontal force output. We then calculate a theoretical maximum walking force measure that represents the highest amount of force that a person can generate in the forward, propulsive direction during walking. Figure 3.8 demonstrates the results of two participants, one person with no neurological impairment and another person with poststroke hemiplegia. The individual poststroke shows an extrapolated maximum horizontal force value of 120.8 N while the non-impaired person shows a value of 307.6 N. We are now confirming these results in a larger number of individuals poststroke and relating the measured parameters to walking speed and mobility participation scores.

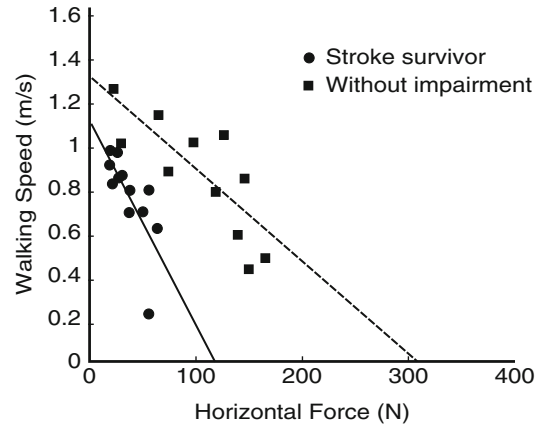

Fig. 3.8 Data comparing two subjects (one without impairment and one individual poststroke) as they walk on the KineAssist MX during progressively higher levels of resistance. As resistance increased, people slowed down until a resistance level was too high to overcome and the velocity nears zero m/s. The stroke survivor reached the zero velocity value at a much lower level of force

Once the maximal propulsive force capability during walking is determined, the individual can engage in a progressive resistive exercise (PRE) regimen where a percent of maximum is applied for a predetermined number of steps. This PRE approach is very common in the strength training literature and enables an exerciser to constantly progress and increase the level of effort that they apply as they get stronger and more able to generate propulsive force during walking.

Speed challenge: *Individuals with poststroke hemiplegia move slowly*. After stroke, most patients walk at speeds that range from approximately 0.2 to 0.8 m/s [63–66] when asked to walk at a comfortable pace; these velocities are significantly lower than age-matched individuals (1.3–1.4 m/s) [64, 65, 67]. Also, when stroke survivors were encouraged to walk at their self-selected maximum walking speed, they achieved walking speeds from 0.3 m/s to 1.3 m/s [63, 65, 66, 68]. This suggests that this population has limited capability to adapt comfortable gait in order to increase walking speed to reach higher functional levels.

To assess the highest level of speed capability, the robotic interface can provide assistive

horizontal forces to the pelvis interface so that a person can be "pushed" to walk at faster speeds without the added requirement of needing to generate propulsive forces. Since the robotic system is providing the horizontal propulsive forces, the individual is challenged to move the legs in successive steps at the fastest speeds possible until a speed is found where the person fails to keep up with the treadmill belt, and the device safely catches the person and prevents a fall from occurring. With this method, the clinician can find the fastest speed that a person is capable of achieving while walking.

We compared the "push" mode to the overhead harness treadmill mode in a recent published study [69]. Stroke survivors were able to walk at self-selected comfortable speeds (SSCWS) overground of 0.67 ± 0.04 m/s. Stroke survivors reached significantly faster speeds in the push mode (1.92 ± 0.06 m/s; $p < 0.05$) than on the treadmill (1.67 ± 0.11 m/s; $p < 0.05$), and both were faster than overground (1.19 ± 0.09 m/s; $p < 0.05$), as seen in Fig. 3.9, and show the speed, average step length, and average cadence achieved by participants during the greatest maximum walking speed.

Once the fastest possible speed of walking is obtained, the clinician can then apply sprint training methods to expose the person to brief bouts of high speed sprinting, followed by adequate recovery walking at much slower speeds.

Dynamic balance challenge: *Individuals with poststroke hemiplegia are at high risk for falls due to poor balance and inability to tolerate environmental challenges*. We have selected specific environmental hazards by turning to the current literature related to why people fall in the home or nonclinical environment. Research has identified specific risk factors for falls in people with stroke [70]. Fallers have shown poorer balance [70], lower physical function measures than non-fallers [70], greater standing sway [71], impulsivity [72], and slowed response times [73], in addition to greater postural sway and reduced force generation when standing up and sitting down [74]. Forster and Young [75] found that fallers were more depressed and less socially active that non-fallers. They found that most falls occurred in patients' homes while walking or during transfers. Individuals reported loss of balance, getting their foot stuck, and difficulty performing transfers as reasons why they fell. Hyndman et al. [76] found that repeat fallers had significantly reduced arm function and ADL ability compared with those who did not fall, and the measure of mobility showed a trend for repeat fallers to have greater mobility deficits than non-fallers, although the difference was not significant. However, fallers had a significantly higher depression score.

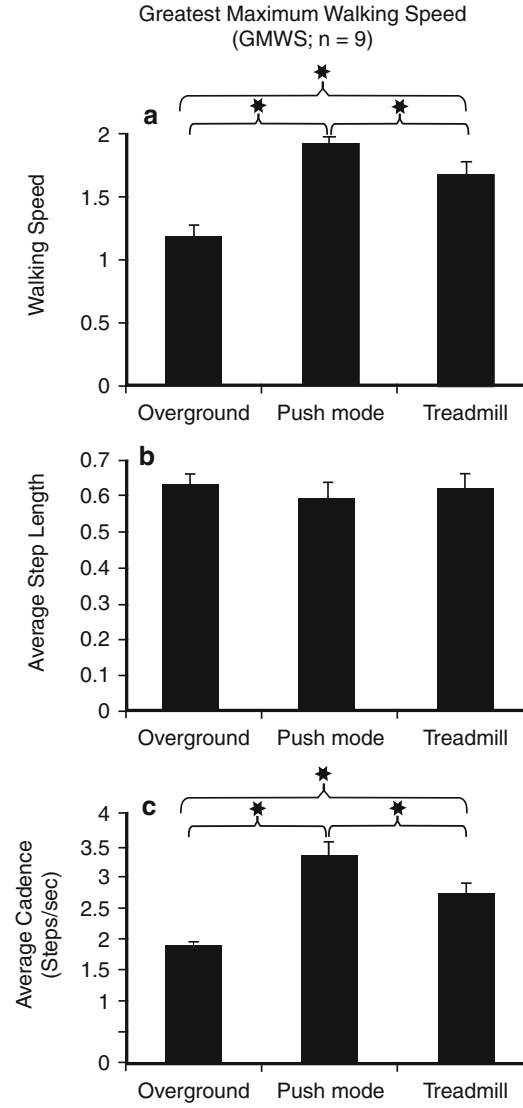

Fig. 3.9 *Bar graphs* illustrating the average top walking speeds that can be obtained by individuals poststroke while in the "push mode" of the KineAssist MX. The second and third *bar graphs* show the average step length and cadence associated with these top speeds

To assess the highest level of dynamic balance capability, we developed nine different dynamic balance tasks that are related to real-world balance activities. These nine tasks are (1) responding to a forward push, (2) responding to a backward push, stepping up onto a step, (3) stepping up onto a compliant surface, (4) stepping onto a slippery surface, (5) reaching forward as far as possible, (6) stepping forward as far as possible, (7) standing up out of a chair, (8) and stepping over a hurdle. Each task is gradable so that there is a very low level to a very high level of challenge. For example, with the stepping onto step task, the height of the step can be made progressively challenging by successively adding one of each platform to the height of the step until a height is reached where the person is no longer able to step up successfully. With each of the nine tasks, we can determine the highest level of performance for the individual.

We determined the concurrent and construct validity of a new balance measure, the KineAssist 9 Task Balance Test (K-9), by comparison to a gold standard, the Berg Balance Scale (BBS). The K-9 represented 9 dynamic balance tasks, such as stepping on to a high step, stepping over a hurdle, forward reaching, and responding to forward and backward pushes, that were tested at a range of levels of difficulty until we determined the highest level where the participant was able to succeed at the task. There was a statistically significant correlation ($R^2=0.632$; $p<0.0004$) between the scores on the K-9 and the BBS in chronic stroke survivors but not with non-impaired subjects. The non-impaired subjects scored significantly higher that the chronic stroke survivors on the K-9 ($p<0.0001$; $t=-6.341$). The K-9 was able to discriminate between subjects with balance impairments poststroke and non-impaired subjects. Thus, the K-9 is a valid measure of balance impairment in the clinic for community-dwelling stroke survivors but now must be tested using the new KineAssist MX.

Once the highest level of performance is reached, then the clinician can choose a level of challenge that will optimize the learning of the task. In our laboratory, we challenge the individual to attempt to succeed at levels which are just one grade above the highest level that they were able to perform during the testing. This approach has resulted in some very successful performances during training week after week (Fig. 3.10).

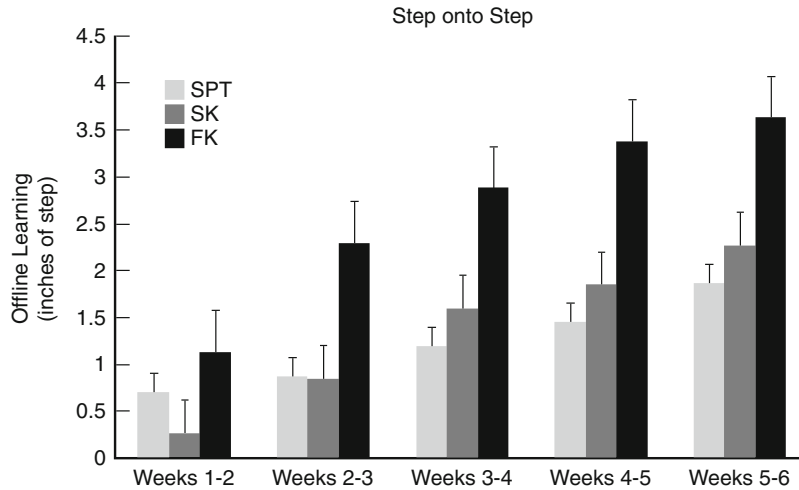

Fig. 3.10 This graph shows the results of a randomized controlled trial (Brown DA et al. 2014, unpublished) for week after week changes in task performance for stepping up onto a step of a specific height. *SPT* clinician-guarded training group ($n=12$), *SK* robot guarded, where the participant was trained on the highest height that they were capable of performing ($n=12$), and *FK* robot guarded, where the participant was asked to perform beyond their initial capability ($n=12$). All participants gained in performance week after week; however, the FK group showed the greatest gains over the 6-week period

Clinicians understand that many neurologic conditions leave an individual with limits to recovery, and adjunctive therapies such as pharmacologic agents and electrical stimulation may help a person to compensate for lost neurologic function. Perhaps the only way to truly recognize a person's limitations to recovery is to provide consistently high challenges to movement and then observe if the behavior can or cannot match the challenge requirements. Our experience seems to suggest that, if given enough time to attempt multiple strategies, stroke survivors have a more expanded capacity to meet higher expectations than might be presumed by considering only physiologic factors.

Conclusion

This chapter described important considerations for design and implementation of rehabilitation robotics in order to enable exercise and motor learning under optimal challenge conditions. In Table 3.1, we have summarized the aspects of challenge that were discussed in this chapter. Individuals engaged in developing new robotics may wish to use this table as a guide for determining the extent to which their system allows for adequate provision of challenge during training. We suggest that there is still much work to be done to design and implement safe and effective robotic tools for allowing optimal motor recovery during the rehabilitation process and forward as the person continues to move toward to the goal of high quality of life. Clearly, more research into the science of motor learning and the ideal conditions for a person to reacquire lost motor skills is needed. New developments in rehabilitation robotics might be best informed by asking questions about how the interface between the person and the machine will facilitate optimal motor learning and exercise training parameters. Elegant mechanical robotic systems that under-challenge, or even ignore, the physical involvement of the user run the risk of facilitating passivity and an expectation for movement assistance, even when the person has great potential to recover function. Rather, the flexibility of robotic systems can be used as a tool to grade challenge. Our challenge to the rehabilitation robotics community is to begin the development of any new project by asking the question, how can a new robot optimize motor learning and exercise effectiveness?

Table 3.1 Summary of factors related to challenge discussed in this chapter

Challenge factor	Robotic application
Random vs blocked practice	Manipulating presentation sequence of task difficulty level
Guidance restriction	Allowing varying degrees of freedom; removing restrictions
Success vs failure	Degree to which failure is allowed to occur
Mechanical assistance	Degree to which the device intervenes to allow completion of movement
Adaptability	Ability to increase/decrease parameters based on performance metrics
Motivation/ self-efficacy	Provision of feedback that facilitates interest and desire to achieve task
Movement validity	Movement reflects true representation of a desired activity of daily living
Biomechanical requirements	Manipulation of key kinematics and kinetic task parameters
Assessment	Identifying an individual's highest performance capacity

References

1. Guadagnoli MA, Lee TD. Challenge point: a framework for conceptualizing the effects of various practice conditions in motor learning. J Mot Behav. 2004;36:212–24.
2. Bjork R. Assessing our own competence: heuristics and illusions. Cambridge: The MIT Press; 1999.
3. Kelley CR. What is adaptive training? Hum Factors J Hum Factors Ergon Soc. 1969;11:547–56.
4. Lintern G, Gopher D. Adaptive training of perceptual-motor skills: issues, results, and future directions. Int J Man Mach Stud. 1978;10:521–51.
5. Williges BH, Williges RC. Learner-centered versus automatic adaptive motor skill training. J Mot Behav. 1977;9:325–31.
6. Lee TD, Schmidt RA. PaR (Plan-act-Review) golf: motor learning research and improving golf skills. Int J Golf Sci. 2014;3:2–25.

7. Griffiths JS. Optimal challenge point training for the post-stroke arm and hand: a randomized controlled pilot trial. Unpublished Master's thesis, Faculty of Health Science, McMaster University, Hamilton, ON, Canada, 2009.
8. Pollock CL, Boyd LA, Hunt MA, Garland SJ. Use of the challenge point framework to guide motor learning of stepping reactions for improved balance control in people with stroke: a case series. Phys Ther. 2014; 94:562–70.
9. Van der Loos M, Reinkensmeyer D. Health care and rehabilitation robotics. In: Siciliano B, Khatib O, editors. Springer handbook of robotics. Berlin Heidelberg. Springer; 2008. p. 1223–51.
10. Aisen ML, Krebs HI, Hogan N, McDowell F, Volpe B. The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. Arch Neurol. 1997;54:443–6.
11. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002;83:952–9.
12. Kahn LE, Zygman ML, Rymer WZ, Reinkensmeyer DJ. Robot-assisted reaching exercise promotes arm movement recovery in chronic hemiparetic stroke: a randomized controlled pilot study. J Neuroeng Rehabil. 2006;3:12.
13. Dietz V, Colombo G, Jensen L, Baumgartner L. Locomotor capacity of spinal cord in paraplegic patients. Ann Neurol. 1995;37:574–82.
14. Uhlenbrock D, Sarkodie-Gyan T, Reiter F, Konrad M, Hesse S. Development of a servo-controlled gait trainer for the rehabilitation of non-ambulatory patients. Biomed Tech. 1997;42:196–202.
15. Reinkensmeyer DJ, Housman SJ. If I can't do it once, why do it a hundred times?: connecting volition to movement success in a virtual environment motivates people to exercise the arm after stroke. Proc Virtual Rehabil Conf. 2007:44–8.
16. Rowe JB. Benefits of robotic assistance for retraining finger movement ability after chronic stroke. Irvine: University of California; 2015.
17. Ryan R. Control and information in the intrapersonal sphere: an extension of cognitive evaluation theory. J Pers Soc Psychol. 1982;43:450–61.
18. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39:1786–92.
19. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, Hornby TG. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23:5–13.
20. Wolbrecht ET, Chan V, Reinkensmeyer DJ, Bobrow JE. Optimizing compliant, model-based robotic assistance to promote neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2008;16:286–97.
21. Reinkensmeyer DJ, Akoner OM, Ferris DP, Gordon KE. Slacking by the human motor system: computational models and implications for robotic orthoses. Proc 2009 IEEE Eng Med Biol Conf. 2009:2129–32.
22. Emken JL, Benitez R, Sideris A, Bobrow JE, Reinkensmeyer DJ. Motor adaptation as a greedy optimization of error and effort. J Neurophysiol. 2007;97:3997–4006.
23. Israel JF, Campbell DD, Kahn JH, Hornby TG. Metabolic costs and muscle activity patterns during robotic- and therapist-assisted treadmill walking in individuals with incomplete spinal cord injury. Phys Ther. 2006;86:1466–78.
24. Hu XL, Tong K-YY, Song R, Zheng XJ, Leung WWF. A comparison between electromyography-driven robot and passive motion device on wrist rehabilitation for chronic stroke. Neurorehabil Neural Repair. 2009;23:837–46.
25. Patton JL, Stoykov ME, Kovic M, Mussa-Ivaldi FA. Evaluation of robotic training forces that either enhance or reduce error in chronic hemiparetic stroke survivors. Exp Brain Res. 2006;168:368–83.
26. Emken JL, Reinkensmeyer DJ. Robot-enhanced motor learning: accelerating internal model formation during locomotion by transient dynamic amplification. IEEE Trans Neural Syst Rehabil Eng. 2005;13:33–9.
27. Abdollahi F, Case Lazarro ED, Listenberger M, Kenyon RV, Kovic M, Bogey RA, Hedeker D, Jovanovic BD, Patton JL. Error augmentation enhancing arm recovery in individuals with chronic stroke: a randomized crossover design. Neurorehabil Neural Repair. 2014;28:120–8.
28. Duarte JE, Reinkensmeyer DJ. Effects of robotically modulating kinematic variability on motor skill learning and motivation. J Neurophysiol. 2015;113:2682–91.
29. Milot M-H, Marchal-Crespo L, Green CS, Cramer SC, Reinkensmeyer DJ. Comparison of error-amplification and haptic-guidance training techniques for learning of a timing-based motor task by healthy individuals. Exp Brain Res. 2010;201:119–31.
30. Marchal-Crespo L, van Raai M, Rauter G, Wolf P, Riener R. The effect of haptic guidance and visual feedback on learning a complex tennis task. Exp Brain Res. 2013;231:277–91.
31. Marchal-Crespo L, Schneider J, Jaeger L, Riener R. Learning a locomotor task: with or without errors? J Neuroeng Rehabil. 2014;11:25.
32. Marchal-Crespo L, López-Olóriz J, Jaeger L, Riener R. Optimizing learning of a locomotor task: amplifying errors as needed. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2014;2014:5304–7.
33. Marchal-Crespo L, Reinkensmeyer DJ. Review of control strategies for robotic movement training after neurologic injury. J Neural Eng Rehabil. 2008;6:20.
34. Taheri H, Rowe JB, Gardner D, Chan V, Gray K, Bower C, Reinkensmeyer DJ, Wolbrecht ET. Design and preliminary evaluation of the FINGER rehabilitation robot: controlling challenge and quantifying finger individuation during musical computer game play. J Neuroeng Rehabil. 2014;11:10.

35. Spencer SJ. Movement training and post-stroke rehabilitation using a six degree of freedom upper-extremity robotic orthosis and virtual environment. Irvine: University of California; 2011.
36. Choi Y, Gordon J, Park H, Schweighofer N. Feasibility of the adaptive and automatic presentation of tasks (ADAPT) system for rehabilitation of upper extremity function post-stroke. J Neuroeng Rehabil. 2011;8:42.
37. Caurin GAP, Siqueira AAG, Andrade KO, Joaquim RC, Krebs HI. Adaptive strategy for multi-user robotic rehabilitation games. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2011;2011:1395–8.
38. Metzger J-C, Lambercy O, Califfi A, Dinacci D, Petrillo C, Rossi P, Conti FM, Gassert R. Assessment-driven selection and adaptation of exercise difficulty in robot-assisted therapy: a pilot study with a hand rehabilitation robot. J Neuroeng Rehabil. 2014;11:154.
39. Zimmerli L, Krewer C, Gassert R, Müller F, Riener R, Lünenburger L. Validation of a mechanism to balance exercise difficulty in robot-assisted upper-extremity rehabilitation after stroke. J Neuroeng Rehabil. 2012; 9:6.
40. Lohse KR, Lang CE, Boyd LA. Is more better? Using metadata to explore dose-response relationships in stroke rehabilitation. Stroke. 2014;45:2053–8.
41. Duarte JE. Effects of robotic challenge level on motor learning, rehabilitation, and motivation: the real-world challenge point framework. Irvine: University of California; 2014.
42. Inkpen P, Parker K, Kirby RL. Manual wheelchair skills capacity versus performance. Arch Phys Med Rehabil. 2012;93:1009–13.
43. Bailey RR, Klaesner JW, Lang CE. Quantifying real-world upper-limb activity in nondisabled adults and adults with chronic stroke. Neurorehabil Neural Repair. 2015.
44. Bandura A. Self-efficacy: the exercise of control. New York: US. Times Books; 1997.
45. Chiviacowsky S, Wulf G, Lewthwaite R. Self-controlled learning: the importance of protecting perceptions of competence. Front Psychol. 2012;3:458.
46. Chiviacowsky S. Self-controlled practice: autonomy protects perceptions of competence and enhances motor learning. Psychol Sport Exerc. 2014;15:505–10.
47. O'Leary A. Self-efficacy and health. Behav Res Ther. 1985;23:437–51.
48. McAuley E, Lox C, Duncan TE. Long-term maintenance of exercise, self-efficacy, and physiological change in older adults. J Gerontol. 1993;48:218–24.
49. Robinson-Smith G, Johnston MV, Allen J. Self-care self-efficacy, quality of life, and depression after stroke. Arch Phys Med Rehabil. 2000;81:460–4.
50. Hampton NZ. Subjective well-being among people with spinal cord injuries: the role of self-efficacy, perceived social support, and perceived health. Rehabil Couns Bull. 2004;48:31–7.
51. Middleton J, Tran Y, Craig A. Relationship between quality of life and self-efficacy in persons with spinal cord injuries. Arch Phys Med Rehabil. 2007;88:1643–8.
52. Hellström K, Lindmark B, Wahlberg B, Fugl-Meyer AR. Self-efficacy in relation to impairments and activities of daily living disability in elderly patients with stroke: a prospective investigation. J Rehabil Med. 2003;35:202–7.
53. Kwakkel G, Kollen BJ, Wagenaar RC. Long term effects of intensity of upper and lower limb training after stroke: a randomised trial. J Neurol Neurosurg Psychiatry. 2002;72:473–9.
54. Bandura A. Self-efficacy mechanism in human agency. Am Psychol Am Psychol Assoc. 1982;37: 122.
55. Feltz DL, Lirgg CD. Self-efficacy beliefs of athletes, teams, and coaches. Handb Sport Psychol. 2001;2: 340–61.
56. Schweighofer N, Han CE, Wolf SL, Arbib MA, Winstein CJ. A functional threshold for long-term use of hand and arm function can be determined: predictions from a computational model and supporting data from the Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial. Phys Ther. 2009;89:1327–36.
57. Bohannon RW. Strength deficits also predict gait performance in patients with stroke. Percept Mot Skills. 1991;73:146.
58. Bohannon RW, Hull D, Palmeri D. Muscle strength impairments and gait performance deficits in kidney transplantation candidates. Am J Kidney Dis. 1994; 24:480–5.
59. Kim CM, Eng JJ. The relationship of lower-extremity muscle torque to locomotor performance in people with stroke. Phys Ther. 2003;83:49–57.
60. Milot M-H, Nadeau S, Gravel D, Bourbonnais D. Effect of increases in plantar flexor and hip flexor muscle strength on the levels of effort during gait in individuals with hemiparesis. Clin Biomech (Bristol, Avon). 2008;23:415–23.
61. Nadeau S, Gravel D, Arsenault AB, Bourbonnais D. A mechanical model to study the relationship between gait speed and muscular strength. IEEE Trans Rehabil Eng. 1996;4:386–94.
62. Richards CL, Malouin F, Wood-Dauphinee S, Williams JI, Bouchard JP, Brunet D. Task-specific physical therapy for optimization of gait recovery in acute stroke patients. Arch Phys Med Rehabil. 1993;74:612–20.
63. Bohannon RW. Walking after stroke: comfortable versus maximum safe speed. Int J Rehabil Res. 1992; 15:246–8.
64. Jonkers I, Delp S, Patten C. Capacity to increase walking speed is limited by impaired hip and ankle power generation in lower functioning persons post-stroke. Gait Posture. 2009;29:129–37.
65. Jonsdottir J, Recalcati M, Rabuffetti M, Casiraghi A, Boccardi S, Ferrarin M. Functional resources to increase gait speed in people with stroke: strategies adopted compared to healthy controls. Gait Posture. 2009;29:355–9.
66. Turnbull GI, Charteris J, Wall JC. A comparison of the range of walking speeds between normal and hemiplegic subjects. Scand J Rehabil Med. 1995;27:175–82.

67. Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. Age Ageing. 1997;26:15–9.
68. Kollen B, Kwakkel G, Lindeman E. Hemiplegic gait after stroke: is measurement of maximum speed required? Arch Phys Med Rehabil. 2006;87: 358–63.
69. Capó-Lugo CE, Mullens CH, Brown DA. Maximum walking speeds obtained using treadmill and overground robot system in persons with post-stroke hemiplegia. J Neuroeng Rehabil. 2012;9:80.
70. Mackintosh SF, Hill KD, Dodd KJ, Goldie PA, Culham EG. Balance score and a history of falls in hospital predict recurrent falls in the 6 months following stroke rehabilitation. Arch Phys Med Rehabil. 2006;87:1583–9.
71. Sackley CM. Falls, sway, and symmetry of weight-bearing after stroke. Int Disabil Stud. 1991;13: 1–4.
72. Rapport LJ, Webster JS, Flemming KL, Lindberg JW, Godlewski MC, Brees JE, Abadee PS. Predictors of falls among right-hemisphere stroke patients in the rehabilitation setting. Arch Phys Med Rehabil. 1993;74:621–6.
73. Mayo NE, Korner-Bitensky N, Kaizer F. Relationship between response time and falls among stroke patients undergoing physical rehabilitation. Int J Rehabil Res. 1990;13:47–55.
74. Cheng PT, Liaw MY, Wong MK, Tang FT, Lee MY, Lin PS. The sit-to-stand movement in stroke patients and its correlation with falling. Arch Phys Med Rehabil. 1998;79:1043–6.
75. Forster A, Young J. Incidence and consequences of falls due to stroke: a systematic inquiry. BMJ. 1995;311:83–6.
76. Hyndman D, Ashburn A, Stack E. Fall events among people with stroke living in the community: circumstances of falls and characteristics of fallers. Arch Phys Med Rehabil. 2002;83:165–70.

Multisystem Neurorehabilitation in Rodents with Spinal Cord Injury

4

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

G. Courtine, PhD (✉) • R. van den Brand, MSc
Department of Neurology,
Experimental Neurorehabilitation Laboratory,
August-Forel-Strasse 7, FOS B23,
Zurich, CH 8008, Switzerland
e-mail: gregoire.courtine@uzh.ch

R.R. Roy, BS, MS, PhD
Department of Integrative Biology and Physiology
and Brain Research Institute, University of California,
Terasaki Life Sciences Building,
610 Charles E. Young Drive, East, Los Angeles,
CA 90095-7239, USA

V.R. Edgerton, PhD
Departments of Integrative Biology and Physiology
and Neurobiology and Brain Research Institute,
University of California, Los Angeles,
Los Angeles, CA, USA

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mode, can strongly enhance the effect of locomotor rehabilitation. We suggest that all 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 toward 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

4.1 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. 4.1). 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.

4.2 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

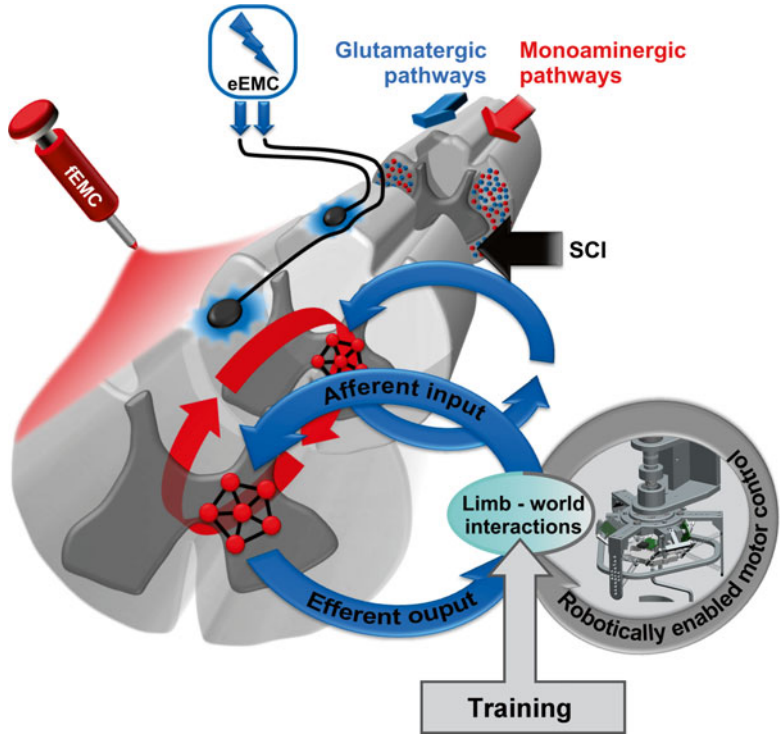

Fig. 4.1 Multisystem neurorehabilitation to restore motor functions after a severe SCI. Schematic drawings of locomotor circuits are shown after a SCI at the thoracic level that interrupts both glutamatergic (*blue*) and monoaminergic (*red*) descending pathways originating from various brainstem areas. 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 efEMC, 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

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 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 time frame 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.

4.3 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. 4.1).

4.3.1 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, three to four well-defined motor responses in lower limb muscles can be classified based on their respective latencies and threshold (Fig. 4.2). The early response (ER), which only 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. 4.2). 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. 4.2). We also surmise that EES recruits large-diameter cutaneous afferent fibers that contact multisensorial interneurons (Fig. 4.2), 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].

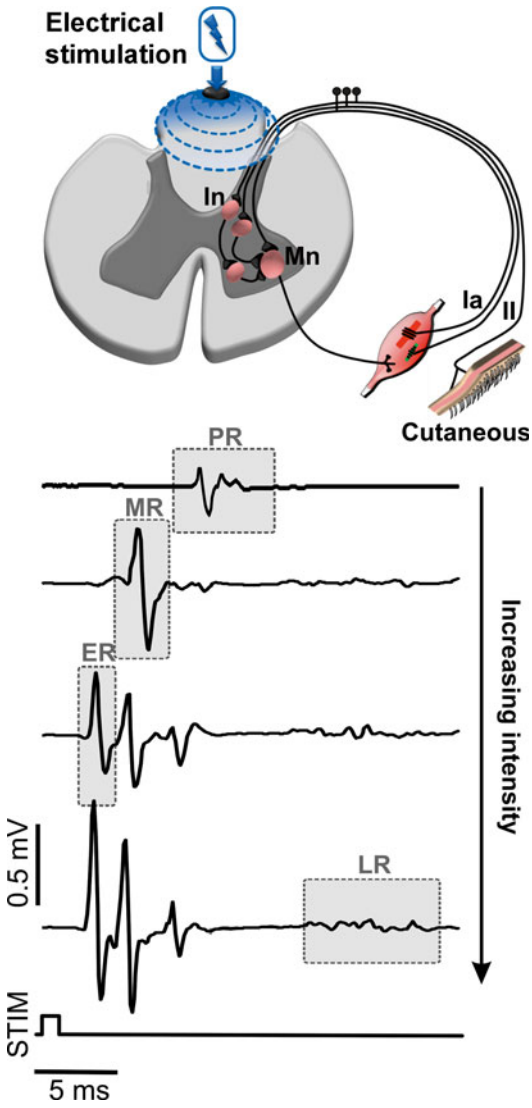

Fig. 4.2 EES elicits distinct motor responses through the recruitment of specific pathways. Schematic illustration of the afferent systems putatively recruited when delivering single-pulse EES over spinal segment S1. When applied over the dorsal aspect of the spinal cord, the electrical stimulus typically 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

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. 4.3) [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. 4.3). 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. 4.3). 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. 4.3) [25]. Both responses are markedly modulated in amplitude throughout the gait cycle according to the phase of the movement [25, 49, 51] (Fig. 4.3). 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 steplike 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

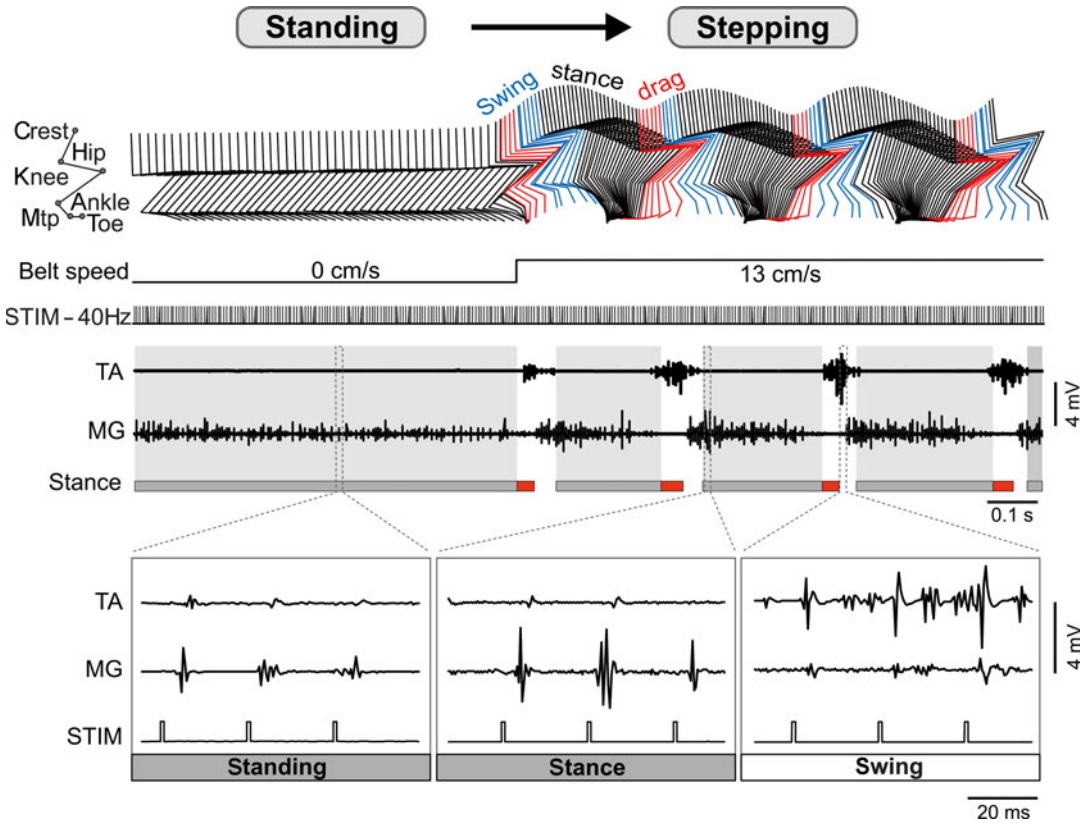

Fig. 4.3 Modulation of spinal circuits with EES during stepping in spinal rats. Hindlimb kinematics and EMG activity from tibialis anterior (*TA*) and medial gastrocnemius (*MG*) muscles are shown for a spinal rat receiving continuous (40 Hz) EES at the sacral (S1) level. During the represented sequence, 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

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. 4.4a) and stepping (Fig. 4.4b). Moreover, the combination of two [28], and even more efficiently three [41], sites of *eEMC* promoted 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. 4.1). In the complete absence of monoaminergic input, however, *eEMC* alone

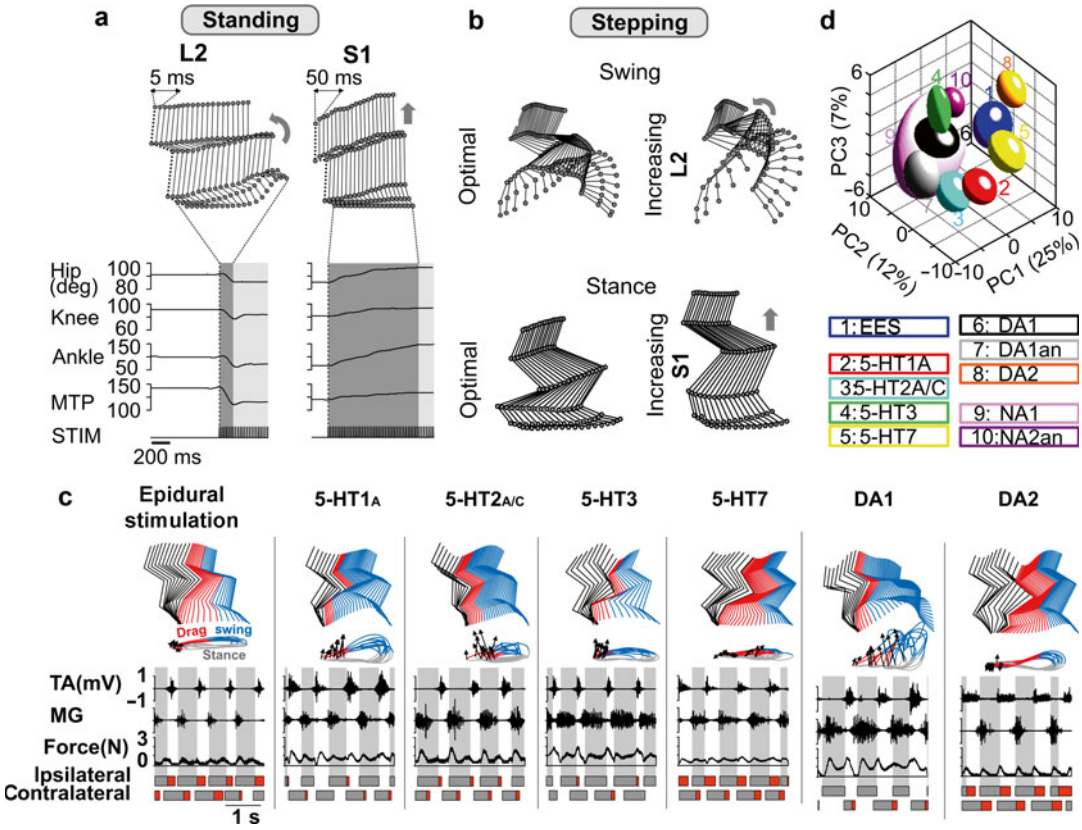

Fig. 4.4 Specific modulation of hindlimb movements mediated by EES and monoaminergic agonists during standing and stepping. (**a**) Stick diagram decomposition of hindlimb movements and associated time course of changes in hindlimb joint angles (increase toward extension) when delivering EES at L2 (*left*) 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]

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 steplike 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.

4.3.2 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. 4.4d). 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 toward flexion (Fig. 4.4c). 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. 4.4c), 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. 4.1).

4.3.3 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 midthoracic 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 identi-

fied 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. 4.1). 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].

4.3.4 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. 4.5a). 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. 4.5a). 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. 4.5b). 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

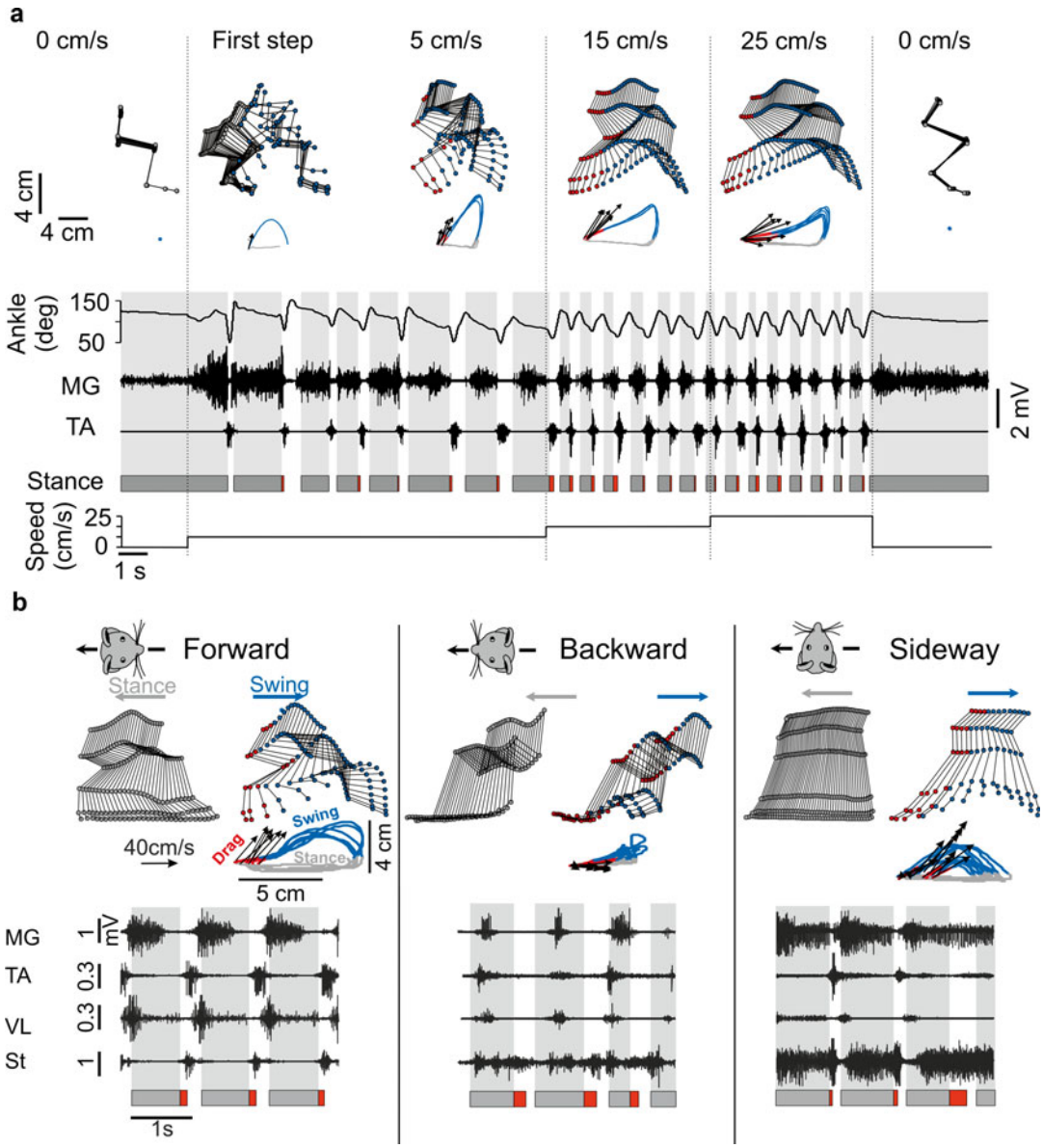

Fig. 4.5 Effects of velocity- and direction-sensitive afferent input on the characteristics of hindlimb movements in spinal rats. (**a**) Representative example of hindlimb kinematics and EMG activity recorded from a continuous sequence of steps during a gradual increase of treadmill belt speed including running velocities. Stick diagram decomposition of the first step shows the smooth transition from standing to stepping. Conventions are the same as in Fig. 4.3. (**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. 4.3, 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]

characteristics of the motor outputs [28] (Fig. 4.5b). 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 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. 4.5) 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 sensorimotor 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. 4.1).

4.4 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 toward 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. 4.6a, 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. 4.6b, 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 patterns when pharmacological and/or electrical interventions are administered. These results are compatible with the emergence of abnormal reflexes [78, 79],

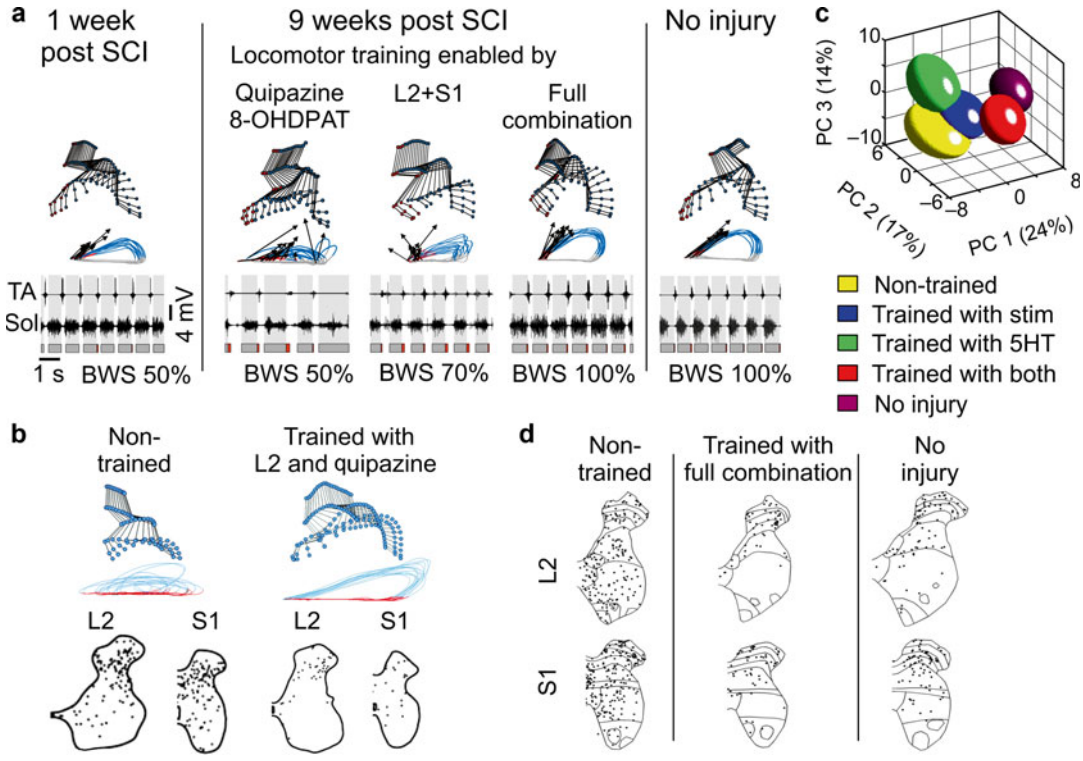

Fig. 4.6 Locomotor training enabled by selective pharmacological and/or electrical stimulation paradigms promotes the recovery of intervention-specific gait patterns in rats deprived of supraspinal input. (**a**) Representative illustrations of EMG and kinematic features during stepping under the full 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. 4.3. (**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]

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?

4.5 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. 4.6b). 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. 4.6b), this combination enabled more normal stepping patterns and effectively promoted locomotion as early as 1 week post-injury (Fig. 4.6a). 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. 4.6b, 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. 4.6a–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. 4.6b–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. 4.6c). 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.

4.6 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. 4.3.3).

4.7 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.

References

1. Sherrington C. Flexion-reflex of the limb, crossed extension reflex, and reflex stepping and standing. J Physiol (Lond). 1910;40:28–121.
2. Philippson M. L'autonomie et la centrilasation dans le système nerveux des animaux. Trav Lab Physiol Inst Solvay (Bruxelle). 1905;7:1–208.

3. Grillner S, Zangger P. The effect of dorsal root transection on the efferent motor pattern in the cat's hindlimb during locomotion. Acta Physiol Scand. 1984;120(3):393–405.
4. Burke RE. Sir Charles Sherrington's the integrative action of the nervous system: a centenary appreciation. Brain. 2007;130(Pt 4):887–94.
5. Lovely RG, Gregor RJ, Roy RR, Edgerton VR. Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. Exp Neurol. 1986; 92(2):421–35.
6. Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in the adult cat. Brain Res. 1987;412(1):84–95.
7. De Leon RD, Hodgson JA, Roy RR, Edgerton VR. Full weight-bearing hindlimb standing following stand training in the adult spinal cat. J Neurophysiol. 1998; 80(1):83–91.
8. de Leon RD, Tamaki H, Hodgson JA, Roy RR, Edgerton VR. Hindlimb locomotor and postural training modulates glycinergic inhibition in the spinal cord of the adult spinal cat. J Neurophysiol. 1999;82(1):359–69.
9. Tillakaratne NJ, de Leon RD, Hoang TX, Roy RR, Edgerton VR, Tobin AJ. Use-dependent modulation of inhibitory capacity in the feline lumbar spinal cord. J Neurosci. 2002;22(8):3130–43.
10. Hebb DO. The organization of behavior: a neuropsychological theory. New York: Wiley; 1949.
11. Cai LL, Courtine G, Fong AJ, Burdick JW, Roy RR, Edgerton VR. Plasticity of functional connectivity in the adult spinal cord. Philos Trans R Soc Lond B Biol Sci. 2006;361(1473):1635–46.
12. Edgerton VR, Courtine G, Gerasimenko YP, et al. Training locomotor networks. Brain Res Rev. 2008; 57(1):241–54.
13. Dietz V, Harkema SJ. Locomotor activity in spinal cord-injured persons. J Appl Physiol. 2004;96(5): 1954–60.
14. Harkema SJ, Schmid-Read M, Lorenz D, Edgerton VR, Behrman AL. Balance and ambulation improvements in individuals with chronic incomplete spinal cord injury using locomotor training-based rehabilitation. Arch Phys Med Rehab. 2012;93:1508–17.
15. Wernig A, Muller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia. 1992;30(4):229–38.
16. Barbeau H, Ladouceur M, Norman KE, Pepin A, Leroux A. Walking after spinal cord injury: evaluation, treatment, and functional recovery. Arch Phys Med Rehabil. 1999;80(2):225–35.
17. Behrman AL, Harkema SJ. Locomotor training after human spinal cord injury: a series of case studies. Phys Ther. 2000;80(7):688–700.
18. Dietz V, Colombo G, Jensen L. Locomotor activity in spinal man. Lancet. 1994;344(8932):1260–3.
19. Dobkin B, Barbeau H, Deforge D, et al. The evolution of walking-related outcomes over the first 12 weeks of rehabilitation for incomplete traumatic spinal cord injury: the multicenter randomized spinal cord injury locomotor trial. Neurorehabil Neural Repair. 2007; 21(1):25–35.
20. Dietz V. Body weight supported gait training: from laboratory to clinical setting. Brain Res Bull. 2009; 78(1):I–VI.
21. Harkema SJ. Plasticity of interneuronal networks of the functionally isolated human spinal cord. Brain Res Rev. 2008;57(1):255–64.
22. Mushahwar VK, Jacobs PL, Normann RA, Triolo RJ, Kleitman N. New functional electrical stimulation approaches to standing and walking. J Neural Eng. 2007;4(3):S181–97.
23. Mushahwar VK, Horch KW. Muscle recruitment through electrical stimulation of the lumbo-sacral spinal cord. IEEE Trans Rehabil Eng. 2000;8(1):22–9.
24. Barthelemy D, Leblond H, Rossignol S. Characteristics and mechanisms of locomotion induced by intraspinal microstimulation and dorsal root stimulation in spinal cats. J Neurophysiol. 2007;97(3):1986–2000.
25. Lavrov I, Dy CJ, Fong AJ, et al. Epidural stimulation induced modulation of spinal locomotor networks in adult spinal rats. J Neurosci. 2008;28(23):6022–9.
26. Musienko PE, Zelenin PV, Orlovsky GN, Deliagina TG. Facilitation of postural limb reflexes with epidural stimulation in spinal rabbits. J Neurophysiol. 2010;103(2):1080–92.
27. Musienko PE, Bogacheva IN, Gerasimenko IP. Significance of peripheral feedback in stepping movement generation under epidural spinal cord stimulation. Ross Fiziol Zh Im I M Sechenova. 2005; 91(12):1407–20.
28. Courtine G, Gerasimenko Y, van den Brand R, et al. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. Nat Neurosci. 2009;12(10):1333–42.
29. Gerasimenko YP, Ichiyama RM, Lavrov IA, et al. Epidural spinal cord stimulation plus quipazine administration enable stepping in complete spinal adult rats. J Neurophysiol. 2007;98(5):2525–36.
30. Landry ES, Lapointe NP, Rouillard C, Levesque D, Hedlund PB, Guertin PA. Contribution of spinal 5-HT1A and 5-HT7 receptors to locomotor-like movement induced by 8-OH-DPAT in spinal cord-transected mice. Eur J Neurosci. 2006;24(2):535–46.
31. Lapointe NP, Guertin PA. Synergistic effects of D1/5 and 5-HT1A/7 receptor agonists on locomotor movement induction in complete spinal cord-transected mice. J Neurophysiol. 2008;100(1):160–8.
32. Rossignol S, Giroux N, Chau C, Marcoux J, Brustein E, Reader TA. Pharmacological aids to locomotor training after spinal injury in the cat. J Physiol. 2001;533(Pt 1):65–74.
33. Cai LL, Fong AJ, Otoshi CK, et al. Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. J Neurosci. 2006;26(41):10564–8.
34. Fong AJ, Cai LL, Otoshi CK, et al. Spinal cord-transected mice learn to step in response to quipazine treatment and robotic training. J Neurosci. 2005; 25(50):11738–47.
35. Kazennikov OV, Shik ML, Iakovleva GV. Stepping movements caused by stimulation of the cat spinal

cord dorsolateral funiculus. Biull Eksp Biol Med. 1983;96(8):8–10.
36. Prochazka A, Mushahwar V, Yakovenko S. Activation and coordination of spinal motoneuron pools after spinal cord injury. Prog Brain Res. 2002;137:109–24.
37. Mushahwar VK, Collins DF, Prochazka A. Spinal cord microstimulation generates functional limb movements in chronically implanted cats. Exp Neurol. 2000;163(2):422–9.
38. Barthelemy D, Leblond H, Provencher J, Rossignol S. Nonlocomotor and locomotor hindlimb responses evoked by electrical microstimulation of the lumbar cord in spinalized cats. J Neurophysiol. 2006;96(6):3273–92.
39. Iwahara T, Atsuta Y, Garcia-Rill E, Skinner RD. Spinal cord stimulation-induced locomotion in the adult cat. Brain Res Bull. 1992;28(1):99–105.
40. Ichiyama RM, Gerasimenko YP, Zhong H, Roy RR, Edgerton VR. Hindlimb stepping movements in complete spinal rats induced by epidural spinal cord stimulation. Neurosci Lett. 2005;383(3):339–44.
41. Musienko P, van den Brand R, Maerzendorfer O, Larmagnac A, Courtine G. Combinatory electrical and pharmacological neuroprosthetic interfaces to regain motor function after spinal cord injury. IEEE Trans Biomed Eng. 2009;56(11 Pt 2):2707–11.
42. Musienko PE, Bogacheva IN, Gerasimenko YP. Significance of peripheral feedback in the generation of stepping movements during epidural stimulation of the spinal cord. Neurosci Behav Physiol. 2007;37(2): 181–90.
43. Minassian K, Jilge B, Rattay F, et al. Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials. Spinal Cord. 2004;42(7):401–16.
44. Harkema SJ, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y, Ferreira C, Willhite A, Rejc E, Grossman RG, Edgerton VR. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet. 2011; 377(9781):1938–47.
45. Bamford JA, Todd KG, Mushahwar VK. The effects of intraspinal microstimulation on spinal cord tissue in the rat. Biomaterials. 2010;31(21):5552–63.
46. Rattay F, Minassian K, Dimitrijevic MR. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 2. quantitative analysis by computer modeling. Spinal Cord. 2000;38(8): 473–89.
47. Kilgore KL, Hoyen HA, Bryden AM, Hart RL, Keith MW, Peckham PH. An implanted upper-extremity neuroprosthesis using myoelectric control. J Hand Surg Am. 2008;33(4):539–50.
48. Gerasimenko Y, Roy RR, Edgerton VR. Epidural stimulation: comparison of the spinal circuits that generate and control locomotion in rats, cats and humans. Exp Neurol. 2008;209(2):417–25.
49. Gerasimenko YP, Lavrov IA, Courtine G, et al. Spinal cord reflexes induced by epidural spinal cord stimulation in normal awake rats. J Neurosci Methods. 2006;157(2):253–63.
50. Holsheimer J. Computer modelling of spinal cord stimulation and its contribution to therapeutic efficacy. Spinal Cord. 1998;36(8):531–40.
51. Courtine G, Harkema SJ, Dy CJ, Gerasimenko YP, Dyhre-Poulsen P. Modulation of multisegmental monosynaptic responses in a variety of leg muscles during walking and running in humans. J Physiol. 2007;582(Pt 3):1125–39.
52. Schomburg ED, Steffens H, Kniffki KD. Contribution of group III and IV muscle afferents to multisensorial spinal motor control in cats. Neurosci Res. 1999; 33(3):195–206.
53. Rossignol S, Dubuc R, Gossard JP. Dynamic sensorimotor interactions in locomotion. Physiol Rev. 2006;86(1):89–154.
54. Fong AJ, Roy RR, Ichiyama RM, et al. Recovery of control of posture and locomotion after a spinal cord injury: solutions staring us in the face. Prog Brain Res. 2009;175:393–418.
55. Hultborn H. State-dependent modulation of sensory feedback. J Physiol. 2001;533(Pt 1):5–13.
56. Vrieseling E, Arber S. Target-induced transcriptional control of dendritic patterning and connectivity in motor neurons by the ETS gene Pea3. Cell. 2006; 127(7):1439–52.
57. Hagglund M, Borgius L, Dougherty KJ, Kiehn O. Activation of groups of excitatory neurons in the mammalian spinal cord or hindbrain evokes locomotion. Nat Neurosci. 2010;13(2):246–52.
58. Hentall ID, Pinzon A, Noga BR. Spatial and temporal patterns of serotonin release in the rat's lumbar spinal cord following electrical stimulation of the nucleus raphe magnus. Neuroscience. 2006;142(3):893–903.
59. Agnati LF, Guidolin D, Guescini M, Genedani S, Fuxe K. Understanding wiring and volume transmission. Brain Res Rev. 2010;64(1):137–59.
60. Zoli M, Jansson A, Sykova E, Agnati LF, Fuxe K. Volume transmission in the CNS and its relevance for neuropsychopharmacology. Trends Pharmacol Sci. 1999;20(4):142–50.
61. Musienko P, van den Brand R, Märzendorfer O, Roy RR, Gerasimenko Y, Edgerton VR, Courtine G. Controlling specific locomotor behaviors through multidimensional monoaminergic modulation of spinal circuitries. J Neurosci. 2011;31(25):9264–78.
62. Edgerton VR, Roy RR. Robotic training and spinal cord plasticity. Brain Res Bull. 2009;78(1):4–12.
63. de Leon RD, Kubasak MD, Phelps PE, et al. Using robotics to teach the spinal cord to walk. Brain Res Brain Res Rev. 2002;40(1–3):267–73.
64. Ziegler MD, Zhong H, Roy RR, Edgerton VR. Why variability facilitates spinal learning. J Neurosci. 2010;30(32):10720–6.
65. Dominici N, Keller U, Friedli L. A novel multidirectional robotic support uncovers unexpected functional capacities of the injured spinal cord. In: Society for neuroscience. San Diego: Neuroscience Meeting Planner; 2010. Program No. 684.689.

66. Pearson KG. Generating the walking gait: role of sensory feedback. Prog Brain Res. 2004;143:123–9.
67. Beres-Jones JA, Harkema SJ. The human spinal cord interprets velocity-dependent afferent input during stepping. Brain. 2004;127(Pt 10):2232–46.
68. Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR. Human lumbosacral spinal cord interprets loading during stepping. J Neurophysiol. 1997;77(2):797–811.
69. Guertin PA. Recovery of locomotor function with combinatory drug treatments designed to synergistically activate specific neuronal networks. Curr Med Chem. 2009;16(11):1366–71.
70. Barriere G, Leblond H, Provencher J, Rossignol S. Prominent role of the spinal central pattern generator in the recovery of locomotion after partial spinal cord injuries. J Neurosci. 2008;28(15):3976–87.
71. Van de Crommert HW, Mulder T, Duysens J. Neural control of locomotion: sensory control of the central pattern generator and its relation to treadmill training. Gait Posture. 1998;7(3):251–63.
72. Rossignol S, Barriere G, Frigon A, et al. Plasticity of locomotor sensorimotor interactions after peripheral and/or spinal lesions. Brain Res Rev. 2008;57(1): 228–40.
73. Boulenguez P, Liabeuf S, Bos R, et al. Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury. Nat Med. 2010;16(3):302–7.
74. Edgerton VR, Roy RR. Spasticity: a switch from inhibition to excitation. Nat Med. 2010;16(3):270–1.
75. Hou S, Duale H, Cameron AA, Abshire SM, Lyttle TS, Rabchevsky AG. Plasticity of lumbosacral propriospinal neurons is associated with the development of autonomic dysreflexia after thoracic spinal cord transection. J Comp Neurol. 2008;509(4):382–99.
76. Courtine G, Song B, Roy RR, et al. Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. Nat Med. 2008;14(1):69–74.
77. Ichiyama RM, Broman J, Roy RR, Zhong H, Edgerton VR, Havton LA. Locomotor training maintains normal inhibitory influence on both alpha- and gamma-motoneurons after neonatal spinal cord transection. J Neurosci. 2011;31(1):26–33.
78. Calancie B, Alexeeva N, Broton JG, Molano MR. Interlimb reflex activity after spinal cord injury in man: strengthening response patterns are consistent with ongoing synaptic plasticity. Clin Neurophysiol. 2005;116(1):75–86.
79. Dietz V, Grillner S, Trepp A, Hubli M, Bolliger M. Changes in spinal reflex and locomotor activity after a complete spinal cord injury: a common mechanism? Brain. 2009;132(Pt 8):2196–205.
80. Dietz V. Behavior of spinal neurons deprived of supraspinal input. Nat Rev Neurol. 2010;6(3):167–74.
81. Maegele M, Muller S, Wernig A, Edgerton VR, Harkema SJ. Recruitment of spinal motor pools during voluntary movements versus stepping after human spinal cord injury. J Neurotrauma. 2002;19(10):1217–29.
82. Hiersemenzel LP, Curt A, Dietz V. From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. Neurology. 2000;54(8):1574–82.
83. Edgerton VR, Leon RD, Harkema SJ, et al. Retraining the injured spinal cord. J Physiol. 2001;533(Pt 1):15–22.
84. Kubasak MD, Jindrich DL, Zhong H, et al. OEG implantation and step training enhance hindlimb-stepping ability in adult spinal transected rats. Brain. 2008;131(Pt 1):264–76.
85. Ichiyama RM, Courtine G, Gerasimenko YP, et al. Step training reinforces specific spinal locomotor circuitry in adult spinal rats. J Neurosci. 2008;28(29):7370–5.
86. Lavrov I, Courtine G, Dy CJ, et al. Facilitation of stepping with epidural stimulation in spinal rats: role of sensory input. J Neurosci. 2008;28(31):7774–80.
87. de Leon RD, Hodgson JA, Roy RR, Edgerton VR. Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats. J Neurophysiol. 1998;79(3):1329–40.
88. Edgerton VR, Roy RR, de Leon RD. Neural Darwinism in the mammalian spinal cord. In: Patterson MM, Grau JW, editors. Spinal cord plasticity: alterations in reflex function. Boston: Kluwer Academic Publishers; 2001. p. 185–206.
89. Gad P, Woodbridge J, Lavrov I, Development of an electronic spinal bridge between the forelimbs and hindlimbs to facilitate quadrupedal stepping after a complete spinal cord transection. In: editors. Society for neuroscience. San Diego: Neuroscience Meeting Planner; 2010. Program No. 588.511.
90. DiGiovanna J, Mahmoudi B, Fortes J, Principe JC, Sanchez JC. Co-adaptive brain-machine interface via reinforcement learning. IEEE Trans Biomed Eng. 2009;56(1):54–64.
91. Fitzsimmons NA, Lebedev MA, Peikon ID, Nicolelis MAL. Extracting kinematic parameters for monkey bipedal walking from cortical neuronal ensemble activity. Front Integr Neurosci. 2009;3:3.
92. Nicolelis MAL, Lebedev MA. Principles of neural ensemble physiology underlying the operation of brain-machine interfaces. Nat Rev Neurosci. 2009;10:530–40.
93. Edgerton VR, Tillakaratne NJ, Bigbee AJ, de Leon RD, Roy RR. Plasticity of the spinal neural circuitry after injury. Annu Rev Neurosci. 2004;27:145–67.

Sensory-Motor Interactions and Error Augmentation

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 signals that were employed prior to injury may no longer be appropriate for controlling the muscles for the intended movement. Hence, a new pattern of signals may need to be learned that appropriately uses the residual resources. The learning required in these circumstances might in fact share features with sports, music performance, surgery, teleoperation, piloting, and child development. Our lab has leveraged key findings in neural adaptation as well as established principles in engineering control theory to develop and test new interactive environments that enhance learning (or relearning). Successful application comes from the use of robotics and video feedback technology to augment error signals. These applications test standing hypotheses about error-mediated neuroplasticity and illustrate an exciting prospect for rehabilitation environments of tomorrow. This chapter highlights our works, identifies our acquired knowledge, and outlines some of the successful pathways for restoring function to brain-injured individuals.

Keywords

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

J.L. Patton, PhD (✉)
Sensory Motor Performance Program,
Rehabilitation Institute of Chicago,
Chicago, IL, USA

Department of Physical Medicine Rehabilitation,
Northwestern University, Chicago, IL, USA

Department of Bioengineering,
Universities of Illinois at Chicago,
Chicago, IL, USA
e-mail: jPatton@ric.org

F.C. Huang, PhD
Sensory Motor Performance Program,
Rehabilitation Institute of Chicago,
Chicago, IL, USA

Department of Physical Medicine Rehabilitation,
Northwestern University, Chicago, IL, USA
e-mail: f-huang@northwestern.edu

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5.1 Introduction

As rehabilitation research continues to provide support for prolonged practice of functionally relevant activities for restoration of function, integration of therapy with technology has revealed new prospects for motor teaching. For many researchers the central issue to be addressed is how technology can provide therapeutic advantages over simply administering greater intensity or prolonged treatment in traditional approaches. 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 and present some early examples.

5.2 Experience Enables Prediction of Consequences

While the fundamental principles of neurorehabilitation are still being actively debated, 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 associated deficits that may not be directly involved in such neural reorganization (contractures, weakness, cognitive deficits, attentional deficits, etc.), one mode of recovery is certainly to *learn* how to perform normal functions with what is effectively a new brain. Hence, the capacity of neuroplasticity is believed to be one of the most powerful resources that can be leveraged to foster functional recovery through the proper conditions of training, feedback, encouragement, motivation, and time.

Early investigations of training-induced neuroplasticity were motivated by results of studies of sensorimotor adaptation in healthy individuals. Earlier studies dating back to the 1950s used a variety of more traditional motor learning tasks to understand many of these processes (for an excellent review, see Schmidt and Lee [1]). 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 [2], long feedback delays [3], and slow activation times for muscle [4]. 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 a lifetime of experience [5]. Yet research has shown that distorting sensory-motor relationships in a variety of ways can alter these representations at least for a short period of time following training. For example, *mechanical distortions—unexpected changes to mechanics*—such as the introduction of a heavy weight in one's hand cause initial errors in reaching accuracy, but people adapt and recover their ability to move normally within a single motion [6]. More complex loads can take hundreds of movements [7–9]. People often stiffen (i.e., co-contract their muscles) as a first strategy [10, 11] in response to external force perturbation. However, the stiffness quickly fades as they learn to counteract the forces, leading to *aftereffects* when forces are unexpectedly removed (Fig. 5.1) [12, 13]. It is important to note that both the adaptation and aftereffects can occur implicitly with minimal conscious attention to any goal. Beyond the investigation of basic motor control principles, we have shown that this type of training can be used constructively to teach a desired set of new movements [14, 15].

Motor learning is strongly driven to reduce performance errors [16, 17]. Particular tests in experiments often use simple tasks to explore how humans respond to such errors. In reaching, these errors are presumed to be simply deviations away from the straight-line hand path to a target [18, 19]. Experiments have demonstrated that it is possible to train subjects to produce new movements, such as a prespecified (but straight) path during reaching. Such *adaptive training* has resulted in altered motion patterns in both the arms [20, 21] and legs [22] by accentuating trajectory errors using robotic forces. Subjects in those studies were exposed to custom-designed

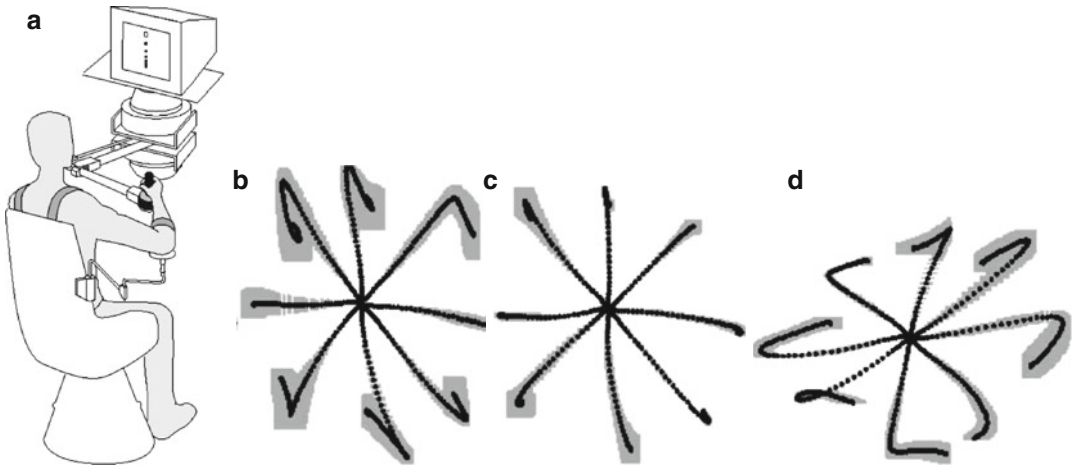

Fig. 5.1 A classic adaptation experiment in which a robot exerts a mechanical distortion. The subject attempted reaching movements to targets in eight different directions. (**a**) Subject seated at the robot. (**b**) Initial exposure to the force field. (**c**) At the end of training, movements appear normal. (**d**) Removing the force field unexpectedly results in aftereffects (Adapted from Shadmehr and Mussa-Ivaldi [9])

force fields that promoted the learning of specific movements by exploiting short-term adaptive processes [23].

5.2.1 The Nervous System Responds Dramatically to Visual and Mechanical Distortions

Similar to the error-based learning described above, adaptation can occur when exposed to a visuomotor distortion. Motor learning as mediated by robotic devices shares many similarities with an older body of research on visuomotor adaptations, such as those induced by prisms [see [24] for a review], rotations, stretches, and other distortions of the conventional hand-to-screen mapping [18, 25, 26]. It is worth noting that beyond effecting a change in overall force-motion relationships, robotic training can introduce haptic interactions at the point of contact [27, 28]. In contrast to prism adaptation, such interactions can alter both the energetics and sensory information in a task and hence could elicit additional neural responses [29]. All of these distortions appear to induce learning and can reduce sensory dysfunction such as hemispatial neglect [30].

5.2.2 Neuroplasticity, Learning, Adaptation, and Recovery

Motor adaptation induced by interactive forces and visual distortion might not necessarily reflect long-term learning, however. 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 [31–33]. Such findings would at first seem to undermine any prospects of successfully transferring the skills acquired in an engineered environment to functional ability in the real world. However, 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 [31, 34, 35]. 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.

Quite importantly, the adaptive responses described here can also be observed in stroke survivors, and evidence is found in the oculomotor [36] and limb motor systems [21, 37, 38] for neuroplasticity, induced by enriched interactive experiences. In fact, errors seen in stroke reflect poor compensation for interaction torques [39], and resemble the problems seen in healthy subjects when they are exposed to force fields. At least part of impairment has been attributed to "learned nonuse" that can be reversed by encouraging individuals to practice and relearn how to move their affected arm [40].

5.3 Multiple Forms of Neuroplasticity

Plasticity comes in many forms across many timescales making it difficult to fully identify all underlying mechanisms at work in a given therapeutic context. Changes can range from very temporary shifts in neurotransmitter concentrations, facilitation or inhibition from collateral neurons, neural growth to establish synapses, or actual neurogenesis where entire neurons are established. Making matters more complicated, neuroplasticity can be described as residing within a much larger spectrum of mechanisms with overlapping times scales that span short-term adaptation in milliseconds, long-term potentiation over minutes, permanent leaning, muscle hypertrophy, and 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 even 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 kinetic and kinematic adaptations are separate and independent processes. Krakauer et al. [32] 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. Basic modeling assumptions can easily show that separate error-motivated adaptation processes could arise (different red lines of Fig. 5.2). Flanagan and colleagues also showed similar results with a visuomotor rotation and a viscous force field [41]. However, Tong and colleagues argued that these studies should not be expected to 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 [33]. They demonstrated that when both the force field and the visuomotor rotation depended on position (or on acceleration), interference was observed. These results strongly suggest that kinetic and kinematic adaptation share at least some common neural resources in motor working memory. As a logical extension of this concept of shared resources, we might employ multiple environmental effects to "trick" the nervous system into learning more. One possibility is to *facilitate* (rather than interfere with) learning. Consequently mixed experience of both force and visual feedback distortions can enhance learning even further [42].

5.4 The Crutch Effect

It is clear that human-machine interactions have the extremely powerful ability to foster learning; but it is less obvious how to precisely program them to alter these interactions 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 approach only provides the correct kinematics without the correct kinetics. While there have been a few studies that

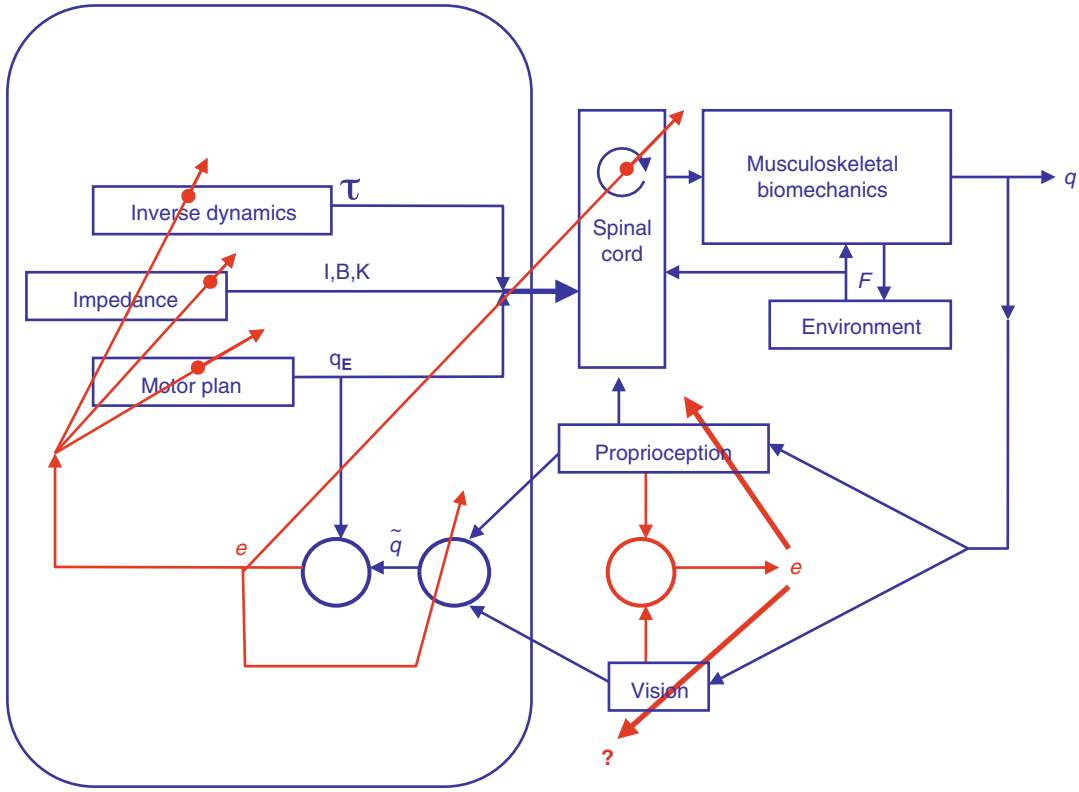

Fig. 5.2 A schematic flowchart that illustrates the believed error-mediated adaptation for the control of movement. News of outcome movements are fed back to the central nervous system to calculate errors that are used for adjusting (adapting). Several known mechanisms exist that use error (*red lines*)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

have shown a benefit for haptic guidance in learning motions [43–46], 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 people when they practiced using robotic guidance [47].

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 [48, 49], 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 [50]. People could literally fall asleep practicing.

5.5 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 aged-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. This field generated forces that were proportional to hand speed, perpendicular to movement direction—either clockwise or counterclockwise

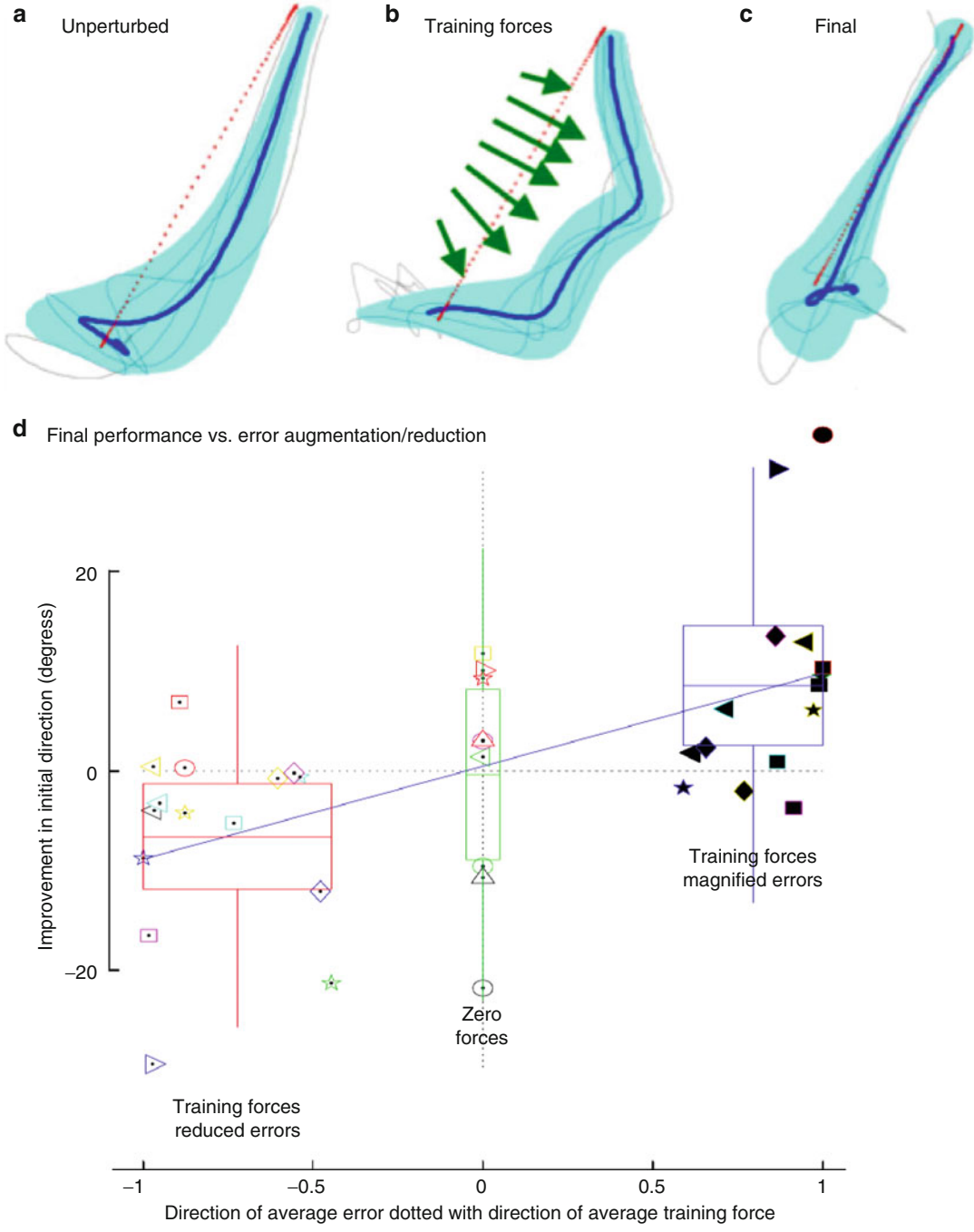

Fig. 5.3 (**a**) One stroke survivor's response to training forces that amplify the original counterclockwise movement error. The force field during training (*arrows* in **b**) resulted in a reduction of error following training that was sustained until the end of the experiment (**c**). (**d**) Cross 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 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. [21])

(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 [21]. Importantly, significant improvements occurred only when the training forces magnified the original errors and not when the training forces reduced the errors or when there were no forces (Fig. 5.3d). Interestingly, adaptation during practice in stroke survivors is concurrent with anatomical and cellular evidence that the nervous system is reorganizing and areas of activity are changing [51]. These results point to a unifying concept—errors induce motor learning, and judicious manipulation of error can lead to lasting desired changes.

5.6 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 novel distortions to perception, essentially creating a "lie" to the interacting subject in a variety of ways. This approach to facilitating training offers a bright prospect, not only in the world of engineering for rehabilitation but in many areas in which people must learn to make new actions. One key implementation 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 [23, 52–54]. 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 [22]. In another study, providing feedback that was less than the actual force production has caused subjects to apply larger forces to compensate [55]. Several studies have shown how the nervous system can be "tricked" by giving altered sensory feedback [18, 56–61]. Conversely, suppression of visual feedback has slowed the unlearning process [15]. 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 [62]. It may be that there are limits to the amount of error augmentation that is useful [63–65]. Robotically reducing kinematic errors in a golf putting training session improved skill more for the less skilled, but increasing errors had no effect and additionally decreased motivation [66]. More error might mean more learning, but it would not seem plausible for error augmentation to work limitlessly.

5.7 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 simple evaluation of the rate change of hand path error while subjects made point-to-point reaching movements of the unseen arm [67, 68]. Error deviations from a straight-line trajectory were visually augmented with either a 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 [69].

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 [57, 64, 70], error magnification may be practicably limited to small gains. On the

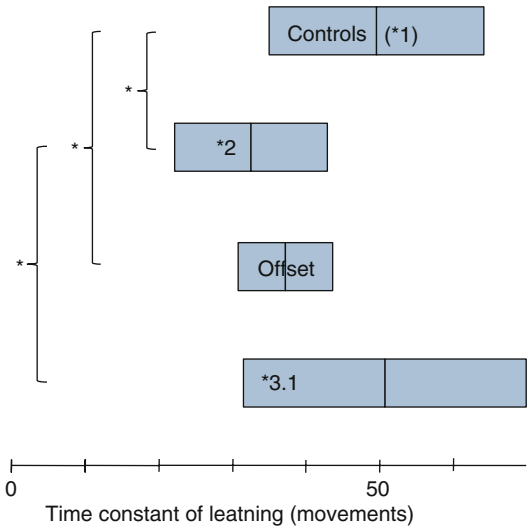

Fig. 5.4 Time constant of error decay during in a visual error augmentation trial on healthy subjects, revealing a breakdown in higher gain of error augmentation of 3.1. *Error bars* indicate 95 % confidence intervals. Horizontal lines indicate significant differences (post hoc) between groups (Adapted from Patton et al. [68])

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 *post-movement evaluations* imply that we often are able to gain insights into the nature of the learning process from one attempt to the next. Such colearning 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.

5.8 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 [71, 72]. Such approaches use active impedance, such as *negative damping*, which constantly pushes you along in the direction you are going. Beyond altering online performance, negative damping can increase awareness of deviations from expected behavior—information critical for driving adaptation. Furthermore, a major advantage is that it allows training even when weakness limits voluntary motion. Most importantly, however, such environments facilitate training and still allow easy transition to unassisted conditions.

To test negative damping as a supplement to training, we investigated the efficacy in a skills training experiment using a robotic interface. One key feature of our approach was to allow self-directed movement during training. While goal-directed movement typically focuses on kinematic performance, we expected that allowing training via exploratory movements would emphasize relevant force and motion relationship and provide better improvement in overall function than repetition of the same task [73, 74]. This free training paradigm also served as an excellent way to test subjects' abilities to *generalize* what they learned, since the structured evaluations after training (making circles) differed from practice.

We found that improvements in performance persisted even when the negative damping portion of the forces was removed [75]. In a follow-up study with stroke survivors (Fig. 5.5), similar training with negative viscosity resulted in improved skill within a single training session, while no improvement was observed in the control group where no forces were administered

[76]. It is important to emphasize that each group was evaluated in the absence of applied forces, which demonstrates that patients' training with negative viscosity transferred their learned skills to better actions in the real world.

The studies described above freely explore using negative damping, which could be thought of as an extension of the principles of error augmentation. In contrast to focusing on prescribed movement trajectories, the space of error could instead be a specific workspace or a rich set of behaviors that require modification. Such behaviors are quite critical when one considers the rich set of behaviors necessary for functional everyday tasks.

5.9 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 [77, 78]. 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.

Recent work, however, reflects a more careful approach to understanding retention and, more importantly, the accumulation of benefit from repeated visits [79, 80]. In this 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 and then another 2 weeks of the other 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 ($F = 100[N/m] \cdot e$) and visual ($x = 1.5 \cdot e$) 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. This was a small but significant benefit to robotic training over simple repetitive practice, with a mean 2-week gain in Fugl-Meyer UE motor score of 2.08 and Wolf Motor Function Test of timed tasks of 1.48 s. This small amount is encouraging, however, because the interactive technology was only applied for 2 weeks although a significant gain was observed. Such an effect may improve more given a longer course of therapy.

5.10 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 [16, 52, 81, 82]. 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

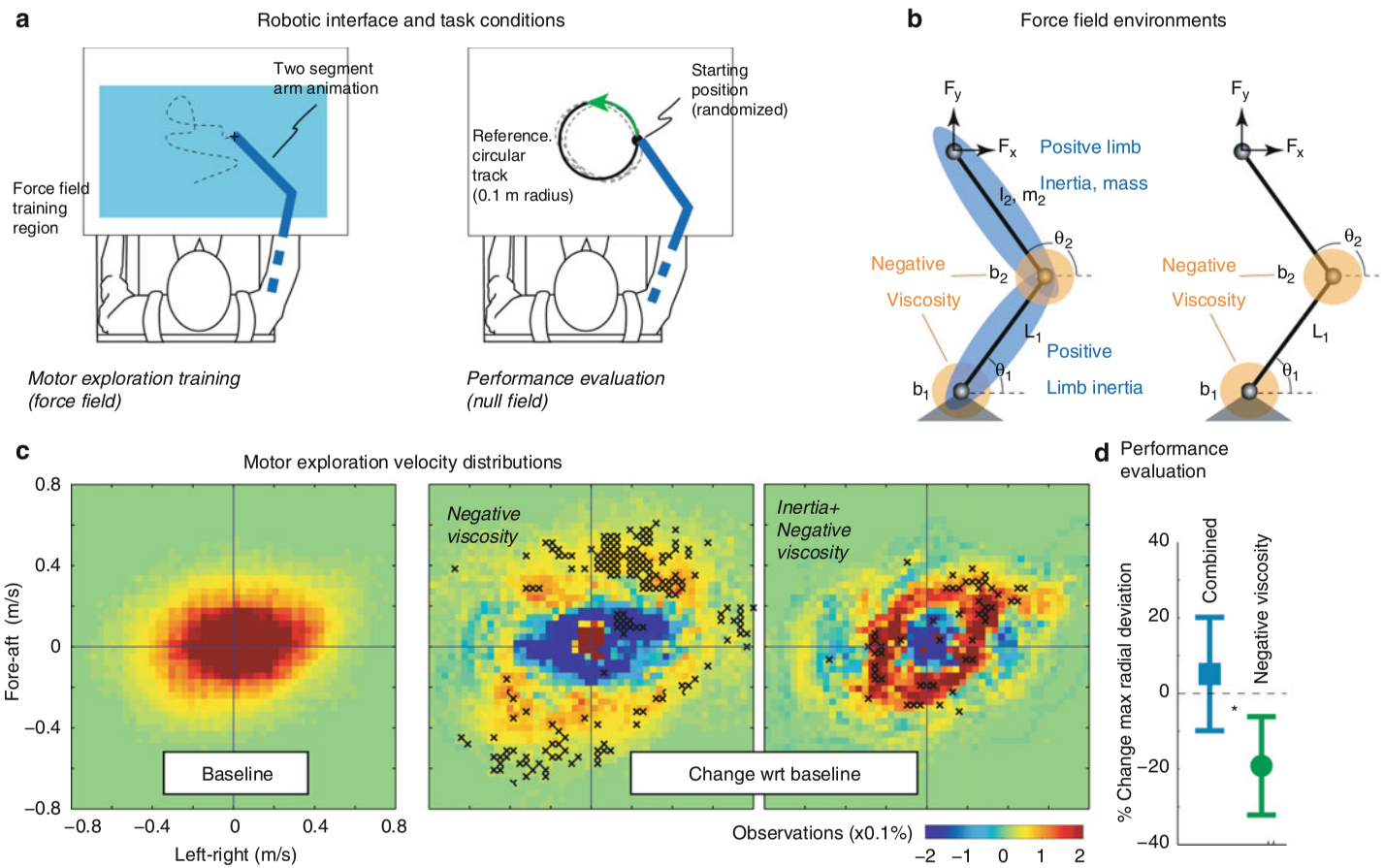

Fig. 5.5 Patients benefit from free exploration training with robot-applied negative viscosity to augment error. (**a**) The robot interfaced to the arm about a free pivot at the wrist. Subjects were allowed to freely interact with each load in a "motor exploration" stage. Following exploration, subjects 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) especially in elbow flexion-extension. (**d**) Tests of learning show error decreased ($-19.1 \pm 0.1\,\%$, $p=1.3\text{e-}2$) from negative viscosity training, while no change was found from inertia + negative viscosity training ($+5.1 \pm 16.2\,\%$, $p=4.3\text{e-}1$) [76]

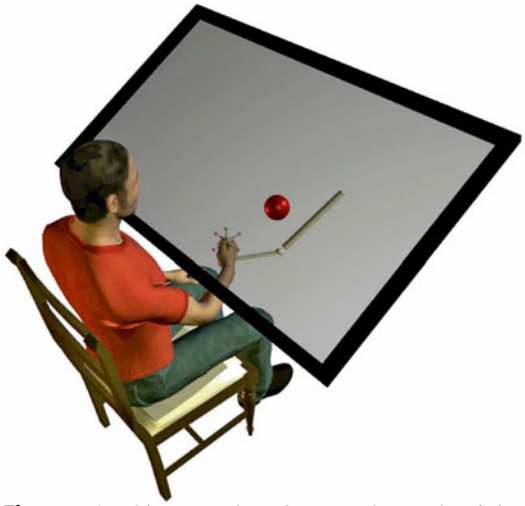

Fig. 5.6 A subject seated at a large-workspace haptic/graphic display

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 [83]. 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 [84] and suppression of visual feedback has been shown to slow down the de-adaptive process [15]. 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 [64]. These and other studies that induce sensorimotor conflict suggest that the nervous system can quickly *adapt its adaptation*—or in other words, it can reweigh the interpretation of sensory information if it no longer is perceived reliable [57, 85].

In summary, 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. Error augmentation has emerged from the recent insights on how the nervous system learns and recovers.

5.11 Statistical Approaches to Error Augmentation

While error augmentation might be quite effective in healthy individuals, one concern is the lack of one powerful tool commonly used by clinicians—*customizing* treatment for each patient. This limitation is the reason interactive therapies have not been effective for some patients. Studies in customization have had preliminary success by assisting the patient only as much as needed [48, 86], by gradually reducing assistance [87–89], and by using patient-customized forces [20, 90, 91]. What is missing, however, is a principled method that relates errors to intervention. The answer to this may lie in statistical modeling of a patient's motor deficits, which can be used to customize therapy [92].

Recent work has shown how interactive machines can inform a direct mathematical relationship between patient deficits and applied interventions [93]. This builds upon some recent and exciting aspects that consider the statistical relationship of errors to learning. Recent research has shown that the nervous system is quite clever—it takes advantage of information on error *statistics* to shape learning [94, 95]. First, spurious errors are discarded [69]. More importantly, prior experience of error alone appears to govern the amount of learning [96]. Our current paradigm ensures that only repeatable errors are augmented in regions of the *error space* where errors were part of previous experience. This greatly aligns with recent findings that learning is greatest when errors can be expected [97]. Because the learning part of the nervous system

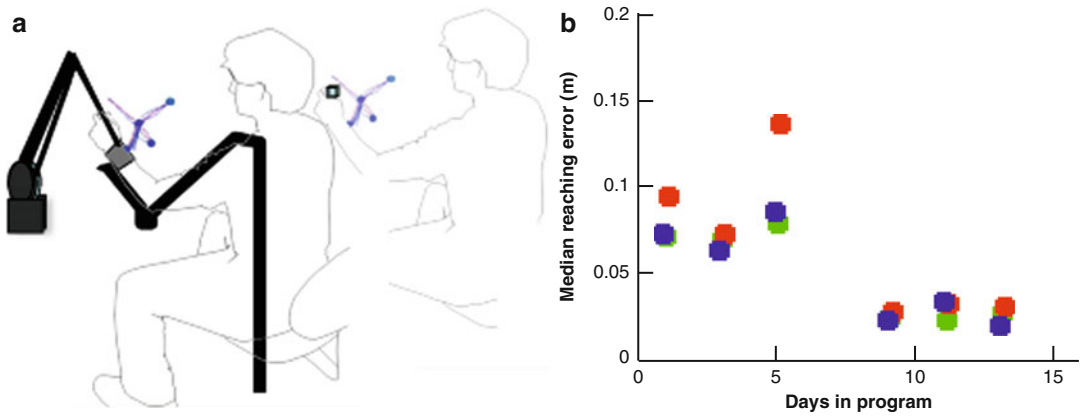

Fig. 5.7 (**a**) An error augmentation application for stroke rehabilitation where a subject and therapist work together, seated and using the large-workspace haptic/graphic display to practice movement. The therapist provides a cue for the subject and can tailor conditioning to the needs of the patient. The robot provides forces that put 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

appears to hinge on error, we suggest that approaches should consider how error probabilities also change during learning and should be updated. Because the error experience plays a clear and prominent role in learning, it follows that neurorehabilitation should consider error statistics in its arsenal for recovery.

Using the statistics of an individual's error is fairly straightforward extension of the already tested methods, which allows us to further customize training and provide an even better error augmentation that varies appropriately as needed [98]. While "offset" used the average initial error and was a step in the right direction, our most recent efforts employ more comprehensive statistics. A statistical profile of error, created from the patient's own assessment data, is used to construct a probability density function. A typical statistical profile from a healthy individual's 100 movements is shown in Fig. 5.8. For this subject, the concentration of errors was centered in a small region to the side of zero error.

Next, a statistical model of error informs the design of customized therapy [99]. The innovation is that the error distribution is used to directly determine the appropriate training forces that one might experience throughout reaching. Forces magnify one's often-repeated error tendencies and leave spurious and rare errors alone. Very large errors are also not further enlarged, making the system gentler. Hence, the algorithm first learns the human, gaining an individualized probabilistic "picture" of error tendencies, which then serves as a basis for the forces that augment error—only in these error-prone regions where they were observed.

As an example, we show a chronic stroke subject training across several days (Fig. 5.9). For this particular direction of motion, the subject first was assessed for 2 days before being treated with an error field. Error varied across the motion and did not change across the 2 days of assessment. Only after the error field treatment began did the errors decline.

One can speculate on other exciting applications of such techniques. Training over a broader domain on a larger variety of tasks should provide functional improvements that are better than from simple repetitions of the same task [73, 74] and will facilitate "system identification" as a part of learning [27]. Importantly, any task from simple to complicated is applicable. Because they only amplify *repeatable* negative actions but otherwise do not impede, error fields should also benefit highly impaired patients who are often excluded from clinical trials because of their inability to move [100]. Success may be further

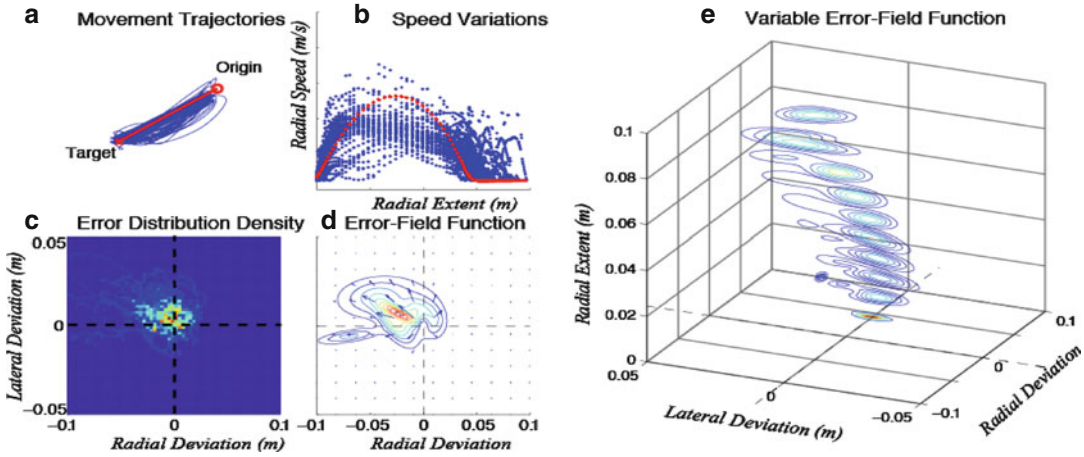

Fig. 5.8 Illustration of the construction of error fields. Based on the individual's patterns of error from ideal straight-line motion (**a**). Profiles of movement speed also showed large variability and deviation from a specified goal profile (**b**). A distribution of observed error patterns in a two-dimensional space is modeled as a linear combination of Gaussian distributions (**c**). An error field is based on this statistical probability of error times the actual magnitude (**d**). This error field function is shown as probability contours in progressive slices along the extent of the movement toward the target (**e**)

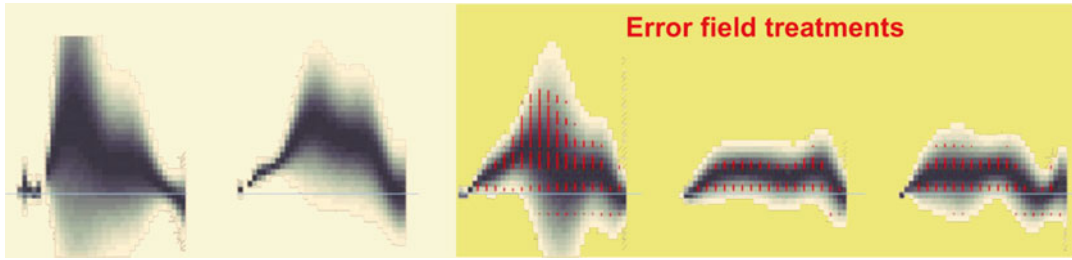

Fig. 5.9 Application of the error field approach on a chronic stroke survivor, with each plot showing successive days visiting the laboratory. Error vs. time shows a probability (indicated by a degree of shading) to curve in the counterclockwise direction. Probabilities of error times the magnitude of error lead to a magnification of error only where errors are likely to occur (indicated by *red arrows*) and where they have repeatedly occurred. Error field treatments began only on visit three, where error began to reduce. Each pixel represents 5 mm^2, and forces were tuned such that the maximum force was 15 N

improved because rehabilitation is typically most effective in these less impaired patients [101, 102], mainly because residual capabilities are normally required to perform therapy [100, 103].

This proposed framework should also stimulate new research on how such error distributions might be linked to specific motor pathologies (such spasticity, weakness, synergies, contractures, etc.). Once better known, the error statistics of each individual might guide therapy, and a person's error signature should provide a unique and valuable assessment of their motor deficits and how they may be resolving over time. While here our focus was on error, it is actually part of a family of methods for therapy that concentrate on a variety of motor deficits that first identifies the statistical tendencies of deficits and then uses it to create a training environment.

5.12 Summary and Conclusions

Regardless of the details of the mechanism, the bioengineering community is now observing successes with error augmentation, and the clinical research world calls for more studies to

discover its optimal application [104]. Statistical techniques provide an enhanced approach that is tailored to the individual's more likely errors. The work outlined in the chapter provides early evidence. Once these approaches are even better understood, they should provide a broad approach to serve therapeutic goals and questions. Even more broadly, these approaches should provide a powerful strategy to improve capabilities for healthy and patient activities alike, covering any situation requiring repetitive motor skill training.

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References

1. Schmidt R, Lee T. Motor control and learning. A behavioral emphasis. 5th ed. Champaign: Human Kinetics; 2011.
2. Hollerbach JM, Flash T. Dynamic interactions between limb segments during planar arm movements. Biol Cybern. 1982;44:67–77.
3. Hogan N. Mechanical impedance of single and multi-articular systems. In: Winters JM, Woo SL-Y, editors. Multiple muscle systems. New York: Springer; 1990. p. 149–64.
4. Zajac FE. Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. CRC Crit Rev Bioeng. 1989;17:359–411.
5. Ghez C. The control of movement. In: Kandel ER, Scwartz JH, Jessel TM, editors. Principles of neural science. 1991. p. 533–47.
6. Bock O. Load compensation in human goal-directed arm movements. Behav Brain Res. 1990;41: 167–77.
7. Lackner JR, DiZio P. Rapid adaptation to Coriolis force perturbations of arm trajectories. J Neurophysiol. 1994;72:299–313.
8. Sainburg RL, Ghez C, Kalakanis D. Intersegmental dynamics are controlled by sequential anticipatory, error correction, and postural mechanisms. J Neurophysiol. 1999;81(3):1045–56.
9. Shadmehr R, Mussa-Ivaldi FA. Adaptive representation of dynamics during learning of a motor task. J Neurosci. 1994;14(5):3208–24.
10. Tee KP, Franklin DW, Kawato M, Milner TE, Burdet E. Concurrent adaptation of force and impedance in the redundant muscle system. Biol Cybern. 2010; 102(1):31–44.
11. Franklin DW, So U, Kawato M, Milner TE. Impedance control balances stability with metabolically costly muscle activation. J Neurophysiol. 2004; 92(5):3097–105.
12. Osu R, Burdet E, Franklin DW, Milner TE, Kawato M. Different mechanisms involved in adaptation to stable and unstable dynamics. J Neurophysiol. 2003;90(5): 3255–69.
13. Thoroughman KA, Shadmehr R. Electromyographic correlates of learning an internal model of reaching movements. J Neurosci. 1999;19(19):8573–88.
14. Mussa-Ivaldi FA, Patton JL. Robots can teach people how to move their arm. Paper presented at: IEEE International Conference on Robotics and Automation (ICRA), 2000, San Francisco.
15. Patton JL, Mussa-Ivaldi FA. Robot-assisted adaptive training: custom force fields for teaching movement patterns. IEEE Trans Biomed Eng. 2004;51(4): 636–46.
16. Kawato M. Feedback-error-learning neural network for supervised learning. In: Eckmiller R, editor. Advanced neural computers. Amsterdam: North-Holland; 1990. p. 365–72.
17. Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. Science. 1995; 269(5232):1880–2.
18. Flanagan JR, Rao AK. Trajectory adaptation to a nonlinear visuomotor transformation: evidence of motion planning in visually perceived space. J Neurophysiol. 1995;74(5):2174–8.
19. Scheidt RA, Reinkensmeyer DJ, Conditt MA, Rymer WZ, Mussa-Ivaldi FA. Persistence of motor adaptation during constrained, multi-joint. Arm Mov J Neurophys. 2000;84(2):853–62.
20. Patton JL, Kovic M, Mussa-Ivaldi FA. Custom-designed haptic training for restoring reaching ability to individuals with poststroke hemiparesis. J Rehabil Res Dev. 2006;43(5):643–56.
21. Patton JL, Stoykov ME, Kovic M, Mussa-Ivaldi FA. Evaluation of robotic training forces that either enhance or reduce error in chronic hemiparetic stroke survivors. Exp Brain Res. 2006;168(3):368–83.
22. Emken JL, Reinkensmeyer DJ. Robot-enhanced motor learning: accelerating internal model formation during locomotion by transient dynamic amplification. IEEE Trans Neural Syst Rehabil Eng. 2005;13(1):33–9.
23. Scheidt RA, Dingwell JB, Mussa-Ivaldi FA. Learning to move amid uncertainty. J Neurophysiol. 2001; 86(2):971–85.
24. Harris C. Perceptual adaptation to inverted, reversed, and displaced vision. Psychol Rev. 1965; 72:419–44.
25. Imamizu H, Miyauchi S, Tamada T, et al. Human cerebellar activity reflecting an acquired internal model

of a new tool. [see comments]. Nature. 2000; 403(6766):192–5.
26. Krakauer JW, Pine ZM, Ghilardi MF, Ghez C. Learning of visuomotor transformations for vectorial planning of reaching trajectories. J Neurosci (Online). 2000;20(23):8916–24.
27. Huang FC, Gillespie RB, Kuo AD. Visual and haptic feedback contribute to tuning and online control during object manipulation. J Mot Behav. 2007;39(3): 179–93.
28. Huang FC, Gillespie RB, Kuo AD. Human adaptation to interaction forces in visuo-motor coordination. IEEE Trans Neural Syst Rehabil Eng. 2006;14(3):390–7.
29. Lackner JR, DiZio P. Motor control and learning in altered dynamic environments. Curr Opin Neurobiol. 2005;15(6):653–9.
30. Rossetti Y, Rode G, Pisella L, et al. Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature. 1998;395(6698):166–9.
31. Shadmehr R, Holcomb HH. Neural correlates of motor memory consolidation. Science. 1997;277:821–5.
32. Krakauer JW, Ghilardi MF, Ghez C. Independent learning of internal models for kinematic and dynamic control of reaching. Nat Neurosci. 1999;2(11):1026–31.
33. Tong C, Wolpert DM, Flanagan JR. Kinematics and dynamics are not represented independently in motor working memory: evidence from an interference study. J Neurosci. 2002;22(3):1108–13.
34. Shadmehr R, Brashers-Krug T. Functional stages in the formation of human long-term motor memory. J Neurosci. 1997;17(1):409–19.
35. Brashers-Krug T, Shadmehr R, Bizzi E. Consolidation in human motor memory. Nature. 1996;382(6588): 252–5.
36. Weiner MJ, Hallett M, Funkenstein HH. Adaptation to lateral displacement of vision in patients with lesions of the central nervous system. Neurology. 1983;33(6):766–72.
37. Dancause N, Ptitob A, Levin MF. Error correction strategies for motor behavior after unilateral brain damage: short-term motor learning processes. Neuropsychologia. 2002;40(8):1313–23.
38. Takahashi CG, Reinkensmeyer DJ. Hemiparetic stroke impairs anticipatory control of arm movement. Exp Brain Res. 2003;149:131–40.
39. Beer RF, Given JD, Dewald JPA. Task-dependent weakness at the elbow in patients with hemiparesis. Arch Phys Med Rehabil. 1999;80:766–72.
40. Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among stroke and head-injured patients. Exp Neurol. 1989;104:125–32.
41. Flanagan J, Nakano E, Imamizu H, Osu R, Yoshioka T, Kawato M. Composition and decomposition of internal models in motor learning under altered kinematic and dynamic environments. J Neurosci. 1999;19:RC34. 31–35.
42. Wei Y, Patton J. Forces that supplement visuomotor learning: a 'Sensory Crossover' experiment. Paper presented at: Symposium on Haptic Interfaces, a satellite to the IEEE Conference on Virtual Reality, 2004, Chicago.
43. Chib VS, Patton JL, Lynch KM, Mussa-Ivaldi FA. The effect of stiffness and curvature on the haptic identification of surfaces. Paper presented at: first joint eurohaptics conference and symposium on haptic Interfaces for Virtual Environment and Teleoperator Systems (IEEE-WHC), 18–20 March 2005, Pisa.
44. Heuer H, Rapp K. Active error corrections enhance adaptation to a visuo-motor rotation. Exp Brain Res. 2011;211:97–108.
45. van Asseldonk EH, Wessels M, Stienen AH, van der Helm FC, van der Kooij H. Influence of haptic guidance in learning a novel visuomotor task. J Physiol Paris. 2009;103(3–5):276–85.
46. Chib VS, Patton JL, Lynch KM, Mussa-Ivaldi FA. Haptic identification of surfaces as fields of force. J Neurophysiol. 2006;95(2):1068–77.
47. Liu J, Cramer SC, Reinkensmeyer DJ. Learning to perform a new movement with robotic assistance: comparison of haptic guidance and visual demonstration. J Neural Eng Rehabil. 2006;3:20.
48. Emken JL, Benitez R, Reinkensmeyer DJ. Human-robot cooperative movement training: learning a novel sensory motor transformation during walking with robotic assistance-as-needed. J Neural Eng Rehabil. 2007;4:8.
49. Emken JL, Benitez R, Sideris A, Bobrow JE, Reinkensmeyer DJ. Motor adaptation as a greedy optimization of error and effort. J Neurophysiol. 2007;97(6):3997–4006.
50. Hornby TG, Reinkensmeyer DJ, Chen D. Manually-assisted versus robotic-assisted body weight-supported treadmill training in spinal cord injury: what is the role of each? PM & R. J Inj Funct Rehabil. 2010;2(3):214–21.
51. Nudo RJ, Friel KM. Cortical plasticity after stroke: implications for rehabilitation. Rev Neurol. 1999; 155(9):713–7.
52. Rumelhart DE, Hinton GE, Williams RJ. Learning representations by back-propagating errors. Nature (London). 1986;323:533–6.
53. Thoroughman KA, Shadmehr R. Learning of action through adaptive combination of motor primitives. [see comments]. Nature. 2000;407(6805):742–7.
54. Wolpert DM, Kawato M. Multiple paired forward and inverse models for motor control. Neural Netw. 1998;11(7–8):1317–29.
55. Brewer B, Klatky R, Matsuoka Y. Perceptual limits for a robotic rehabilitation environment using visual feedback distortion. IEEE Trans Neural Syst Rehabil Eng. 2005;13(1):1–11.
56. Srinivasan MA, LaMotte RH. Tactual discrimination of softness. J Neurophysiol. 1995;73:88–101.
57. Ernst M, Banks M. Humans integrate visual and haptic information in a statistically optimal fashion. Nature. 2002;415:429–33.

58. Robles-De-La-Torre G, Hayward V. Force can overcome object geometry in the perception of shape through active touch. Nature. 2001;412:445–8.
59. Brewer BR, Klatzky R, Matsuoka Y. Effects of visual feedback distortion for the elderly and the motor-impaired in a robotic rehabilitation environment. Paper presented at: IEEE International Conference on Robotics and Automation (ICRA), 2004, New Orleans.
60. Sainburg RL, Lateiner JE, Latash ML, Bagesteiro LB. Effects of altering initial position on movement direction and extent. J Neurophysiol. 2003;89(1):401–15.
61. Kording KP, Wolpert DM. Bayesian integration in sensorimotor learning. Nature. 2004;427(6971): 244–7.
62. Winstein CJ, Merians AS, Sullivan KJ. Motor learning after unilateral brain damage. Neuropsychologia. 1999;37(8):975–87.
63. Wei Y, Bajaj P, Scheidt RA, Patton JL. A real-time haptic/graphic demonstration of how error augmentation can enhance learning. IEEE International Conference on Robotics and Automation (ICRA), 2005, Barcelona.
64. Kording KP, Wolpert DM. The loss function of sensorimotor learning. Proc Natl Acad Sci U S A. 2004;101(26):9839–42.
65. Duarte JE, Gebrekristos B, Perez S, Rowe JB, Sharp K, Reinkensmeyer DJ. Effort, performance, and motivation: insights from robot-assisted training of human golf putting and rat grip strength. Seattle: IEEE International Conference on Rehabilitation Robotics (ICORR); 2013:6650461.
66. Duarte JE, Reinkensmeyer DJ. Effects of robotically modulating kinematic variability on motor skill learning and motivation. J Neurophysiol. 2015;113(7):2682–91.
67. Wei Y, Bajaj P, Scheidt RA, Patton JL. Visual error augmentation for enhancing motor learning and rehabilitative relearning. Paper presented at: IEEE-International Conference on Rehabilitation Robotics (ICORR), 2005, Chicago.
68. Patton JL, Wei YJ, Bajaj P, Scheidt RA. Visuomotor learning enhanced by augmenting instantaneous trajectory error feedback during reaching. PLoS One. 2013;8(1):e46466.
69. Wei K, Kording K. Relevance of error: what drives motor adaptation? J Neurophysiol. 2009;101(2): 655–64.
70. Todorov E, Jordan MI. Optimal feedback control as a theory of motor coordination.[see comment]. Nat Neurosci. 2002;5(11):1226–35.
71. Kazerooni H. The human power amplifier technology at the University of California. Berkeley Robotics Auton Syst. 1996;19(2):179–87.
72. Aguirre-Ollinger G, Colgate JE, Peshkin MA, Goswami A. Active-impedance control of a lower-limb assistive exoskeleton. Noordwijk: International Conference on Rehabilitation Robotics (ICORR); 13–15 June, 2007.
73. Hanlon RE. Motor learning following unilateral stroke. Arch Phys Med Rehabil. 1996;77(8):811–5.
74. Jarus T, Gutman T. Effects of cognitive processes and task complexity on acquisition, retention, and transfer of motor skills. Can J Occup Ther. 2001; 68(5):280–9.
75. Huang FC, Patton JL, Mussa-Ivaldi FA. Manual skill generalization enhanced by negative viscosity. J Neurophysiol. 2010;104(4):2008–19.
76. Huang FC, Patton JL. Augmented dynamics and motor exploration as training for stroke. IEEE Trans Biomed Eng. 2013;60(3):838–44.
77. Patton JL, Dawe G, Scharver C, Muss-Ivaldi FA, Kenyon R. Robotics and virtual reality: a perfect marriage for motor control research and rehabilitation. Assist Technol. 2006;18(2):181–95.
78. Patton JL, Wei Y, Scharver C, Kenyon RV, Scheidt R. Motivating rehabilitation by distorting reality. Paper presented at: BioRob: The first IEEE/RAS-EMBS International Conference on Biomedical Robotics and Biomechatronics, 20–22 Feb, 2006, Pisa, Tuscany.
79. Abdollahi F, Rozario S, Case E, et al. Arm control recovery enhanced by error augmentation IEEE International Conference on Rehabilitation Robotics (ICORR), 2011, Zurich.
80. Abdollahi F, Case ED, Listenberger M, et al. Error augmentation enhancing arm recovery in individuals with chronic hemiparetic stroke: a randomized crossover design. Neurorehab Neural Repair (NNR). 2014;128(2):120–8.
81. Dancausea N, Ptitob A, Levin MF. Error correction strategies for motor behavior after unilateral brain damage: short-term motor learning processes. Neuropsychologia. 2002;40(8):1313–23.
82. Lisberger S. The neural basis for the learning of simple motor skills. Science. 1988;242(4879): 728–35.
83. Alleva E, Santucci D. Psychosocial vs. "physical" stress situations in rodents and humans: role of neurotrophins. Physiol Behav. 2001;73(3):313–20.
84. Scheidt RA, Conditt MA, Secco EL, Mussa-Ivaldi FA. Interaction of visual and proprioceptive feedback during adaptation of human reaching movements. J Neurophysiol. 2005;93(6):3200–13.
85. Ravaioli E, Oie KS, Kiemel T, Chiari L, Jeka JJ. Nonlinear postural control in response to visual translation. Exp Brain Res. 2005;160(4):450–9.
86. Krebs HI, Palazzolo JJ, Dipietro L, et al. Rehabilitation robotics: performance-based progressive robot-assisted therapy. Auton Robots. 2003;15(1):7–20.
87. Kahn LE, Rymer WZ, Reinkensmeyer DJ. Adaptive assistance for guided force training in chronic stroke. San Francisco: Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); 2004.
88. Kahn LE, Rymer WZ, Reinkensmeyer DJ. Adaptive assistance for guided force training in chronic stroke. Proc Annu Int Conf IEEE Eng Med Biol Conf (EMBC). 2004;4:2722–5.
89. Colombo R, Sterpi I, Mazzone A, Delconte C, Pisano F. Taking a lesson from patients' recovery strategies to optimize training during robot-aided

rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2012;20(3):276–85.
90. Kahn LE, Lum PS, Rymer WZ, Reinkensmeyer DJ. Robot-assisted movement training for the stroke-impaired arm: does it matter what the robot does? J Rehabil Res Dev. 2006;43(5):619–30.
91. Johnson MJ, Van der Loos HF, Burgar CG, Shor P, Leifer LJ. Experimental results using force-feedback cueing in robot-assisted stroke therapy. IEEE Trans Neural Syst Rehabil Eng. 2005;13(3):335–48.
92. Wright ZA, Fisher ME, Huang FC, Patton JL. Data sample size needed for prediction of movement distributions. Conf Proc IEEE Eng Med Biol Soc (EMBC). 2014;2014:5780–3.
93. Sundaram H, Chen Y, Rikakis T. A computational framework for constructing interactive feedback for assisting motor learning. Conf Proc IEEE Eng Med Biol Soc (EMBC). 2011;2011:1399–402.
94. Wei Y, Kording KP. Relevance of error: what drives motor adaptation? J Neurophys. 2009;101(2):655–4.
95. Herzfeld DJ, Shadmehr R. Motor variability is not noise, but grist for the learning mill. Nat Neurosci. 2014;17(2):149–50.
96. Herzfeld DJ, Vaswani PA, Marko MK, Shadmehr R. A memory of errors in sensorimotor learning. Science. 2014;12(345):1349–53.
97. Takiyama K, Hirashima M, Nozaki D. Prospective errors determine motor learning. Nat Commun. 2015;6:5925.
98. Fisher ME, Huang FC, Wright ZA, Patton JL. Distributions in the error space: goal-directed movements described in time and state-space representations. Conf Proc IEEE Eng Med Biol Soc (EMBC). 2014;2014:6953–6.
99. Fisher ME, Huang FC, Klamroth-Marganska V, Riener R, Patton JL. Haptic error fields for robotic training. Evanston: World Haptics Conference (WHC); 2015.
100. Buch ER, Modir Shanechi A, Fourkas AD, Weber C, Birbaumer N, Cohen LG. Parietofrontal integrity determines neural modulation associated with grasping imagery after stroke. Brain. 2012;135(Pt 2):596–614.
101. Parry R, Lincoln N, Vass C. Effect of severity of arm impairment on response to additional physiotherapy early after stroke. Clin Rehabil. 1999;13(3):187–98.
102. Winstein CJ, Rose DK, Tan SM, Lewthwaite R, Chui HC, Azen SP. A randomized controlled comparison of upper-extremity rehabilitation strategies in acute stroke: a pilot study of immediate and long-term outcomes. Arch Phys Med Rehabil. 2004;85(4):620–8.
103. Nowak DA, Grefkes C, Ameli M, Fink GR. Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. Neurorehabil Neural Repair (NNR). 2009;23(7):641.
104. Parmar PN, Patton JL. Optimal gain schedules for visuomotor skill training using error-augmented feedback. Seattle: Proceedings 2015 IEEE International Conference on Robotics and Automation (ICRA), 26–30 May, 2015.

Normal and Impaired Cooperative Hand Movements: Role of Neural Coupling

6

Miriam Schrafl-Altermatt and Volker Dietz

Abstract

Recent research indicates that a task-specific, interhemispheric neural coupling is involved in the control of cooperative hand movements required for activities of daily living. This neural coupling is manifested in bilateral electromyographic reflex responses in the arm muscles to unilateral arm nerve stimulation. In addition, fMRI recordings show a bilateral task-specific activation and functional coupling of the secondary somatosensory cortical areas (S2) during the cooperative, but not during bimanual control tasks. This activation is suggested to reflect processing of shared cutaneous input during the cooperative task in both cortical areas. In chronic poststroke patients, arm nerve stimulation of the unaffected arm also leads to bilateral electromyographic responses, similar to those seen in healthy subjects in the cooperative task. However, stimulation of the affected side is frequently followed only by ipsilateral responses. The presence/absence of contralateral electromyographic responses correlates with the clinical motor impairment measured by the Fugl-Meyer score. The observations suggest impaired processing of afferent input from the affected side leading to defective neural coupling during cooperative hand movements after stroke. In moderately affected patients, movement execution seems to rely on the involvement of the ipsilateral corticospinal tract arising in the non-damaged hemisphere. According to these results, hand rehabilitation of stroke patients, currently focused on reach and grasp movements of the affected side, should be supplemented with the training of cooperative hand movements required during activities of daily living.

Keywords

Stroke • Hand function • Rehabilitation • Neural limb coupling • Reflex activity • fMRI recordings

M. Schrafl-Altermatt, PhD (✉) • V. Dietz, MD
Spinal Cord Injury Center, Balgrist University Hospital,
Forchstrasse 340, CH-8008 Zurich, Switzerland
e-mail: mschrafl@paralab.balgrist.ch

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6.1 Introduction

In contrast to lower limb movements, a great variety of uni- and bimanual functional hand/arm movements exist that require a specific neural control. In monkeys, it was suggested that the supplementary motor area (SMA) of one hemisphere influences the motor outflow of both hemispheres [1, 2]. Furthermore, the primary [3, 4] and non-primary motor cortex [5] as well as the prefrontal cortex [6] are assumed to play an essential role in the execution of bimanual tasks. Previous research has indicated that distributed neural networks coordinate interlimb coordination of bimanual tasks, including cortical and subcortical areas [3, 7–11].

Alongside these general control mechanisms, task specificity of neural control seems to exist for various bimanual movements (for review cf. [12]). It has been shown that interhemispheric connections between the primary motor cortices are involved in the control of uni- and bilateral in-phase movements while connections between the premotor cortex and the contralateral primary motor cortex regulate bimanual antiphase movements [13]. In bimanual reactive restrain tasks, digits are coupled by a neural control that facilitates reaction of one digit when another digit is preloaded and when digit-specific afferent input is present [14]. Furthermore, rapid grip force adjustments are modulated by sensory input from the contralateral hand, whereas arm reaction movements in the same task are independent from the contralateral arm [15]. During a two-hand grasp, bimanual reflex responses occur following a unilateral mechanical hand perturbation with short latency (30 ms) and a delay in the non-perturbed side of about 15 ms [16].

Cooperative hand movements represent a special type of bimanual tasks. They differ from other bimanual movements in that not only both hands are acting in synchrony but that, in order to accomplish the task, the action of one hand is counteracted by the other, e.g., in opening a bottle. Although many daily tasks involve cooperative hand movements, little is known about the underlying neural mechanism. This chapter gives an overview of recent research on the neural mechanism underlying cooperative hand movements. A task-specific neural coupling will be demonstrated as the main mechanism controlling cooperative hand movements and its function and dysfunction in poststroke subjects will be discussed. These novel aspects of normal and impaired hand movement control have consequences for rehabilitation of hand function in poststroke subjects. In the first part of this chapter, we will describe specific aspects of neural control of cooperative hand movements. In the second part, we will discuss the neural adaptations of the impaired task-specific control in poststroke subjects and in the last part we will establish the consequences of the first two parts for the rehabilitation of hand function and implementation of new technology.

6.2 Task-Specific Neural Control of Hand Function: Neural Coupling

Many daily life activities require cooperative hand movements. Therefore it is surprising to see that little is known about their neural control [17]. Recently, a task-specific neural coupling during cooperative hand movements has been described [18]. Exclusively during dynamic cooperative hand movements (e.g., opening a bottle), a distinct contralateral EMG response pattern (N2–P2 complex) appears in forearm muscles with approximately the same latency (80 ms) as the late reflex complex (N2–P2) in the forearm muscles of the ipsilateral, stimulated side (Fig. 6.1). In accordance with previous electrophysiological research on hand function that has focused mainly on the execution of unilateral or separate bimanual movements, a task-dependent amplitude modulation of unilateral EMG responses in upper limb muscles with larger amplitudes during a dynamic compared with a static muscle contraction was described [18–20]. Also, only ipsilateral EMG responses to arm nerve stimulations were recorded in synchronously performed pro-/supination movements of both hands [11, 18]. This reflex behavior differs profoundly from that found during

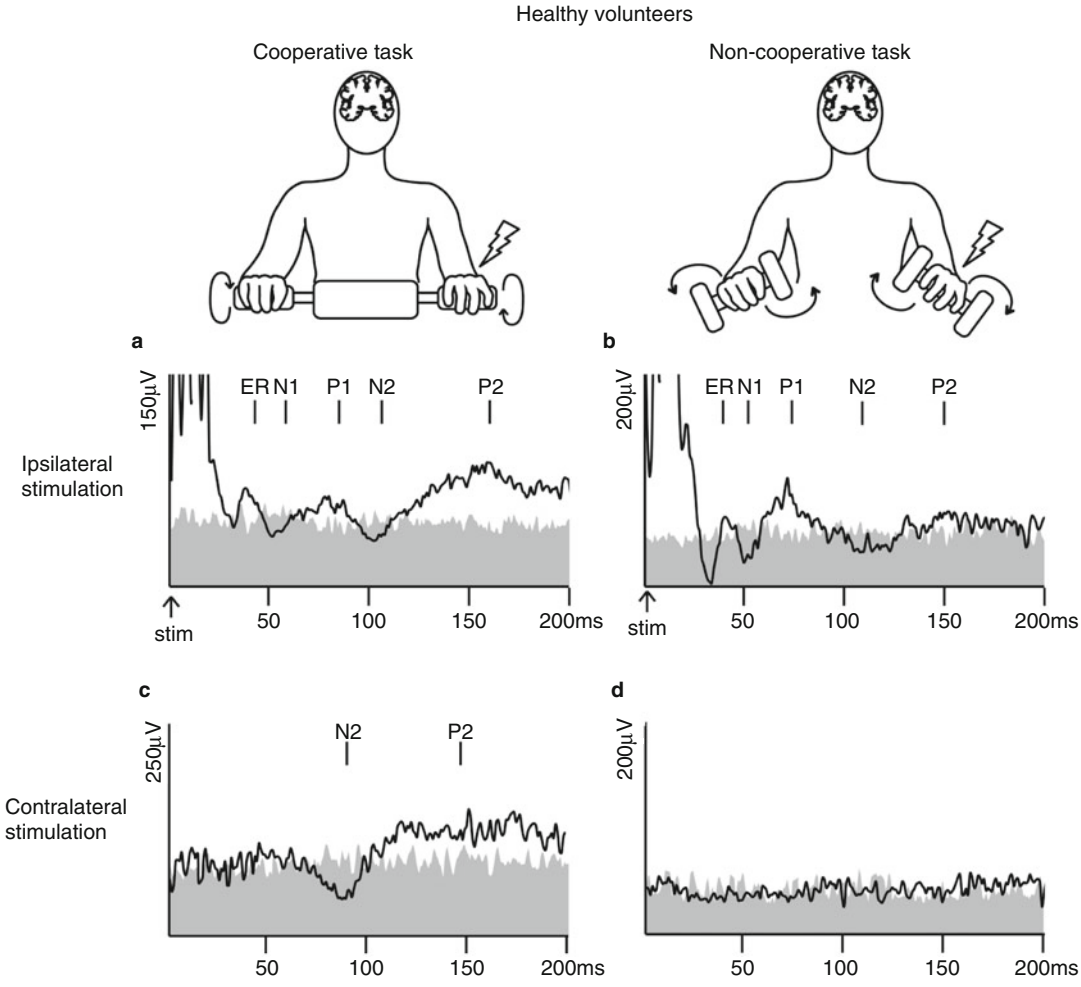

Fig. 6.1 Reflex responses during a cooperative and a noncooperative control task in healthy volunteers. Grand averages ($n = 24$) of the EMG recordings in forearm muscles of the nondominant (**a**, **b**) and the dominant (**c**, **d**) arm following electrical unilateral ulnar nerve stimulation on the nondominant arm. Ipsilateral responses (**a**, **b**) are similar for both task and consist of an early reflex response (ER) followed by a first component composed of a first negativity (N1) and a first positivity (P1) followed by a late component (N2 and P2). On the contralateral side, a reflex response is only observed during the cooperative task. This response only consists of the late components, i.e., N2 and P2. The stimulation artifact lasting for the first 20 ms is seen in both tasks in the ipsilateral muscles. *Upper* part: schematic drawings of the movement tasks performed and stimulation site. *Shaded* areas represent the level of background EMG. *Vertical arrows* in (**a**) and (**b**) indicate the onset of electrical stimulation. Note the different calibrations

cooperative hand movements, the latter being a novel observation. Therefore, different neural circuitries are suggested to be involved during cooperative and noncooperative bimanual hand movements.

The bilateral distribution of reflex responses elicited by a unilateral afferent volley reflects a task-specific, functionally meaningful, neural coupling of upper limbs. That is, the processing of an artificial afferent input produced by nerve stimulations is processed by coupled neural circuits within both hemispheres. This coupling seems to depend on the execution of cooperative hand movements, as the neural coupling does not occur when the task is mimicked in a static condition or during a bimanual pro-/supination task.

A corresponding observation of a task-specific neural coupling, i.e., the appearance of bilateral

arm muscle responses to unilateral leg nerve stimulation during locomotion in healthy subjects [21], has recently been described. Although locomotor function differs basically from cooperative hand movements, the underlying mechanism of a task-dependent neural coupling of limbs might be achieved in a similar way [22].

Based on fMRI findings [18], it is suggested that the pathways and brain areas involved in the control of cooperative hand movements and in the generation of the bilateral reflex responses to unilateral nerve stimulation are partly reflected in the task-specific bilateral activation of secondary somatosensory (S2) cortical areas. Using a different setup, this assumption is supported by observations in humans [23] and nonhuman primates [24] where it could be shown that S2 cortical areas of both hemispheres receive afferent inputs from receptor fields of both hands.

S2 is suggested to be involved in the exchange and integration of information from both sides of the body [25]. After unilateral limb stimulation, S2 cortices of both hemispheres are activated and thus S2 is thought to have a role in combining somatosensory information from the two sides of the body to allow its interhemispheric unification [26]. This assumption is in line with the fMRI results obtained during cooperative hand movements [18]. In addition, the spatial extent of fMRI activation in the S2 (and ventral parietal) cortical areas in humans is larger for bilateral than for unilateral hand stimulations [23]. This further supports the suggestion that the S2 areas are engaged and required in the interhemispheric processing of afferent input during cooperative hand movements. In addition, a functional connectivity analysis shows that the left and right S2 areas (in addition to M1) are functionally connected only during the cooperative task [18]. Thus, a stronger connectivity between the right and the left S2 exists for a cooperative hand movement task in comparison to a bimanual pro-/supination task. This finding supports the idea of an interaction and coupling between the two cortical areas involved in the execution of the cooperative task.

Nonsubtracted fMRI data show robust non-task-specific activation of the SMA, PMC, and M1 in many bimanual and also cooperative, hand movements. Consequently, these cortical areas are obviously nonspecifically involved in bimanual movement tasks. The main difference in the neural organization of cooperative hand movements is the stronger involvement of the S2 cortical areas compared to other bimanual in- and out-phase movement tasks.

The role of sensory input to both the ipsi- and contralateral cortex during a cooperative hand movement task becomes apparent when somatosensory evoked potentials (SSEP) from the ulnar nerve are recorded over the ipsi- and contralateral cortex during cooperative and noncooperative hand movements [27]. In relation to the resting condition, the amplitudes of both the ipsi- and the contralateral potential are reduced during cooperative and noncooperative tasks. The reduction in amplitude is similar for the ipsi- and the contralaterally recorded potentials in the noncooperative task. However, during the cooperative task the ipsilateral potential is less reduced compared to the contralateral side. Consequently, the ratio of ipsi-/contralateral SSEP amplitude is significantly larger during the cooperative task when compared to the control task. This indicates a major functional role of ipsilateral pathways connecting the cervical spinal cord with the cortex during the cooperative hand movement task. These observations favor the idea of a task-specific mediation of sensory input from both hands to the ipsi- and contralateral hemispheres, respectively, as the basis of neural coupling.

6.3 Neural Control of Cooperative Hand Movements in Poststroke Subjects

In poststroke patients, it is known that both anticipatory postural adjustments [28] and bimanual coordination, due to somatosensory limitations [29], are reduced. Also the task-specific neural coupling previously discussed in this chapter is defective after a stroke [30]. The extent of the impairment is related to the clinical impairment of motor function. Electrical nerve stimulation of the unaffected arm leads to bilateral forearm EMG responses with characteristics similar to those obtained in healthy subjects. In contrast,

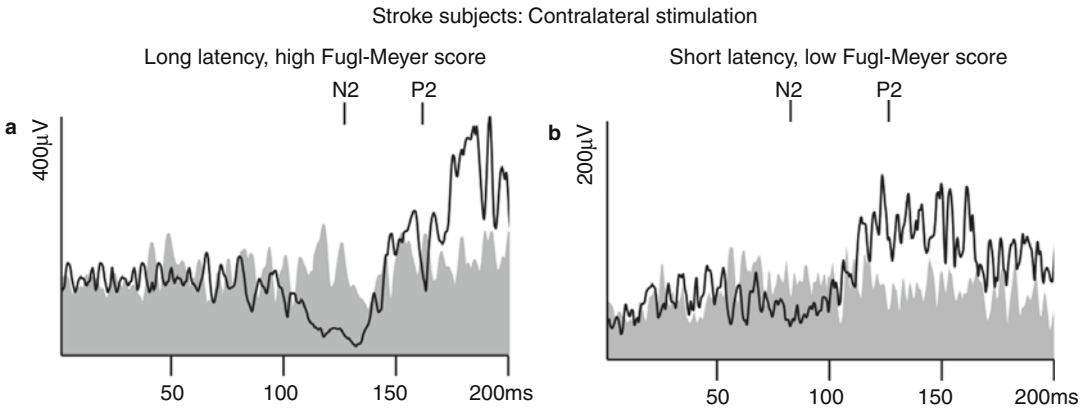

Fig. 6.2 Contralateral reflex responses in stroke subjects during cooperative movement task. Averages of EMG recordings from the affected side to 15 nerve stimulations of the unaffected side of an exemplary patient with a high Fugl-Meyer score and longer (compared to healthy subjects) N2 latency (**a**) and a low Fugl-Meyer score and shortened N2 latency (**b**). The N2 latency seen in A is somewhat longer than that observed in healthy volunteers, indicating a slower processing of afferent input. The latency seen in B is shorter than those observed in healthy volunteers, indicating an involvement of ipsilateral efferent, non-crossing pathways. Shaded areas represent the level of background EMG. Note the different calibrations

nerve stimulation of the affected arm usually elicits only ipsilateral EMG responses [30].

This striking discrepancy in poststroke patients between the lack of contralateral responses in unaffected arm muscles following stimulation of the affected arm and the frequently preserved contralateral responses on the paretic side following stimulation of the unaffected arm indicates an impaired processing of afferent input from the paretic side but a largely preserved efferent reflex transmission to affected arm muscles. This suggests that the processing of afferent input by the corticospinal tract [31] is disproportionately affected after stroke with regard to the generation of efferent output. This is the case although in the clinical testing of these patients the paresis dominates while light touch perception is only slightly impaired on the affected side. The findings are in line with the alteration of a task-specific neural coupling during locomotion in stroke subjects [32]. Stimulation of the tibial nerve of the unaffected leg produces normal EMG responses in bilateral proximal arm muscles, but stimulation of the paretic leg elicits neither ipsilateral nor contralateral reflex responses in the arms. This was also assumed to be due to an impaired processing of afferent input by the damaged corticospinal tract.

The defective neural coupling is related to the severity of paresis of the affected arm. In patients with a low Fugl-Meyer (FM) score, both contralateral reflex responses, i.e., in the paretic as well as in the unaffected arm, are absent while moderately affected patients show the above-described preservation of the contralateral reflex in the affected arm and mildly affected patients do not differ from healthy individuals. Such an observation is important as, after CNS damage, improvement in function depends on the training of both motor tasks required in daily life activities (ADL) and those based on specific neural control [33]. Consequently, cooperative hand movements should be included in training approaches following a stroke. However, rehabilitation of hand function is currently mainly focused on unimanual reach and grasp function of the affected arm and hand.

The largely preserved efferent output on the paretic side may be explained by transmission of the efferent EMG volley to the contralateral, paretic limb via an alternative pathway. A suggestion for this pathway is the ipsilateral, non-crossing corticospinal tract or the cortico-reticulo-propriospinal pathway of the undamaged hemisphere. These fibers can in healthy subjects be activated under specific conditions [34, 35]. It is also assumed that ipsilateral tract fibers become involved in movement performance after stroke for a partial compensation of the deficit on the

paretic side [36]. The observation that severely affected patients with low FM scores show shorter N2 latencies of the contralateral responses in the affected arm than healthy volunteers (Fig. 6.2) would support such an assumption. It would imply the recruitment of ipsilateral pathways replacing or compensating for the defective interhemispheric interactions [37]. Ipsilateral fibers of the corticospinal tract may, in fact, play an important role in stroke recovery especially in patients with more severe lesions (for a review see [38]). However, one has to be aware that in such cases motor deficits and functional impairments can concern both ipsi- and contralesional arms [39]. The pathways suggested to be involved in bimanual separate and cooperative movements in healthy subjects as well as in poststroke subjects are displayed in Fig. 6.3.

6.4 Consequences for Therapy and Robotic Devices

After stroke, impairment of the affected limb is usually compensated by utilizing the unaffected limb, leading to the nonuse phenomenon [40]. To avoid this, constraint-induced movement therapy (CIMT) [41] is well established. This approach demands exclusive training of the affected arm/hand. No clear evidence of superiority has been demonstrated when CIMT became compared with bimanual training [42–44]. However, bimanual training of reaching and grasping tasks in stroke patients has been shown to be more

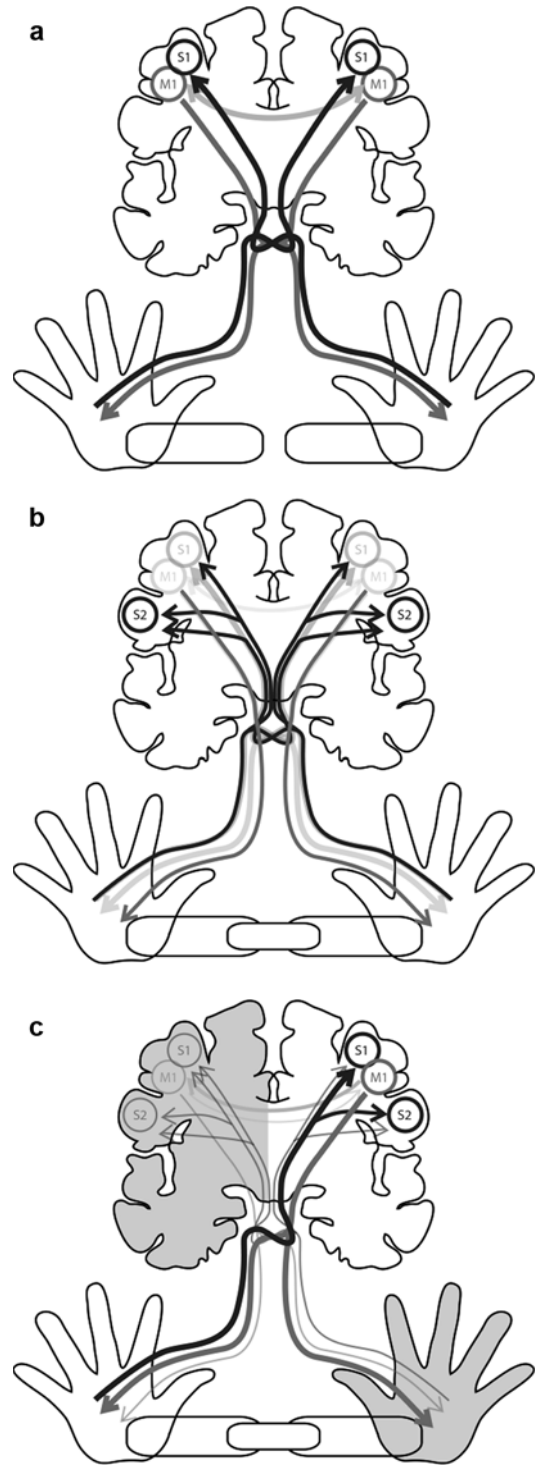

Fig. 6.3 Schematic illustration of the pathways involved in bimanual movement control. This illustration shows the pathways suggested being involved in the neural control of bimanual separate (e.g., pro-/supination movements (**a**) and in cooperative movements of healthy (**b**) and poststroke (**c**) subjects. During cooperative movements in addition to the pathways involved controlling bimanual separate hand movements, ipsilateral, non-crossing ascending and descending pathways as well as S2 cortical areas become involved and play a role in the compensation of sensorimotor deficits after stroke

effective in improving unilateral execution of these tasks with the affected arm than unilateral training alone [45]. And there is also some evidence in poststroke patients that ipsilateral pathways from the unaffected hemisphere support movement performance of the affected limb during bimanual movements. For example, the observation that stroke patients perform a simple tapping task faster when they use both arms/hands compared to execution of the task only with the paretic arm/hand [46] is in line with the idea of an involvement of the unaffected hemisphere in task performance. Furthermore, children with cerebral palsy can use mirrored movements to accomplish a task with the more affected arm [47, 48].

Based on experiments in rodents, improvement of function appears to depend on the specific task and its underlying neural control to be trained (for a review [33, 49]). Therefore, current approaches to exploit neuroplasticity after stroke are directed at training specific motor tasks required during ADL. The neural coupling mechanism underlying cooperative bimanual movements should therefore also be included in the rehabilitation of hand function after a stroke as many ADL require bimanual cooperation. A single-subject pilot study comparing cooperative training to conventional occupational therapy has in fact indicated an enhanced improvement in affected hand function due to cooperative training [50]. This field nevertheless remains in need of further experimental and clinical studies [51].

A wide variety of rehabilitation technologies for upper limb training after stroke are available today (for review cf. [52]). Robot-assisted training has shown superior effects on functional improvements in poststroke patients when compared to conventional therapy [53, 54]. Currently available robotic devices provide training for the affected hand, e.g., Amadeo [55], or arm, e.g., Armeo [56] or MIT-Manus [57], or for bimanual training, e.g., Bi-Manu-Track [58], or mirror movement training, e.g., MIME [59] (for review cf. [60]). However, none of these devices enables support for the training of cooperative hand movements and, thereby, the neural coupling mechanism. We suggest that robot-assisted therapy should be complemented by a technology that allows training of cooperative hand and arm movements covering a great range of upper limb tasks needed in ADL.

References

1. Jenny AB. Commissural projections of the cortical hand motor area in monkeys. J Comp Neurol. 1979;188(1):137–45.
2. Rouiller EM, Babalian A, Kazennikov O, Moret V, Yu XH, et al. Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. Exp Brain Res. 1994;102(2):227–43.
3. Donchin O, Gribova A, Steinberg O, Bergman H, Vaadia E. Primary motor cortex is involved in bimanual coordination. Nature. 1998;395(6699):274–8.
4. Kermadi I, Liu Y, Tempini A, Calciati E, Rouiller EM. Neuronal activity in the primate supplementary motor area and the primary motor cortex in relation to spatio-temporal bimanual coordination. Somatosens Mot Res. 1998;15(4):287–308.
5. Tanji J, Okano K, Sato KC. Relation of neurons in the nonprimary motor cortex to bilateral hand movement. Nature. 1987;327(6123):618–20.
6. Theorin A, Johansson RS. Selection of prime actor in humans during bimanual object manipulation. J Neurosci. 2010;30(31):10448–59.
7. Debaere F, Swinnen SP, Beatse E, Sunaert S, Van Hecke P, et al. Brain areas involved in interlimb coordination: a distributed network. Neuroimage. 2001;14:947–58.
8. Kazennikov O, Hyland B, Corboz M, Babalian A, Rouiller EM, et al. Neural activity of supplementary and primary motor areas in monkeys and its relation to bimanual and unimanual movement sequences. Neuroscience. 1999;89:661–74.
9. Kermadi I, Liu Y, Rouiller EM. Do bimanual motor actions involve the dorsal premotor (PMd), cingulate (CMA) and posterior parietal (PPC) cortices? Comparison with primary and supplementary motor cortical areas. Somatosens Mot Res. 2000;17(3):255–71.
10. Stephan KM, Binkofski F, Halsband U, Dohle C, Wunderlich G, et al. The role of ventral medial wall motor areas in bimanual co-ordination. A combined lesion and activation study. Brain. 1999;122(Pt 2):351–68.
11. Swinnen SP. Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci. 2002;3:348–59.

12. Wiesendanger M, Serrien DJ. The quest to understand bimanual coordination. Prog Brain Res. 2004;143: 491–505.
13. Liuzzi G, Horniss V, Zimerman M, Gerloff C, Hummel FC. Coordination of uncoupled bimanual movements by strictly timed interhemispheric connectivity. J Neurosci. 2011;31(25):9111–7.
14. Ohki Y, Johansson RS. Sensorimotor interactions between pairs of fingers in bimanual and unimanual manipulative tasks. Exp Brain Res. 1999;127(1):43–53.
15. White O, Dowling N, Bracewell RM, Diedrichsen J. Hand interactions in rapid grip force adjustments are independent of object dynamics. J Neurophysiol. 2008;100:2738–45.
16. Lum PS, Reinkensmeyer DJ, Lehman SL. A Bimanual reflex during two hand grasp. Conference proceedings IEEE, Med Biol Soc, San Diego, 1993. p. 1163–4.
17. Obhi SS. Bimanual coordination: an unbalanced field of research. Motor Control. 2004;8(2):111–20.
18. Dietz V, Macauda G, Schrafl-Altermatt M, Wirz M, Kloter E, et al. Neural coupling of cooperative hand movements: a reflex and FMRI study. Cereb Cortex. 2015;25(4):948–58.
19. Datta AK, Harrison LM, Stephens JA. Task-dependent changes in the size of response to magnetic brain stimulation in human first dorsal interosseous muscle. J Physiol. 1989;418:13–23.
20. Zehr EP, Kido A. Neural control of rhythmic, cyclical human arm movement: task dependency, nerve specificity and phase modulation of cutaneous reflexes. J Physiol. 2001;537(Pt 3):1033–45.
21. Michel J, van Hedel HJ, Dietz V. Obstacle stepping involves spinal anticipatory activity associated with quadrupedal limb coordination. Eur J Neurosci. 2008;27(7):1867–75.
22. Dietz V, Fouad K, Bastiaanse CM. Neuronal coordination of arm and leg movements during human locomotion. Eur J Neurosci. 2001;14(11):1906–14.
23. Disbrow E, Roberts T, Poeppel D, Krubitzer L. Evidence for interhemispheric processing of inputs from the hands in human S2 and PV. J Neurophysiol. 2001;85(5):2236–44.
24. Whitsel BL, Petrucelli LM, Werner G. Symmetry and connectivity in the map of the body surface in somatosensory area II of primates. J Neurophysiol. 1969; 32(2):170–83.
25. Lin YY, Forss N. Functional characterization of human second somatosensory cortex by magnetoencephalography. Behav Brain Res. 2002;135(1–2):141–5.
26. Hari R, Hanninen R, Makinen T, Jousmaki V, Forss N, et al. Three hands: fragmentation of human bodily awareness. Neurosci Lett. 1998;240(3):131–4.
27. Schrafl-Altermatt M, Dietz V. Task-specific role of ipsilateral pathways: somatosensory evoked potentials during cooperative hand movements. Neuroreport. 2014;25(18):1429–32.
28. Massion J, Ioffe M, Schmitz C, Viallet F, Gantcheva R. Acquisition of anticipatory postural adjustments in a bimanual load-lifting task: normal and pathological aspects. Exp Brain Res. 1999;128(1–2):229–35.
29. Torre K, Hammami N, Metrot J, van Dokkum L, Coroian F, et al. Somatosensory-related limitations for bimanual coordination after stroke. Neurorehabil Neural Repair. 2013;27(6):507–15.
30. Schrafl-Altermatt M, Dietz V. Cooperative hand movements in stroke patients: neural reorganization. Under revision. 2016.
31. Lemon RN. Descending pathways in motor control. Annu Rev Neurosci. 2008;31:195–218.
32. Kloter E, Wirz M, Dietz V. Locomotion in stroke subjects: interactions between unaffected and affected sides. Brain. 2011;134(Pt 3):721–31.
33. Edgerton VR, Tillakaratne NJ, Bigbee AJ, de Leon RD, Roy RR. Plasticity of the spinal neural circuitry after injury. Annu Rev Neurosci. 2004;27: 145–67.
34. Bradnam LV, Stinear CM, Byblow WD. Theta burst stimulation of human primary motor cortex degrades selective muscle activation in the ipsilateral arm. J Neurophysiol. 2010;104(5):2594–602.
35. Howatson G, Taylor MB, Rider P, Motawar BR, McNally MP, et al. Ipsilateral motor cortical responses to TMS during lengthening and shortening of the contralateral wrist flexors. Eur J Neurosci. 2011;33(5): 978–90.
36. Baker SN. The primate reticulospinal tract, hand function and functional recovery. J Physiol. 2011; 589(Pt 23):5603–12.
37. Edwards JD, Meehan SK, Linsdell MA, Borich MR, Anbarani K, et al. Changes in thresholds for intracortical excitability in chronic stroke: more than just altered intracortical inhibition. Restor Neurol Neurosci. 2013; 31:693.
38. Teasell R, Bayona NA, Bitensky J. Plasticity and reorganization of the brain post stroke. Top Stroke Rehabil. 2005;12(3):11–26.
39. Schaefer SY, Haaland KY, Sainburg RL. Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. Brain. 2007; 130(Pt 8):2146–58.
40. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys. 2006;42:241–56.
41. Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation – a clinical review. J Rehabil Res Dev. 1999;36(3):237–51.
42. Stoykov ME, Lewis GN, Corcos DM. Comparison of bilateral and unilateral training for upper extremity hemiparesis in stroke. Neurorehabil Neural Repair. 2009;23:945–53.
43. van Delden AL, Peper CL, Beek PJ, Kwakkel G. Match and mismatch between objective and subjective improvements in upper limb function after stroke. Disabil Rehabil. 2013;35(23):1961–7.
44. Lin KC, Chen YA, Chen CL, Wu CY, Chang YF. The effects of bilateral arm training on motor control and functional performance in chronic stroke: a randomized controlled study. Neurorehabil Neural Repair. 2010;24(1):42–51.

45. Mudie MH, Matyas TA. Can simultaneous bilateral movement involve the undamaged hemisphere in reconstruction of neural networks damaged by stroke? Disabil Rehabil. 2000;22(1–2):23–37.
46. Jung R, Dietz V. Delayed initiation of voluntary movements after pyramidal lesions in man (author's transl). Arch Psychiatr Nervenkr. 1975 Dec 31;221(2): 87–109.
47. Carr LJ, Harrison LM, Evans AL, Stephens JA. Patterns of central motor reorganization in hemiplegic cerebral palsy. Brain. 1993;116(Pt 5):1223–47.
48. Mayston MJ, Harrison LM, Stephens JA. A neurophysiological study of mirror movements in adults and children. Ann Neurol. 1999;45(5):583–94.
49. Buma F, Kwakkel G, Ramsey N. Understanding upper limb recovery after stroke. Restor Neurol Neurosci. 2013;31(6):707–22.
50. Schrafl-Altermatt M, Dietz V. Effect of cooperative hand movement training in post-stroke subjects: a single case study. Under review. 2016.
51. Sleimen-Malkoun R, Temprado JJ, Berton E. A dynamic systems approach to bimanual coordination in stroke: implications for rehabilitation and research. Medicina. 2010;46(6):374–81.
52. Laffont I, Bakhti K, Coroian F, van Dokkum L, Mottet D, et al. Innovative technologies applied to sensorimotor rehabilitation after stroke. Ann Phys Rehabil Med. 2014;57(8):543–51.
53. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002;83:952–9.
54. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2): 159–66.
55. Sale P, Lombardi V, Franceschini M. Hand robotics rehabilitation: feasibility and preliminary results of a robotic treatment in patients with hemiparesis. Stroke Res Treat. 2012;2012:820931.
56. Guidali M, Duschau-Wicke A, Broggi S, Klamroth-Marganska V, Nef T, et al. A robotic system to train activities of daily living in a virtual environment. Med Biol Eng Comput. 2011;49(10):1213–23.
57. Ang KK, Chua KS, Phua KS, Wang C, Chin ZY, et al. A Randomized controlled trial of EEG-based motor imagery brain-computer interface robotic rehabilitation for stroke. Clin EEG Neurosci. 2015;46(4):310–20.
58. Formaggio E, Storti SF, Boscolo Galazzo I, Gandolfi M, Geroin C, et al. Modulation of event-related desynchronization in robot-assisted hand performance: brain oscillatory changes in active, passive and imagined movements. J Neuroeng Rehabil. 2013;10:24.
59. Lum PS, Burgar CG, Shor PC. Evidence for improved muscle activation patterns after retraining of reaching movements with the MIME robotic system in subjects with post-stroke hemiparesis. IEEE Trans Neural Syst Rehabil Eng. 2004;12(2):186–94.
60. Basteris A, Nijenhuis SM, Stienen AH, Buurke JH, Prange GB, et al. Training modalities in robot-mediated upper limb rehabilitation in stroke: a framework for classification based on a systematic review. J Neuroeng Rehabil. 2014;11:111.

7 Clinical Assessment and Rehabilitation of the Upper Limb Following Cervical Spinal Cord Injury

Michelle Louise Starkey and Armin Curt

Abstract

The impairment of upper extremity function following a cervical spinal cord injury (SCI) has a significant impact on independence and quality of life due to its bilateral and often symmetrical nature. Upper extremity function following spinal cord injury is commonly assessed with clinical measures of capacity, performance, quantitative sensory testing, and surrogate markers such as electrophysiological and biomedical recordings. More recently novel techniques, such as the use of robotics and senor technology, are beginning to be employed for this purpose. Most currently these assessments are based on ordinal scales with rather subjective rating criteria, and for this reason, a new generation of objective and precise upper extremity functional assessment tests is required. For example, the RULER is a novel scale developed by the authors which is a detailed functional classification of the upper extremity and can distinguish different levels of impairment where changes between these levels can be considered clinically meaningful.

In order to effect changes in function that can be assessed with various devices, physical therapy training is essential. Therapy increases neural plasticity and thereby improves motor function. New rehabilitation therapies based on robots, passive workstations, functional electrical stimulation (FES) systems and novel sensor technology have been developed but mostly focus on the stroke field. Thus, despite huge promise and a large amount of research in stroke, the overall clinical value of these new technology-based therapies in SCI patients' still needs to be evaluated fully.

M.L. Starkey, MA, MSc, PhD (✉) • A. Curt
Spinal Cord Injury Research Lab,
Spinal Cord Injury Centre,
Balgrist University Hospital, University of Zurich,
340 Forchstrasse, 8008 Zurich, Switzerland
e-mail: mstarkey@paralab.balgrist.ch

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Keywords
Spinal cord injury • Upper extremity • Upper limb • Assessment • RULER • Rehabilitation • Robot • Sensor • Training

7.1 Introduction

Cervical spinal cord injury (SCI) results in either complete or incomplete paralysis of the upper and lower limbs due to either a total or partial loss, respectively, of motor and sensory function below the level of lesion [1, 2]. The functional impairment depends on which spinal cord segments are affected, but due to the somatotopic organisation of the spinal cord, i.e. the segmental innervation of sensory and motor nerves, the impairment of upper limb function following SCI can be accurately predicted once the location and extent of the injury are known (Fig. 7.1) [3]. As brain function is not usually affected after an SCI (unlike in stroke), motor planning and other functions related to movement initiation and control remain intact at the cortical level. Despite this, after a cervical SCI, movement control is affected by the disruption of afferent input to the spinal cord and the impairment of efferent output from the spinal cord. Therefore, in order to appropriately address the specific needs for recovery of arm and hand (upper extremity) function in tetraplegics, the exact impairment needs to be accurately assessed and the underlying pathophysiology needs to be taken into consideration.

In most cases cervical SCI leads to a bilateral impairment of upper extremity function, meaning that bimanual tasks, such as opening a jar, are affected. This means that, unlike in stroke, the SCI sufferer is not able to compensate for the loss of function in one limb with the less (or even non-affected) limb and therefore they are dependent on recovery of upper extremity function. This is in contrast to people suffering a stroke, peripheral nerve damage, and to a variable extent multiple sclerosis where impairments are either focal (in

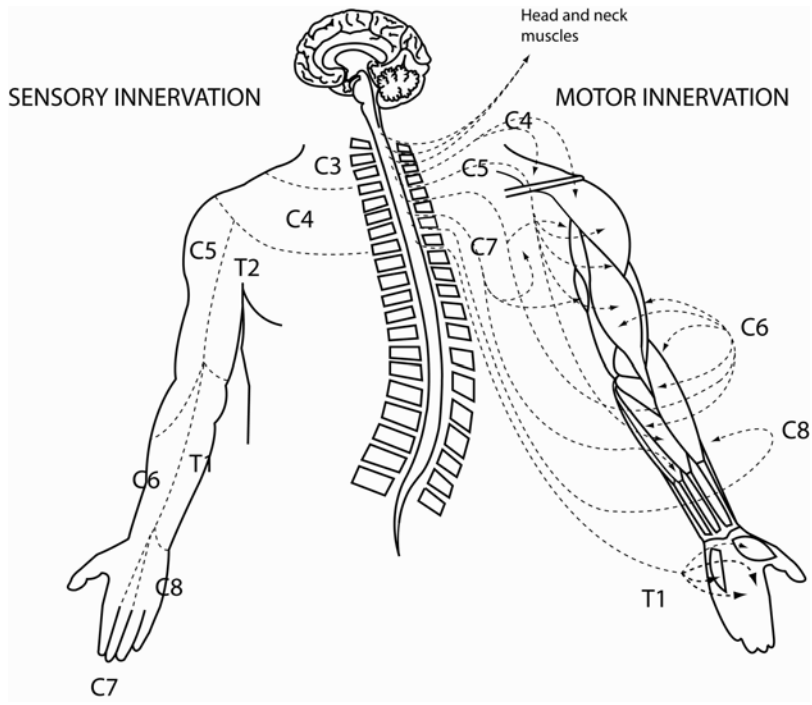

Fig. 7.1 Dermatomes (*left*) and myotomes (*right*) of the upper limbs are specifically innervated leaving typical maps of sensory and motor functions and deficits, respectively

stroke unilateral) or can affect multiple areas (in MS) of the CNS where one limb often remains, at best, functionally intact or at worst less affected than the other. Consequently, following a cervical SCI, one of the highest priorities for sufferers is recovery of upper extremity function [4, 5]. This is because useful function of the arms and hands is one of the main determinants of independence in activities of daily living (ADL) [6] which has a significant impact on quality of life. Therefore, the development and validation of suitable assessments and rehabilitation methods for the upper extremities following cervical SCI remains a highly relevant clinic goal.

To address this goal, considerable effort has been, and remains to be, focussed on the development of a number of novel devices for their ability to firstly assess functional loss of the upper extremity following SCI and secondly to aid rehabilitation in persons with tetraplegia. In the SCI field the most notable are robots [7–11], passive workstations [12–14], functional electrical stimulation (FES) [15–17], and sensor-based technology systems [18–20] which will be discussed in detail below. However, the clinical significance of these devices for evaluating and assessing recovery as well as their value in SCI rehabilitation remains to be established.

This chapter is organised as follows: Sect. 7.2 summarises the methods used to assess a spinal cord injury neurologically and functionally; Sect. 7.3 introduces methods used to measure upper extremity capabilities after spinal cord injury; Sect. 7.4 presents the RULER which is an important measure used for classifying upper limb and hand capacity following spinal cord injury; and finally Sect. 7.5 reviews the novel therapeutic approaches currently being used and developed for the rehabilitation of upper extremity function following spinal cord injury.

7.2 Neurological Assessment of the Functional Impairment After Spinal Cord Injury

Clinically an SCI is characterised by a combination of the neurological sensory and motor level, the completeness or incompleteness of the lesion, and the american spinal injury association (ASIA) impairment scale (AIS). There are International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) which are approved by the ASIA and the International Spinal Cord Injury Society (ISCoS) [21]. Multiple clinical measures, e.g. assessments of activity including quantitative motor and sensory function (motor-sensory scores), performance measures (ADLs), as well as clinical surrogate measures, e.g. electrophysiological and biomechanical recordings, are used to determine the initial deficit and subsequent recovery of upper extremity function following a cervical SCI. Except for measures of performance, these assessments evaluate specific, detailed functions and are mainly used to reveal the specific effects of interventions such as the torque generated, the joint angles achieved, and the range of motion (ROM) accomplished. These assessments tend to be carried out soon after the injury and throughout rehabilitation to document any changes in sensory and motor function that occur. The most common assessments are discussed below.

7.2.1 Electrophysiology

Electrophysiological measures used to assess an SCI consist of somatosensory evoked potentials (SSEP), contact heat evoked potentials (CHEP), motor evoked potentials (MEP), nerve conduction study (NCS), and electromyogram (EMG) recordings. SSEPs, CHEPs, and MEPs are electrical potentials recorded from predefined locations (i.e. scalp and muscles) following the stimulation of a sensory or motor nerve and reflect conditions within the peripheral and central nervous system, whereas NCS specifically reflects the condition of peripheral nerves and EMG and directly assesses the condition of the muscles.

7.2.1.1 Somatosensory Evoked Potential (SSEP)

SSEP are elicited by an electrical stimulus of a peripheral sensory or mixed nerve [22, 23]. The stimulus is applied to the skin and the evoked potential is recorded from the subject's scalp. The time taken for the sensory nerve fibres to

transmit the stimulus to the sensory areas of the brain is measured. These recordings can be used to assess the integrity of the spinal cord because when the nerve pathway is damaged, the signals from the peripheral nerve to the brain become either slowed, in the case of an incomplete lesion, or completely abolished, in the case of a complete lesion. Hence, during the course of rehabilitation, changes in the latency or amplitudes of the signal can be used to indicate changes in spinal cord and brain function.

7.2.1.2 Contact Heat Evoked Potential (CHEP)

The mechanisms underlying the generation of pain in pathogenic conditions following an SCI can be studied using a CHEP stimulator [24–26]. In CHEPs the stimulus is applied with a thermode that is placed directly on the skin to stimulate the thermal pain sensory receptors on Aδ (delta) and C fibres. The pulses of heat are delivered rapidly, with adjustable peak temperatures, to elicit the different warm/heat thresholds of the receptors. The resulting evoked potentials can be measured using scalp electrodes. CHEP are used to assess the condition of the spino-thalamic pathways (thermal and nociceptive sensation) and their relation to pain.

7.2.1.3 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 [3]. Transcranial electrical stimulation (TES) is applied through cutaneous electrodes, whereas transcranial magnetic stimulation (TMS) is generated with a magnetic field. In comparison to TMS, the main limitation of TES is that the electrical currents applied to the scalp can cause local discomfort. Either way the stimulus results in the contraction of a muscle contralateral to where the MEPs were applied and are recorded with surface electrodes. TMS is used as a diagnostic and follow-up tool for neurological disorders where the impairment and eventual recovery of the corticospinal tract are assessed.

7.2.1.4 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 corresponding muscle [27, 28]. In sensory NCS, the electrical stimulation is applied to a sensory peripheral nerve and electrical potentials are recorded from the sensory dermatome of the nerve. The F-wave and H-reflex are examples of NCS and represent different reflex responses within peripheral nerves and spinal segments, respectively. Although NCS is mainly used to diagnose peripheral nerve dysfunction (such as carpal tunnel and Guillain-Barré syndromes) and muscle disorders (such as muscle atrophy), it also provides useful information on spinal cord function, specifically when damage of alpha-motoneurons (traumatic or nontraumatic) results in an alteration of motor (but not sensory) NCS resulting in reduced or abolished compound muscle action potentials.

7.2.1.5 Electromyography (EMG)

EMG uses changes in the electrical potentials of muscle cells for diagnostic purposes [27, 28]. 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 localised muscle activity. Surface EMGs are used to assess gross muscle activation, whereas needle EMGs assess single muscle fibres. EMG is used to diagnose neurological and muscular disorders.

7.2.2 Biomechanical (Kinetic, Kinematic) Measures

Changes in biomechanical parameters of upper extremity function, such as muscle activity, muscle strength, joint angles, ROM and movement trajectories, can be measured with specific techniques, such as EMG, instrumented gloves, robotics and 3D motion capture systems as summarised in more detail below.

7.2.2.1 Assessment of Muscle Activity

The EMG recordings applying cup (surface) electrodes can also be used in biomechanics to measure muscular activity of the upper extremity during movements and thereby can be used to

evaluate the efficacy of new technology-based rehabilitation treatments.

7.2.2.2 Assessment of Muscle Strength

Digital-palmar prehensile strength can be measured using a Jamar dynamometer [29], a vigorimeter (a manometer with tubing and rubber ball) [30] or another type of manometer; for review see [31]. Unlike EMG the measured strength is generated by several muscles rather than a single muscle. The Jamar dynamometer displays a mass unit (kg or lb), whereas the manometers express a force unit (kp) or pressure unit (mmHg). According to Gansel, manometry is more sensitive and has a better reproducibility than the Jamar dynamometer for muscle forces below 2.3 kg [32]. Alternatively, thumb-index lateral prehensile strength can be measured using a Preston dynamometer (kgms or kg) [33], a B and L pinch gauge dynamometer (N) [29] or a pinch dynamometer (kg) [32].

7.2.2.3 Assessment of Angles, Range of Motion (ROM) and Trajectories

Upper limb passive and active joint flexion as well as ROM can be measured using traditional goniometry. However, simultaneous recordings of dynamic changes in joint angles and movement trajectories require the use of motion capture systems or instrumented gloves. For example, upper limb movements can be tracked with three dimensional motion systems. The most commonly used are based on optical tracking, for example, the Vicon system [34] and Qualisys [35]. In recent times gaming systems, such as the optical tracking system Kinect, are now also being used in the rehabilitation and assessment of upper limb function [36–38]. Additionally, inertial measurement systems such as the Xsens [39] can be used.

7.2.2.4 Assessment Using Instrumented Gloves

Instrumented gloves, often in combination with virtual reality, offer a relatively low-cost solution for tracking motion of the hand and fingers are increasingly being used in clinical research as novel assessment tools. For example, custom-designed gloves equipped with force and position transducers have been used to evaluate grasping in tetraplegic subjects [40], whereas other custom-designed gloves have been used to measure specific motor tasks performed with the hands during behavioural and functional magnetic resonance imaging studies [41]. Instrumented gloves have also been used to track the hand during training in virtual reality [42]. In another study the MusicGlove was used by stroke subjects to test its suitability as both an assessment tool and a training device [43]. The MusicGlove is an instrumented glove that helps the user train various hand movements whilst engaging in a motivating, music-based video game. The authors compared training with this glove to conventional therapy to see whether it provided better training and also to see if it could predict clinical scores. The authors reported that grasping functions were better after using the MusicGlove than after conventional therapy and that these effects lasted for up to one month post-training. Scores measured by the MusicGlove were also highly correlated with the Box and Block clinical assessments. Whilst the MusicGlove remains to be tested for its effectiveness in spinal cord injured subjects, these are promising initial findings.

However, as a word of caution, in a recent study the accuracy and precision of the measured joint angles of one example of such gloves, specifically the CyberGlove III, were evaluated [44]. The authors found that these gloves produced substantial errors so it follows that some caution should be applied to using such devices for clinical assessment. Recently, however, commercially available versions have been employed in rehabilitation research, such as the YouGrabber (YouRehab Ltd., Switzerland) which was not so far tested as an assessment device but was used to provide intensive virtual reality-based training for upper extremity in stroke subjects [45]. The YouGrabber has not been tested for clinical assessment and has not been used with SCI subjects thus far although it could potentially be useful for motivating rehabilitation in this population in the future. For a review of the use of virtual reality in upper extremity rehabilitation, see [46–49]. In conclusion, a proper evaluation of the value of

Fig. 7.2 Upper extremity training and assessment devices. This figure shows some devices that are already used for the training of the upper extremity. (**a**) The ARMinII device (Photo used with permission from Tobis Nef), (**b**) ReJoyce (Photo used with permission from Rehabtronics Inc.), (**c**) MIT-Manus (Photo used with permission from Joshua Dalsimer), (**d**) Ness Handmaster H200-3 (Photo used with permission from Bioness)

instrumented gloves in SCI rehabilitation and assessment remains to be performed.

7.2.2.5 Assessment Using Robotics and Other Novel Technologies

Robotics are also beginning to be applied in the assessment field for measuring upper extremity impairments and dysfunction as most are able to collect quantitative data about the users movements. Linking information collected by robotics with traditional clinical scores may allow more precise and perhaps also quicker assessments. Using robotics as novel assessment devices in the stroke field has been an area of research for a number of years. There are a broad range of devices used and outcomes assessed, for example [50–52]. However, it is much less common in the SCI field. In this context, the ArmeoSpring, a commercial gravity compensated device based on the T-WREX upper extremity robot (see below for further details), was tested to determine whether measurements taken by the robot are able to predict clinical scores in SCI subjects [53]. The authors showed that measurements taken with the device were able to provide relevant clinical predictions for a number of clinical scores and that the results were in line with previous similar studies with stroke subjects. Recently, in a significant advance, the specific assessment associated with the passive workstation ReJoyce (Fig. 7.2b), the ReJoyce Arm and Hand Function Test (RAHFT), was evaluated against standardised tests of arm function in stroke and SCI subjects and was shown to be valid. This means

that the RAHFT can provide a standardised assessment of arm and dexterous hand function either performed in the clinic or home environment by being administered remotely via the Internet [54], a first in this field.

In addition to novel robotic approaches to assessment, various other technologies are now being employed to assess function following spinal cord injury, for example, instrumented gloves [55] and novel sensor-based technology [56, 57, 58].

7.2.3 Discussion

Surrogate measurements are important to reveal changes in the neural and biomechanical conditions underlying impairments of upper extremity function. Such measures are important because they make it possible to evaluate the efficacy of new technology-based therapies and surgical interventions. Furthermore, seeing as the motivation of the subject plays an important role in the rehabilitation process even if these methods only pick up small, positive changes, this might be enough to positively influence the subject's motivation. However, it is important to note that it remains to be determined whether surrogate measurements actually correlate with clinically important changes in upper limb function.

7.3 Clinical Assessment of Upper Extremity Capabilities After Spinal Cord Injury

In addition to the measures and assessments mentioned above, following an SCI the patient's ability to accomplish tasks is also assessed. Clinical measures of capacity and performance typically consist of specific movements and/or ADL tasks that the patient has to perform within a standardised environment from which defined parameters are measured and scored according to a predefined scale. Various classifications exist (discussed in more detail below); the initial intention of developing such classifications was to provide a scale upon which the function of the upper extremity following tetraplegia or surgery (e.g. tendon transfers) could be compared [32, 59, 60]. Fattal distinguished two different classifications. The first was based on a metameric structure describing residual or lost dermatomes and myotomes, whilst the second was based on remaining or lost functions [32]. His classifications have been used to define upper extremity function in a wide number of settings. However, one of the most prominent upper extremity classifications in surgical restoration was the system developed by Moberg [61] and later modified by McDowell and co-workers [62]. This classification is based both on a metameric and functional description of the forearm and hand and consists of 11 groups. Groups 0–9 correspond to active muscles below the elbow, whilst the remaining group, called X, brings together all atypical functions. Except for group X, each group is characterised at the (metameric) sensory and motor level, as well as at the functional level. In addition, since grip is controlled by both vision and sensibility in the hand [61], vision is also tested in this classification. The sensory level is described by measuring cutaneous sensibility, whereas the motor level, by contrast, is defined by the remaining active muscles with a minimum strength of four on the MRC (British Medical Research Council) scale [63]. Finally, the functional level is characterised by the movements that can be carried out by the elbow, wrist and fingers.

7.3.1 Basic Characteristics of the Tests

The methods used to rate upper extremity 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. Of the tests developed specifically for SCI sufferers (Table 7.1), 40 % are based on single-handed movements and/or ADL tasks. It follows that tests based on single-handed and bimanual tasks are more suitable to assess upper limb function of cervical SCI as typically both arms are affected. The majority of tests detailed

Table 7.1 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-handed 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-anded/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 $r=0.87$ 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-anded/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-handed 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
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

(continued)

Table 7.1 (continued)

Instrument	Purpose	Proximal arm	Distal arm/hand	Time to complete	Method used	Parameter measured	Scoring	Reliability	Validity	Advantages	Disadvantages
GRT (Grasp and Release Test), 1994 [41]	Research tool, hand function in C5–C6 patients, neuroprosthesis evaluation	Not assessed	Forearm, wrist, hand grasp	90–150 min (both with/without neuropro-sthesis)	6 single-anded 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-handed 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 administration	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

in Tables 7.1, 7.2 and 7.3 evaluate the proximal arm and the distal arm/hand. However, some, e.g. the Thorsen Functional Test (Table 7.1) [69], the Sollerman Hand Function Test (Table 7.1) [71], the Grasp and Release Test (GRT, Table 7.1) [72], the Vanden Berghe Hand Function Test (Table 7.1) [73], the Jebsen Hand Function Test (Table 7.3) [77], the Minnesota Rate of Manipulation Test for Disability Evaluation (MRM, Table 7.3) [78] and the Box and Block test (Table 7.3) [76], concentrate on the distal arm/hand and do not assess the proximal part of the upper extremity at all. Although the Jebsen test does not fulfil the selection criteria owing to the fact that it failed in a validation test [79], we have included it in our table because it is frequently used with SCI sufferers.

7.3.2 Purpose of the Tests

The "Purpose" section of Tables 7.1, 7.2 and 7.3 indicates whether the tests were initially developed for use in the clinic, in occupational therapy practice, in research or in industry, for example, the MRM test was developed for industry in order to select workers with good manual skills. Furthermore, some tests were designed to evaluate specific interventions such as surgery, e.g. the Motor Capacity Scale (MCS, Table 7.1) [67] and the Vanden Berghe test (Table 7.1); FES-based therapy, e.g. the Thorsen test (Table 7.1); forced nonuse of the nonaffected arm, e.g. the Wolf Motor Function Test (WMFT) Table 7.2 [75]; or use of learned skills and orthotic devices after discharge, e.g. the Ranchos Los Amigos Hospital Functional Activities (RLAH, Table 7.1) test [74]. It follows that tests developed to assess changes in upper extremity function within a specific setting should be good for that specific purpose, for example, a test designed to evaluate FES-based therapies should be most sensitive and responsive for FES interventions, but is likely to be less optimal for assessing the effects of other interventions or for assessing general upper limb function. It is assumed that tests developed specifically for SCI subjects will be more sensitive and responsive for this community than general tests that are also applied in other neurological disorders. Although a large number of tests have been developed to assess upper limb function, only a limited number are specific for use after cervical SCI (Table 7.1).

7.3.3 Questionnaires

Some tests, such as the Tetraplegia Hand Activity Questionnaire (THAQ, Table 7.1) [68], the Capabilities of Upper Extremity Instrument (CUE, Table 7.1) [70], the RLAH (Table 7.1), the Disabilities of the Arm, Shoulder, and Hand (DASH, Table 7.3) [80] and the Canadian Occupational Performance Measure (COPM, Table 7.3) [81], are presented in the form of a questionnaire. The tests base their assessments on questions regarding the subject's ability to carry out either raw movements, specific ADL tasks or other activities that occur in daily life. In most cases the subject rates his/her own capacity to perform the task as well as their proficiency. The COPM questionnaire is an exception however. In the COPM the patient identifies the areas of daily functioning that he/she experiences as specifically problematic (personal goal setting) and, together with the therapist, establishes therapeutic goals and specific treatments and evaluates the outcome. In the evaluation of the outcome, the patient rates his/her ability to perform the task and their satisfaction with their current performance. Thus, the COPM emphasises the importance of the subject's perception of their needs and their self-satisfaction with the therapy and gives the subject the notion that he/she is a fundamental part of the therapeutic process. The advantage of questionnaires is that the answers can be collected by telephone interview and the raw movements and/or ADL tasks involved can be performed by the patient themselves. However, for most questionnaires there is no examiner present to verify that the patient has performed the ADL task correctly. Furthermore, if the patient wants to please the interviewer, this can generate a bias in the answers [32].

Table 7.2 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
GRASSP (Graded and Redefined Assessment of Strength, Sensibility and Prehension), 2008 [64, 65]	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 filament 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	[32] $n=72$, inter-rater ICC = 0.84–0.96, test-retest ICC = 0.86–0.98 $p<0.0001$	[32] $n=72$, 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-handed specific; test kit has to be purchased
VLT-SV (Short Version of the Van Lieshout Test for Arm/ Hand Function), 2006 [66]	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 [67]	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 [68]	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 [69]	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-handed specific
CUE (Capabilities of Upper Extremity Instrument), 1998 [70]	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
Sollerman Hand Function Test, 1995 [71]	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 [72]	Research tool, hand function in C5–C6 patients, neuropro-sthesis evaluation	Not assessed	Forearm, wrist, hand grasp	90–150 min (both with/without neuropro-sthesis)	6 single-handed basic ADL tasks	Ability to pass or fail task within a given time	Number of passed/failed tasks	[40] $n=19$, test-retest ICC = 0.87–1 $P<0.01$	[40] $n=19$, 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-handed specific, based only on time not on movement quality

(continued)

Table 7.2 (continued)

Instrument	Purpose	Proximal arm	Distal arm/hand	Time to complete	Method used	Parameter measured	Scoring	Reliability	Validity	Advantages	Disadvantages
Vanden Berghe Hand Function Test, 1991 [73]	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	Ti-me (s), 0–3	Not available	Not available	Easy administration	Neither tested for validity nor reliability, proximal arm not assessed, specific for surgery evaluation
RLAH (the Ranchos Los Amigos Hospital Functional Activities Test), 1980 [74]	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 7.3 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 [75]	Research tool, upper limb function, forced nonuse 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 (lbs)	[44] $n=19$, inter-rater ICC = 0.95–0.99 $P<0.0001$	[44] $n=19$, FMA $\rho=0.61$ $P<0.02$	Norm values	Low validation correlation, specific for forced nonuse of non-affected arm therapy evaluation, single-handed specific, movement quality scoring reported to be described in non-existing reference
ARAT (Action Research Arm Test), 1981 [76]	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-handed specific
Fugl-Meyer Test, 1975 [76]	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-handed/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	[49] $n=12$, inter-rater ICC = 0.97 [50] $n=19$ intra-rater $r=0.995$ $p<0.001$, inter-rater $r=0.990$ $p<0.001$	[51] $n=50$, DeSouza test $r=0.97$ $\rho=0.95$	Assesses different parameters, very rapid	Whole body function test, no ADL tasks, single-handed/arm specific, ceiling effect observed [44]

7.3.4 Measures of Capacity and Performance

Clinically, speaking measurement of capacity refers to the ability of the subject to carry out a task, such as an assessment task, whereas measurement of performance assesses how well the subject actually did the task, how good their execution of the task was or how well they performed. Thus, whereas tests of capacity tend to measure specific parameters precisely, and therefore are reliable, they do not reflect reality because the subject was asked to perform a specific test for assessment rather than the rater observing how they behave in daily life. On the other hand, tests of performance evaluate the accomplishment of tasks in daily life and therefore better reflect reality but are less precise because they do not measure a specific parameter but rather how the subject is able to do things in their daily life. An example of this is the SCIM test. The SCIM is scored following the observation of what a patient actually does in their daily life and not what he/she might be able to do, although some caution needs to be taken with such measures as the patient-reported abilities and independence scores can differ from investigator-determined scores [82].

Clinical measures of upper extremity capacity and performance tend to be based on various items, such as time and ordinal ratings as well as counts, or weighing.

7.3.5 Measurement of Time

The time necessary to complete a test is not only a sensitive assessment parameter to assess function but is also relevant in clinical practice where tests lasting less than 30 min are optimal because they can be easily applied during clinical sessions that often last one hour. Tests based mainly on timing, such as the Jebsen test, the MRM, the GRT and the Box and Block test, are objective but do not rate quality of movement and as a result they cannot differentiate normal from compensatory movements nor can they distinguish between a subject who cannot perform a grasp pattern and one who can execute a grasp pattern but cannot complete a given task. Of the tests in Tables 7.1, 7.2 and 7.3, 89 % are based on ordinal rating, 42 % on timing, 16 % on counting and 5 % on weighing.

7.3.6 Ordinal Scales

Ordinal scales generally rate the grasp pattern or the capacity to execute a task and hence are subjective and somewhat imprecise. Among the 19 tests summarised in Tables 7.1, 7.2 and 7.3, only ten use ordinal rating alone whilst seven use it in combination with another type of measurement. For example, in the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) counting, ordinal rating (when scoring the Semmes-Weinstein Monofilaments) and time to complete a task are all used as factors. Thus, most of the tests of upper extremity capacity and performance are based on ordinal ratings and are, as a result, subjective and somewhat imprecise. Assessments of capacity such as GRASSP (Table 7.1) [64, 65, 83], the Van Lieshout Test Short Version (VLT-SV, Table 7.1) [66] and the MCS (Table 7.1) are based on specific movements and/or ADL tasks that the subject carries out in an artificial environment (in a laboratory or in the clinic) for evaluation, whereas tests of performance such as the THAQ (Table 7.1), the RLAH (Table 7.1) and the COPM (Table 7.1) instead assess ADL tasks that the patient executes in daily life (at home or work).

7.3.7 Prehension Patterns

The analysis of prehension patterns during the performance of ADL tasks plays an important role in tests that evaluate upper extremity function, in particular in tests of capacity. Indeed, most capacity tests are based on raw movements and/or ADL tasks that are selected to test specific types of grasp. Numerous taxonomies of prehension have been established as described by McKenzie and Iberall [84]. We have identified the most common types of grasp from the taxonomies of Sollerman [85], Schlesinger [86] and Light [87] (Fig. 7.3). It should be noted that in the

literature some of these grasps are referred to by other names, for example, the pulp pinch is often also referred to as the palmar pinch and the transverse volar grip is commonly called the cylindrical grasp.

From both an anatomical and a functional perspective, Napier distinguishes two basic patterns of hand movement called precision and power grip [88]. Accordingly the precision grip is performed during activities that require high precision, whilst the power grip is used in activities that necessitate power. These grips can be performed either separately or in combination and embody the whole range of prehensile patterns. In the precision grip, the object is pinched between the flexor side of the fingers and the opposing thumb. In the power grip, by contrast, the object is held in a clamp between the flexed fingers and the palm with the thumb applying more or less counterpressure. Thus, these two movements are distinct both in the anatomical and functional sense. The theory of Napier is that although the size and shape of an object may influence the type of prehension employed, it is

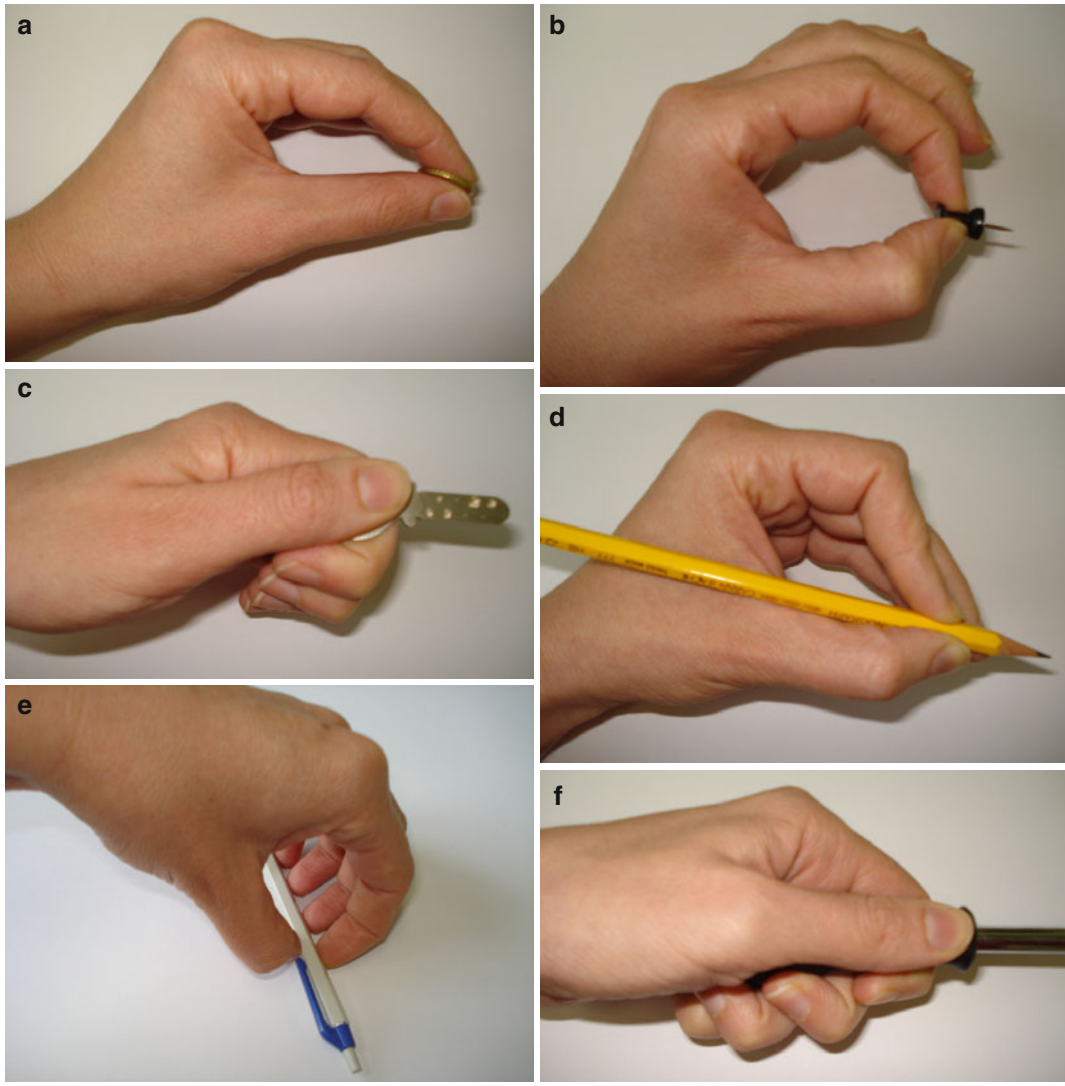

Fig. 7.3 (**a**) The pulp pinch, (**b**) the tip pinch, (**c**) the lateral pinch, (**d**) the tripod pinch, (**e**) the five-finger pinch, (**f**) the diagonal volar grip, (**g**) the transversal volar grip, (**h**) the spherical volar grip, (**i**) the extension grip and (**j**) the hook grip

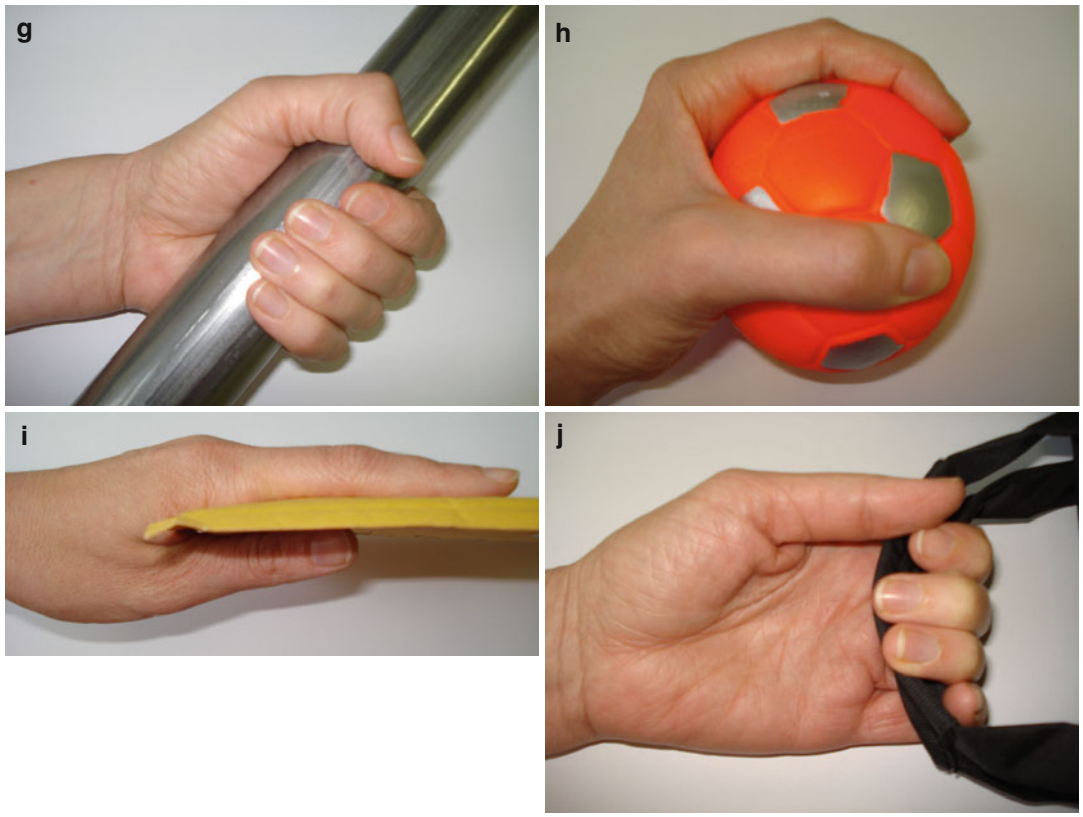

Fig. 7.3 (continued)

actually the nature of the intended activity that ultimately influences the type of grip. This theory is shared by Cutkosky, who constructed a taxonomy of manufacturing grasps [89]. In his classification, grasp patterns are divided into two main types, power grips and precision grips. Some grips belong to one group, whereas others, such as the spherical volar grip, belong to both.

7.3.8 Minimal Clinically Important Difference

Clinical measures of capacity evaluate very specific details and hence the observed changes might not correlate well with the clinical appreciation, i.e. the clinicians' or the patients' perceived value of the outcome. The minimal clinically important difference (MCID) is defined as the smallest change in a measurement that signifies an important improvement from the patients' and/or clinicians' perspective [90]. MCID should not be confused with the minimum detectable difference (MDD) which is a statistical concept that determines the smallest real change in an outcome which is beyond measurement error. A valid MCID therefore cannot be less than the MDD. MCID was first introduced in 1989 as a way of determining whether a difference in a treatment effect between the experimental and control group was of value to the people with the disorder [91]. At this time the exact definition of MCID was "the smallest difference in score, within the domain of interest, which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive costs, a change in the patients management" [91]. Hence, the definition of MCID is not only subjective but also needs to be defined for every outcome (measurement device) and potentially

every stage of injury as someone that has lived with a spinal cord injury for some time may have a different perception of the value of a treatment than someone who is acutely experiencing it. Thus, MCID estimates are very difficult to determine. A discussion of the considerations when defining MCID is reviewed here [92]. Regardless, the MCID is required for an appropriate understanding of the effects on the person of a particular treatment. 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 effect on ADL is probably less important. Whilst both changes might be significant in a group evaluation, they are likely to have a different impact on the patient's condition due to where they lie in the scoring scale. Ultimately, however, the MCID is based on judgement of clinicians and/or patients about how they rate the observed changes with regard to a meaningful change, and hence, this is a subjective judgement and the reason for a lot of debate over this score.

7.3.9 Reliability and Validity of Testing

The reliability and validity of tests that assess upper limb function has been studied to ensure that the tests are precise and accurate. Reliability is defined as the reproducibility of the results obtained when the test is administrated repeatedly [93]. Evaluation of the reproducibility can be performed by the same rater (intra-rater reliability), by different raters (inter-rater reliability) or on two different occasions in order to evaluate the stability of the test (test-retest). The most commonly used index of reproducibility is the intraclass correlation coefficient (ICC). It represents the proportion of the variability that is due to the subject; the subject variance (σ_s^2) is divided by the total variance of the observations and is given by [94]: $\rho_c = \sigma_s^2 / \left(\sigma_s^2 + \sigma_e^2\right)$, where σ_e^2 is the variance of the measurement error. The ICC ranges from 0 (no agreement between repeated measurements) to 1 (perfect agreement between repeated measurements). For ordinal measures, the weighted Cohen kappa (k) coefficient is commonly used. In general, the criteria for accepting the ICC and k (kappa) are a value equal to or greater than 0.70 [93]. By contrast, the validity is defined as the degree to which a test actually measures what it intends to measure. There are three basic types of validity: content validity, construct validity and criterion validity [93]. Content validity is the extent to which the items of the instrument reflect the domain of interest, i.e. 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 of course implies that a theoretical rationale has been developed that underlies the tested instrument. Criterion validity on the other hand is the extent to which the results of an instrument are related to results of another instrument, a criterion standard, which has previously been shown to be accurate. Among the ten tests listed in Table 7.1, six (the GRASSP, the VLT-SV, the MCS, the CUE, the Sollerman test and the GRT) have been assessed for reliability and validity; the GRT was shown to be only partly valid. Some tests, which were initially developed for individuals with stroke (Table 7.2) and other diagnoses (Table 7.3), are also frequently used in the clinic to evaluate people who suffer an SCI. Of these tests we have selected those which have been tested for reliability and validity.

7.3.10 Discussion

Most of the traditional upper extremity 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 assessments of upper extremity function for people with cervical SCI is required. These tests 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 able to

be performed rapidly and should also rate the grasp pattern. Finally, this new generation of tests should be evaluated for reliability and validity.

7.4 RULER: Classification of Upper Extremity Function After Spinal Cord Injury

In the interest of being able to make comparisons between different approaches to the treatment and rehabilitation of upper limb function following SCI, an appropriate classification was needed. The framework for the RULER (Table 7.4), originally presented in the previous edition of this book, includes an algorithm for the classification of upper extremity function and a measure of upper extremity performance. The RULER does not require any specific tests or measurement tools, is applicable at the bedside in acute and chronic SCI and is complementary to more elaborate tests and assessments. The RULER has now been implemented by the International Spinal Cord Injury Society and is considered to be one of the core elements for describing upper limb function and hence it is included in the International Dataset of Upper Extremity Function (www.iscos.org.uk/international-sci-upper-extremity-data-sets).

The RULER describes motor function of the hand, forearm and shoulder as related to spinal myotomes. It is based, to some extent, on previous classifications, such as the modified classification of Moberg (functional part) [62] and the classifications of Freehafer [95] and Hentz [96], but unlike these previous classifications, it is instead focussed on SCI rather than the specific needs following hand surgery. The RULER distinguishes five different levels of hand function that are considered to be of highest clinical relevance. The levels are designed such that measured changes between the five levels, either improvement or deterioration, can be considered clinically meaningful. The five stages (Table 7.4) are discussed within the framework of a Delphi study.

RULER Level 1—No hand function: individuals have no voluntary control of the muscles controlling the elbow, wrist or hand. Additionally, they have no grasping function and active placing or reaching of the arm is severely limited.

RULER Level 2—Passive tenodesis hand: individuals have neither voluntary control of extrinsic and intrinsic hand muscles nor the ability to actively extend the wrist. Opening and closing of the hand are only possible using the 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 stabilising objects between the hands or passive tenodesis grasp is effective but only in a limited workspace.

RULER Level 3—Active tenodesis hand: individuals 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.

RULER Level 4—Active extrinsic (tenodesis hand): individuals 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.

RULER Level 5—Active extrinsic (intrinsic hand): individuals have voluntary control of extrinsic and intrinsic hand muscles within their entire workspace. Furthermore, they have the ability to perform different grasp forms but muscle strength and dexterity can be limited.

The spinal cord independence measure (SCIM) is a performance test that reveals clinically relevant changes in upper extremity function by assessing the affected person's ability to complete ADL tasks. Three versions of the scale exist (SCIM I–III) and all have been validated and are in use clinically [97–99]. The SCIM protocol scores the ability of the subject to complete self-care tasks, respiration, sphincter management

Table 7.4 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 [80]	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 [81]	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 centred, not diagnosis specific, crosses developmental stages	Not upper limb specific, scores between patients not comparable
JebsenHand Function Test, 1969 [77][a]	Clinical and research tool, hand function in patients with various diagnoses	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	[59] $n=111$, 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-handed specific; test kit has to be purchased

(continued)

Table 7.4 (continued)

Instrument	Purpose	Proximal arm	Distal arm/hand	Time to complete	Method used	Parameter measured	Scoring	Reliability	Validity	Advantages	Disadvantages
MRM (Minnesota Rate of Manipulation Test for Disability Evaluation), 1965 [78]	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)	[61] $n=118$, inter-rater $r=0.75$ (we assume Pearson's correlation coefficient)	[61] $n=118$, 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 although strong correlation mentioned
Box and Block test, 1960 [76]	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	[63] $n=69$, test-retest ICC = 0.89–0.97	[63] $n=69$, ARAT $r=0.80$–0.82, SMAF $r=0.42$–0.54	Objective, norm values [63], [69], rapid	Single-handed specific, proximal arm not assessed, based only on time not on movement quality

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, *ASIA-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 fulfil the selection criterions (it failed a validation test [59]), we have included it in this table given that it is very frequently used in SCI patients

and mobility, and the self-care items of the SCIM III test describe independence when using the upper extremities. The most recent version, the SCIM III, therefore represents a valid scale of disability which is routinely used in clinical practice as a reference for upper extremity function in SCI. For each level of the RULER, the SCIM III (self-care items) scores have been estimated (see Table 7.4). The estimated SCIM III score for level 1 of the RULER is 0 point, whilst the score calculated for level 2 is 0–4 points. Level 3 of the RULER is equivalent to a SCIM III score of 4–13 points, whereas level 4 of the RULER is linked to a SCIM III score of 4–16 points. Finally, the SCIM III score estimated for level 5 of the RULER is 12–18 points. The maximum score of the SCIM III (self-care items) that a subject sitting in a wheelchair can reach is 18 points because the items "bathing-lower body" and "dressing-lower body" cannot be performed if the subject is restricted to a wheelchair.

The comparison of the RULER with functional scoring (SCIM III) allows the user to distinguish different patterns of innervation and levels of independence for a particular degree of upper extremity function. Comparison of the SCIM III score to the specific levels of the RULER also provides information on how well the subject within one of the levels performs ADLs. Thus, the combination of the two measures gives a better overall impression of the impairment to the upper limb function. An additional advantage of these measures (RULER and SCIM III) in comparison to the neurological classification using the ASIA scoring is that they translate directly into clinically meaningful changes.

7.5 Therapeutic Approaches for the Rehabilitation of Upper Extremity Function

The other focus of this chapter is the current and novel methods being used for upper extremity rehabilitation. Both preclinical and clinical studies have shown the benefits of physical activities on recovery of upper extremity function [12, 100–107]. Studies carried out in rats with partial SCIs affecting the upper limb have demonstrated that training and enhanced activity increase neural plasticity and thereby improve motor recovery [100, 102–104]. Accordingly, after an incomplete cervical SCI, diverse training therapy of the upper limb is required to avoid muscular atrophy of the remaining (active) motor functions and recover, to variable extents, lost neuromotor functions [101]. For these reasons considerable effort has been placed in the clinical field on the development of upper limb training devices, such as robots, MIT-Manus [7] (Fig. 7.2c) and ARMin [11] (Fig. 7.2a); passive workstations, T-WREX [13] and ReJoyce [12]; FES systems, Compex Motion-based neuroprosthesis [15]; ETHZ-ParaCare [15]; Ness Handmaster [108]; Bionic Glove [109] and NEC-FES system [16]; as well as novel sensor-based technology [20] and video gaming systems [110]. The most commonly used are reviewed below.

7.5.1 Robotic Systems for Upper Limb Training

In clinical research positive results have been presented for robot-assisted training [11, 111, 112] and there are clear advantages to technology-based therapies. For example, robot-supported training can be more intensive, of longer duration and more repetitive than manual arm training. Additionally, the motivation of the subject to perform repeated training exercises can be enhanced if they are embedded within entertaining computer games, for example, in a study comparing technological-based therapy (T-WREX) with conventional therapy, the subjects reported a preference for training with the T-WREX [13]. If the device also collects relevant data in a standardised way, then there are additional benefits to the devices [11]. Hence, a number of robots have been developed to train upper extremity function following damage; however thus far they have only been tested in stroke subjects. For example, ARMin III is an exoskeleton robot used for arm-supported training therapy after stroke [11]. 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. 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 (Fig. 7.2a) on four subjects with stroke showed that intensive robot-assisted arm therapy can significantly improve motor function in some stroke subjects [112]. More recently the ARMin III was used to assess if robotic training of the affected arm resulted in task-specific training and whether this training was more effective than conventional therapy [11]. The authors found that subjects that received training with the ARMin III had significantly greater improvements in motor function of the affected arm than those that underwent conventional therapy [11]. Whilst these are promising results, the effect size was small and so the clinical meaning is unclear. In another study the ARMin III and HandSOME, a passive hand exoskeleton [113], were combined to provide novel robotic training of reach and grasp compared to conventional therapy in stroke subjects. It was shown that the combined robotic therapy leads to improvements in arm and hand function which were distinct from the improvements seen with conventional therapy [111]. To date there are no published studies using the ARMin III with spinal cord injured subjects. Whilst these robots currently provide only unilateral training, it would be interesting to investigate their further use following SCI.

The MIT-Manus robot comprises two modules with five degrees of freedom, two for elbow and forearm motion and three for wrist motion [7]. The robot can move, guide or perturb the movement of a subject's upper extremity whilst recording measures, such as position, velocity and force. The patient-robot interface consists of video-game exercises for the elbow, shoulder and wrist. However, a multicentre, randomised, controlled study comparing intensive robot-assisted therapy, using the MIT-Manus, with intensive conventional therapy and usual care after stroke showed that after 12 weeks of training intensive robot-assisted therapy did not significantly improve motor function compared to either of the other two therapies. In fact, in comparison to those receiving intensive conventional therapy, the subjects using the robot did worse. The subjects using the robot did however do better than those receiving usual care; however the results were not significant at the 12-week time point [114]. However, after 36 weeks of training robot-assisted therapy, robot-trained subjects showed significant improvements compared to usual care but not when compared with those receiving intensive therapy [114]. Recently the MIT-Manus device was used in combination with an electroencephalography (EEG)-based motor imagery brain-computer interface system to test the efficacy of providing rehabilitation in chronic stroke subjects and showed positive effects in various clinical outcome measures [115]. Again, to date there are no published studies with SCI subjects so whilst the results with stroke subjects are promising studies with SCI subjects should be planned.

7.5.2 Passive Workstations for Upper Limb Training

The T-WREX, a forerunner of the ArmeoSpring, was initially developed to enable stroke sufferers with chronic hemiparesis to practise arm movements without the continuous supervision of a therapist. It consists of an orthosis that assists arm movement, a grip sensor that senses hand grip pressure and software that simulates functional activities. The exoskeleton has five degrees of freedom and passively counterbalances the weight of the arm against gravity by means of elastic bands [13]. A study comparing motor training with T-WREX versus conventional training with a table top for gravity support in chronic stroke sufferers showed that all subjects significantly improved motor function [14]. In addition, rehabilitation therapy with T-WREX was associated with modest maintenance of progress at the 6-month follow-up as compared with conventional therapy [14]. Later the T-WREX was commercialised being renamed the ArmeoSpring. The gravity compensated ArmeoSpring robot, an example of passive workstations, has been tested

with SCI subjects with promising results. For example, subacute cervical SCI subjects completed five weeks of training with the device. The results were very interesting because there were no statistically significant differences between the robot-trained and the control arm for any outcome measured except for in those individuals with some preserved hand function which reported increased scores in the GRASSP-Sensibility component [107].

Additionally, ReJoyce is of particular note because it can assess hand function and provide upper limb rehabilitation training for individuals with stroke as well as those with SCI. The apparatus consists of a four degrees-of-freedom spring-loaded arm (joystick), attached to a table or desk. The automated exercises are incorporated into games that comprise ADL tasks played 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 [12].

Apart from the ArmeoSpring and ReJoyce, the other passive devices currently in use, like the robots mentioned above, have mostly been tested in stroke sufferers; the HandSOME device, another passive workstation, was shown to increase finger range of motion when used for training with stroke subjects [113].

7.5.3 FES Systems for Upper Limb Training

Promisingly many FES systems have been tested in the SCI field and have been shown to provide effective rehabilitation. In particular, FES-based neuroprosthesis devices for grasping, such as the Compex Motion-based neuroprosthesis [15], the ETHZ-Paracare [15], the Freehand [116], the Ness Handmaster [108] (Fig. 7.2d) and the Bionic Glove [109], all incorporate FES and are designed to restore or improve grasping function [16]. FES uses electrical currents to stimulate nerves innervating the paralysed extremities and is often used with SCI subjects, in particular the Ness Handmaster [108, 117] and the Bionic Glove [118]. For example, a number of acute SCI subjects reported improved grasping function with FES assistance to such an extent that they no longer needed the FES system [16]. However, other acute SCI subjects were not able to improve their functional output with the aid of FES [16]. In particular, the Ness Handmaster device was shown to improve hand function when SCI subjects trained with it two to three times a week for 3 weeks [117]. The Ness Handmaster showed benefits within a limited group of subjects with a specific SCI after 2 months of training [108]. Finally, the Bionic Glove has also shown significant effects with the SCI subjects that used it [118]. Despite these promising findings, in order to better determine which types of SCI patients benefit the most from FES-based therapies and why, detailed investigations will be required.

7.5.4 Novel Sensors-Based Technology for Upper Limb Training

In SCI subjects, precise and accurate measures of the overall amount of activity, both during specific rehabilitation sessions and during everyday life, as well as more specific measures such as energy expenditure and specific upper extremity movements are limited. Wearable sensor modules present a promising approach for enhancing functional motor activities [20] and they have been shown to provide motivating, personalised and effective therapy for SCI patients [119]. The data collected from accelerometers can also be used in various ways, for example: to control FES setups [120], to motivate patients to move [121], to train algorithms for analysis of the type of movements made [19] or even to train artificial neural networks that control arm-specific neural prostheses [122]. Although most of these examples remain to be tested for their feasibility in individuals with SCI, sensors have a huge, potential in upper limb

rehabilitation [20]. Inertial measurement units (IMUs) which combine accelerometers, gyroscopes and magnetometers have recently become the focus of increasing research due to the many possible novel applications [20, 123, 124] and in particular with SCI patients [125–129]. Wearable sensor technology is fast becoming a promising approach to rapidly and unobtrusively collect objective movement information repeatedly and over the long term or to immerse the patient into a motivating virtual reality training environment. Hence, using novel wearable sensors is one way of firstly measuring what actually goes on in and out of the specific training session and secondly to feedback this information is a way of motivating subjects.

7.5.5 Video Game Consoles for Upper Limb Training

Finally, video game consoles are increasingly being used for the purpose of rehabilitation of arm function and in this field the Wii gaming system (Nintendo) dominates. The gaming system is based on the Wii controller which can detect movements in three dimensions and therefore can be used as a handheld pointing device. It is this feature of the gaming system that gives it its clear application in the rehabilitation field. However, as with the abovementioned systems, research with the Wii gaming system has been almost entirely focused on stroke subjects. For example, in a recent study the effectiveness of the Wii system for rehabilitation of fine motor control in chronic stroke subjects was tested. Following 16 sessions using the device, the authors reported significant improvements in all clinical measures assessed including an increase in measures of quality of life [130]. In recent years there have been a number of clinical studies with the Wii device which have reported a range of findings; for a review of these studies, see [110, 131]. In conclusion, whilst interesting the Wii system studies have not yet reached any consensus about relevance and effectiveness for rehabilitation and the system has not yet been tested for its effectiveness with SCI subjects.

7.5.6 Discussion

The robotic systems and passive workstations mentioned above were developed to generate movements and task-specific recovery of motor function of the upper limb, but, apart from the ReJoyce passive workstation and some of the FES systems, all of the devices mentioned were initially developed for stroke subjects with a chronic hemiparesis and were assessed in such subjects. Hence, these devices do not provide the bimanual training that would be required for SCI subjects. Novel sensor technology is promising, but the field is still in its infancy with useable algorithms and devices now becoming available. Thus, whilst all of these devices can also be used for training with SCI patients, the overall clinical value of these technologies in SCI and a thorough evaluation of their specific advantages/disadvantages over conventional therapies for SCI need to be investigated fully.

Conclusion

Therapy of the upper extremity in people rendered tetraplegic due to an SCI is of high clinical importance. For this reason, training devices using novel technology, such as robots, passive workstations, FES and sensor technology, are continuously being developed and improved. The clinical value of novel rehabilitation devices can be evaluated by determining whether, following therapy, subjects manage to pass clinically meaningful thresholds using hand function classification systems such as the RULER and SCIM III with the MCID being defined as the smallest change in a measurement that signifies a clinically important improvement. During rehabilitation from cervical SCI, changes in upper limb function and structure can be established with the ASIA classification which is an important tool that enables clinicians to make precise neurological diagnoses about a spinal cord lesion. Nevertheless, changes measured with the ASIA scale do not necessarily relate to clinically relevant changes in upper limb function. Traditional upper limb capacity and performance tests are in general subjective and

somewhat imprecise given that they are mainly based on ordinal ratings. Also, they target very specific detailed functions of the upper limb. Similarly to the ASIA classification, changes measured with capacity tests and surrogates do not necessarily correlate with clinically meaningful changes. However, measures of capacity and surrogate markers do play an important role in the evaluation of upper limb function because in the absence of clinically meaningful changes, kinetics and kinematics and other surrogates can reveal small changes that do not have any obvious clinical effects but that provide insight into activity-dependent changes and if fed back to the subject may be important for their motivation. Such markers can be used to predict outcomes and, where clinically relevant changes are not obvious, potentially the underlying mechanisms which might have been missed with other clinical methods. Ideally, relevant levels of capacity that represent (beneficial or detrimental) changes in upper limb function, e.g. time to accomplish a task, muscle strength, finger joint ROM, muscular activity, NCS latency and amplitude, would need to be defined a priori in order to determine their significance. A new generation of objective and precise tests, evaluated for reliability and validity, is required.

References

1. Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? Spinal Cord. 2006; 44(9):523–9 [Meta-Analysis Review].
2. Curt A, Dietz V. Ambulatory capacity in spinal cord injury: significance of somatosensory evoked potentials and ASIA protocol in predicting outcome. Arch Phys Med Rehabil. 1997;78(1):39–43.
3. Curt A, Keck ME, Dietz V. Functional outcome following spinal cord injury: significance of motor-evoked potentials and ASIA scores. Arch Phys Med Rehabil. 1998;79(1):81–6.
4. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma. 2004;21(10):1371–83.
5. Snoek GJ, IJzerman MJ, Hermens HJ, Maxwell D, Biering-Sorensen F. Survey of the needs of patients with spinal cord injury: impact and priority for improvement in hand function in tetraplegics. Spinal Cord. 2004;42(9):526–32 [Clinical Trial Controlled Clinical Trial Multicenter Study Research Support, Non-U.S. Gov't].
6. Waters RL, Adkins RH, Yakura JS, Sie I. Motor and sensory recovery following complete tetraplegia. Arch Phys Med Rehabil. 1993;74(3):242–7 [Research Support, U.S. Gov't, Non-P.H.S.].
7. Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neurorehabilitation. IEEE Trans Rehabil Eng. 1998;6(1):75–87 [Clinical Trial Controlled Clinical Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.].
8. Nef T, Mihelj M, Riener R. ARMin: a robot for patient-cooperative arm therapy. Med Biol Eng Comput. 2007;45(9):887–900 [Research Support, Non-U.S. Gov't].
9. Colombo R, Pisano F, Micera S, Mazzone A, Delconte C, Carrozza MC, et al. Robotic techniques for upper limb evaluation and rehabilitation of stroke patients. IEEE Trans Neural Syst Rehabil Eng. 2005;13(3):311–24 [Clinical Trial Controlled Clinical Trial Research Support, Non-U.S. Gov't].
10. Vanmulken DA, Spooren AI, Bongers HM, Seelen HA. Robot-assisted task-oriented upper extremity skill training in cervical spinal cord injury: a feasibility study. Spinal Cord. 2015;35(7):547–51.
11. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2):159–66 [Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't].
12. Kowalczewski J, Chong SL, Galea M, Prochazka A. In-home tele-rehabilitation improves tetraplegic hand function. Neurorehabil Neural Repair. 2011;25(5):412–22 [Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't].
13. Sanchez RJ, Liu J, Rao S, Shah P, Smith R, Rahman T, et al. Automating arm movement training following severe stroke: functional exercises with quantitative feedback in a gravity-reduced environment. IEEE Trans Neural Syst Rehabil Eng. 2006;14(3):378–89 [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.].
14. Housman SJ, Scott KM, Reinkensmeyer DJ. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. Neurorehabil Neural Repair. 2009;23(5):505–14 [Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.].
15. Popovic MR, Keller T. Modular transcutaneous functional electrical stimulation system. Med Eng Phys. 2005;27(1):81–92 [Case Reports Research Support, Non-U.S. Gov't].
16. Popovic MR, Curt A, Keller T, Dietz V. Functional electrical stimulation for grasping and walking: indications and limitations. Spinal Cord. 2001;39(8):403–12 [Research Support, Non-U.S. Gov't Review].

17. Kapadia NM, Bagher S, Popovic MR. Influence of different rehabilitation therapy models on patient outcomes: hand function therapy in individuals with incomplete SCI. J Spinal Cord Med. 2014;37(6):734–43 [Research Support, Non-U.S. Gov't].
18. Leuenberger K, Gassert R. Low-power sensor module for long-term activity monitoring. Conf Proc IEEE Eng Med Biol Soc. 2011;2011:2237–41. doi:10.1109/IEMBS.2011.6090424.
19. Moncada-Torres A, Leuenberger K, Gonzenbach R, Luft A, Gassert R. Activity classification based on inertial and barometric pressure sensors at different anatomical locations. Physiol Meas. 2014;35(7):1245–63.
20. Dobkin BH, Dorsch A. The promise of mHealth: daily activity monitoring and outcome assessments by wearable sensors. Neurorehabil Neural Repair. 2011;25(9):788–98.
21. Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, et al. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med. 2011;34(6):535–46.
22. Spiess M, Schubert M, Kliesch U, Halder P. Evolution of tibial SSEP after traumatic spinal cord injury: baseline for clinical trials. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2008;119(5):1051–61 [Research Support, Non-U.S. Gov't].
23. Kramer JL, Moss AJ, Taylor P, Curt A. Assessment of posterior spinal cord function with electrical perception threshold in spinal cord injury. J Neurotrauma. 2008;25(8):1019–26 [Research Support, Non-U.S. Gov't].
24. Chen AC, Niddam DM, Arendt-Nielsen L. Contact heat evoked potentials as a valid means to study nociceptive pathways in human subjects. Neurosci Lett. 2001;316(2):79–82 [Research Support, Non-U.S. Gov't].
25. Kramer JL, Haefeli J, Curt A, Steeves JD. Increased baseline temperature improves the acquisition of contact heat evoked potentials after spinal cord injury. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2012;123(3):582–9 [Research Support, Non-U.S. Gov't].
26. Ulrich A, Haefeli J, Blum J, Min K, Curt A. Improved diagnosis of spinal cord disorders with contact heat evoked potentials. Neurology. 2013;80(15):1393–9 [Research Support, Non-U.S. Gov't].
27. Kimura J. Nerve conduction studies and electromyography. Dyck PJ, Thomas PK, editors. Philadelphia: Saunders; 1993.
28. Kimura J. Electrodiagnosis in diseases of nerve and muscle: principles and practices. Philadelphia: Davis; 1983.
29. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. J Hand Surg [Am]. 1984;9(2):222–6.
30. Jaber R, Hewson DJ, Duchene J. Design and validation of the grip-ball for measurement of hand grip strength. Med Eng Phys. 2012;34(9):1356–61 [Research Support, Non-U.S. Gov't Validation Studies].
31. Sisto SA, Dyson-Hudson T. Dynamometry testing in spinal cord injury. J Rehabil Res Dev. 2007;44(1):123–36 [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Review].
32. Fattal C. Critical review of the evaluation of the results of upper limb functional surgery in tetraplegia since 50 years. Ann Readapt Med Phys. 2004;47(1):30–47 [Meta-Analysis].
33. Shin H, Moon SW, Kim GS, Park JD, Kim JH, Jung MJ, et al. Reliability of the pinch strength with digitalized pinch dynamometer. Ann Rehabil Med. 2012;36(3):394–9.
34. Hingtgen B, McGuire JR, Wang M, Harris GF. An upper extremity kinematic model for evaluation of hemiparetic stroke. J Biomech. 2006;39(4):681–8 [Clinical Trial].
35. Alt Murphy M, Willen C, Sunnerhagen KS. Kinematic variables quantifying upper-extremity performance after stroke during reaching and drinking from a glass. Neurorehabil Neural Repair. 2011;25(1):71–80 [Research Support, Non-U.S. Gov't].
36. Lange B, Chang CY, Suma E, Newman B, Rizzo AS, Bolas M. Development and evaluation of low cost game-based balance rehabilitation tool using the Microsoft Kinect sensor. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng. 2011;2011:1831–4 [Research Support, Non-U.S. Gov't].
37. Pastor I, Hayes HA, Bamberg SJ. A feasibility study of an upper limb rehabilitation system using kinect and computer games. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng. 2012;2012:1286–9 [Research Support, Non-U.S. Gov't].
38. Kurillo G, Han JJ, Obdrzalek S, Yan P, Abresch RT, Nicorici A, et al. Upper extremity reachable workspace evaluation with Kinect. Stud Health Tech Inform. 2013;184:247–53 [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.].
39. Gil-Agudo A, de Los Reyes-Guzman A, Dimbwadyo-Terrer I, Penasco-Martin B, Bernal-Sahun A, Lopez-Monteagudo P, et al. A novel motion tracking system for evaluation of functional rehabilitation of the upper limbs. Neural Regen Res. 2013;8(19):1773–82.
40. de Castro MC, Cliquet Jr A. An artificial grasping evaluation system for the paralysed hand. Med Biol Eng Comput. 2000;38(3):275–80.
41. Vanello N, Hartwig V, Tesconi M, Ricciardi E, Tognetti A, Zupone G, Gassert R, Chapuis D, Sgambelluri N, Scilingo EP, Giovannetti G, Positano V, Santarelli MF, Bicchi A, Pietrini P, de Rossi D, Landini L. Sensing glove for brain studies: design and assessment of its compatibility for fMRI with a robust test. Mechatron IEEE/ASME Trans 2008. 2008;13(3):345–54.
42. Merians AS, Tunik E, Fluet GG, Qiu Q, Adamovich SV. Innovative approaches to the rehabilitation of upper extremity hemiparesis using virtual environments. Eur J Phys Rehabil Med. 2009;45(1):123–33.
43. Friedman N, Chan V, Reinkensmeyer AN, Beroukhim A, Zambrano GJ, Bachman M, et al. Retraining and

assessing hand movement after stroke using the MusicGlove: comparison with conventional hand therapy and isometric grip training. J Neuroeng Rehabil. 2014;11:76 [Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't].
44. Buffi JH, Sancho Bru JL, Crisco JJ, Murray WM. Evaluation of hand motion capture protocol using static computed tomography images: application to an instrumented glove. J Biomech Eng. 2014;136(12):124501 [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't].
45. Schuster-Amft C, Henneke A, Hartog-Keisker B, Holper L, Siekierka E, Chevrier E, et al. Intensive virtual reality-based training for upper limb motor function in chronic stroke: a feasibility study using a single case experimental design and fMRI. Disabil Rehabil Assist Technol. 2014;10(5):385–92.
46. Dipietro L, Sabatini AM, Dario P. A survey of glove-based systems and their applications. Syst Man Cybern Part C Appl Rev IEEE Trans. 2008;38(4):461–82.
47. Laver K, George S, Thomas S, Deutsch JE, Crotty M. Cochrane review: virtual reality for stroke rehabilitation. Eur J Phys Rehabil Med. 2012;48(3):523–30.
48. Laver KE, George S, Thomas S, Deutsch JE, Crotty M. Virtual reality for stroke rehabilitation. Cochrane Database Syst Rev. 2015;2:CD008349.
49. Balasubramanian S, Klein J, Burdet E. Robot-assisted rehabilitation of hand function. Curr Opin Neurol. 2010;23(6):661–70.
50. Cusmano I, Sterpi I, Mazzone A, Ramat S, Delconte C, Pisano F, et al. Evaluation of upper limb sense of position in healthy individuals and patients after stroke. J Healthc Eng. 2014;5(2):145–62 [Research Support, Non-U.S. Gov't].
51. Simo L, Botzer L, Ghez C, Scheidt RA. A robotic test of proprioception within the hemiparetic arm post-stroke. J Neuroeng Rehabil. 2014;11:77 [Research Support, N.I.H., Extramural].
52. Colombo R, Cusmano I, Sterpi I, Mazzone A, Delconte C, Pisano F. Test-retest reliability of robotic assessment measures for the evaluation of upper limb recovery. IEEE Trans Neural Syst Rehabil Eng. 2014;22(5):1020–9 [Research Support, Non-U.S. Gov't].
53. Zariffa J, Kapadia N, Kramer J, Taylor P, Alizadeh-Meghrazi M, Zivanovic V, et al. Relationship between clinical assessments of function and measurements from an upper-limb robotic rehabilitation device in cervical spinal cord injury. IEEE Trans Neural Syst Rehabil Eng. 2011;20(3):341–50.
54. Prochazka A, Kowalczewski J. A fully automated, quantitative test of upper limb function. J Mot Behav. 2015;47(1):19–28 [Research Support, Non-U.S. Gov't].
55. Oess NP, Wanek J, Curt A. Design and evaluation of a low-cost instrumented glove for hand function assessment. J Neuroeng Rehabil. 2012;9:2 [Research Support, Non-U.S. Gov't Validation Studies].
56. Kiuchi K, Inayama T, Muraoka Y, Ikemoto S, Uemura O, Mizuno K. Preliminary study for the assessment of physical activity using a triaxial accelerometer with a gyro sensor on the upper limbs of subjects with paraplegia driving a wheelchair on a treadmill. Spinal Cord. 2014;52(7):556–63.
57. Brogioli M, Popp WL, Albisser U, Brust AK, Frotzler A, Gassert R, et al. Novel sensor technology to assess independence and limb-use laterality in cervical spinal cord injury. J Neurotrauma. 2016. [Epub ahead of print].
58. Popp WL, Brogioli M, Leuenberger K, Albisser U, Frotzler A, Curt A, et al. A novel algorithm for detecting active propulsion in wheelchair users following spinal cord injury. Med Eng Phys. 2016;38(3):267–74. doi:10.1016/j.medengphy.2015.12.011.
59. Buck M, Beckers D. Rehabilitation bei Querschnittlähmung: Ein multidisziplinärer Leitfaden (Rehabilitation und Prävention). Berlin: Springer; 1993.
60. Nigst H. Operationen an Tetraplegikern. In: Buck-Gramcko D, Nigst H, editors. Motorische Ersatzoperationen der Oberen Extremität. Stuttgart: Hippokrates-Verlag; 1991. p. 11–8.
61. Moberg E. Surgical treatment for absent single-hand grip and elbow extension in quadriplegia. Principles and preliminary experience. J Bone Joint Surg Am. 1975;57(2):196–206.
62. McDowell CL, Moberg EA, Smith AG. International conference on surgical rehabilitation of the upper limb in tetraplegia. J Hand Surg [Am]. 1979;4(4):387–90 [Congresses].
63. MacAvoy MC, Green DP. Critical reappraisal of medical research council muscle testing for elbow flexion. J Hand Surg [Am]. 2007;32(2):149–53.
64. Velstra IM, Curt A, Frotzler A, Abel R, Kalsi-Ryan S, Rietman JS, et al. Changes in strength, sensation, and prehension in acute cervical spinal cord injury: European multicenter responsiveness study of the GRASSP. Neurorehabil Neural Repair. 2015;29(8):755–66.
65. Kalsi-Ryan S, Beaton D, Curt A, Duff S, Popovic MR, Rudhe C, et al. The Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP): reliability and validity. J Neurotrauma. 2011;29(5):905–14.
66. Post MW, Van Lieshout G, Seelen HA, Snoek GJ, Ijzerman MJ, Pons C. Measurement properties of the short version of the Van Lieshout test for arm/hand function of persons with tetraplegia after spinal cord injury. Spinal Cord. 2006;44(12):763–71 [Validation Studies].
67. Fattal C. Motor capacities of upper limbs in tetraplegics: a new scale for the assessment of the results of functional surgery on upper limbs. Spinal Cord. 2004;42(2):80–90 [Evaluation Studies Validation Studies].
68. Land NE, Odding E, Duivenvoorden HJ, Bergen MP, Stam HJ. Tetraplegia Hand Activity Questionnaire (THAQ): the development, assessment of arm-hand function-related activities in tetraplegic patients with

a spinal cord injury. Spinal Cord. 2004;42(5): 294–301.
69. Thorsen R, Ferrarin M, Spadone R, Frigo C. Functional control of the hand in tetraplegics based on residual synergistic EMG activity. Artif Organs. 1999;23(5): 470–3 [Research Support, Non-U.S. Gov't].
70. Marino RJ, Shea JA, Stineman MG. The capabilities of upper extremity instrument: reliability and validity of a measure of functional limitation in tetraplegia. Arch Phys Med Rehabil. 1998;79(12):1512–21.
71. Sollerman C, Ejeskar A. Sollerman hand function test. A standardised method and its use in tetraplegic patients. Scand J Plast Reconstr Surg Hand Surg. 1995;29(2):167–76 [Comparative Study].
72. Wuolle KS, Van Doren CL, Thrope GB, Keith MW, Peckham PH. Development of a quantitative hand grasp and release test for patients with tetraplegia using a hand neuroprosthesis. J Hand Surg [Am]. 1994;19(2):209–18 [Research Support, U.S. Gov't, Non-P.H.S.].
73. Vanden Berghe A, Van Laere M, Hellings S, Vercauteren M. Reconstruction of the upper extremity in tetraplegia: functional assessment, surgical procedures and rehabilitation. Paraplegia. 1991;29 (2):103–12.
74. Rogers JC, Figone JJ. Traumatic quadriplegia: follow-up study of self-care skills. Arch Phys Med Rehabil. 1980;61(7):316–21.
75. Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. Exp Neurol. 1989;104(2):125–32 [Research Support, U.S. Gov't, Non-P.H.S.].
76. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer test, action research arm test and box and block test: a multicentre study. Clin Rehabil. 2005;19(4):404–11. Multicenter Study Research Support, Non-U.S. Gov't Validation Studies.
77. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. Arch Phys Med Rehabil. 1969;50 (6):311–9.
78. Gloss DS, Wardle MG. Use of the minnesota rate of manipulation test for disability evaluation. Percept Mot Skills. 1982;55(2):527–32.
79. Sears ED, Chung KC. Validity and responsiveness of the Jebsen-Taylor hand function test. J Hand Surg [Am]. 2010;35(1):30–7 [Comparative Study Research Support, N.I.H., Extramural Validation Studies].
80. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med. 1996;29(6):602–8 [Research Support, Non-U.S. Gov't].
81. Law M, Baptiste S, McColl M, Opzoomer A, Polatajko H, Pollock N. The Canadian occupational performance measure: an outcome measure for occupational therapy. Can J Occup Ther. 1990;57(2):82–7 [Research Support, Non-U.S. Gov't].
82. van Hedel HJ, Dokladal P, Hotz-Boendermaker S. Mismatch between investigator-determined and patient-reported independence after spinal cord injury: consequences for rehabilitation and trials. Neurorehabil Neural Repair. 2011;25(9):855–64 [Research Support, Non-U.S. Gov't].
83. Kalsi-Ryan S, Beaton D, Curt A, Popovic MR, Verrier MC, Fehlings MG. Outcome of the upper limb in cervical spinal cord injury: profiles of recovery and insights for clinical studies. J Spinal Cord Med. 2014;37(5):503–10.
84. MacKenzie CI, Iberall T. The grasping hand. Advances in psychology. Amsterdam: North-Holland; 1994. p. 370.
85. Mulcahey MJ, Smith BT, Betz RR. Psychometric rigor of the grasp and release test for measuring functional limitation of persons with tetraplegia: a preliminary analysis. J Spinal Cord Med. 2004;27(1):41–6 [Research Support, Non-U.S. Gov't Validation Studies].
86. Schlesinger G. Der mechanische Aufbau der kunstlichen Glieder. In: Schlesinger G, editor. Ersatzglieder und Arbeitshilfen. Berlin: Springer; 1919.
87. Light CM, Chappell PH, Kyberd PJ. Establishing a standardized clinical assessment tool of pathologic and prosthetic hand function: normative data, reliability, and validity. Arch Phys Med Rehabil. 2002;83(6):776–83 [Evaluation Studies].
88. Napier JR. The prehensile movements of the human hand. J Bone Joint Surg (Br). 1956;38-B(4): 902–13.
89. Cutkosky MR. On grasp choice, grasp models, and the design of hands for manufacturing tasks. Robot Autom IEEE Trans 1989. 1989;5(3):269–79.
90. Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean? Ann Rheum Dis. 2007;66 Suppl 3:iii40–1 [Review].
91. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10 (4):407–15 [Clinical Trial Research Support, Non-U.S. Gov't].
92. Wu X, Liu J, Tanadini LG, Lammertse DP, Blight AR, Kramer JL, et al. Challenges for defining minimal clinically important difference (MCID) after spinal cord injury. Spinal Cord. 2015;53(2):84–91 [Review].
93. van de Ven-Stevens LA, Munneke M, Terwee CB, Spauwen PH, van der Linde H. Clinimetric properties of instruments to assess activities in patients with hand injury: a systematic review of the literature. Arch Phys Med Rehabil. 2009;90(1):151–69 [Review].
94. Rousson V, Gasser T, Seifert B. Assessing intrarater, interrater and test-retest reliability of continuous measurements. Stat Med. 2002;21(22):3431–46

[Comparative Study Research Support, Non-U.S. Gov't].
95. Freehafer AA, Vonhaam E, Allen V. Tendon transfers to improve grasp after injuries of the cervical spinal cord. J Bone Joint Surg Am. 1974;56(5):951–9.
96. Hentz VR, Brown M, Keoshian LA. Upper limb reconstruction in quadriplegia: functional assessment and proposed treatment modifications. J Hand Surg [Am]. 1983;8(2):119–31.
97. Catz A, Itzkovich M, Agranov E, Ring H, Tamir A. SCIM – spinal cord independence measure: a new disability scale for patients with spinal cord lesions. Spinal Cord. 1997;35(12):850–6 [Clinical Trial Research Support, Non-U.S. Gov't].
98. Catz A, Itzkovich M, Steinberg F, Philo O, Ring H, Ronen J, et al. The catz-itzkovich SCIM: a revised version of the spinal cord independence measure. Disabil Rehabil. 2001;23(6):263–8 [Evaluation Studies Research Support, Non-U.S. Gov't].
99. Catz A, Itzkovich M, Tesio L, Biering-Sorensen F, Weeks C, Laramee MT, et al. A multicenter international study on the spinal cord independence measure, version III: rasch psychometric validation. Spinal Cord. 2007;45(4):275–91 [Multicenter Study Research Support, Non-U.S. Gov't Validation Studies].
100. Starkey ML, Bleul C, Maier IC, Schwab ME. Rehabilitative training following unilateral pyramidotomy in adult rats improves forelimb function in a non-task specific way. Exp Neurol. 2011;232(1):81–9.
101. Starkey ML, Bleul C, Kasper H, Mosberger AC, Zorner B, Giger S, et al. High-impact, self-motivated training within an enriched environment with single animal tracking dose-dependently promotes motor skill acquisition and functional recovery. Neurorehabil Neural Repair. 2014;28(6):594–605.
102. Maier IC, Baumann K, Thallmair M, Weinmann O, Scholl J, Schwab ME. Constraint-induced movement therapy in the adult rat after unilateral corticospinal tract injury. J Neurosci. 2008;28(38):9386–403.
103. Carmel JB, Berrol LJ, Brus-Ramer M, Martin JH. Chronic electrical stimulation of the intact corticospinal system after unilateral injury restores skilled locomotor control and promotes spinal axon outgrowth. J Neurosci. 2010;30(32):10918–26.
104. Girgis J, Merrett D, Kirkland S, Metz GA, Verge V, Fouad K. Reaching training in rats with spinal cord injury promotes plasticity and task specific recovery. Brain. 2007;130(Pt 11):2993–3003.
105. Krajacic A, Weishaupt N, Girgis J, Tetzlaff W, Fouad K. Training-induced plasticity in rats with cervical spinal cord injury: effects and side effects. Behav Brain Res. 2010;214(2):323–31.
106. Nooijen CF, de Groot S, Postma K, Bergen MP, Stam HJ, Bussmann JB, et al. A more active lifestyle in persons with a recent spinal cord injury benefits physical fitness and health. Spinal Cord. 2012;50(4):320–3.
107. Zariffa J, Kapadia N, Kramer JL, Taylor P, Alizadeh-Meghrazi M, Zivanovic V, et al. Feasibility and efficacy of upper limb robotic rehabilitation in a subacute cervical spinal cord injury population. Spinal Cord. 2011;50(3):220–6.
108. Snoek GJ, IJzerman MJ, in 't Groen FA, Stoffers TS, Zilvold G. Use of the NESS handmaster to restore handfunction in tetraplegia: clinical experiences in ten patients. Spinal Cord. 2000;38(4):244–9 [Clinical Trial].
109. Popovic D, Stojanovic A, Pjanovic A, Radosavljevic S, Popovic M, Jovic S, et al. Clinical evaluation of the bionic glove. Arch Phys Med Rehabil. 1999;80(3):299–304 [Research Support, Non-U.S. Gov't].
110. Thomson K, Pollock A, Bugge C, Brady M. Commercial gaming devices for stroke upper limb rehabilitation: a systematic review. Int J Stroke. 2014;9(4):479–88.
111. Brokaw EB, Nichols D, Holley RJ, Lum PS. Robotic therapy provides a stimulus for upper limb motor recovery after stroke that is complementary to and distinct from conventional therapy. Neurorehabil Neural Repair. 2014;28(4):367–76 [Randomized Controlled Trial Research Support, U.S. Gov't, Non-P.H.S.].
112. Staubli P, Nef T, Klamroth-Marganska V, Riener R. Effects of intensive arm training with the rehabilitation robot ARMin II in chronic stroke patients: four single-cases. J Neuroeng Rehabil. 2009;6:46.
113. Brokaw EB, Black I, Holley RJ, Lum PS. Hand Spring Operated Movement Enhancer (HandSOME): a portable, passive hand exoskeleton for stroke rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2011;19(4):391–99 [Research Support, U.S. Gov't, Non-P.H.S.].
114. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362(19):1772–83.
115. Ang KK, Chua KS, Phua KS, Wang C, Chin ZY, Kuah CW, et al. A randomized controlled trial of EEG-based motor imagery brain-computer interface robotic rehabilitation for stroke. Clin EEG Neurosci. 2014 Apr 21.
116. Taylor P, Esnouf J, Hobby J. The functional impact of the freehand system on tetraplegic hand function. Clinical results. Spinal Cord. 2002;40(11):560–6 [Clinical Trial Research Support, Non-U.S. Gov't].
117. Alon G, McBride K. Persons with C5 or C6 tetraplegia achieve selected functional gains using a neuroprosthesis. Arch Phys Med Rehabil. 2003;84(1):119–24 [Evaluation Studies Research Support, Non-U.S. Gov't].
118. Prochazka A, Gauthier M, Wieler M, Kenwell Z. The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. Arch Phys Med Rehabil. 1997;78(6):608–14 [Clinical Trial Multicenter Study Research Support, Non-U.S. Gov't].
119. Szturm T, Peters JF, Otto C, Kapadia N, Desai A. Task-specific rehabilitation of finger-hand func-

tion using interactive computer gaming. Arch Phys Med Rehabil. 2008;89(11):2213–7 [Case Reports Clinical Trial Research Support, Non-U.S. Gov't].
120. Tong KY, Mak AF, Ip WY. Command control for functional electrical stimulation hand grasp systems using miniature accelerometers and gyroscopes. Med Biol Eng Comput. 2003;41(6):710–7 [Evaluation Studies Research Support, Non-U.S. Gov't].
121. Markopoulos P, Timmermans AA, Beursgens L, van Donselaar R, Seelen HA. Us'em: the user-centered design of a device for motivating stroke patients to use their impaired arm-hand in daily life activities. Conf Proc IEEE Eng Med Biol Soc. 2011;2011: 5182–7.
122. Mijovic B, Popovic MB, Popovic DB. Synergistic control of forearm based on accelerometer data and artificial neural networks. Braz J Med Biol Res. 2008;41(5):389–97. 41.
123. Lee JK, Park EJ. 3D spinal motion analysis during staircase walking using an ambulatory inertial and magnetic sensing system. Med Biol Eng Comput. 2011;49(7):755–64.
124. Luinge HJ, Veltink PH, Baten CT. Ambulatory measurement of arm orientation. J Biomech. 2007;40 (1):78–85.
125. Warms CA, Belza BL. Actigraphy as a measure of physical activity for wheelchair users with spinal cord injury. Nurs Res. 2004;53(2):136–43 [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.].
126. Bussmann JB, Kikkert MA, Sluis TA, Bergen MP, Stam HJ, van den Berg-Emons HJ. Effect of wearing an activity monitor on the amount of daily manual wheelchair propulsion in persons with spinal cord injury. Spinal Cord. 2010;48(2):128–33 [Evaluation Studies].
127. Postma K, van den Berg-Emons HJ, Bussmann JB, Sluis TA, Bergen MP, Stam HJ. Validity of the detection of wheelchair propulsion as measured with an activity monitor in patients with spinal cord injury. Spinal Cord. 2005;43(9):550–7 [Clinical Trial Research Support, Non-U.S. Gov't Validation Studies].
128. Wilson SK, Hasler JP, Dall PM, Granat MH. Objective assessment of mobility of the spinal cord injured in a free-living environment. Spinal Cord. 2008;46(5):352–7.
129. Coulter EH, Dall PM, Rochester L, Hasler JP, Granat MH. Development and validation of a physical activity monitor for use on a wheelchair. Spinal Cord. 2011;49(3):445–50 [Research Support, Non-U.S. Gov't].
130. Paquin K, Ali S, Carr K, Crawley J, McGowan C, Horton S. Effectiveness of commercial video gaming on fine motor control in chronic stroke within community-level rehabilitation. Disabil Rehabil. 2015;14:1–8.
131. Thomson K, Pollock A, Bugge C, Brady MC. Commercial gaming devices for stroke upper limb rehabilitation: a survey of current practice. Disabil Rehabil Assist Technol. 2015;30:1–8.

Part II

Human-Machine Interaction in Rehabilitation Practice

Application Issues for Robotics

8

Markus Wirz and Rüdiger 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 end users. End users in this case are patients with neurological conditions but also therapists who operate rehabilitation robots. 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 which allow the continuation of a robotic therapy at home will further enlarge the range of applications.

M. Wirz, PT, PhD (✉)
Health Department, Institute of Physiotherapy, Zurich University of Applies Sciences,
Technikumstrasse 71, Winterthur CH-8401,
Switzerland
e-mail: markus.wirz@zhaw.ch

R. Rupp, PhD
Spinal Cord Injury Center,
Heidelberg University Hospital,
Schlierbacher Landstrasse 200a, Heidelberg 69118,
Germany
e-mail: ruediger.rupp@med.uni-heidelberg.de

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Keywords

End user requirements • Complexity vs. usability • Safety issues • Human-machine interfaces • Robotic assessments

8.1 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 machine 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., the support of an insufficient respiratory function by artificial ventilators. Technology becomes smarter, not only in daily life 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 the end users. End users 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. End users 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. Hence, 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. It is recommended that engineers regard patients and therapists as integral components of the therapy who need to be involved throughout the whole process of development. Patients and therapists are likely to set priorities in the development of robotic therapy devices differently than engineers. The potential clinical application has to be borne in mind throughout the whole developmental process. A widely adopted classification of developmental stages of technology is the technology readiness level (TRL, see Table 8.1) which has originally been established for the aerospace engineering by the National Aeronautics and Space

Table 8.1 Technology readiness level (TRL) according to the European Horizon 2020 – Work Programme 2014–2015 [2] and their translation to the development of rehabilitation robotics

TRL	Description	Translation to rehabilitation robotics
TRL 1	Basic principles observed	Proof of principle observed in animal models and in pilot human applications (e.g., on motor learning)
TRL 2	Technology concept formulated	Technical requirements and specifications including safety measures with regard to the application in patients defined. Review of these concepts by end users (patients and therapists) is recommended
TRL 3	Experimental proof of concept	Development and implementation of an experimental model
TRL 4	Technology validated in lab	First usability studies in healthy volunteers (human factor study) for the refinement of technical specifications in a user-centered design process. Development of training scenarios for the application in patients
TRL 5	Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)	First usability studies in selected patients representing typical use cases. These studies do not focus on investigating efficacy but feasibility of both hard- and software components as well as acceptance by end users. Establishment of reliability and validity of the devices measurement capacities. Ethical approval and involvement of regulatory authorities required. Aim: certification of the product
TRL 6	Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies)	Clinical trials with broader inclusion criteria and a larger number of patients to investigate efficacy. Health technology assessment
TRL 7	System prototype demonstration in operational environment	Effectiveness studies
TRL 8	System complete and qualified	Broader application, commercialization
TRL 9	Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)	Ongoing refinement according to end user feedback and to the technological progress. Different manufacturers with comparable products

Administration (NASA) [1]. Nowadays this classification represents the standard of reference (ISO 16290:2013) and is widely accepted by several organizations (e.g., the European Commission [2]). The TRL is not directly fit to the dedicated requirements of the development of rehabilitative robotics but may serve as a structural framework for the 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.

8.2 Human Issues

8.2.1 Patient Requirements

8.2.1.1 Autonomous Nervous System

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 [3–5]. The latter include among others lack of bladder and bowel voiding function and/or lack of blood pressure adaptation as a response to upright position named orthostatic hypotension. 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.

8.2.1.2 Musculoskeletal System

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.

8.2.1.3 Cognitive Prerequisites

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 [6]. 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.

8.2.2 Therapist Requirements

The usage of robotic devices is only partially 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 and that not all clinics where students are placed provide robotic-assisted training. Different approaches to make use of new technology for rehabilitation are in development or already commercially available. The International Industry Society in Advanced Rehabilitation Technology (IISART) is formed by manufacturers of robotic devices and equipment for virtual rehabilitation and therapeutic electrical stimulation. The society's Internet resources provide a comprehensive overview of the actual state of various devices in this fast advancing area [7].

8.2.2.1 Instruction of Therapists

Despite the level of matureness of robotic technology is quite high, the proper use of robotic devices is critical for the success of the training with respect to the rehabilitation outcome. For complex devices, 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. If a robotic training is associated with a high risk for severe adverse events (e.g., large and powerful devices, which are mounted to the whole body), 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. For the use of smaller and less strong devices (e.g., where a patient remains seated) with fewer operating modes, a basic instruction is sufficient. However, other devices require extensive training and experience in order to respond to variations and irregularities.

8.2.2.2 Implementation of Robotic Therapy

For the practical implementation, it is recommended to evaluate 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 a complex device. On the other hand when only few staff members know how to run such a 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. However, there are other constellations conceivable, where teams of specialized therapists are exclusively responsible for the technology-assisted training applied as an adjunct to the regular therapy program. In those cases several devices are grouped in one room, and few therapists assist the patients in the setup of the devices and the adaptation of the training parameter. This allows for supervision of multiple patients during the technology-assisted training similar to a gym with strength training equipment for able-bodied subjects.

8.2.3 Principles of Robotic Training

At the current stage, robots do not introduce completely new rehabilitation strategies [8]. 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 are 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 [9].

8.2.3.1 Training Parameters

The question pertaining to the principles behind robotic training is the question regarding the principles of neurological rehabilitation. To date little is known about the choice of intervention, the timing of its application, and the intensity

required to maximally exploit rehabilitative capacity. Thus, training varies considerably between institutions. This holds not only true for robotic-assisted training but for rehabilitative interventions in general. There is preclinical evidence that suggests a strong influence of the abovementioned factors [10]. Studies addressing sequencing and intensity as well as individual tailoring of rehabilitation interventions need to be conducted in order to get a better understanding of the exposure-outcome association. In recent years there have been many reports on the principles and strategies on which neurological rehabilitation is based [11–17]. 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.

8.2.3.2 Principles of Motor Learning

One major and persistent principle of neurological rehabilitation is that of motor learning [15, 16, 18]. 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 restoration of motor functions by neuroplasticity or compensation [15, 19]. Regardless the underlying mechanism, the principles of motor learning apply in both cases [16, 20]. These principles comprise among others task specificity, goal orientation, meaningfulness, active involvement, 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 leg movements of patient to successfully perform the motor task of 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 [21–24]. The correct unloading and loading of the legs as well as hip extension at the end of stance phase seem to be key afferent stimuli for the appropriate facilitation of neural structures which are involved in the control of walking. A recent systematic review of 23 studies in 999 patients with stroke concluded that the combination of electromechanical-assisted gait training with physiotherapy is associated with a higher likelihood of achieving independent walking than gait training without robotic assistance. This observation seems to be valid in particular if such a training is applied in the acute to subacute phase early after the event (i.e., within 3 months) in patients with severe activity-related limitations [25].

Also, devices for the training of upper limb functions are most valuable for improvement of rehabilitation outcomes. 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 bed for most of the time [26]. A number of devices work in conjunction with a display, on which the patient completes meaningful tasks of daily living within a virtual environment [27]. 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 [28, 29]. Other approaches aim at minimizing the lack of coordination between shoulder and elbow joint during reaching movements [30]. Upper extremity robots in combination with virtual environments allow for the implementation of relatively unconventional concepts of occupational therapy. Among them is the so-called error augmentation concept, where haptic (via robot-rendered forces) and graphic (via a virtual environment) distortions are used to amplify upper extremity tracking errors and thereby maximizing therapy outcome [31].

Without the support of electromechanical devices, patients will not be able to start functional exercises (e.g., walking) at such 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 with severe

disabilities, robotic devices allow longer training durations and a higher number of repetitions. Studies have shown that augmented exercise results in an improved outcome [32]. However, it seems not sufficient just to repeat a specific movement or completion of a task. Task variability improves the acquisition of that task [18]. 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. This is in particular true for systems which are used in combination with a body-weight support system either on a treadmill or for overground walking. Walking speed during training is considered important to warrant further improvements [33].

8.2.3.3 Feedback and Virtual Reality

In order to maintain physiological movement trajectories in different operating conditions 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. There is evidence that the use of virtual reality and interactive video gaming may be beneficial in improving upper and lower limb function and activities of daily living when used as an adjunct to usual care or when compared with the same dose of conventional therapy [34, 35]. However, to date only little is known, which characteristics of virtual reality are most important, and it is unknown whether effects are sustained in the longer term.

A comparison of the data of all sensors with reference data from able-bodied subjects or previous sessions of patients serves the therapist to document the progression within a training series. 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.

Robotic devices represent a useful tool for therapists as well as patients to implement the principles of motor learning from the very beginning of rehabilitation and to measure and control for the progress of motor function.

8.3 Technical Issues

8.3.1 Complexity of Robotic Devices

The main goal of 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 task repetitions and the generation of physiological afferent stimuli [36]. For achieving a meaningful improvement of motor functions by mass practice therapy regimes, supportive devices are beneficial and valuable tools.

8.3.1.1 Complexity of Training Devices

The complexity of electromechanical training 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 particularly 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, and stationary and mobile versions of the 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. More complex devices such as the ArmeoSpring (Hocoma AG, Volketswil, Switzerland) have integrated sensors, whose data may be used for performing motor tasks in a virtual environment and thereby providing a patient with feedback about the performance. 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, nonphysiological 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.

8.3.1.2 End-Effector Devices Versus Exoskeletons

Within the class of active devices, there are technically more simple devices, which are mainly based on an end-effector approach, and complex exoskeleton 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 [37–39] (Fig. 8.1). 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 of the guided body segments (e.g., the foot) looks similar to the physiological situation—the kinetics of the generated movements in the adjacent joints (e.g., knee) and the principle of weight bearing may not be perfectly physiological [40]. However, this seems to be crucial for the success of the therapy [24]. 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 [41] or the ReJoyce (Rehabtronics, Edmonton, Canada) and for the lower extremity the gait trainer [42] (Reha-Stim, Berlin, Germany), the LYRA (ABILITY, Zurich, Switzerland), or the GEO (Fig. 8.1, Reha Technology AG, Olten, Switzerland).

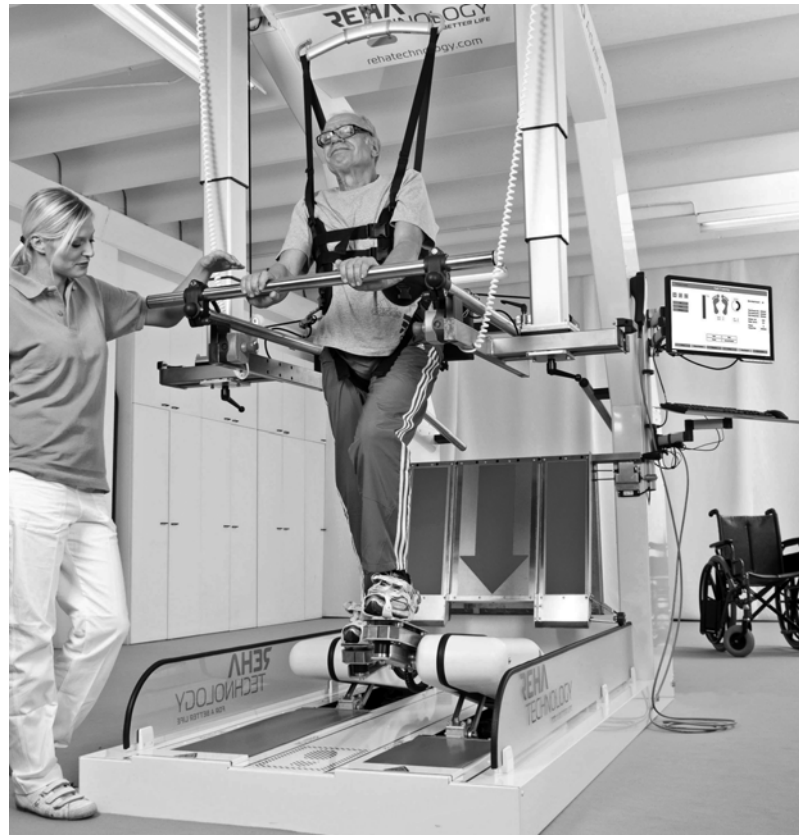

Fig. 8.1 The GEO System assists the patient during gait training using an end-effector-based approach combined with a system for partial unloading of the body weight (Photo courtesy Reha Technology AG, Olten, Switzerland. Used with permission)

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 either in conjunction with a system for partial body-weight unloading and a moving treadmill (Fig. 8.2) [43–46] or as a fully mobile device for overground walking such as the commercially available ReWalk (ReWalk Robotics,Yokneam Ilit, Israel) and the Ekso (Ekso Bionics, Richmond, California, USA). Since active components form the most expensive parts of a robotic device, usually a compromise between costs and functionality in terms of 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 application. Examples for actively driven exoskeletons are the Lokomat and Lopes I devices for the lower extremity [45] and the ARMin (Armeo Power, Hocoma AG, Volketswil, Switzerland) and RUPERT device for the upper extremity [47, 48]. The first prototypes of exoskeleton locomotion robots such as the Lopes II, in which an alignment of technical and anatomical joints is not needed by design, are currently undergoing clinical testing [49].

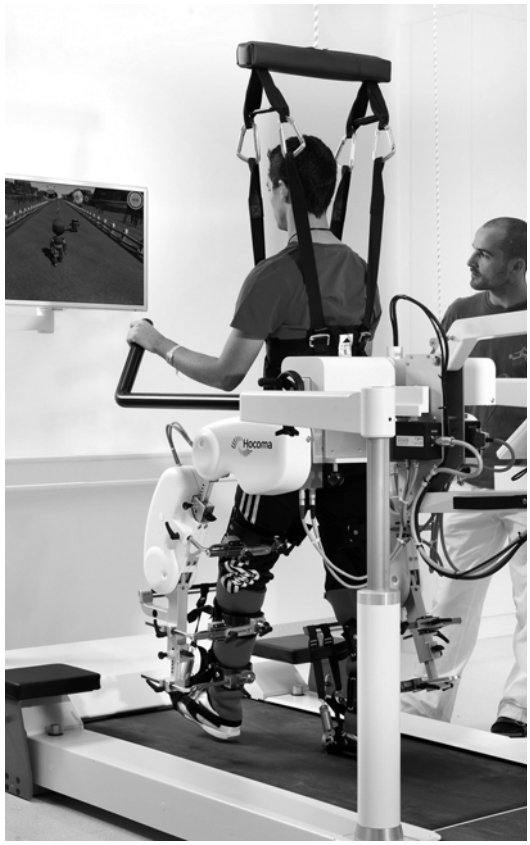

Fig. 8.2 The Lokomat is an exoskeleton which is operated in conjunction with a moving treadmill (Photo courtesy Hocoma AG, Volketswil, Switzerland. Used with permission)

8.3.1.3 Controller for Robotic Training Devices

Although 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. This control concept has the disadvantage that even if movements in the robot look normal, the underlying muscle activation may still be non-physiological. As a consequence, an open-loop position control mode should only be used in conjunction with a feedback of joint torques. Using an open-loop position control, the patient's movements are supported even during phases, where the voluntary force of the patient would be sufficient to follow a physiological trajectory. 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 [50]. Although a variety of control methods to achieve "assist as needed" have been investigated so far in research prototypes in particular of locomotion robots, their translation into clinically applicable, easy-to-use, and robust implementations is still lacking [51]. 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 [52]. Therefore, robotic devices should also incorporate a control scheme that does allow for small deviations from the reference trajectory, e.g., the nonlinear control scheme of the "force fields" implemented in the T-/Pneu-WREX device [53] or an impedance control scheme of the Lokomat [54]. In this way users will be allowed to check out different motor strategies, and a true cooperative robot-assisted therapy will become reality.

8.3.1.4 Combination of Training Devices with Functional Electrical Stimulation

Nevertheless, all motor-driven orthotic devices only generate movements of totally or partially paralyzed muscles in a passive way. However, from the results of a few clinical studies, it may be concluded that an additional activation of paralyzed muscles by externally applied electrical currents leads to a better outcome [55–57]. 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 in clinical routine [58].

However, such hybrid systems offer the possibility that not only 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 [59]. To achieve this functionality novel light-weight drives and multichannel, easy-to-handle electrode concepts need to be evaluated in end users in a real-life setting [60].

8.3.2 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 toward 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 3rd edition of the standard published in 2005 [61] 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
- IEC 62304: Medical device software, software life cycle processes
- 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 non-certified 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 has 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-specific limit 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 a exceeding of safe torque limits.

The most apparent adverse events of robotic devices in particular of active exoskeletons for locomotion training are skin erythema [62]. Though skin erythema is not a life-threatening condition, they 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 [63]. This will allow checking 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 check-ups and maintenance of the device.

8.3.3 Customization

8.3.3.1 Anthropometrics

Human beings vary to a great degree in their anthropometric data like size and weight and body proportions such as 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.

8.3.3.2 Severity of Impairment and Functional Limitations

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 the mechanical components of the machine as well as the training paradigms including feedback modalities.

8.3.3.3 Setup Time Prior to Execution of Training

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 setup.

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.

8.3.3.4 Individualized Training

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, 38].

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.

8.4 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 for therapists. 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 nontechnical professional background. Therefore, the ISO 9241–210 standard, which refers to "Ergonomics of human-system interaction—Part 210: Human-centered 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.

8.4.1 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.

8.4.2 Control and Feedback Interfaces

An important component of the robotic system is the control and the feedback interface. The control interface is used by the therapist to set and adapt the most important therapy parameters like speed, amount of support, or range of motion. The feedback interface provides 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 operate 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.

8.4.3 Automated Adaptation of Training

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.

8.4.4 Feedback

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 her/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 need to be chosen individually 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 [64].

8.5 Assessment and Documentation

Rehabilitation robots are not only equipped with motors but also with multiple sensors. These sensor signals 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. 8.3).

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 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. Detection of any functional gains is important to generate motivation [65]. 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.

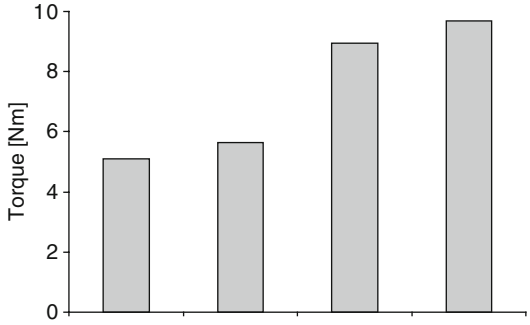

Fig. 8.3 Example of a series of force measurements recorded with the Lokomat system. The columns represent the maximum force in direction of unilateral hip flexion during successive sessions from a patient recovering from Guillain-Barré syndrome (the respective value of healthy volunteers amounts to 74 Nm)

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; e.g., 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 errors, e.g., the instruction of the therapist or pain may influence measurements. Few studies pertaining to this issue affirmed feasibility and reliability [66–68]. 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 [69]. Additionally, robots allow for assessments which are hard to perform without the robot like the measurement of lower limb joint position sense with the patient in an upright position [70].

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.

8.6 Continuation of a Robotic Therapy at Home

Due to increasing economical restrictions in the healthcare 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 [71]. 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 homes 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 [71, 72]. 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.

8.6.1 Safety of Home-Based Robotic Systems

The main challenges of therapeutic 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 loco-

motion 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 [9, 73, 74]. In locomotion robotics, a key method to minimize the risk of injuries is to put the user in a safe training position, like a semi-recumbent position of the body in the MoreGait device (Fig. 8.4).

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 [75].

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.

8.6.2 Conventional Gaming Consoles

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 camera-based KINECT option [76, 77]. 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 non-limited 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

Fig. 8.4 The MoreGait is a pneumatically actuated robot for the training of ambulatory function. The device allows the use at the patient's home

time to the user. On the one hand, moderate evidence from clinical studies exists that a console-based (tele-) rehabilitation is efficient, but on the other hand systematic evaluation of systems' usability, cost-effectiveness, and data privacy concerns still requires major attention [78–80]. Furthermore, it has to be investigated in the future if the option of commercial video games for an Internet-based multiplayer mode may be used for supervision of home-based training by a qualified therapist [81].

8.7 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 is 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. Nevertheless, multiple patients, who are compliant and familiar with the details of the robot-assisted rehabilitation training, may be supervised by a single therapist.

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 [82], 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 healthcare providers to give every patient with a motor disorder the chance to profit from such training.

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 neurobiological 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 therapies with 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 complies 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 simultaneously guiding movements of several joints can be overcome.

References

1. Mankins JC. Technology readiness levels. 1995. Available from: http://www.hq.nasa.gov/office/codeq/trl/trl.pdf.
2. Horizon 2020—work programme 2014–2015. Annex G: technology readiness levels (TRL). 2014.
3. Alexander MS, Biering-Sorensen F, Bodner D, Brackett NL, Cardenas D, Charlifue S, et al. International standards to document remaining autonomic function after spinal cord injury. Spinal Cord. 2009;47(1):36–43.
4. Kelly-Hayes M, Robertson JT, Broderick JP, Duncan PW, Hershey LA, Roth EJ, et al. The American Heart Association Stroke Outcome Classification. Stroke. 1998;29(6):1274–80.
5. NSCISC. The 2012 annual statistical report for the model spinal cord injury care system: National SCI Statistical Center. 2012. Available from: www.uab.edu/NSCISC.
6. Jackson AB, Dijkers M, Devivo MJ, Poczatek RB. A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. Arch Phys Med Rehabil. 2004;85(11):1740–8.
7. IISART. 2015. Available from: www.iisartonline.org.
8. Reinkensmeyer DJ, Maier MA, Guigon E, Chan V, Akoner O, Wolbrecht ET, et al. Do robotic and non-robotic arm movement training drive motor recovery after stroke by a common neural mechanism? Experimental evidence and a computational model. Conference proceedings of IEEE engineering in medicine and biology society. 2009;2009:2439–41. PMID 19965205.
9. Sanchez RJ, Liu J, Rao S, Shah P, Smith R, Rahman T, et al. Automating arm movement training following severe stroke: functional exercises with quantitative feedback in a gravity-reduced environment. IEEE Trans Neural Syst Rehabil Eng. 2006;14(3):378–89.
10. Wahl AS, Schwab ME. Finding an optimal rehabilitation paradigm after stroke: enhancing fiber growth and training of the brain at the right moment. Front Hum Neurosci. 2014;8:381.
11. Floel A, Cohen LG. Translational studies in neurorehabilitation: from bench to bedside. Cogn Behav Neurol. 2006;19(1):1–10.
12. Hubbard IJ, Parsons MW, Neilson C, Carey LM. Task-specific training: evidence for and translation to clinical practice. Occup Ther Int. 2009;16(3–4):175–89.
13. Graham JV, Eustace C, Brock K, Swain E, Irwin-Carruthers S. The Bobath concept in contemporary clinical practice. Top Stroke Rehabil. 2009;16(1):57–68.
14. Kalra L. Stroke rehabilitation 2009: old chestnuts and new insights. Stroke. 2010;41(2):e88–90.
15. Dobkin BH. Strategies for stroke rehabilitation. Lancet Neurol. 2004;3(9):528–36.
16. Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. Curr Opin Neurobiol. 2006;19(1):84–90.
17. Oujamaa L, Relave I, Froger J, Mottet D, Pelissier JY. Rehabilitation of arm function after stroke. Literature review. Ann Phys Rehab Med. 2009;52(3):269–93.
18. Hanlon RE. Motor learning following unilateral stroke. Arch Phys Med Rehabil. 1996;77(8):811–5.
19. Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensation" mean in patients following stroke? Neurorehabil Neural Repair. 2009;23(4):313–9.
20. Curt A, Van Hedel HJ, Klaus D, Dietz V. Recovery from a spinal cord injury: significance of compensation, neural plasticity, and repair. J Neurotrauma. 2008;25(6):677–85.
21. Dietz V, Duysens J. Significance of load receptor input during locomotion: a review. Gait Posture. 2000;11(2):102–10.
22. Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR. Human lumbosacral spinal cord interprets loading during stepping. J Neurophysiol. 1997;77(2):797–811.
23. Lunenburger L, Bolliger M, Czell D, Muller R, Dietz V. Modulation of locomotor activity in complete spinal cord injury. Exp Brain Res Exp Hirnforsch. 2006;174(4):638–46.
24. Dietz V, Muller R, Colombo G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. Brain. 2002;125(Pt 12):2626–34.
25. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2013;(7):CD006185.
26. Rosati G, Gallina P, Masiero S. Design, implementation and clinical tests of a wire-based robot for neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(4):560–9.
27. Ferraro M, Palazzolo JJ, Krol J, Krebs HI, Hogan N, Volpe BT. Robot-aided sensorimotor arm training improves outcome in patients with chronic stroke. Neurology. 2003;61(11):1604–7.
28. van Vliet PM, Wulf G. Extrinsic feedback for motor learning after stroke: what is the evidence? Disabil Rehabil. 2006;28(13–14):831–40.
29. Wulf G, Shea C, Lewthwaite R. Motor skill learning and performance: a review of influential factors. Med Educ. 2010;44(1):75–84.
30. Sukal TM, Ellis MD, Dewald JP. Source of work area reduction following hemiparetic stroke and preliminary intervention using the ACT3D system. Conf Proc IEEE Eng Med Biol Soc. 2006;1:177–80.
31. Abdollahi F, Case Lazarro ED, Listenberger M, Kenyon RV, Kovic M, Bogey RA, Hedeker D, Jovanovic BD, Patton JL. Error augmentation enhancing arm recovery in individuals with chronic stroke: a randomized crossover design. Neurorehabil Neural Repair. 2014;28(2):120–8.

32. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. Lancet. 1999;354(9174):191–6.
33. Sullivan KJ, Knowlton BJ, Dobkin BH. Step training with body weight support: effect of treadmill speed and practice paradigms on poststroke locomotor recovery. Arch Phys Med Rehabil. 2002;83(5):683–91.
34. Laver KE, George S, Thomas S, Deutsch JE, Crotty M. Virtual reality for stroke rehabilitation. Cochrane Database Syst Rev. 2015;(2):CD008349.
35. Lohse KR, Hilderman CG, Cheung KL, Tatla S, Van der Loos HF. Virtual reality therapy for adults post-stroke: a systematic review and meta-analysis exploring virtual environments and commercial games in therapy. PLoS One. 2014;9(3):e93318.
36. Prange GB, Jannink MJ, Groothuis-Oudshoorn CG, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev. 2006;43(2):171–84.
37. Hesse S, Uhlenbrock D. A mechanized gait trainer for restoration of gait. J Rehabil Res Dev. 2000;37(6):701–8.
38. Hesse S, Waldner A, Tomelleri C. Innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients. J Neuroeng Rehabil. 2010;7:30.
39. Freivogel S, Mehrholz J, Husak-Sotomayor T, Schmalohr D. Gait training with the newly developed 'LokoHelp'-system is feasible for non-ambulatory patients after stroke, spinal cord and brain injury. A feasibility study. Brain Inj. 2008;22(7–8):625–32.
40. Hesse S, Sarkodie-Gyan T, Uhlenbrock D. Development of an advanced mechanised gait trainer, controlling movement of the centre of mass, for restoring gait in non-ambulant subjects. Biomed Tech (Berl). 1999;44(7–8):194–201.
41. Hogan N, Krebs H, Sharon A, Charnnarong J., inventor. Massachusetts Institute of Technology, assignee. Interactive robotic therapist. USA. 1995.
42. Hesse S, Werner C, Uhlenbrock D, von Frankenberg S, Bardeleben A, Brandl-Hesse B. An electromechanical gait trainer for restoration of gait in hemiparetic stroke patients: preliminary results. Neurorehabil Neural Repair. 2001;15(1):39–50.
43. Banala SK, Kim SH, Agrawal SK, Scholz JP. Robot assisted gait training with active leg exoskeleton (ALEX). IEEE Trans Neural Syst Rehabil Eng. 2009;17(1):2–8.
44. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37(6):693–700.
45. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379–86.
46. Mantone J. Getting a leg up? Rehab patients get an assist from devices such as HealthSouth's AutoAmbulator, but the robots' clinical benefits are still in doubt. Mod Healthc. 2006;36(7):58–60.
47. Nef T, Mihelj M, Riener R. ARMin: a robot for patient-cooperative arm therapy. Med Biol Eng Comput. 2007;45(9):887–900.
48. Sugar TG, He J, Koeneman EJ, Koeneman JB, Herman R, Huang H, et al. Design and control of RUPERT: a device for robotic upper extremity repetitive therapy. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):336–46.
49. Lopes II. 2015. Available from: http://www.utwente.nl/en/newsevents/2014/5/332856/unique-walking-robot-moves-into-rehabilitation-clinic.
50. Edgerton VR, Courtine G, Gerasimenko YP, Lavrov I, Ichiyama RM, Fong AJ, et al. Training locomotor networks. Brain Res Rev. 2008;57(1):241–54.
51. Cao J, Xie SQ, Das R, Zhu GL. Control strategies for effective robot assisted gait rehabilitation: the state of art and future prospects. Med Eng Phys. 2014;36(12):1555–66.
52. Kruger M, Eggert T, Straube A. Joint angle variability in the time course of reaching movements. Clin Neurophysiol. 2011;122(4):759–66.
53. Wolbrecht ET, Chan V, Reinkensmeyer DJ, Bobrow JE. Optimizing compliant, model-based robotic assistance to promote neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2008;16(3):286–97.
54. Duschau-Wicke A, Caprez A, Riener R. Patient-cooperative control increases active participation of individuals with SCI during robot-aided gait training. J Neuroeng Rehabil. 2010;7:43.
55. Hesse S, Werner C, Bardeleben A. Electromechanical gait training with functional electrical stimulation: case studies in spinal cord injury. Spinal Cord. 2004;42(6):346–52.
56. Daly JJ, Ruff RL. Construction of efficacious gait and upper limb functional interventions based on brain plasticity evidence and model-based measures for stroke patients. ScientificWorldJournal. 2007;7:2031–45.
57. Bae YH, Ko YJ, Chang WH, Lee JH, Lee KB, Park YJ, et al. Effects of robot-assisted gait training combined with functional electrical stimulation on recovery of locomotor mobility in chronic stroke patients: a randomized controlled trial. J Phys Ther Sci. 2014;26(12):1949–53.
58. del Ama AJ, Gil-Agudo A, Pons JL, Moreno JC. Hybrid FES-robot cooperative control of ambulatory gait rehabilitation exoskeleton. J Neuroeng Rehabil. 2014;11:27.
59. Schill O, Wiegand R, Schmitz B, Matthies R, Eck U, Pylatiuk C, Reischl M, Schulz S, Rupp R. OrthoJacket—an active FES-hybrid orthosis for the paralysed upper extremity. Biomed Eng. 2011;56(1):35–44.
60. Indego. 2015. Available from: www.indego.com.
61. Medical electrical equipment—part 1: general requirements for basic safety and essential performance, IEC 60601–1 (2005).
62. Borggraefe I, Klaiber M, Schuler T, Warken B, Schroeder SA, Heinen F, et al. Safety of robotic-assisted treadmill therapy in children and adolescents with gait impairment: a bi-centre survey. Dev Neurorehabil. 2010;13(2):114–9.

63. Toth A, Nyitrai D, Jurak M, Merksz I, Fazekas G, Denes Z. Safe robot therapy: Adaptation and usability test of a three-position enabling device for use in robot mediated physical therapy of stroke, in IEEE 2009. Int Conf Rehabil Robot, 2009, pp. 940–5.
64. Koritnik T, Koenig A, Bajd T, Riener R, Munih M. Comparison of visual and haptic feedback during training of lower extremities. Gait Posture. 2010;32(4):540–6.
65. Banz R, Riener R, Lunenburger L, Bolliger M. Assessment of walking performance in robot-assisted gait training: a novel approach based on empirical data. Conference proceedings of IEEE engineering in medicine and biology society. 2008:1977–80. PMID: 19163079.
66. Bolliger M, Banz R, Dietz V, Lunenburger L. Standardized voluntary force measurement in a lower extremity rehabilitation robot. J Neuroeng Rehabil. 2008;5:23.
67. Schmartz AC, Meyer-Heim AD, Muller R, Bolliger M. Measurement of muscle stiffness using robotic assisted gait orthosis in children with cerebral palsy: a proof of concept. Disabil Rehabil Assist Technol. 2011;6(1):29–37.
68. Bosecker C, Dipietro L, Volpe B, Krebs HI. Kinematic robot-based evaluation scales and clinical counterparts to measure upper limb motor performance in patients with chronic stroke. Neurorehabil Neural Repair. 2010;24(1):62–9.
69. Craven BC, Morris AR. Modified Ashworth scale reliability for measurement of lower extremity spasticity among patients with SCI. Spinal Cord. 2010;48(3):207–13.
70. Domingo A, Lam T. Reliability and validity of using the Lokomat to assess lower limb joint position sense in people with incomplete spinal cord injury. J Neuroeng Rehabil. 2014;11(1):167.
71. Center NSCIS. Spinal cord injury: annual statistical report. Birmingham: The University of Alabama; 2007.
72. Wirz M, Zemon DH, Rupp R, Scheel A, Colombo G, Dietz V, et al. Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil. 2005;86(4):672–80.
73. Hicks AL, Adams MM, Martin Ginis K, Giangregorio L, Latimer A, Phillips SM, et al. Long-term body-weight-supported treadmill training and subsequent follow-up in persons with chronic SCI: effects on functional walking ability and measures of subjective well-being. Spinal Cord. 2005;43(5):291–8.
74. Rupp R, Plewa H, Schuld C, Gerner HJ, Hofer EP, Knestel M. MotionTherapy@Home—first results of a clinical study with a novel robotic device for automated locomotion therapy at home. Biomed Tech (Berl). 2011;56(1):11–21.
75. Rupp R, Schliessmann D, Plewa H, Schuld C, Gerner HJ, Weidner N, et al. Safety and efficacy of at-home robotic locomotion therapy in individuals with chronic incomplete spinal cord injury: a prospective, pre-post intervention proof-of-concept study. PLoS One. 2015;10(3):e0119167.
76. Anderson KR, Woodbury ML, Phillips K, Gauthier LV. Virtual reality video games to promote movement recovery in stroke rehabilitation: a guide for clinicians. Arch Phys Med Rehabil. 2015;96(5):973–6.
77. Webster D, Celik O. Systematic review of Kinect applications in elderly care and stroke rehabilitation. J Neuroeng Rehabil. 2014;11:108.
78. Putrino D. Telerehabilitation and emerging virtual reality approaches to stroke rehabilitation. Curr Opin Neurol. 2014;27(6):631–6.
79. Ravenek KE, Wolfe DL, Hitzig SL. A scoping review of video gaming in rehabilitation. Disabil Rehabil Assist Technol. 2015:1–9.
80. Lauritzen J, Munoz A, Luis Sevillano J, Civit A. The usefulness of activity trackers in elderly with reduced mobility: a case study. Stud Health Technol Inform. 2013;192:759–62.
81. Pietrzak E, Cotea C, Pullman S. Using commercial video games for upper limb stroke rehabilitation: is this the way of the future? Top Stroke Rehabil. 2014;21(2):152–62.
82. Pohl M, Werner C, Holzgraefe M, Kroczek G, Mehrholz J, Wingendorf I, et al. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). Clin Rehabil. 2007;21(1):17–27.

The Human in the Loop

9

Alexander C. Koenig and Robert Riener

Abstract

In conventional man-machine interfaces applied to rehabilitation, the primary goal is to control the biomechanical 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

A.C. Koenig, PhD
Sensory-Motor Systems Lab, Institute of Robotics and Intelligent Systems, Department of Health Sciences and Technology, ETH Zurich, Tannenstrasse 1, Zurich 8092, Switzerland

Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, 125 Nashua Street, Boston, MA 02114, USA

R. Riener, MD, PhD (✉)
Sensory-Motor Systems Lab, Institute of Robotics and Intelligent Systems, Department of Health Sciences and Technology, ETH Zurich, Tannenstrasse 1, Zurich 8092, Switzerland

Medical Faculty, University Hospital Balgrist, University of Zurich, Forchstrasse 340, 8008 Zurich, Switzerland

Department of Health Sciences and Technology, Spinal Cord Injury Center, Balgrist University Hospital, Zurich, Switzerland
e-mail: riener@hest.ethz.ch

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9.1 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 efforts of that particular person. For instance, many actuated orthoses apply 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. 9.1) [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. 9.2) [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]. For an up-to-date review about rehabilitation robotics, please see [10].

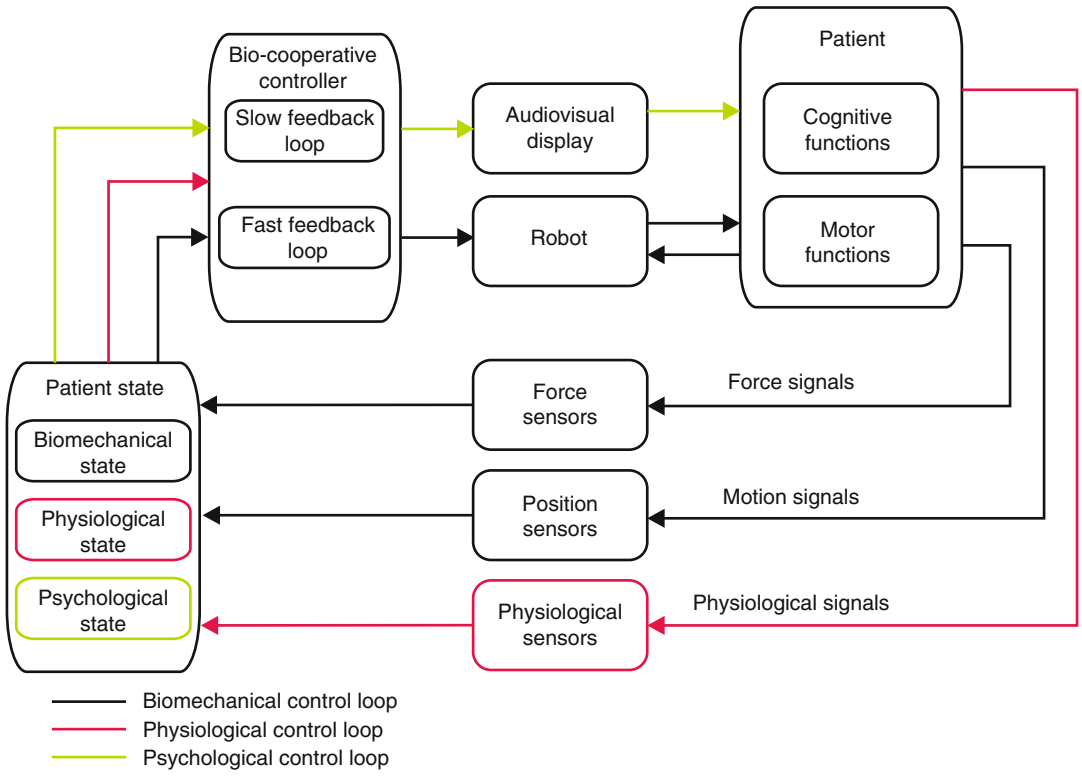

Fig. 9.1 The human is in the loop with respect to biomechanical (*black*), physiological (*red*), and psychological aspects (*green*). A fast feedback loop with update frequencies in the millisecond range controls the robot. A slow feedback loop adapts robot and audiovisual display with an updating frequency of several seconds (Adapted from Riener and Munih [1] (© 2010, IEEE); used with permission)

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

9.2.1 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 [2]. 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 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. 9.3).

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" [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 [13] demonstrated that intralimb coordination and self-selected walking speed after stroke were

Fig. 9.2 Patient exercising with the Lokomat® (Courtesy Hocoma AG, Switzerland, www.hocoma.com; used with permission)

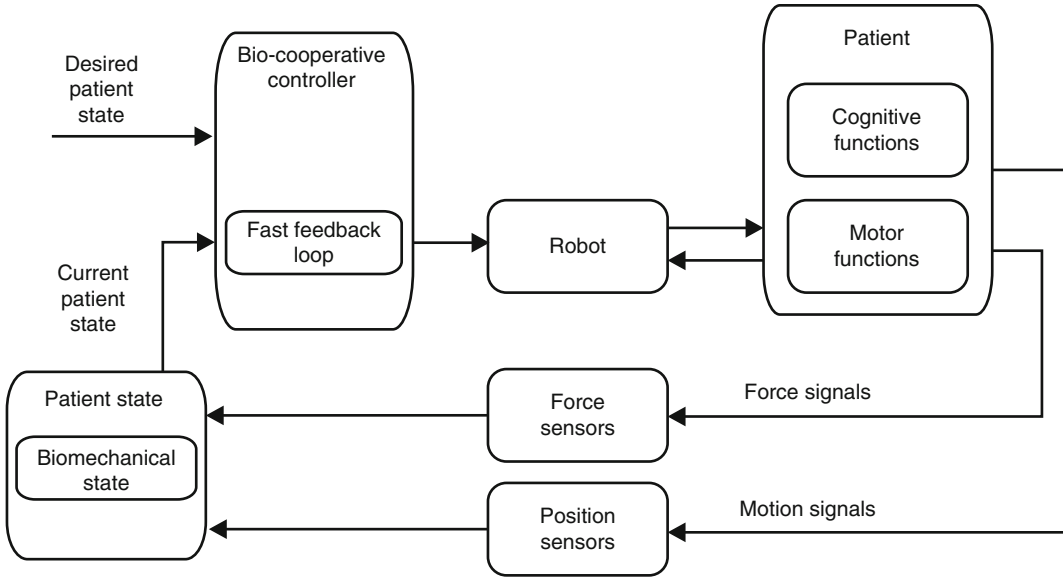

Fig. 9.3 The human in the biomechanical control loop. The user-cooperative controller provides a training environment where the human can actively control his/her movements. A visual display provides feedback about the quality of the movement (deviation between desired and actual one)

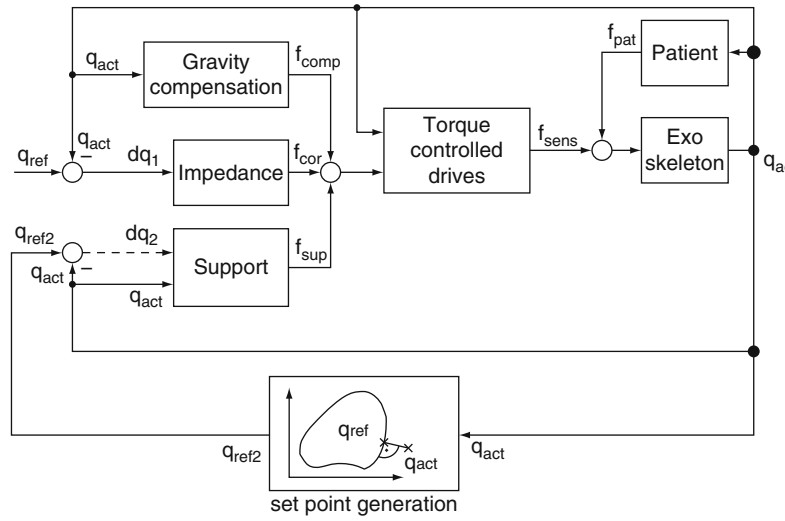

Fig. 9.4 Path control strategy as derived by Duschau-Wicke et al. [16]: q is the vector of generalized joint angles; F is the vector of joint forces (From Duschau-Wicke et al. [16] (© 2010, IEEE); used with permission)

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 [14–16]. 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 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 [17]. Figure 9.4 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 [15]. 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. Also, the patient might trip or fall when the impedance controller becomes too compliant. 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.

An extension of the impedance-based controller was implemented and tested by Emken et al.

[14], who used an iterative learning controller to adapt the impedance within each gait cycle. The controller identified points within the gait cycle where the patient consistently deviated from the desired trajectory. At these locations within each gait cycle, the controller became stiffer and thereby provided more guidance force.

9.2.2 The Path Controller

Therefore, the features of the impedance controller have been extended into a novel "path controller" [16] in which the time-dependent walking trajectories are converted to walking paths with user-determined free timing (Fig. 9.4). 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 [16]). 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 [16].

In an initial study, 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 [18]. 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 [16, 19]).

Two recent case studies evaluated the feasibility of patient-cooperative robotic gait training for improving locomotor function in a chronic stroke survivor with severe lower extremity motor impairments [20]. A 52-year-old man suffering from right hemiparesis due to a left corona radiata infarct underwent 4 weeks of path control Lokomat therapy and showed considerable improvements in self-selected walking speed and the 6-min walking test, two important clinical quantifiers of gait recovery. Also, the patient showed larger propulsive forces, more symmetric ground reaction forces, and improvements in muscle coordination [21]. Contrasting position control with path control mode, a 62-year-old man with right temporal lobe ischemic stroke underwent 4 weeks of intense Lokomat with full robotics guidance before undergoing 4 weeks of similarly intensive training in Lokomat path control mode. Among others, the self-selected walking speed and the 6-min walking test changed minimally after full guidance robotic training but improved considerably after 4 weeks of path control Lokomat therapy [20].

The initial results show that the subjects are able to freely influence their movements within the spatial constraints of the desired walking pattern which can ultimately lead to improved gait recovery. Although the controller leaves maximum freedom, it still ensures functional gait in critical situations. Particularly during stance phase, where subjects are not able to keep their knee joints extended, the controller assists 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.

9.2.3 Patient-Cooperative Control Based on Muscle Activity Recognition

The path control strategy takes into account interaction forces as well as joint positions and velocities to quantify the patients' intention and their individual ability to perform the gait movement themselves. The interaction forces between the patients' limbs and the rehabilitation robot are, however, the result of complex muscle activation patterns in the limbs, generated by the major muscle groups such as the gluteus, the quadriceps, the hamstrings, or the gastrocnemius muscles.

EMG-based control strategies utilize not only recordings of force, position, and velocity but integrate information recorded directly from the major muscle groups of the legs into the control scheme. Recent research efforts are directed toward stable and reliable recording and interpretation of EMG data for motion and intention recognition [22]. Using signal processing for filtering and decomposing the EMG signals in combination with real-time, online machine learning techniques, the EMG data of

subjects can be interpreted to modify the control strategy. However, usability of such EMG-driven approaches in daily clinical routine is still limited, as they require the use of contact-based electrodes, which is time consuming as compared to the ready-to-use force sensors build into many rehabilitation robots.

9.2.4 The Next Step: Movement Intention Detection

Whereas the control approaches presented so far limit the patients to movement in the sagittal plane on a treadmill, future rehabilitation could well take place overground using a wearable exoskeleton. Besides freedom in gait timing as permitted by the path controller, in these scenarios the patient would be able to experience an even great variety of movement patterns through voluntary turning movements or gait initiation or termination. Reliably detecting the patient's intentions to ambulate in the presence of incomplete control over the movement generation presents a challenge which is unsolved so far. In healthy subjects, however, wearable inertial measurement units and pressure-sensitive insoles have successfully be used to detect voluntary gait initiation and termination [23] and turning movements [24]. Results on gait initiation and termination showed that gait initiation can be detected timely and accurately, with few errors in the case of within-subject cross-validation and overall good performance in subject-independent cross-validation. The proposed gait initiation detection method recognized an anticipatory movement preceding foot lifting and toe-off. Gait termination could be predicted in over 80 % of trials well before the subject came to a complete stop. Results on predicting turning onset, orientation (left or right), and angular turning velocity showed that turning onset could be most accurately detected with inertial sensors on the back and using a combination of orientation and angular velocity estimation. The same setup also gave the best prediction of turn direction and amplitude.

9.3 Human Physiology in the Loop

9.3.1 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 [25]. 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 [26]. 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 [27, 28].

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 [29–31], 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

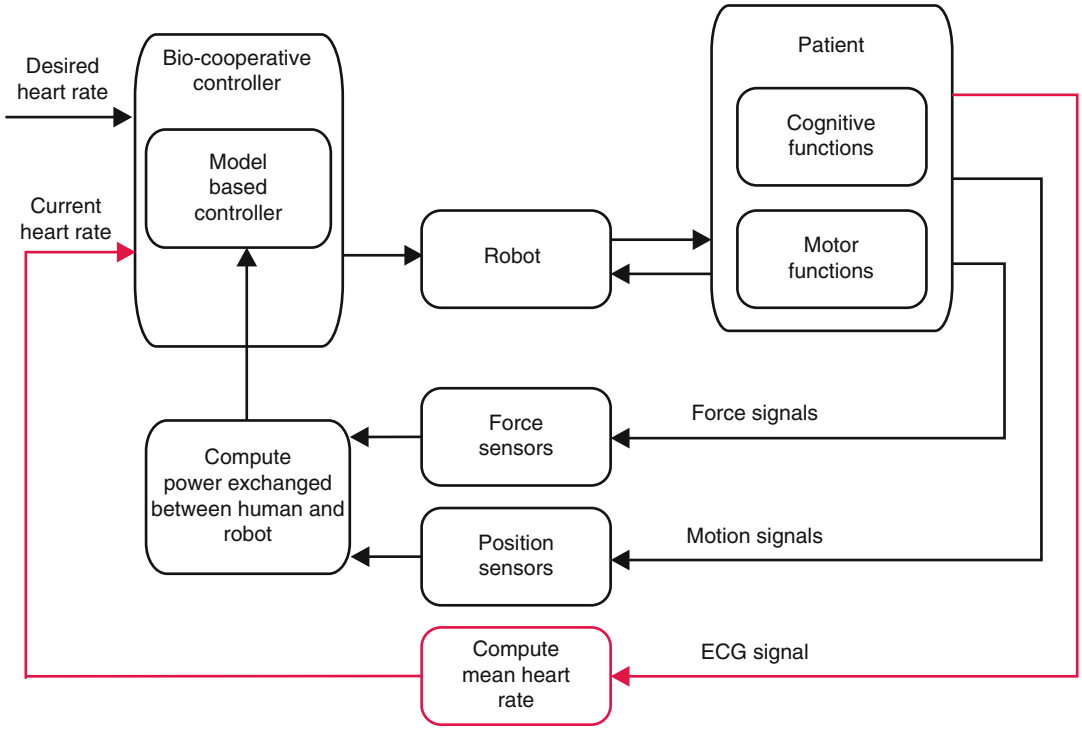

Fig. 9.5 Model-based control of heart rate as derived by [34]. Heart rate control is performed based on a model by taking power exchange between patient and robot into account

rate control was performed with walking speeds greater than 3.6 km/h [32]. Second, for facilitation of stance, the patient can be body weight supported, which will decrease heart rate with increasing body weight support (BWS) [33]. 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. 9.5).

9.3.2 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 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. 9.2). 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 [35, 36]. 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 [37–39]. 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 [38, 40], 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 [41]. 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 [42]. The power expenditure of a subject during exercise on a bicycle ergometer [43] and during arm cranking [44] 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 [38, 45]. 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 [32]. However, PID or H_∞ control strategies have so far only been used with healthy subjects. A model-based approach as described above can not only be applied to healthy subjects but also to stroke patients: as energy expenditure is one of the key drivers of changes in heart rate, the change in heart rate as a function of energy exchanged between human and robot (as described above as a first-order PT element) can then explicitly be taken into account as a model parameter. 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.

9.3.3 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 [34].

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 [46]. However, it was possible to control heart rate of stroke patients in a range between resting heart rate and plus 10 beats/min.

9.3.4 Implementing Model-Based Heart Rate into Daily Clinical Routine

The major holdback in utilizing heart rate control schemes in daily clinical routines has so far been the necessity of using sensors that require contact to the body for recording of the subject's heart rate. While ECG electrodes, chest belts, or even wrist watches for monitoring HR are commonly available, they all require the use of devices that need to be attached to the patient and later be disinfected, which are time-consuming processes in the already time-consuming clinical routine of physical therapy staff.

An image processing algorithm, recently developed at MIT, allows quantifying HR through changes in the blood flow, invisible to the human eye [47]. As each heart beat pumps blood through the veins and, therefore, through the head, small changes in red color channel of the head occur. By magnifying these color changes, an algorithm can evaluate the frequency at which these changes occur and compute the current HR from it. This could, in the future, allow therapists to simply direct a webcam toward the face of the patient and start the training.

9.4 Human Psychology in the Loop

9.4.1 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 [48]. 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 [49, 50]. 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 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. 9.6). 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

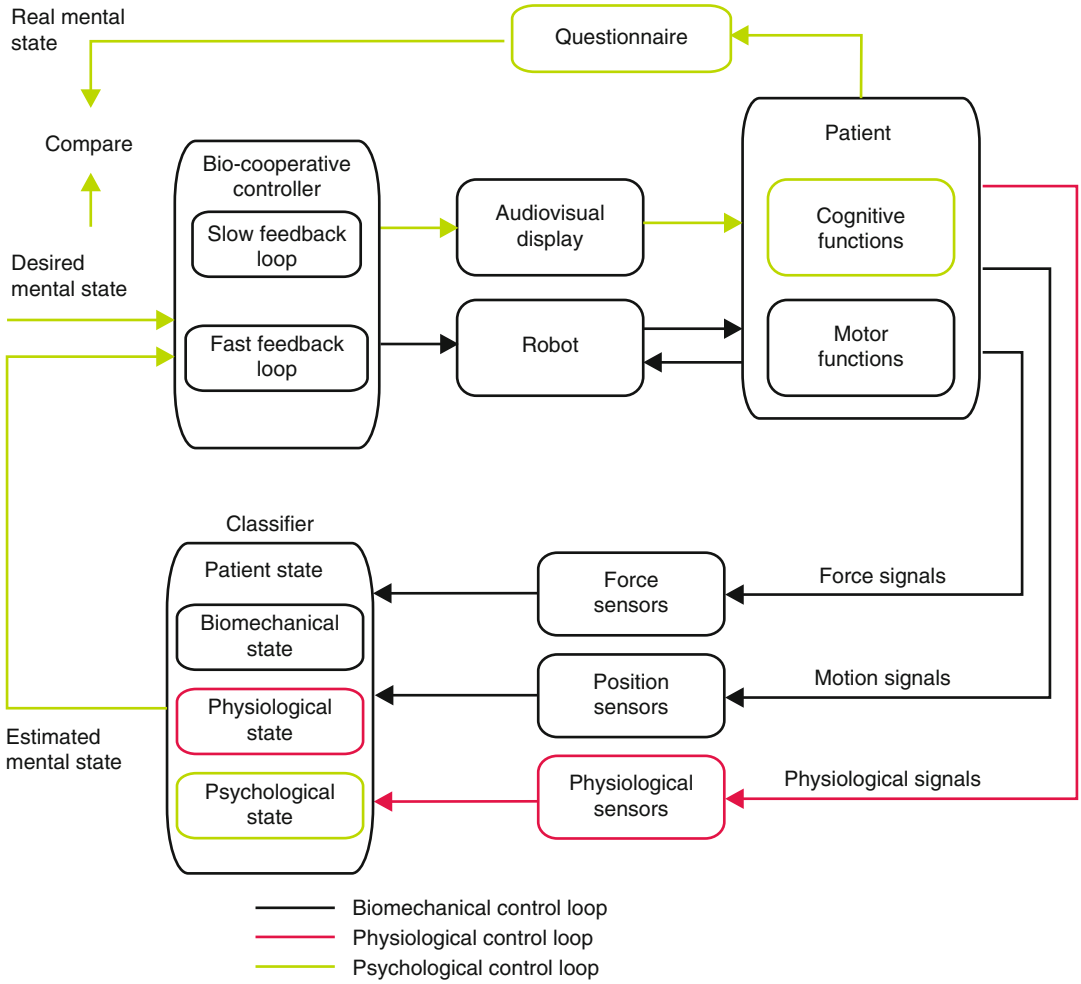

Fig. 9.6 Closed-loop control scheme for automated control of cognitive load during robot-assisted gait training. Questionnaires can be used to ensure that the desired mental state can really be established in the subject

and the virtual task, the mental state of the subject can be altered, which causes a psychological reaction.

Changes in the mental state, particularly arousal and valence of a subject, are reflected in numerous physiological signals, as summarized in Table 9.1 [51–57]. These human "output" signals are affected by the autonomic nervous system [58]. We selected heart rate and heart rate variability (HRV) obtained by electrocardiogram (ECG) recordings [59], skin conductance response (SCR) [60], skin temperature, breathing frequency, and joint torques (Table 9.1). 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 [61]. Heart rate variability was computed as a discrete time series of consecutive RR intervals. Using a thermistor

Table 9.1 Overview of physiological signals recorded for determination of psychological states

Signal	Time	ECG frequency	SCR	Skin temperature	Breathing	Joint torques
Quantity	Mean heart rate	Spectral power of HRV				
Psychological interpretation	Physical effort, arousal [51]	Arousal [52]	Cognitive load, arousal [53, 54]	Valence [55, 56]	Physical effort, arousal [57]	Physical effort

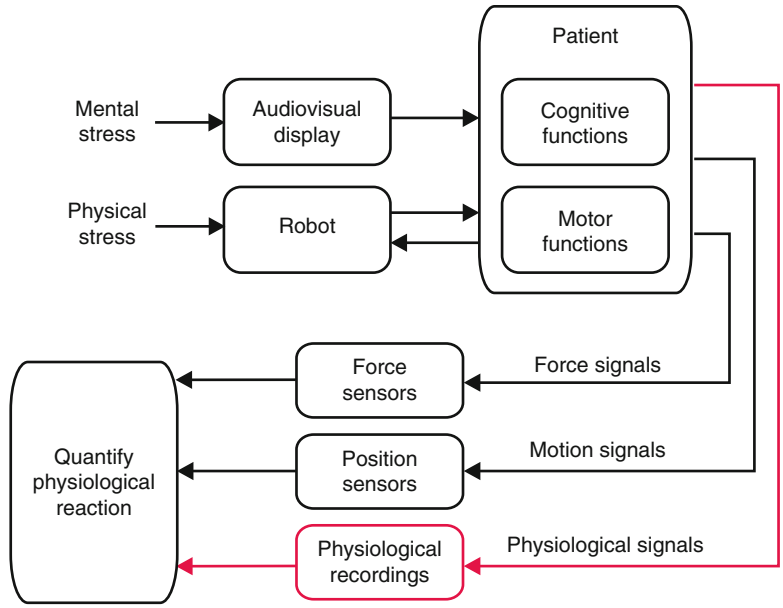

Fig. 9.7 Quantifying the effects of mental and physical stress on physiological signals (From Riener et al. [19] (copyright IEEE); used with permission)

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 [54]. Skin temperature was measured on the fifth finger. Signals were sampled at 512 Hz according to the recommendations of Malik [59]. Force data from the Lokomat were weighted and summed for each step such that it reflected the current physical effort of the subjects [62].

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.

9.4.2 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. 9.7) [19]. 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

Table 9.2 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	–

From Riener et al. [19] (copyright IEEE); used with permission)
Breathing frequency during arithmetic tasks could not be recorded as subjects had to talk, which prevented analysis of the thermistor signal [19]
SCR skin conductance responses

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 9.2; they showed that the number of SCR events increased significantly when subjects had to perform mental arithmetic tasks [60], whereas skin temperature decreased significantly during mental arithmetic tasks. Heart rate increased with physical load, but it also increased with mental workload [63].

The isolated findings are congruent with the literature. An increase in heart rate was found due to negative emotions or stress [64, 65]. 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 [53, 65]. 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 [65]. An increase of sympathetic activity, and therefore a decrease in skin temperature, was found in the study of Ohsuga et al. [66] 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 [67]. An increase in breathing frequency was also found in different studies during excitement or during pleasant attentive states [67]. 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 [67].

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

9.4.3 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 [68]. 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 9.3).

Table 9.3 Characteristics of patients of open-loop identification experiments

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

From Koenig et al. [68] (copyright IEEE), used with permission
F Female, *M* Male

Table 9.4 Classification results of healthy subjects with a Kalman adaptive linear discriminant analysis (KALDA) classifier

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

From Koenig et al. [68] (copyright IEEE), used with permission

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 [69] and adapted to rehabilitation [70]. 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.

Table 9.5 Classification results of neurological patients with a Kalman adaptive linear discriminant analysis (KALDA) classifier

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

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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 9.4 and 9.5).

9.4.4 Evaluation of Psychological Closed-Loop Control

Using the open-loop classifier trained with data of nine healthy subjects and four stroke patients,

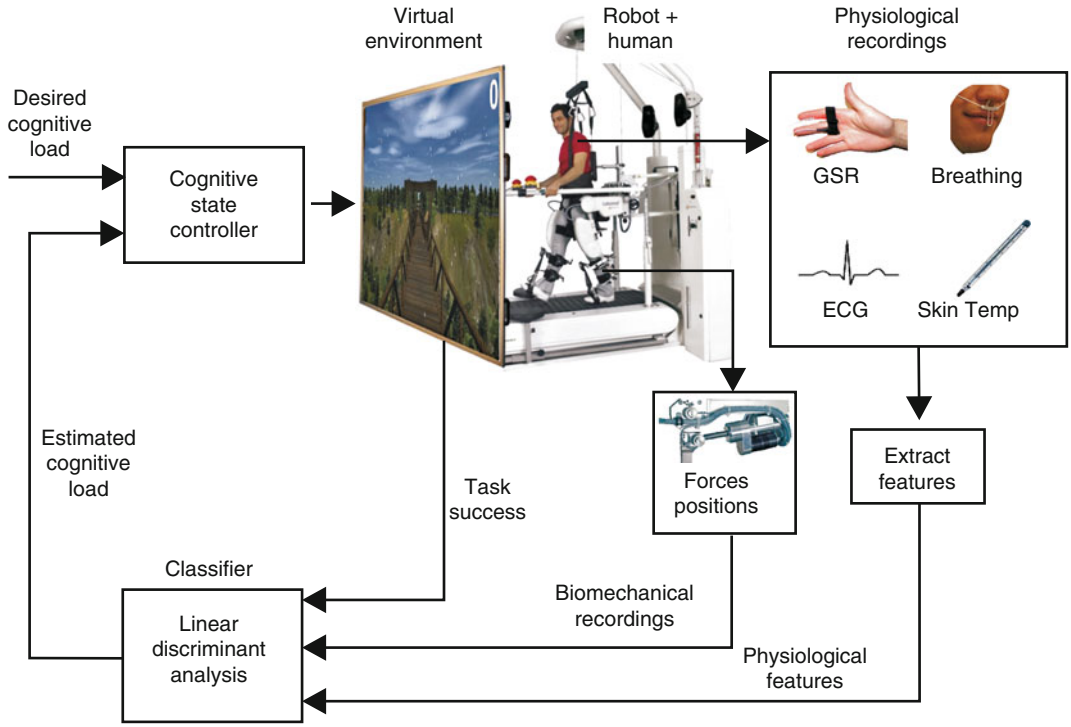

Fig. 9.8 System setup for control of cognitive load (Adapted from Koenig et al. [68] (copyright IEEE), used with permission)

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. 9.8). 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 9.6.

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

Table 9.6 Classification results in % correctly classified decisions of five healthy subjects

		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

From Koenig et al. [68] (copyright IEEE), used with permission
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)

success data was superior in the amount of correct decisions compared to the classifier that only received task success as input (Table 9.6).

While the patients in this study were nonaphasic and could therefore verbalize their own preferences, 10–20 % of patients suffer from aphasia [71] and could therefore benefit from this approach when undergoing rehabilitation training. 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.

9.4.5 Implementing Cognitive Load Evaluation and Control into Daily Clinical Routine

Despite the clinical advantages of enabling patients to exercise at their individually optimal cognitive levels, one major drawback of quantifying and controlling cognitive load during neurorehabilitation is the increased effort for preparation caused by sensor placement. As discussed above, similar to heart rate control, contactless sensors will in the future enable clinicians to implement cognitive control training schemes more efficiently. A recent study performed in healthy subjects obtained HR, HRV, and breathing frequency from ten subjects using a digital camera from a distance of up to 3 m [72] during varying levels of cognitive load. Quantifying situations of high cognitive load, it was possible to achieve 85 % correct classification of high cognitive load in a two-class problem (50 % would denote chance). In combination with performance metrics obtained from the virtual task, these classification rates should theoretically increase further while enabling clinicians to minimize time for setup.

9.5 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 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. [73], 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 [48]. 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 [25], exemplarily implemented in closed-loop heart rate control. Heart rate control in the Lokomat

thereby allows cardiovascular training of non-ambulatory 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 [74, 75]. 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 [76, 77].

Detection and control of physiological and psychological states are 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 autoadaptive 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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References

1. Riener R, Munih M. Guest editorial: special section on rehabilitation via bio-cooperative control. IEEE Trans Neural Syst Rehabil Eng. 2010;18(4):2.
2. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37(6):693–700. Epub 2001/04/26.
3. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379–86. Epub 2007/09/27.
4. Stauffer Y, Allemand Y, Bouri M, Fournier J, Clavel R, Metrailler P, et al. The WalkTrainer; a new generation of walking reeducation device combining orthoses and muscle stimulation. IEEE Trans Neural Syst Rehabil Eng. 2009;17(1):38–45. Epub 2009/02/13.
5. Hesse S, Sarkodie-Gyan T, Uhlenbrock D. Development of an advanced mechanised gait trainer, controlling movement of the centre of mass, for restoring gait in non-ambulant subjects. Biomed Tech (Berl). 1999;44(7–8):194–201. Epub 1999/09/03.
6. Nef T, Guidali M, Riener R. ARMin III; arm therapy exoskeleton with an ergonomic shoulder actuation. Appl Bionics Biomech. 2009;6(2):16.
7. Nef T, Mihelj M, Riener R. ARMin: a robot for patient-cooperative arm therapy. Med Biol Eng Comput. 2007;45(9):887–900. Epub 2007/08/04.
8. Houtsma JA, Van Houten FJ. Virtual reality and a haptic master-slave set-up in post-stroke upper-limb rehabilitation. Proc Inst Mech Eng H. 2006;220(6):715–8. Epub 2006/09/12.
9. Aisen ML, Krebs HI, Hogan N, McDowell F, Volpe BT. The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. Arch Neurol. 1997;54(4):443–6. Epub 1997/04/01.
10. Riener R. Rehabilitation robotics. Found Trends Robot. 2013;3(1–2):1–137.
11. Bernstein NA. The co-ordination and regulation of movements. Ltd PP, Oxford, New York, Pergamon Press 1967.
12. Huang VS, Krakauer JW. Robotic neurorehabilitation: a computational motor learning perspective. J Neuroeng Rehabil. 2009;6:5. Epub 2009/02/27.
13. Lewek MD, Cruz TH, Moore JL, Roth HR, Dhaher YY, Hornby TG. Allowing intralimb kinematic variability during locomotor training poststroke improves kinematic consistency: a subgroup analysis from a randomized clinical trial. Phys Ther. 2009;89(8):829–39. Epub 2009/06/13.
14. Emken JL, Harkema SJ, Beres-Jones JA, Ferreira CK, Reinkensmeyer DJ. Feasibility of manual teach-and-replay and continuous impedance shaping for robotic locomotor training following spinal cord injury. Biomed Eng IEEE Trans On. 2008;55(1):322–34.
15. Riener R, Lunenburger L, Jezernik S, Anderschitz M, Colombo G, Dietz V. Patient-cooperative strategies

for robot-aided treadmill training: first experimental results. IEEE Trans Neural Syst Rehabil Eng. 2005;13(3):380–94. Epub 2005/10/05.
16. Duschau-Wicke A, von Zitzewitz J, Caprez A, Lunenburger L, Riener R. Path control: a method for patient-cooperative robot-aided gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2010;18:38–48.
17. Hogan N. Impedance control: an approach to manipulation. J Dyn Syst-T ASME. 1985;107:1–23.
18. Barbeau H, Wainberg M, Finch L. Description and application of a system for locomotor rehabilitation. Med Biol Eng Comput. 1987;25(3):341–4. Epub 1987/05/01.
19. Riener R, Koenig A, Bolliger M, Wieser M, Duschau-Wicke A, Vallery H, editors. Bio-cooperative robotics: controlling mechanical, physiological and psychological patient states. Kyoto: ICORR; 2009.
20. Krishnan C, Kotsapouikis D, Dhaher YY, Rymer WZ. Reducing robotic guidance during robot-assisted gait training improves gait function: a case report on a stroke survivor. Arch Phys Med Rehabil. 2013;94(6):1202–6.
21. Krishnan C, Ranganathan R, Kantak SS, Dhaher YY, Rymer WZ. Active robotic training improves locomotor function in a stroke survivor. J Neuroeng Rehabil. 2012;9:57. Epub 2012/08/22.
22. Wei M, Yilin Z, Zude Z, Kun C, Qingsong A, editors. Active interaction control of a rehabilitation robot based on motion recognition and adaptive impedance control. 2014 IEEE international conference on Fuzzy Systems (FUZZ-IEEE), 6–11 July 2014. 1436–41
23. Novak D, Rebersek P, De Rossi SM, Donati M, Podobnik J, Beravs T, et al. Automated detection of gait initiation and termination using wearable sensors. Med Eng Phys. 2013;35(12):1713–20. Epub 2013/08/14.
24. Novak D, Goršič M, Podobnik J, Munih M. Toward real-time automated detection of turns during gait using wearable inertial measurement units. Sensors. 2014;14(10):18800–22.
25. Gordon NF, Gulanick M, Costa F, Fletcher G, Franklin BA, Roth EJ, et al. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. Stroke. 2004;35(5):1230–40. Epub 2004/04/24.
26. Shumway-Cook A, Woollacott M. Motor control: theory and practical applications. Philadelphia: Lippincott Williams & Wilkins; 1995.
27. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke. 2007;38(2):349–54. Epub 2007/01/06.
28. Mayr A, Kofler M, Quirbach E, Matzak H, Frohlich K, Saltuari L. Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair. 2007;21(4):307–14. Epub 2007/05/04.
29. Su SW, Wang L, Celler BG, Savkin AV, Guo Y. Identification and control for heart rate regulation during treadmill exercise. IEEE Trans Biomed Eng. 2007;54(7):1238–46. Epub 2007/07/04.
30. Cheng T, Savkin A, Su S, Celler B, Wang L. A robust control design for heart rate tracking during exercise. IEEE EMBS, Vancouver, 2008. P. 4.
31. Cheng T, Savkin A, Celler B, Su S, Wang L, editors. Heart rate regulation during exercise with various loads: identification and nonlinear H infinity control. 17th world congress of the international federation of automatic control, Seoul, 2008.
32. Su S, Huang S, Wang L, Celler B, Savkin A, Guo Y, et al., editors. Nonparametric Hammerstein model based model predictive control for heart rate regulation. Lyon: IEEE EMBS; 2007.
33. Colby SM, Kirkendall DT, Bruzga RF. Electromyographic analysis and energy expenditure of harness supported treadmill walking: implications for knee rehabilitation. Gait Posture. 1999;10(3):200–5. Epub 1999/11/24.
34. Koenig A, Caruso A, Bolliger M, Somaini L, Omlin X, Morari M, et al., editors. Model-based heart rate control during robot-assisted gait training. International conference robotics and automation, Singapore, 2011.
35. Dietz V, Duysens J. Significance of load receptor input during locomotion: a review. Gait Posture. 2000;11:9.
36. Dietz V, Muller R, Colombo G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. Brain. 2002;125(Pt 12):2626–34. Epub 2002/11/14.
37. Achten J, Jeukendrup AE. Heart rate monitoring: applications and limitations. Sports Med. 2003;33(7):517–38. Epub 2003/05/24.
38. Hajek M, Potucek J, Brodan V. Mathematical-model of heart rate regulation during exercise. Automatica. 1980;16(2):5.
39. Pierpont GL, Stolpman DR, Gornick CC. Heart rate recovery post-exercise as an index of parasympathetic activity. J Auton Nerv Syst. 2000;80(3):169–74. Epub 2000/04/28.
40. Baum K, Essfeld D, Leyk D, Stegemann J. Blood pressure and heart rate during rest-exercise and exercise-rest transitions. Eur J Appl Physiol Occup Physiol. 1992;64(2):134–8. Epub 1992/01/01.
41. Holmgren A. Circulatory changes during muscular work in man; with special reference to arterial and central venous pressures in the systemic circulation. Scand J Clin Lab Invest. 1956;8 Suppl 24:1–97. Epub 1956/01/01.
42. Feroldi P, Belleri M, Ferretti G, Veicsteinas A. Heart rate overshoot at the beginning of muscle exercise. Eur J Appl Physiol Occup Physiol. 1992;65(1):8–12. Epub 1992/01/01.
43. Vokac Z, Bell H, Bautz-Holter E, Rodahl K. Oxygen uptake/heart rate relationship in leg and arm exercise,

sitting and standing. J Appl Physiol. 1975;39(1):54–9. Epub 1975/07/01.
44. Borg G, Hassmen P, Lagerstrom M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Eur J Appl Physiol Occup Physiol. 1987;56(6):679–85. Epub 1987/01/01.
45. Fagraeus L, Linnarsson D. Autonomic origin of heart rate fluctuations at the onset of muscular exercise. J Appl Physiol. 1976;40(5):679–82. Epub 1976/05/01.
46. Tokgözoglu SL, Batur MK, Topçuoglu MA, Saribas O, Kes S, Oto A. Effects of stroke localization on cardiac autonomic balance and sudden death. Stroke. 1999;30(7):1307–11.
47. Wu H-Y, Rubinstein M, Shih E, Guttag J, et al. Eulerian video magnification for revealing subtle changes in the world. ACM Trans Graph. 2012;31(4): 1–8.
48. Lotze M, Braun C, Birbaumer N, Anders S, Cohen LG. Motor learning elicited by voluntary drive. Brain. 2003;126(Pt 4):866–72. Epub 2003/03/05.
49. Holden MK. Virtual environments for motor rehabilitation: review. Cyberpsychol Behav. 2005;8(3): 187–211; discussion 2–9. Epub 2005/06/24.
50. Labruyere R, Gerber CN, Birrer-Brutsch K, Meyer-Heim A, van Hedel HJ. Requirements for and impact of a serious game for neuro-pediatric robot-assisted gait training. Res Dev Disabil. 2013;34(11):3906–15. Epub 2013/09/13.
51. Den Otter AR, Geurts AC, Mulder T, Duysens J. Gait recovery is not associated with changes in the temporal patterning of muscle activity during treadmill walking in patients with post-stroke hemiparesis. Clin Neurophysiol: Off J Int Fed Clin Neurophysiol. 2006;117(1):4–15. Epub 2005/12/13.
52. Delaney JPA, Brodie DA. Effects of short-term psychological stress on the time and frequency domains of heart-rate variability. Percept Mot Skills. 2000;91(2):515–24.
53. Boucsein W, Backs R. Methods and models for the psychophysiology of emotion, arousal and personality. In: Francis T, editor. Handbook of digital human modelling. Boca Raton, FL. CRC Press; 2008
54. Dawson ME, Schell AM, Filion DL. In: Cacioppo JT, Tassinary LG, Berntson GG, editors. The Electrodermal System, Handbook of psychophysiology. Cambridge University Press, New York. 3rd ed. 2007.
55. Suess WM, Alexander AB, Smith DD, Sweeney HW, Marion RJ. The effects of psychological stress on respiration: a preliminary study of anxiety and hyperventilation. Psychophysiology. 1980;17(6):535–40. Epub 1980/11/01.
56. Carroll D, Turner JR, Prasad R. The effects of level of difficulty of mental arithmetic challenge on heart rate and oxygen consumption. Int J Psychophysiol: Off J Int Organ Psychophysiol. 1986;4(3):167–73. Epub 1986/11/01.
57. Mancuso DL, Knight KL. Effects of prior physical activity on skin surface temperature response of the ankle during and after a 30-minute ice pack application. J Athl Train. 1992;27(3):242. 4, 6, 8–9.
58. Duffy VG. Handbook of digital human modeling: research for applied ergonomics and human factors engineering: Boca Raton, FL. CRC Press, Inc.; 2008. 738 p.
59. Malik M. Heart rate variability; standards of measurement, physiological interpretation and clinical use. Eur Heart J. 1996;17:28.
60. Fowles DC, Christie MJ, Edelberg R, Grings WW, Lykken DT, Venables PH. Publication recommendations for electrodermal measurements. Committee report. Psychophysiology. 2007;18:232–9. PMID 7291438 p.
61. Christov I. Real time electrocardiogram QRS detection using combined adaptive threshold. Biomed Eng OnLine. 2004;3(28):8.
62. Banz R, Bolliger M, Colombo G, Dietz V, Lunenburger L. Computerized visual feedback: an adjunct to robotic-assisted gait training. Phys Ther. 2008;88(10):1135–45. Epub 2008/09/06.
63. Neumann SA, Waldstein SR. Similar patterns of cardiovascular response during emotional activation as a function of affective valence and arousal and gender. J Psychosom Res. 2001;50:245–53.
64. Levenson RW, Ekman P, Friesen WV. Voluntary facial action generates emotion-specific autonomic nervous system activity. Psychophysiology. 1990;27(4):363–84. Epub 1990/07/01.
65. Andreassi JL. Psychophysiology: human behavior and physiological response. 5th ed. Associates MLE; New Jersey, USA; 2007.
66. Ohsuga M, Shimono F, Genno H. Assessment of phasic work stress using autonomic indices. Int J Psychophysiol. 2001;40(3):211–20.
67. Boiten FA, Frijda NH, Wientjes CJ. Emotions and respiratory patterns: review and critical analysis. Int J Psychophysiol Off J Int Organ Psychophysiol. 1994;17(2):103–28. Epub 1994/07/01.
68. Koenig A, Novak D, Omlin X, Pulfer M, Perreault E, Zimmerli L, et al. Real-time closed-loop control of cognitive load in neurological patients during robot-assisted gait training. IEEE Trans Neural Syst Rehabil Eng. 2011;19(4):453–64. Epub 2011/08/11.
69. Vidaurre C, Schlogl A, Cabeza R, Scherer R, Pfurtscheller G. Study of on-line adaptive discriminant analysis for EEG-based brain computer interfaces. IEEE Trans Biomed Eng. 2007;54(3):550–6. Epub 2007/03/16.
70. Novak D, Mihelj M, Ziherl J, Olensek A, Munih M, editors. Measuring motor actions and psychophysiology for task difficulty estimation in human-robot interaction. Proceedings of measuring behavior, Eindhoven, 2010.
71. Wade DT, Hewer RL, David RM, Enderby PM. Aphasia after stroke: natural history and associated deficits. J Neurol Neurosurg Psychiatry. 1986;49(1):11–6.
72. McDuff D, Gontarek S, Picard R, editors. Remote measurement of cognitive stress via heart rate variability. Engineering in medicine and biology society

(EMBC), 2014. 36th annual international conference of the IEEE, Chicago, IL. 26–30 Aug 2014. 2957–60
73. Rani P, Sims J, Brackin R, Sarkar N. Online stress detection using psychophysiological signals for implicit human-robot cooperation. Robotica. 2002;20:13.
74. Loureiro R, Amirabdollahian F, Cootes S, Stokes E, Harwin W. Using haptics technology to deliver motivational therapies in stroke patients: concepts and initial pilot studies. Proceedings of EuroHaptics, Birmingham, UK, 2001. P. 6.
75. Robertson IH, Murre JMJ. Rehabilitation of brain damage: brain plasticity and principles of guided recovery. Psychol Bull. 1999;125(32):544.
76. Maclean N, Pound P. A critical review of the concept of patient motivation in the literature on physical rehabilitation. Soc Sci Med. 2000;50(4):495–506. Epub 2000/01/21.
77. Kaelin-Lang A, Sawaki L, Cohen LG. Role of voluntary drive in encoding an elementary motor memory. J Neurophysiol. 2005;93(2):1099–103.

Robotic and Wearable Sensor Technologies for Measurements/ Clinical Assessments

10

Olivier Lambercy, Serena Maggioni, Lars Lünenburger, Roger Gassert, and Marc Bolliger

Abstract

Neurological disorders such as stroke, multiple sclerosis, 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 program, a detailed assessment of the nature and degree of the sensorimotor deficits, as well as their temporal evolution, is crucial. Valid, reliable, and standardized assessments are essential to define the rehabilitation setting, and adapt it over the course of a therapy. Many clinical assessments suffer from limitations such as poor validity, low reliability, and low sensitivity and are often time consuming to administer, which greatly limits their systematic use in daily clinical routine. Rehabilitation robotics and sensor technologies are promising approaches that can provide objective, sensitive, and reliable measurements, which could help overcome the common limitations of conventional clinical assessments. This chapter focuses on the novel possibilities robotic devices and sensor technologies offer in the field of neurorehabilitation. Different strategies to evaluate sensorimotor

O. Lambercy, PhD (✉) • R. Gassert, PhD
Rehabilitation Engineering Laboratory, Department of Health Sciences and Technology, ETH Zurich, BAA Lengghalde 5, 8092 Zurich, Switzerland
e-mail: olivier.lambercy@hest.ethz.ch; roger.gassert@hest.ethz.ch

S. Maggioni, MSc Biomedical Engineering
Hocoma AG, Industriestrasse 4, 8604 Volketswil, Switzerland

Spinal Cord Injury Center, University of Zurich, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland

Sensory-Motor Systems (SMS) Lab, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland
e-mail: serena.maggioni@hocoma.com

L. Lünenburger, PhD
Hocoma AG, Industriestrasse 4, 8604 Volketswil, Switzerland
e-mail: lars.luenenburger@hocoma.com

M. Bolliger, PhD
Spinal Cord Injury Center, University of Zurich, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland
e-mail: mbolliger@paralab.balgrist.ch

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impairments using robotic platforms, as well as wearable sensor technologies, are presented. We discuss how a link between conventional scales and robotic/sensor-based assessments could be established and how this could result in more objective, clinically accepted assessment scales. Such scales have the potential to directly influence the way therapy is provided and to generate new insights into long-term recovery and transfer of therapy into performance in the home environment.

Keywords
Neurorehabilitation • Sensorimotor impairment • Clinical assessment • Medical robotics • Rehabilitation robotics • Robot-assisted assessment • Sensor technologies • Wearable sensors • Long-term activity monitoring

10.1 Introduction/Motivation

Neurological damage following a stroke, spinal cord injury (SCI), 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 are crucial for neurorehabilitation in several ways. In an early phase after the neurological injury, assessments are used to diagnose the level of sensorimotor impairment. 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. In addition valid, reliable, and standardized assessments are needed in order to evaluate the effect of new therapeutic interventions. 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 clinician or therapist. Throughout the course of a rehabilitation therapy, clinical assessments are usually repeated only at a few stages to monitor the patient's status and progress. However, several studies have shown that the long-term evolution in motor function can be well forecasted using predictive models of recovery based on clinical scales early after a stroke [1–5] or spinal cord injury [6, 7]. However, good prediction can only be achieved if clinical scales can assure high-quality data. The quality of an assessment method is defined by its sensitivity, validity, and reliability. Validity describes how precisely a scale assesses what it intends to measure. Hence, validity cannot be described by an all-or-nothing metric, but is rather continuous. Reliability is given if results are consistent on repeated administrations of the same test [8], which can be by the same or different raters (intra- or inter-rater reliability) or at two different points in time (test-retest reliability). Sensitivity, or responsiveness, of an assessment is defined as its ability to detect and quantify real changes (i.e., recovery or decline). For use in a clinical setting, it is essential that an assessment can detect changes due to therapeutic effects of interventions [9]. Nevertheless, many clinical assessments suffer from limitations such as low intra- or inter-rater reliability, low sensitivity, poor validity, or flooring/ceiling effects. Furthermore, they are often time consuming to administer, which limits the number and frequency of assessments that can be performed.

The field of rehabilitation technologies has seen increasing interest and development over the last decades [10–14]. Robotic devices are a promising approach to complement conventional

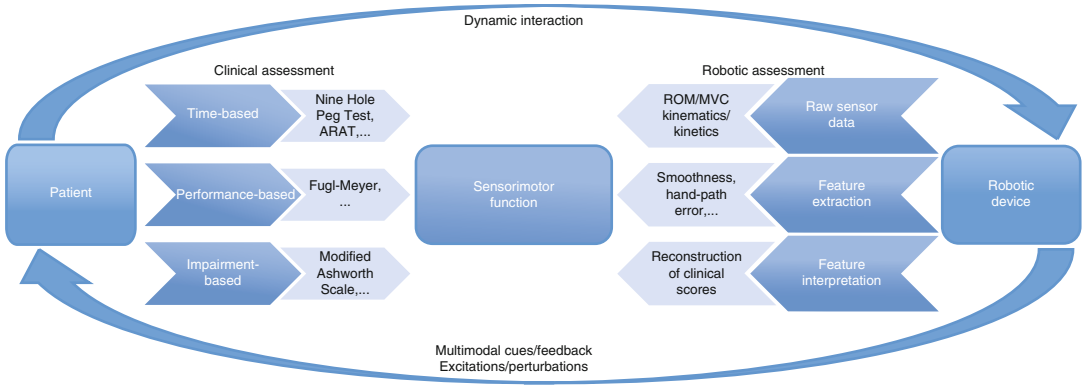

Fig. 10.1 Schematic representation of approaches for clinical and robotic/sensor-based assessments used to evaluate sensorimotor impairment resulting from neurological injuries. *ARAT* Action Research Arm Test, *ROM* range of motion, *MVC* maximal voluntary contraction

therapy and provide a unique platform for more objective and sensitive assessment [15]. By *robotic and sensor-based 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 (both during active/assisted movement of the patient as well as during passive guidance or perturbations), as well as through stationary or wearable sensor technologies. Robotic and sensor-based systems offer – depending on the used technology – the possibility to precisely and objectively record movement trajectories, limb posture, completion time, task precision, etc., and, in the case of robotic systems, measure interaction forces during well-controlled interactions. These allow extracting task-related features descriptive of sensorimotor function of a patient [16]. 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 [17].

Clinical assessments and those based on advanced technology are fundamentally different, but both aim at providing patients and therapists with a precise evaluation of sensorimotor functions or their impact on activities or participation. Both types of assessment provide valuable and complementary information, but the specific characteristics of each assessment may often preclude a direct comparison. 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 [18]. ICF further distinguishes measures of capacity (i.e., what an individual can do in a standardized environment, such as during a clinical evaluation) from measures of performance (i.e., what an individual actually does in his/her usual environment, e.g., at home).

In an attempt to provide a comparison of clinical and technology-based sensorimotor assessments, we propose here to group them according to the measurement domain they characterize, namely, temporal, performance, and impairment (Fig. 10.1). Whereas the *temporal* domain includes the measurement of the time required to

complete a task (e.g., the 10-m-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 Assessment). In the *impairment* domain, the measurement focuses on the direct physiological consequence of a disability (e.g., increased muscle tone related to spasticity, as measured by the Modified Ashworth Scale [19]). 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/sensor-based assessments is to translate raw measurements of physical parameters collected by the various sensors into clinically meaningful scales representative of sensorimotor functions, abilities or 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 and how these can be used to automatically adapt technology-assisted therapy. 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. In addition we will discuss the emerging field of assessments based on wearable sensors. The chapter will conclude with an outlook on the main challenges toward realizing generally accepted robotic and sensor-based assessment scales and making them independent of the technology platform. This independence will help these assessments gain a wider usage and acceptance.

10.2 Impairments of the Upper and Lower Extremity Following Neurological 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, individuals become restricted in their activities and participation in society. Regaining motor abilities is therefore one major focus of neurorehabilitation.

Disturbed gait is a common symptom in patients with neurological disorders and can be observed in more than 60 % of these patients [20]. Gait deficits range from reduced speed and asymmetrical gait – frequently observed after stroke – to the permanent need for a wheelchair for mobility. In stroke and SCI patients, reduced strength of specific muscle groups (mainly hip flexors, ankle plantar flexors, and knee extensors) and somatosensory deficits have a negative impact on spatial and temporal symmetry and on gait speed [21–24], while spasticity may support some movements while hindering others [25, 26]. Leg rigidity, together with cognitive deficits, can lead to reduced step length, increased step-to-step variability, and affect postural stability in Parkinson's disease patients [27, 28]. Assessment of gait is challenging as it consists of a complex set of domains, e.g., in SCI locomotion depends on a variety of factors like level of injury, sensory preservation, proprioception, muscle strength, spasticity, and locomotor mechanics [29].

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 ADL. Therapy and assessment of the upper limb focus both on proximal arm function (shoulder and elbow), which is crucial for gross movements and for assisting the unimpaired limb in bimanual tasks, 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. More distally, 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 [30–32]; (2) the loss of interjoint coordination and control, limiting the ability to move the fingers independently or generate force with individual fingers [33–35]; (3) the inability to control endpoint force; and (4) the inability to explore the environment due to impaired somatosensory function [36]. 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 tasks.

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 (see [37] for a review), thus leading to time-consuming assessment sessions.

10.3 Clinical Assessments

Many clinical assessments for upper- or lower-limb function have been developed for use in different neurological conditions. Unfortunately, many challenges remain with regard to the systematic application of these clinical assessments. In the following, examples of clinical assessments of lower- and upper-limb function 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). Following neurological diseases that affect the lower limbs, time-based walking tests are widely performed. The time required to accomplish the test can also be used to calculate the walking speed, a parameter that has been linked to a number of higher functions, such as cognitive function [38, 39]. 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. An example for a time-based assessment for the upper extremity is the Nine Hole Peg Test (NHPT [40]). The NHPT was developed to measure finger dexterity and can be applied to patients with low to moderate impairment of upper-limb 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.

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 [41]). The SCIM evaluates how well patients with a spinal cord injury can manage ADL. Activities that 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. A typical performance-based clinical assessment in stroke is the Fugl-Meyer Assessment (FMA [42]). The FMA is well established and widely used clinically and in research studies thanks to its good validity and reliability [43]. 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.

Impairment-based assessments measure the direct physiological source of a disability. A common impairment after a neurological lesion is spasticity, which is characterized by disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles [44].

However, the role of spasticity in walking impairment is debated. More recently, a differentiated look at spasticity has been provided [25], based on the different neural and anatomical effects that are relevant in passive conditions, during non-functional and during functional movements. A clinical assessment method of spasticity in the passive condition is the Modified Ashworth Scale (MAS) [19]. 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, while the patient is instructed to remain passive, and rates the perceived resistance on a six-point ordinal scale. The Ashworth Scale and the Modified Ashworth Scale are the most commonly used assessment methods in clinical as well as scientific research to measure spasticity, despite being strongly criticized [45]. Impairments of the sensory pathways are also common, specifically those affecting proprioception. Clinical assessments of proprioception usually focus on detecting or replicating a movement executed by a rater. In the first case, the patient is asked to indicate the direction in which his/her limb was moved by a rater, for example [46]. For assessments using movement replication, the patients have to move their limbs according to previously presented positions [47].

Whereas clinical assessments are widely used to diagnose individuals after a neurological injury, they also suffer from limitations. Time-based assessments are usually fast and easy to administer, provide quantitative values, and usually have good validity and repeatability [40, 48]. However, they do not provide information on movement quality and thus on the impairments or functional limitations underlying the time loss. Typically, time-based assessments such as the Action Research Arm Test (ARAT) [49] were found to be limited when it comes to distinguishing true recovery of motor function from compensatory movements [50]. Performance- and impairment-based assessments are subjective by nature as they rely on the interpretation of trained raters. Furthermore, they typically have limited sensitivity and present ceiling/flooring effects due to the ordinal scales they use [19, 43, 44, 51]. The responsiveness of these tools and consequently their usability in clinical trials to investigate new intervention therapies are limited. The drawbacks of current clinical assessments could in the future be addressed by robotic and sensor-based assessments. Despite still being in their infancy, such technology-based assessments have shown the possibility to quantitatively measure and record several parameters concurrently from multiple joints during well-controlled, highly repeatable tasks.

10.4 Robotic Assessments

Over the last decades, many robotic devices have been developed to provide therapy to the lower and upper extremities, with the main goal of increasing the intensity and duration of rehabilitation therapy. Exoskeleton robotic devices have been developed for gait rehabilitation [52, 53]. Further, robotic systems allow training of proximal joints of the upper limb [14, 16, 54–56], and more recently, devices were developed to also target rehabilitation of hand function [57–64]. Robotic systems can provide therapy under well-controlled and reproducible conditions while assisting the patient in an optimal way (assist-as-needed [65]). A further advantage of robotic systems is that they can reduce the burden on the therapist, especially in gait therapy [52]. 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, the evolution of robotics has 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, has 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., interaction 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.

10.4.1 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 mainly for clinicians but also for the patients themselves. 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 assess motor function [66, 67]. While easily implementable on any 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, the walking speed (e.g., [68]) or the required amount of body weight support to evaluate gait performance. Although these parameters can be set relatively arbitrarily by the therapist during the training, maximum challenge or minimal assistance required for a patient to perform a task with the robot can be used to reflect the sensorimotor ability. If the assistance of the device is automatically adapted through dedicated algorithms, more objective data could be extracted [69, 70].

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 force/torque. Exoskeleton devices provide a simple means to assess joint ROM. For assessment of the passive ROM, the therapist moves the corresponding joint manually through the patient's ROM, 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 (Hocoma, Switzerland) [71] and is generally applicable to all devices with backdrivable joints (i.e., those that can be moved by an external force). When the device is configured to compensate for its own weight and the patient actively moves his/her limb, this method also allows for assessing active ROM. In another example, here for a measurement of maximum voluntary muscle force [72], 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) and in one movement direction (extension or flexion). 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 a patient can generate. Galen et al. showed that this method provides an objective and reliable outcome measure to record changes in muscle strength following robot-aided gait therapy in patients with incomplete spinal cord injury [73]. Simpler devices focusing on single joints (e.g., ankle) were also used to assess isometric force and passive/active ROM [74, 75]. Similar approaches were used at the level of the upper limb using the arm exoskeleton ARMin to evaluate shoulder, elbow, forearm, and wrist ROM, as well as maximal joint torques in spinal cord injury patients [76]. As they do not follow the position of each joint, the raw position measurements of end-effector robots can be used to assess endpoint workspace. For example, the

ACT3D arm robot has been used to evaluate arm-reaching workspace of stroke subjects on a virtual table, as well as the effect of shoulder abduction loading [77].

From joint position readings, attempts have been made to assess proprioception, specifically joint position sense, with robotic devices. While different methodological approaches exist, they all take advantage of the robot to move a limb segment to precise reference positions that patients are asked to either reproduce (i.e., position matching [78]) or compare to a second passive stimulus (i.e., difference threshold; see [79] for a review). Domingo and Lam [80] evaluated a method that uses an exoskeleton robot to move the leg of a patient in an objective and repeatable manner. The robot passively moves the patient's leg to a target position and subsequently to a distractor position. Then the patient controls the robot using a joystick to replicate the target position. The angular difference between the final and the target position is a raw value assessment. This robotic assessment method was found to be reliable and valid in able-bodied subjects and subjects with incomplete spinal cord injury [80]. With stroke patients, a similar approach has been used for arm proprioception assessment where patients mirror-match a movement presented on their impaired side by moving the unimpaired arm using a two-arm robotic apparatus [81–83]. Other robotic assessments focused on the evaluation of difference threshold in joint position sense in stroke patients, at the level of the arm [84], wrist [85], or fingers [86].

10.4.2 Assessment Based on Feature Extraction

More advanced robotic assessment techniques have been proposed with the aim of extracting additional 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 [53], 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. [87] determined stride length, duration of stride, stance, and swing, as well as double-stance ratio kinematic parameters, to assess the subjects' gait. 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 any information on the quality of gait. 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 multiplied by a weighting function selected in order to provide positive values when the patient performs correct movements [88–90]. Averaging for stance and swing phases provides two values per leg and joint that can be displayed to the patient and therapist as an index of the patient's activity, as well as stored for later analysis [90].

Even though devices for lower extremity rehabilitation are mainly designed to support gait movements, they can also be used to perform specific physiological assessments, e.g., to evaluate biomechanical correlates of spasticity. Robot-assisted assessments of spasticity apply passive movements controlled by the device to a single joint, while the torque is recorded and analyzed during repetitive movements [91, 92] (see [93] for a review). The addition of electromyography can help determine the actual muscle activity, but increases the complexity of the measurement. One very interesting direction is the use of pseudorandom binary perturbations, which is based on system identification [94, 95]. Also, stiffness measurement in multi-joint robots has been described [71], where the mechanical stiffness was calculated off-line taking into account the passive effects of the orthosis and of the patient's legs during passive movements using mathematical models. The mentioned assessment methods all focus on nonfunctional movements, typically isokinetic or sinusoidal patterns or passive conditions, whereas most clinical assessments like the Modified Ashworth Scale (MAS) [19] always use

passive conditions. Nevertheless, joint stiffness measured by a device showed a reasonable relation to spasticity measured using the MAS [71]. In principle, robotic devices would have the capability to assess spasticity also during functional movements and could therefore inform clinicians whether treatment of clinical signs of spasticity has a positive or negative effect on functional outcome.

In upper-extremity rehabilitation, movements with a robot are less stereotyped than in the case of gait rehabilitation. This requires the development of performance metrics assessing movement quality without relying on a predefined movement pattern (see [96] for a detailed review). Movement smoothness is a typical performance metric representative of upper-limb coordination that has been extensively studied using robotic devices training arm-reaching movements. In the literature, smoothness has been evaluated based on the jerk as the third derivative of position [97], the ratio of mean speed over peak speed [98], the number of zero crossings of the acceleration reflecting the number of putative submovements the movement is composed of [99], the number peaks in speed [100], or through frequency analysis of the movement speed profile [101] (see [102] for a review). Several studies with stroke patients have shown that movement smoothness improves over the course of rehabilitation [103–106], suggesting that smoothness indicators are valid measures of motor recovery [103]. 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, are also used to evaluate motor control. It has been shown that neurologically impaired patients tend to deviate more from an ideal straight line, reflecting impaired interjoint coordination in the upper limb [66, 107]. 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 [108, 109]. Miller et al. [110] proposed a similar approach with a robotic platform recording isometric flexion and extension forces generated by the fingers, wrist, and thumb during robot-mediated 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 [62, 111]. Bardorfer et al. [112] used a PHANTOM haptic device (Sensable/Geomagic, USA) to create a virtual labyrinth in which subjects have to navigate. Hand and arm function were evaluated using performance metrics such as movement velocity, number of collisions with the labyrinth walls, impact duration, as well as impact force and allowed to distinguish between patients suffering from different types of neurodegenerative diseases. Using a similar approach, Emery et al. proposed the Virtual Peg Insertion Test (VPIT), a virtual reality assessment motivated by movement components of the conventional NHPT, and the Box and Block Test [113], where subjects have to insert nine virtual pegs into nine virtual holes by controlling the position and orientation of an instrumented handle attached to a PHANTOM Omni device [114]. Performance metrics based on the time required to perform meaningful movement segments, movement smoothness, and precision allowed to highlight and quantify upper-limb impairment in patients with different neurological disorders, such as stroke [115], multiple sclerosis [116], and ataxia [117] using a common robotic platform. Other similar approaches using PHANTOM haptic devices in combination with virtual reality to extract features representative of upper-limb function have also been reported [118, 119].

10.4.3 Reconstruction of Clinical Scores

Several research groups have attempted to directly correlate parameters from robotic measurements 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 exercise scores. These reflected the amount of voluntary activity of the subject during the movement, the mean movement velocity, and an active movement index (AMI) quantifying patients' ability to execute the motor task without assistance from the robot [120]. A moderate correlation ($r=0.53$–0.55) was observed between robotic measurements and the FMA scores. In subsequent work with the planar MEMOS arm and 22 chronic stroke patients, these results were confirmed, with only few metrics (smoothness and AMI) directly correlating with the FMA ($r=0.48$–0.58) [121]. In a similar way, Celik et al. analyzed correlations between FMA, Motor Activity Log, ARAT, Jebsen-Taylor Hand Function Test scores, and robotic measures during 2D point-to-point target-reaching movements with a robotic joystick [122]. 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 correlation coefficient between the actual trajectory and a minimal jerk profile) and trajectory error (defined as the normalized error with respect to the straight line) were found to show significant, moderate to strong correlations with all four of the clinical measures ($r=0.49$–0.83). Overall, 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 direct indicators of upper-limb motor function. Regarding assessment of arm and hand function, Feys et al. [67] developed an assessment test with a PHANTOM device where 21 multiple sclerosis patients performed tasks in a virtual environment, such as navigating a cursor to follow a predefined path or picking up and manipulating 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 test. While correlations with the NHPT were not significant, good correlation was found between the performance metrics and the ARAT and Purdue Pegboard ($r=0.48$–0.69). With the Virtual Peg Insertion Test, also using a PHANTOM haptic device in combination with virtual reality, good correlations were found between the total time required for completing the test and the NHPT, both in multiple sclerosis patients ($r=0.66$) [116] and in patients with ataxia ($r=0.85$) [117].

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 (Interactive Motion Technologies, USA) [123]. 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). Krebs et al. recently showed in a study with 208 stroke patients that features extracted from arm movements performed with the InMotion2 robot could be used to reconstruct and predict clinical scales such as the FMA ($r=0.73$), the modified Rankin Scale ($r=0.60$), the National Institutes of Health Stroke Scale ($r=0.63$), and Motor Power ($r=0.75$). Reconstructions were based on nonlinear models with neural networks, taking as input 35 kinematic and kinetic metrics [124]. In SCI patients, Zariffa et al. used a similar approach based on kinematic and kinetic data collected during movements with the ArmeoSpring (Hocoma, Switzerland). Fourteen metrics describing arm ROM, movement smoothness, and grip ability were established, and linear regression models were used to predict upper-limb clinical scores. Good correlations were found with the ARAT, the SCIM, and the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP)

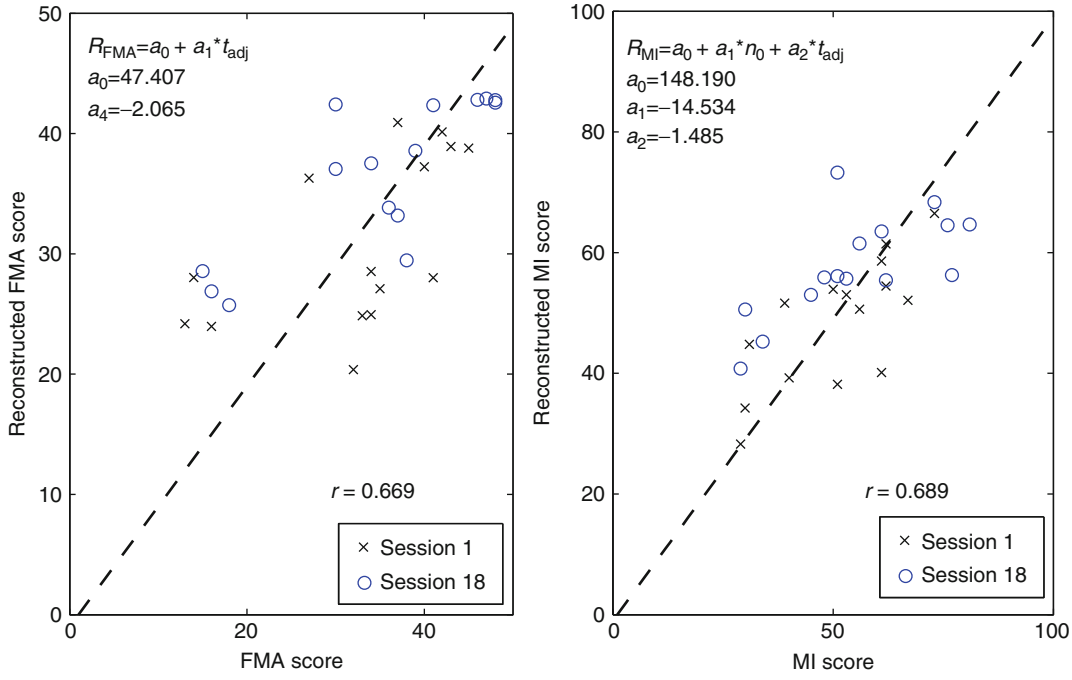

Fig. 10.2 Correlations between Fugl-Meyer (*left*) and Motricity Index (*right*) clinical assessment scores, and reconstructed scores based on performance metrics of hand opening/hand closing and pronation/supination movements with the HapticKnob. Linear models for the reconstruction were computed using stepwise linear regression on data collected 15 chronic stroke patients at beginning (session 1) and end (session 18) of robot-assisted therapy [126]

(r^2=0.54–0.78) [125]. In a study on hand rehabilitation with the HapticKnob, a two-degrees-of-freedom device to train grasping and forearm pronation/supination, a regression analysis was performed in an attempt to reconstruct clinical assessment scores from the kinematic data collected during a 6-week rehabilitation therapy with 15 chronic stroke patients [126]. Robotic assessments were performed on the first and last day 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 a stepwise linear regression analysis showed that clinical scores (FMA, Motricity Index (MI), Motor Assessment Scale (MS), and MAS) could be well explained by only one or a combination of two parameters representative of movement control, namely, a smoothness metric (n_0) and the time to precisely adjust the forearm angle during pronation/supination exercises (t_{adj}) (Fig. 10.2). Good correlation was observed between clinical scores of the upper extremity and their respective reconstructed scores (r=0.67 for FMA, r=0.69 for MI, r=0.60 for MS, and r=0.79 for MAS). The principal parameter used to reconstruct all clinical scores was 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 tasks to be performed and evaluated, with the potential of simplifying and shortening assessment sessions [123].

10.5 Assessments Based on Wearable Sensors

Stationary sensors, such as cameras, motion capture systems, or force plates, have been used extensively in gait labs for biomechanics studies

over the past decades. With the availability of relatively low-cost alternatives, such technology has penetrated the clinics for rehabilitation and assessment applications. For example, instrumented mats such as the GAITRite™ (GAITRite, USA) have proved valid and reliable for estimating spatiotemporal gait patterns [127–129]. 3D cameras, such as the Microsoft Kinect (Microsoft, USA), are also of high interest for assessing balance [130, 131] as well as gait kinematic parameters [132, 133] (see [134] for a review), as they further allow the reconstruction of individual joint angles. They also proved useful for therapy and assessment of arm function (e.g., 3D reachable workspace [135]), providing patients with immersive and motivating training conditions using virtual reality [135–137]. For the evaluation of hand function, which requires the detection of fine movements, gloves instrumented with position sensors (e.g., CyberGlove (Immersion, USA)) have been used in stroke or spinal cord injury patients [138–140]. These can further be complemented by objects instrumented with force sensors allowing the evaluation of grip force control during interaction with real objects, which is often affected after neurological injuries [141–145]. Thanks to such kinematic and kinetic data, it is possible to identify impairments beyond what is achievable with clinical scales.

However, the use of stationary sensors requires a dedicated space (e.g., motion capture volume) and continuous data processing, making them valuable for laboratory experiments, but difficult to translate to the evaluation of real ADL tasks, or to move them out of the research/clinical environment. In that respect, assessments that rely exclusively on wearable sensors (e.g., simple accelerometers, or inertial measurement units (IMUs)) bear high potential to support and improve time-based and performance-based sensorimotor assessments. Today's integrated circuits enable the combination of such sensors into lightweight and compact units that allow easy and comfortable mounting on one or several body segments [146]. One of the main advantages of such wearable sensor technology is the possibility to perform assessments in functional conditions and during ADL, because they only marginally interfere with movements. Another advantage is their relatively low cost, especially compared to robotic devices or optical motion capture equipment.

The most widely used type of wearable sensors is accelerometers, typically placed at the wrist or foot, to record changes in acceleration during movements and offer the possibility to label periods where a subject is active (e.g., time when the acceleration signal is over a certain threshold or simply by integrating acceleration signal [147]). Many wrist-worn devices incorporating accelerometers are available on the market, and most of them are embedded in watch-like devices. As research tools, they are widely used in sports science to measure physical performance (see [148, 149] for reviews), energy expenditure [150, 151], or even in sleep research [152, 153]. Due to their low power consumption, accelerometers are present in most of the modern cell phones and watches, making actigraphy accessible to the public through various health monitoring applications. From a clinical assessment perspective, actigraphy can provide valuable information on activity levels of neurological patients. The type and duration of certain ADL such as walking, sitting, and laying can be detected through triaxial accelerometers placed on the lower back [154–157] or on the sternum [158]. These measures can replace self-reported questionnaires that are subjective and do not provide detailed information on the intensity and frequency of ADL.

Several studies with stroke patients wearing accelerometers on both arms aimed at evaluating the amount of the use of the impaired arm or the ratio of use between impaired and unimpaired arms [159–161] (see [162] for a review). These values are expected to provide information on how patients involve their paretic arm in real-life activities, with the possibility to track patients over several hours or days, which is a real advantage over punctual clinical assessment. Ratios of arm use were found to correlate well with the FMA in a study with 31 chronic stroke patients ($r = 0.85$) [161]. In another study on 169 subacute stroke patients wearing accelerometers on their wrists for 3 days in their home environment, ratios between impaired/non-impaired arm were

found to correlate well with the Motor Activity Log ($r=0.52$), suggesting that actigraphy values can provide objective, real-world upper-extremity motor status [163] and have good psychometric properties [164]. Markopoulos et al. further proposed to use this ratio of arm use as feedback method to directly inform patients on their level of activity (represented by colored bars on a display integrated into the device) and, if required, motivate them to involve their arm more in their daily tasks through written encouragements [165].

IMUs extend the type of kinematic data that can be collected with wearable sensors, typically adding to acceleration information about angular velocity and magnetic field direction. Therefore, IMUs allow to calculate orientation and, to a certain extent, also position in space (see [166] or a review). When walking is the primary focus of the assessment, adding one or more inertial sensors on the lower limbs [167–170] can provide more accurate and detailed gait parameters compared to observational or video gait analysis, while not requiring the setup of a complete gait lab with motion tracking. Numerous parameters can be extracted, including temporal information on heel-strike and toe-off, number of steps, step duration, cadence, step variability, and stance/swing time ratio [171]. These parameters can provide a wide range of clinical information, whose potential has probably not yet been fully explored. Step variability, for example, is altered (both in terms of magnitude and dynamics) in syndromes, such as falling, frailty, and neurodegenerative disease (e.g., Parkinson's and Alzheimer's disease) [172]. In stroke patients, asymmetry and altered stance/swing time ratio were reported [22, 173–175] using IMUs. The detection and quantification of these asymmetries are not possible solely using the current time-based clinical measures of walking, which mainly focus on speed.

Assessments of balance and sway have also been performed using IMUs placed on the lower back, e.g., in Parkinson's disease (see [176] for a review). Systems that reached the commercial stage include SwayStar (Balance International Innovations GmbH, Switzerland) and Opal (APDM, USA). Measures of trunk sway can be obtained during standing and gait tasks similar to the ones performed in well-established clinical assessments like the Tinetti Test and the CTSIB protocol (e.g., standing with eyes open/closed, standing on foam) [177]. The study demonstrated that roll angle and pitch angular velocity were able to distinguish patients with a balance deficit from able-bodied subjects. Inertial sensors can also be used for assessment of fall risk (see [178] for a review). For the upper limb, IMUs have been used to reconstruct arm movements, with the possibility to extract assessment metrics such as arm-reaching workspace [179, 180], or to perform online tracking of arm movement to control virtual reality rehabilitation games [179].

Wearable sensors can also be attached to patients during the execution of conventional clinical assessment, to extract quantitative data that can complement clinical scales or help removing the subjective component of assessments based on ordinal scales. An instrumented Timed Up and Go (TUG) test has been developed and evaluated in patients with Parkinson's disease (PD) [181]. With respect to the traditional TUG, the instrumented version was able to provide a new set of parameters of potential clinical relevance: sit-to-stand and stand-to-sit time, as well as range and slope of the acceleration during the transitions. These measures were sensitive to group differences between PD and age-matched control subjects and could be used to identify PD earlier and document the progression of the disease [181]. For the upper extremity, IMUs have been mounted to the wrist of stroke patients to automatize parts of the Wolf Motor Function Test [182], the FMA [183], or the ARAT [184]. Validity of IMU readings was demonstrated by high correlations between instrumental variables (based on jerk and movement durations) and conventional ARAT scores ($r=0.80$).

Despite providing valuable assessment metrics and unique information on performance in ADL tasks, IMUs are currently only rarely used outside lab environment due to the high power demand of gyroscopes. Some attempts have been made to optimize power usage of IMUs, for example, by selectively switching off gyroscopes

when the patient is not moving (i.e., subthreshold acceleration) [185], to allow for long-term monitoring of activity of patients in their home environment. Using such an approach, Leuenberger et al. classified ambulatory activity in a group of 24 chronic stroke patients wearing IMUs at both wrists, both ankles, and the trunk during 24-h recordings. It was possible to distinguish level walking from stair ascent/descent with high sensitivity, highlighting the potential of wearable sensors for gaining insights on patient behavior outside of the clinic [186].

While conventional assessments may provide valid measures of capacity, the ability to perform assessments outside of the clinical environment is of crucial importance to obtain representative measures of true performance during ADL. This might shed further light on the mechanisms underlying recovery, as well as on the transfer of therapy to ADL.

Conclusions

The promising results of recent studies using advanced technologies such as robotics and wearable sensors demonstrate the potential of using technology not only to complement conventional therapy but also to assess sensorimotor function in a more objective, reliable, and continuous way. Whether relying on raw kinematic and kinetic measures or on more sophisticated feature extraction algorithms, performance metrics obtained from robotic systems offer new possibilities to objectively investigate sensorimotor impairment under reproducible conditions. These metrics can provide unique information on the quality of patients' performance in a defined task, which cannot be captured with conventional clinical scales. Because of the quantifiable assistance that 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. Similarly, sensor-based assessments offer new ways to objectively measure activity levels and complex movements, with the unique ability to monitor daily life activity in the clinic or at home, and over extended periods of time. Table 10.1 aims at providing a (non-exhaustive) overview of clinical and technology-based assessments, and a summary of key opportunities where robotic and sensor-based assessments can advantageously complement conventional clinical scales.

While meaningful assessments can, in principle, be obtained with any robotic platform, in the context of the specific tasks supported by the device, exoskeletons that offer the possibility to assist or perturb a joint or the entire leg while recording the active torque generated by the patient appear to be the preferred choice for assessments of lower-limb sensorimotor function and impairments (e.g., spasticity). For assessing free walking, robots can be advantageously replaced by wearable IMUs providing quantitative gait parameters in daily life situations. End-effector, low impedance (i.e., transparent) robotic devices appear to be well suited to assess functional ability of the upper limb, as they do not constrain the complex and highly dynamic movements of the arm and hand. Additionally, factors such as usability (for patient and therapists), size, and portability should be considered when developing dedicated assessment tools. In that sense, systems based on tabletop haptic devices (such as the VPIT [115]) and IMUs, which could be complemented by cameras or instrumented objects (e.g., [184, 188, 189]), bear high potential. Also, wearable sensor technologies are unique solutions for long-term and unobtrusive monitoring, offering new ways of following patients' physical activity over extended periods of time after discharge from the hospital. This has the potential to provide not only useful information to establish detailed patient profiles but also unique data to help scientists investigate mechanisms of recovery underlying neurological disorders and their evolution over time [50].

Given the promises of technology-based assessments, the question of why such scales are not more rapidly adopted by the clinical and research communities can be raised. Robotic and sensor-based assessments are

Table 10.1 Overview of clinical assessment domains including their advantages and disadvantages, as well as opportunities for robotic and sensor-based technologies to complement these assessments

Assessment domain	Examples of clinical assessments	Pros (+) and cons (−)	Opportunities for technology-based assessments	Examples of technology-based metrics
Temporal	10-m walking test (10-m WT) 6-min walk test (6MWT) Timed up and go (TUG) Action Research Arm Test (ARAT) Nine Hole Peg Test (NHPT) Box and Block Test (BBT)	+ Easy and fast to administer + Reflects overall functional ability + Objective measure + No expensive equipment required – No information about movement quality – Do not distinguish recovery from compensation – Patients must be able to achieve the task	Time can be easily and precisely measured with robotic/sensor-based systems Allow decomposing a task into different sub-times Robotic devices would enable application to more severely impaired patients, e.g., by providing controlled assistance while performing a task	Time to execute a motor task [66, 67, 117] Sub-times for phases of a task [115]
Performance				
Lower limbs and balance	Berg balance scale (BBS) Spinal cord independence measure (SCIM) Fugl-Meyer Assessment (FMA) (lower limb)	+ Subscales providing a detailed overview of functional ability + Many standardized well-validated assessment scales – Subjective (based on perception of therapist or patient) – Require trained therapists – Usually ordinal scales, nonlinear and with limited sensitivity – Suffer from flooring and ceiling effects – Time consuming to administer	Can provide objective and quantitative kinetic and kinematic data From raw sensor measurements, linear and sensitive metrics representative of different types of impairments can be extracted, which can be used to construct models predicting recovery Possibility to extract metrics during robot-assisted therapy and adapt therapy settings online Wearable sensors can monitor activity levels during long-term recording or activities of daily living	Gait spatiotemporal parameters (speed, step length, etc.) [87, 127, 134, 170] Gait symmetry [173] Gait variability [171, 172]
Upper limbs	FMA (upper limb) Motor Assessment Scale (MS) Motricity Index (MI) Chedoke McMaster Stroke Assessment (CMSA)			Movement smoothness [98, 101, 102] Movement speed [112, 120, 122] Trajectory error [66, 112] Interaction force/torque [108–110] Reaching workspace [77, 135, 179, 180]
Activities of daily living	Barthel Index (BI) Motor Activity Log (MAL)			Activity counts [147, 162] Index of arm use in activities of daily life [159, 163]

Table 10.1 (continued)

Assessment domain	Examples of clinical assessments	Pros (+) and cons (−)	Opportunities for technology-based assessments	Examples of technology-based metrics
Impairment	Modified Ashworth Scale (MAS) Somatosensory assessments (e.g., Nottingham Sensory Assessment (NSA)) Range of motion (ROM)	+ Rapid to administer + Impairment evaluation at the joint/limb level − Subjective (based on perception of therapist or patient) − Requires good training of the evaluator to achieve good reliability − Might not reflect functional ability	Robotic technology can impose a movement or force pattern repeatedly in a systematic way while objectively recording the resulting force/motion. This should increase reliability and validity	Joint stiffness [71, 187] Sensory thresholds [79, 80, 82, 86] Passive ROM [71]

Corresponding examples of metrics typically used in studies with neurological patients are listed in an attempt to highlight their relevance. The list of examples is for illustrative purposes only and is not comprehensive

currently still in their infancy, and several important limitations, both theoretical and practical, have to be addressed before novel scales can be adopted in clinical practice. First, since technology-based assessments can provide parameters that were not possible to obtain with existing clinical assessments (at least not in an objective and sensitive manner, such as metrics evaluating movement smoothness), many of the proposed novel metrics remain abstract values that are difficult to interpret for therapists and patients compared to the well-established and standardized clinical measures. Further studies are therefore needed to determine what these parameters represent based on concurrent physiological examinations and how these metrics can document functional changes, predict therapy outcome, and reflect sensorimotor impairment. Some of the signals captured by technological assessments may, for example, represent a purely clinical sign (i.e., different from a healthy subject) which does not, or at least not negatively, affect function.

Secondly, in order to improve clinical acceptance, the psychometric properties of novel performance metrics need to be carefully evaluated and documented. A few studies have suggested that well-defined robotic and sensor-based metrics have good test-retest reliability [72, 76, 80, 190]. However, additional studies with larger sample sizes and patients with different impairment levels are needed to further confirm these results, together with solid normative data sets from healthy subjects to characterize the sensitivity of novel assessment scales. Also, validity is typically evaluated through comparison with established clinical assessments. This highlights one key issue when comparing robotic and sensor-based assessments, which are expected to be more objective and sensitive to clinical assessments that rely on subjective judgment, and that are known to be limited (e.g., ceiling/flooring effect).

Thirdly, wider acceptance of robotic and sensor-based assessments also depends on the technological platforms that are being used. Technology should prove to be safe and robust enough for daily use with patients while minimizing additional effort required from therapists to perform the assessments. Many systems are still too close to research prototypes and require the presence of engineers to properly operate them, which is not clinically viable. In parallel, it seems also important to better inform clinicians and therapists about what is available and how technology can support their daily work, to help them become more confident in the interpretation of the new technology-based assessments.

Finally, robotic assessments will only find wider application and reach their full potential once the community agree on metrics that can be implemented on various robotic platforms with adequate instrumentation. A recent initiative from the European Network on Robotics for Neurorehabilitation targeted this ambitious objective, where experts from over 23 countries attempted to define standards for robotic assessments, as well as guidelines for the use of clinical and robotic outcome measures in neurorehabilitation. The establishment of such standards would be valuable for quality assurance in neurorehabilitation therapy and impact the design of clinical trials comparing treatment outcomes across rehabilitation centers worldwide. Typically, metrics with good reliability and improved sensitivity to sensorimotor changes could ultimately help decrease the large sample sizes that are typically needed in randomized control trials to demonstrate effects of novel therapies [124]. Nevertheless, while the definition of standardized metrics 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 the interpretation of assessments involving active, dynamic movements [191].

It is clear that robotic and sensor-based metrics will play, in the near future, an increasingly prominent role in the assessment of sensorimotor function of the lower and upper extremities. The tight coupling between assessments and therapy and the appealing

possibility of achieving both on the same hardware platform is enticing. By embedding short and independent assessment modules within robotic or sensor-based therapy sessions, it becomes possible to track the performance of patients on a daily basis, without having to perform time-consuming clinical assessments [125]. Robotic assessments based on feature extraction and the reconstruction of clinical scores could also be performed online, during therapy, offering the possibility to continuously and automatically 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. This approach of assessment-driven therapy has recently been successfully implemented in several pilot trials on robot-assisted or sensor-based stroke rehabilitation [179, 192–195].

Nevertheless, the prediction of clinical scales should of course not be seen as the primary reason for the use of robotic and sensor-based assessments. Even if studies showed good correlation between clinical and reconstructed scores, both remain only approximations of the patient's performance, impairments, and abilities. Robotic and sensor-based assessments should be seen as independent but complementary tools to conventional assessments. Technological assessments will never replace neurological examinations, such as reflex testing, but by combining both clinical and technological assessments, clinicians would benefit from more sensitive, reliable, and objective evaluations of different aspects of sensorimotor function/impairment, which could ultimately impact the way neurorehabilitation therapy is administered.

References

1. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. Stroke. 1992;23(8):1084–9.
2. Prabhakaran S, Zarahn E, Riley C, Speizer A, Chong JY, Lazar RM, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. Neurorehabil Neural Repair. 2008;22(1):64–71.
3. Winters C, van Wegen EE, Daffertshofer A, Kwakkel G. Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. Neurorehabil Neural Repair. 2015;29(7):614–22.
4. Kollen B, van de Port I, Lindeman E, Twisk J, Kwakkel G. Predicting improvement in gait after stroke: a longitudinal prospective study. Stroke. 2005;36(12):2676–80.
5. Nijland RH, van Wegen EE, der Harmeling-van Wel BC, Kwakkel G. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: early prediction of functional outcome after stroke: the EPOS cohort study. Stroke. 2010;41(4):745–50.
6. Zorner B, Blanckenhorn WU, Dietz V, Curt A. Clinical algorithm for improved prediction of ambulation and patient stratification after incomplete spinal cord injury. J Neurotraum. 2010;27(1):241–52.
7. Velstra IM, Bolliger M, Tanadini LG, Baumberger M, Abel R, Rietman JS, et al. Prediction and stratification of upper limb function and self-care in acute cervical spinal cord injury with the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP). Neurorehabil Neural Repair. 2014;28(7):632–42.
8. Finch E, Brooks D, Stratford PW, Mayo NE. Physical rehabilitation outcome measures: a guide to enhanced clinical decision-making. 2nd ed. Ontario: B.C. Decker; 2002.
9. Kirshner B, Guyatt G. A methodological framework for assessing health indices. J Chronic Dis. 1985;38(1):27–36.
10. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabil Neural Repair. 2008;22(2):111–21.
11. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2013;(7):CD006185.
12. Mehrholz J, Hadrich A, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Databse Syst Rev. 2012;(6):CD006876.
13. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. New Engl J Med. 2010;362(19):1772–83.
14. Maciejasz P, Eschweiler J, Gerlach-Hahn K, Jansen-Troy A, Leonhardt S. A survey on robotic devices for upper limb rehabilitation. J Neuroeng Rehabil. 2014;11:3.

15. Prange GB, Jannink MJ, Groothuis-Oudshoorn CG, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev. 2006;43(2):171–84.
16. Reinkensmeyer DJ, Emken JL, Cramer SC. Robotics, motor learning, and neurologic recovery. Annu Rev Biomed Eng. 2004;6:497–525.
17. Gassert R, Burdet E, Chinzei K. Opportunities and challenges in MR-compatible robotics: reviewing the history, mechatronic components, and future directions of this technology. IEEE Eng Med Biol Mag. 2008;27(3):15–22.
18. World Health Organization. International classification of functioning, disability and health (ICF). Geneva: World Health Organization; 2001.
19. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67(2):206–7.
20. Stolze H, Klebe S, Baecker C, Zechlin C, Friege L, Pohle S, et al. Prevalence of gait disorders in hospitalized neurological patients. Mov Disord. 2005;20(1):89–94.
21. Hsu AL, Tang PF, Jan MH. Analysis of impairments influencing gait velocity and asymmetry of hemiplegic patients after mild to moderate stroke. Arch Phys Med Rehabil. 2003;84(8):1185–93.
22. Olney S, Richards C. Hemiparetic gait following stroke. Part I: characteristics. Gait Posture. 1996; 4(2):136–48.
23. van der Salm A, Nene AV, Maxwell DJ, Veltink PH, Hermens HJ, IJzerman MJ. Gait impairments in a group of patients with incomplete spinal cord injury and their relevance regarding therapeutic approaches using functional electrical stimulation. Artif Organs. 2005;29(1):8–14.
24. Field-Fote EC, Fluet GG, Schafer SD, Schneider EM, Smith R, Downey PA, et al. The Spinal Cord Injury Functional Ambulation Inventory (SCI-FAI). J Rehabil Med. 2001;33(4):177–81.
25. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6(8):725–33.
26. Dietz V, Fouad K. Restoration of sensorimotor functions after spinal cord injury. Brain. 2014;137:654–67.
27. Stegemoller EL, Wilson JP, Hazamy A, Shelley MC, Okun MS, Altmann LJ, et al. Associations between cognitive and gait performance during single- and dual-task walking in people with Parkinson disease. Phys Ther. 2014;94(6):757–66.
28. Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. Mov Disord. 2013;28(11):1544–51.
29. Jackson AB, Carnel CT, Ditunno JF, Read MS, Boninger ML, Schmeler MR, et al. Outcome measures for gait and ambulation in the spinal cord injury population. J Spinal Cord Med. 2008;31(5):487–99.
30. Cruz EG, Waldinger HC, Kamper DG. Kinetic and kinematic workspaces of the index finger following stroke. Brain. 2005;128:1112–21.
31. Dovat L, Lambercy O, Johnson V, Salman B, Wong S, Gassert R, et al. A cable driven robotic system to train finger function after stroke. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Noordwijk. 2007:222–7.
32. Kamper DG, Fischer HC, Cruz EG, Rymer WZ. Weakness is the primary contributor to finger impairment in chronic stroke. Arch Phys Med Rehabil. 2006;87(9):1262–9.
33. Lang CE, Schieber MH. Human finger independence: limitations due to passive mechanical coupling versus active neuromuscular control. J Neurophysiol. 2004;92(5):2802–10.
34. Raghavan P, Petra E, Krakauer JW, Gordon AM. Patterns of impairment in digit independence after subcortical stroke. J Neurophysiol. 2006;95(1):369–78.
35. Schieber MH, Lang CE, Reilly KT, McNulty P, Sirigu A. Selective activation of human finger muscles after stroke or amputation. Adv Exp Med Biol. 2009;629:559–75.
36. Doyle S, Bennett S, Fasoli SE, McKenna KT. Interventions for sensory impairment in the upper limb after stroke. Cochrane Database Syst Rev. 2010;(6):CD006331.
37. Alt Murphy M, Resteghini C, Feys P, Lamers I. An overview of systematic reviews on upper extremity outcome measures after stroke. BMC Neurol. 2015; 15:29.
38. Gale CR, Allerhand M, Sayer AA, Cooper C, Deary IJ. The dynamic relationship between cognitive function and walking speed: the English Longitudinal Study of Ageing. Age. 2014;36(4):9682.
39. Welmer AK, Rizzuto D, Qiu C, Caracciolo B, Laukka EJ. Walking speed, processing speed, and dementia: a population-based longitudinal study. J Gerontol. 2014;69(12):1503–10.
40. Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the nine hole peg test of finger dexterity. Occup Ther J Res. 1985;5:24–38.
41. Catz A, Itzkovich M, Agranov E, Ring H, Tamir A. SCIM – spinal cord independence measure: a new disability scale for patients with spinal cord lesions. Spinal Cord. 1997;35(12):850–6.
42. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient: a method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13–31.
43. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair. 2002;16(3):232–40.
44. Pandyan AD, Gregoric M, Barnes MP, Wood D, Van Wijck F, Burridge J, et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. Disabil Rehabil. 2005;27(1–2):2–6.
45. Fleuren JFM, Voerman GE, Erren-Wolters CV, Snoek GJ, Rietman JS, Hermens HJ, et al. Stop using the Ashworth Scale for the assessment of spasticity. J Neurol Neurosurg Psychiatry. 2010;81(1): 46–52.

46. Gilman S. Joint position sense and vibration sense: anatomical organisation and assessment. J Neurol Neurosurg Psychiatry. 2002;73(5):473–7.
47. Goble DJ. Proprioceptive acuity assessment via joint position matching: from basic science to general practice. Phys Ther. 2010;90(8):1176–84.
48. Rossier P, Wade DT. Validity and reliability comparison of 4 mobility measures in patients presenting with neurologic impairment. Arch Phys Med Rehabil. 2001;82(1):9–13.
49. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res. 1981;4(4):483–92.
50. Kitago T, Liang J, Huang VS, Hayes S, Simon P, Tenteromano L, et al. Improvement after constraint-induced movement therapy: recovery of normal motor control or task-specific compensation? Neurorehabil Neural Repair. 2013;27(2):99–109.
51. Blackburn M, van Vliet P, Mockett SP. Reliability of measurements obtained with the modified Ashworth scale in the lower extremities of people with stroke. Phys Ther. 2002;82(1):25–34.
52. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37(6):693–700.
53. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379–86.
54. Hogan N, Krebs HI, Sharon A, Charnnarong J, inventors. Interactive robotic therapist. US Patent 5466213, 1995.
55. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002;83(7):952–9.
56. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2):159–66.
57. Bouzit M, Burdea G, Popescu G, Boian R. The Rutgers Master II: new design force-feedback glove. IEEE-ASME Trans Mech. 2002;7(2):256–63.
58. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau ML. Computerized arm training improves the motor control of the severely affected arm after stroke; a single-blinded randomized trial in two centers. Stroke. 2005;36(9):1960–6.
59. Takahashi CD, Der-Yeghiaian L, Le V, Motiwala RR, Cramer SC. Robot-based hand motor therapy after stroke. Brain. 2008;131:425–37.
60. Lambercy O, Dovat L, Gassert R, Burdet E, Teo CL, Milner T. A haptic knob for rehabilitation of hand function. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):356–66.
61. Dovat L, Lambercy O, Gassert R, Maeder T, Milner T, Leong TC, et al. HandCARE: a cable-actuated rehabilitation system to train hand function after stroke. IEEE Trans Neural Syst Rehabil Eng. 2008;16(6):582–91.
62. Metzger JC, Lambercy O, Califfi A, Conti FM, Gassert R. Neurocognitive robot-assisted therapy of hand function. IEEE Trans Haptics. 2014;7(2):140–9.
63. Lum PS, Godfrey SB, Brokaw EB, Holley RJ, Nichols D. Robotic approaches for rehabilitation of hand function after stroke. Am J Phys Med Rehabil. 2012;91(11):242–54.
64. Balasubramanian S, Klein J, Burdet E. Robot-assisted rehabilitation of hand function. Curr Opin Neurol. 2010;23(6):661–70.
65. Marchal-Crespo L, Reinkensmeyer DJ. Review of control strategies for robotic movement training after neurologic injury. J Neuroeng Rehabil. 2009;6:20.
66. Dovat L, Lambercy O, Salman B, Johnson V, Gassert R, Burdet E, et al. Post-stroke training of a pick and place activity in a virtual environment. Proceedings of international conference virtual rehabilitation. IEEE, Vancouver. 2008:28–34.
67. Feys P, Alders G, Gijbels D, De Boeck J, De Weyer T, Coninx K, et al. Arm training in multiple sclerosis using PHANTOM: clinical relevance of robotic outcome measures. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Kyoto. 2009:671–6.
68. Hesse S, Waldner A, Tomelleri C. Innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients. J Neuroeng Rehabil. 2010;7:30.
69. Emken JL, Harkema SJ, Beres-Jones JA, Ferreira CK, Reinkensmeyer DJ. Feasibility of manual teach-and-replay and continuous impedance shaping for robotic locomotor training following spinal cord injury. IEEE Trans Bio Med Eng. 2008;55(1):322–34.
70. Maggioni S, Lunenburger L, Riener R, Melendez-Calderon A. Robot-aided assessment of walking function based on an adaptive algorithm. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Singapore. 2015:804–9.
71. Lunenburger L, Colombo G, Riener R, Dietz V. Clinical assessments performed during robotic rehabilitation by the gait training robot Lokomat. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Chicago. 2005:345–8.
72. Bolliger M, Banz R, Dietz V, Lunenburger L. Standardized voluntary force measurement in a lower extremity rehabilitation robot. J Neuroeng Rehabil. 2008;5:23.
73. Galen SS, Clarke CJ, McLean AN, Allan DB, Conway BA. Isometric hip and knee torque measurements as an outcome measure in robot-assisted gait training. NeuroRehabilitation. 2014;34(2):287–95.
74. Waldman G, Yang CY, Ren Y, Liu L, Guo X, Harvey RL, et al. Effects of robot-guided passive stretching and active movement training of ankle and mobility impairments in stroke. NeuroRehabilitation. 2013;32(3):625–34.

75. Zhang LQ, Chung SG, Bai Z, Xu D, van Rey EM, Rogers MW, et al. Intelligent stretching of ankle joints with contracture/spasticity. IEEE Trans Neural Syst Rehabil Eng. 2002;10(3):149–57.
76. Keller U, Scholch S, Albisser U, Rudhe C, Curt A, Riener R, et al. Robot-assisted arm assessments in spinal cord injured patients: a consideration of concept study. PLoS One. 2015;10(5):e0126948.
77. Ellis MD, Sukal-Moulton T, Dewald JP. Progressive shoulder abduction loading is a crucial element of arm rehabilitation in chronic stroke. Neurorehabil Neural Repair. 2009;23(8):862–9.
78. Carey LM, Oke LE, Matyas TA. Impaired limb position sense after stroke: a quantitative test for clinical use. Arch Phys Med Rehabil. 1996;77(12):1271–8.
79. Han J, Waddington G, Adams R, Anson J, Liu Y. Assessing proprioception: a critical review of methods. J Sport Health Sci. 2015. doi:10.1016/j.jshs.2014.10.004.
80. Domingo A, Lam T. Reliability and validity of using the Lokomat to assess lower limb joint position sense in people with incomplete spinal cord injury. J Neuroeng Rehabil. 2014;11:167.
81. Semrau JA, Herter TM, Scott SH, Dukelow SP. Robotic identification of kinesthetic deficits after stroke. Stroke. 2013;44(12):3414–21.
82. Dukelow SP, Herter TM, Moore KD, Demers MJ, Glasgow JI, Bagg SD, et al. Quantitative assessment of limb position sense following stroke. Neurorehabil Neural Repair. 2010;24(2):178–87.
83. Dukelow SP, Herter TM, Bagg SD, Scott SH. The independence of deficits in position sense and visually guided reaching following stroke. J Neuroeng Rehabil. 2012;9:72.
84. Simo L, Botzer L, Ghez C, Scheidt RA. A robotic test of proprioception within the hemiparetic arm post-stroke. J Neuroeng Rehabil. 2014;11:77.
85. Cappello L, Elangovan N, Contu S, Khosravani S, Konczak J, Masia L. Robot-aided assessment of wrist proprioception. Front Hum Neurosci. 2015;9:198.
86. Rinderknecht M, Popp W, Lambercy O, Gassert R. Experimental validation of a rapid, adaptive robotic assessment of the MCP joint angle difference threshold. Haptics: neuroscience, devices, modeling, and applications. Berlin: Springer; 2014. p. 3–10.
87. van Asseldonk EH, Veneman JF, Ekkelenkamp R, Buurke JH, van der Helm FC, van der Kooij H. The effects on kinematics and muscle activity of walking in a robotic gait trainer during zero-force control. IEEE Trans Neural Syst Rehabil Eng. 2008;16(4):360–70.
88. Banz R, Bolliger M, Colombo G, Dietz V, Lunenburger L. Computerized visual feedback: an adjunct to robotic-assisted gait training. Phys Ther. 2008;88(10):1135–45.
89. Lunenburger L, Colombo G, Riener R. Biofeedback for robotic gait rehabilitation. J Neuroeng Rehabil. 2007;4:1.
90. Lunenburger L, Colombo G, Riener R, Dietz V. Biofeedback in gait training with the robotic orthosis Lokomat. Proceedings of IEEE engineering in medicine and biology conference, San Francisco. 2004;7:4888–91.
91. Wood DE, Burridge JH, van Wijck FM, McFadden C, Hitchcock RA, Pandyan AD, et al. Biomechanical approaches applied to the lower and upper limb for the measurement of spasticity: a systematic review of the literature. Disabil Rehabil. 2005;27(1–2):19–32.
92. Kakebeeke TH, Lechner H, Baumberger M, Denoth J, Michel D, Knecht H. The importance of posture on the isokinetic assessment of spasticity. Spinal Cord. 2002;40(5):236–43.
93. Johnson GR. Outcome measures of spasticity. Eur J Neurol. 2002;9:10–6.
94. Mirbagheri MM, Barbeau H, Kearney RE. Intrinsic and reflex contributions to human ankle stiffness: variation with activation level and position. Exp Brain Res. 2000;135(4):423–36.
95. Mirbagheri MM, Barbeau H, Ladouceur M, Kearney RE. Intrinsic and reflex stiffness in normal and spastic, spinal cord injured subjects. Exp Brain Res. 2001;141(4):446–59.
96. Nordin N, Xie SQ, Wunsche B. Assessment of movement quality in robot-assisted upper limb rehabilitation after stroke: a review. J Neuroeng Rehabil. 2014;11:137.
97. Flash T, Hogan N. The coordination of arm movements; an experimentally confirmed mathematical model. J Neurosci. 1985;5(7):1688–703.
98. Rohrer B, Fasoli S, Krebs HI, Hughes R, Volpe B, Frontera WR, et al. Movement smoothness changes during stroke recovery. J Neurosci. 2002;22(18):8297–304.
99. Burdet E, Milner TE. Quantization of human motions and learning of accurate movements. Biol Cybern. 1998;78(4):307–18.
100. Kahn LE, Zygman ML, Rymer WZ, Reinkensmeyer DJ. Effect of robot-assisted and unassisted exercise on functional reaching in chronic hemiparesis. Proceedings of IEEE engineering in medicine and biology conference, Istanbul. 2001;23:1344–7.
101. Balasubramanian S, Melendez-Calderon A, Burdet E. A robust and sensitive metric for quantifying movement smoothness. IEEE Trans Bio Med Eng. 2012;59(8):2126–36.
102. Hogan N, Sternad D. Sensitivity of smoothness measures to movement duration, amplitude, and arrests. J Mot Behav. 2009;41(6):529–34.
103. Rohrer B, Fasoli S, Krebs HI, Volpe B, Frontera WR, Stein J, et al. Submovements grow larger, fewer, and more blended during stroke recovery. Motor Control. 2004;8(4):472–83.
104. Kahn LE, Zygman ML, Rymer WZ, Reinkensmeyer DJ. Robot-assisted reaching exercise promotes arm movement recovery in chronic hemiparetic stroke: a randomized controlled pilot study. J Neuroeng Rehabil. 2006;3:12.
105. Lambercy O, Dovat L, Yun H, Wee SK, Kuah CW, Chua KS, et al. Effects of a robot-assisted training of grasp and pronation/supination in chronic stroke: a pilot study. J Neuroeng Rehabil. 2011;8:63.

106. Yoo DH, Kim SY. Effects of upper limb robot-assisted therapy in the rehabilitation of stroke patients. J Phys Ther Sci. 2015;27(3):677–9.
107. Levin MF. Interjoint coordination during pointing movements is disrupted in spastic hemiparesis. Brain. 1996;119:281–93.
108. Guidali M, Schmiedeskamp M, Klamroth V, Riener R. Assessment and training of synergies with an arm rehabilitation robot. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Kyoto. 2009:772–6.
109. Dewald JPA, Beer RF. Abnormal joint torque patterns in the paretic upper limb of subjects with hemiparesis. Muscle Nerve. 2001;24(2):273–83.
110. Miller LC, Ruiz-Torres R, Stienen AHA, Dewald JPA. A wrist and finger force sensor module for use during movements of the upper limb in chronic hemiparetic stroke. IEEE Trans Bio Med Eng. 2009;56(9):2312–7.
111. Kazemi H, Kearney R, Milner T. Characterizing coordination of grasp and twist in hand function of healthy and post-stroke subjects. Proceedings of IEEE International Conference Rehabil Robot (ICORR), Seattle. 2013;2013:1–6.
112. Bardorfer A, Munih M, Zupan A, Primozic A. Upper limb motion analysis using haptic interface. IEEE-ASME Trans Mech. 2001;6(3):253–60.
113. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. Am J Occup Ther. 1985;39(6):386–91.
114. Emery C, Samur E, Lambercy O, Bleuler H, Gassert R. Haptic/VR assessment tool for fine motor control. Haptics: generating and perceiving tangible sensations, Proceedings of EuroHaptics 2010. Lecture Notes in Computer Science. Vol. 6192, Springer, Berlin Heidelberg. 2010;6192:186–93.
115. Fluet M-C, Lambercy O, Gassert R. Upper limb assessment using a Virtual Peg Insertion Test. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Zurich. 2011:1–6.
116. Lambercy O, Fluet M-C, Lamers I, Feys P, Gassert R. Assessment of upper limb motor function in patients with multiple sclerosis using the Virtual Peg Insertion Test: a pilot study. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Seattle. 2013:1–6.
117. Gagnon C, Lavoie C, Lessard I, Mathieu J, Brais B, Bouchard J-P, et al. The Virtual Peg Insertion Test as an assessment of upper limb coordination in ARSACS patients: a pilot study. J Neurol Sci. 2014;15(347):341–4.
118. Amirabdollahian F, Johnson G. Analysis of the results from use of haptic peg-in-hole task for assessment in neurorehabilitation. Appl Bionics Biomech. 2011;8(1):1–11.
119. Xydas EG, Louca LS. Upper limb assessment of people with multiple sclerosis with the use of a haptic nine-hole peg-board test. Proceedings of ASME biennial conference on engineering systems design and analysis. ASME, Haifa. 2008:159–66.
120. Colombo R, Pisano F, Micera S, Mazzone A, Delconte C, Carrozza MC, et al. Robotic techniques for upper limb evaluation and rehabilitation of stroke patients. IEEE Trans Neural Syst Rehabil Eng. 2005;13(3):311–24.
121. Colombo R, Pisano F, Micera S, Mazzone A, Delconte C, Carrozza MC, et al. Assessing mechanisms of recovery during robot-aided neurorehabilitation of the upper limb. Neurorehabil Neural Repair. 2008;22(1):50–63.
122. Celik O, O'Malley MK, Boake C, Levin HS, Yozbatiran N, Reistetter TA. Normalized movement quality measures for therapeutic robots strongly correlate with clinical motor impairment measures. IEEE Trans Neural Syst Rehabil Eng. 2010;18(4):433–44.
123. Bosecker C, Dipietro L, Volpe V, Krebs HI. Kinematic robot-based evaluation scales and clinical counterparts to measure upper limb motor performance in patients with chronic stroke. Neurorehabil Neural Repair. 2010;24(1):62–9.
124. Krebs HI, Krams M, Agrafiotis DK, DiBernardo A, Chavez JC, Littman GS, et al. Robotic measurement of arm movements after stroke establishes biomarkers of motor recovery. Stroke. 2014;45(1):200–4.
125. Zariffa J, Kapadia N, Kramer JLK, Taylor P, Alizadeh-Meghrazi M, Zivanovic V, et al. Relationship between clinical assessments of function and measurements from an upper-limb robotic rehabilitation device in cervical spinal cord injury. IEEE Trans Neural Syst Rehabil Eng. 2012;20(3):341–50.
126. Lambercy O, Dovat L, Yun H, Wee SK, Kuah C, Chua K, et al. Robotic assessment of hand function with the HapticKnob. Proceedings of International Convention for Rehabilitation Engineering & Assistive Technology (i-CREATe), Singapore. 2010:1–4.
127. Bilney B, Morris M, Webster K. Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait. Gait Posture. 2003;17(1):68–74.
128. McDonough AL, Batavia M, Chen FC, Kwon S, Ziai J. The validity and reliability of the GAITRite system's measurements: a preliminary evaluation. Arch Phys Med Rehabil. 2001;82(3):419–25.
129. Menz HB, Latt MD, Tiedemann A, Mun San Kwan M, Lord SR. Reliability of the GAITRite walkway system for the quantification of temporo-spatial parameters of gait in young and older people. Gait Posture. 2004;20(1):20–5.
130. Clark RA, Pua YH, Fortin K, Ritchie C, Webster KE, Denehy L, et al. Validity of the Microsoft Kinect for assessment of postural control. Gait Posture. 2012;36(3):372–7.
131. Lange B, Chang CY, Suma E, Newman B, Rizzo AS, Bolas M. Development and evaluation of low cost game-based balance rehabilitation tool using the Microsoft Kinect sensor. Proceedings of IEEE engineering in medicine and biology conference, Boston. 2011:1831–4.
132. Lee MM, Song CH, Lee KJ, Jung SW, Shin DC, Shin SH. Concurrent validity and test-retest reliability of the OPTOGait photoelectric cell system for the

assessment of spatiotemporal parameters of the gait of young adults. J Phys Ther Sci. 2014;26(1):81–5.
133. Clark RA, Vernon S, Mentiplay BF, Miller KJ, McGinley JL, Pua YH, et al. Instrumenting gait assessment using the Kinect in people living with stroke: reliability and association with balance tests. J Neuroeng Rehabil. 2015;12:15.
134. Wikstrom J, Georgoulas G, Moutsopoulos T, Seferiadis A. Intelligent data analysis of instrumented gait data in stroke patients-a systematic review. Comput Biol Med. 2014;51:61–72.
135. Han JJ, Kurillo G, Abresch RT, De Bie E, Nicorici A, Bajcsy R. Upper extremity 3-dimensional reachable workspace analysis in dystrophinopathy using Kinect. Muscle Nerve. 2015;52(3):344–55.
136. Olesh EV, Yakovenko S, Gritsenko V. Automated assessment of upper extremity movement impairment due to stroke. PLoS One. 2014;9(8):e104487.
137. Chang YJ, Chen SF, Huang JD. A Kinect-based system for physical rehabilitation: a pilot study for young adults with motor disabilities. Res Dev Disabil. 2011;32(6):2566–70.
138. Raghavan P, Santello M, Gordon AM, Krakauer JW. Compensatory motor control after stroke: an alternative joint strategy for object-dependent shaping of hand posture. J Neurophysiol. 2010;103(6): 3034–43.
139. Oess NP, Wanek J, Curt A. Design and evaluation of a low-cost instrumented glove for hand function assessment. J Neuroeng Rehabil. 2012;9:2.
140. Gentner R, Classen J. Development and evaluation of a low-cost sensor glove for assessment of human finger movements in neurophysiological settings. J Neurosci Methods. 2009;178(1):138–47.
141. Hermsdorfer J, Hagl E, Nowak DA, Marquardt C. Grip force control during object manipulation in cerebral stroke. Clin Neurophysiol. 2003;114(5): 915–29.
142. Nowak DA, Hermsdorfer J. Grip force behavior during object manipulation in neurological disorders: toward an objective evaluation of manual performance deficits. Mov Disord. 2005;20(1):11–25.
143. Nowak DA, Hermsdorfer J. Objective evaluation of manual performance deficits in neurological movement disorders. Brain Res Rev. 2006;51(1): 108–24.
144. Nowak DA, Hermsdorfer J, Marquardt C, Topka H. Moving objects with clumsy fingers: how predictive is grip force control in patients with impaired manual sensibility? Clin Neurophysiol. 2003;114(3): 472–87.
145. Nowak DA, Hermsdorfer J, Topka H. Deficits of predictive grip force control during object manipulation in acute stroke. J Neurol. 2003;250(7):850–60.
146. Bonato P. Advances in wearable technology and applications in physical medicine and rehabilitation. J Neuroeng Rehabil. 2005;2(1):2.
147. Chen KY, Bassett Jr DR. The technology of accelerometry-based activity monitors: current and future. Med Sci Sports Exerc. 2005;37(1):S490–500.
148. John D, Freedson P. ActiGraph and actical physical activity monitors: a peek under the hood. Med Sci Sports Exerc. 2012;44(1):86–9.
149. Bassett DR. Device-based monitoring in physical activity and public health research. Physiol Meas. 2012;33(11):1769–83.
150. Kinnunen H, Tanskanen M, Kyrolainen H, Westerterp KR. Wrist-worn accelerometers in assessment of energy expenditure during intensive training. Physiol Meas. 2012;33(11):1841–54.
151. Koehler K, Braun H, de Marees M, Fusch G, Fusch C, Schaenzer W. Assessing energy expenditure in male endurance athletes: validity of the sensewear armband. Med Sci Sports Exerc. 2011;43(7):1328–33.
152. Pollak CP, Tryon WW, Nagaraja H, Dzwonczyk R. How accurately does wrist actigraphy identify the states of sleep and wakefulness? Sleep. 2001;24(8): 957–65.
153. So K, Buckley P, Adamson TM, Horne RS. Actigraphy correctly predicts sleep behavior in infants who are younger than six months, when compared with polysomnography. Pediatr Res. 2005; 58(4):761–5.
154. Dijkstra B, Kamsma YP, Zijlstra W. Detection of gait and postures using a miniaturized triaxial accelerometer-based system: accuracy in patients with mild to moderate Parkinson's disease. Arch Phys Med Rehabil. 2010;91(8):1272–7.
155. Godfrey A, Conway R, Meagher D, OL G. Direct measurement of human movement by accelerometry. Med Eng Phys. 2008;30(10):1364–86.
156. Zijlstra W, Hof AL. Assessment of spatiotemporal gait parameters from trunk accelerations during human walking. Gait Posture. 2003;18(2):1–10.
157. Dijkstra B, Zijlstra W, Scherder E, Kamsma Y. Detection of walking periods and number of steps in older adults and patients with Parkinson's disease: accuracy of a pedometer and an accelerometry-based method. Age Ageing. 2008;37(4):436–41.
158. Paraschiv-Ionescu A, Perruchoud C, Buchser E, Aminian K. Barcoding human physical activity to assess chronic pain conditions. PLoS One. 2012;7(2):e32239.
159. Michielsen ME, Selles RW, Stam HJ, Ribbers GM, Bussmann JB. Quantifying nonuse in chronic stroke patients: a study into paretic, nonparetic, and bimanual upper-limb use in daily life. Arch Phys Med Rehabil. 2012;93(11):1975–81.
160. van der Pas SC, Verbunt JA, Breukelaar DE, van Woerden R, Seelen HA. Assessment of arm activity using triaxial accelerometry in patients with a stroke. Arch Phys Med Rehabil. 2011;92(9):1437–42.
161. Thrane G, Emaus N, Askim T, Anke A. Arm use in patients with subacute stroke monitored by accelerometry: association with motor impairment and influence on self-dependence. J Rehabil Med. 2011;43(4):299–304.
162. Noorkoiv M, Rodgers H, Price CI. Accelerometer measurement of upper extremity movement after stroke: a systematic review of clinical studies. J Neuroeng Rehabil. 2014;11:144.

163. Uswatte G, Giuliani C, Winstein C, Zeringue A, Hobbs L, Wolf SL. Validity of accelerometry for monitoring real-world arm activity in patients with subacute stroke: evidence from the extremity constraint-induced therapy evaluation trial. Arch Phys Med Rehabil. 2006;87(10):1340–5.
164. Uswatte G, Foo WL, Olmstead H, Lopez K, Holand A, Simms LB. Ambulatory monitoring of arm movement using accelerometry: an objective measure of upper-extremity rehabilitation in persons with chronic stroke. Arch Phys Med Rehabil. 2005; 86(7):1498–501.
165. Markopoulos P, Timmermans AA, Beursgens L, van Donselaar R, Seelen HA. Us'em: the user-centered design of a device for motivating stroke patients to use their impaired arm-hand in daily life activities. Proceedings of IEEE engineering in medicine and biology conference, Boston. 2011:5182–7.
166. Gebruers N, Vanroy C, Truijen S, Engelborghs S, De Deyn PP. Monitoring of physical activity after stroke: a systematic review of accelerometry-based measures. Arch Phys Med Rehabil. 2010;91(2):288–97.
167. Jasiewicz JM, Allum JH, Middleton JW, Barriskill A, Condie P, Purcell B, et al. Gait event detection using linear accelerometers or angular velocity transducers in able-bodied and spinal-cord injured individuals. Gait Posture. 2006;24(4):502–9.
168. Rueterbories J, Spaich EG, Larsen B, Andersen OK. Methods for gait event detection and analysis in ambulatory systems. Med Eng Phys. 2010;32(6): 545–52.
169. Moore ST, Dilda V, Hakim B, Macdougall HG. Validation of 24-hour ambulatory gait assessment in Parkinson's disease with simultaneous video observation. Biomed Eng Online. 2011;10:82.
170. Aminian K, Najafi B, Bula C, Leyvraz PF, Robert P. Spatiotemporal parameters of gait measured by an ambulatory system using miniature gyroscopes. J Biomech. 2002;35(5):689–99.
171. Hamacher D, Hamacher D, Taylor WR, Singh NB, Schega L. Towards clinical application: repetitive sensor position re-calibration for improved reliability of gait parameters. Gait Posture. 2014;39(4): 1146–8.
172. Hausdorff JM. Gait variability: methods, modeling and meaning. J Neuroeng Rehabil. 2005;2:19.
173. Allen J, Kautz S, Neptune R. Step length asymmetry is representative of compensatory mechanisms used in post-stroke hemiparetic walking. Gait Posture. 2011;33(4):538–43.
174. Chen G, Patten C, Kothari D, Zajac F. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait Posture. 2005;22(1):51–6.
175. Esser P, Dawes H, Collet J, Feltham MG, Howells K. Assessment of spatiotemporal gait parameters using inertial measurement units in neurological populations. Gait Posture. 2011;34(4):558–60.
176. Hubble R, Naughton G, Silburn P, Cole M. Wearable sensor use for assessing standing balance and walking stability in people with Parkinson's disease: a systematic review. PLoS One. 2015;10(4):e0123705.
177. Allum JH, Adkin AL, Carpenter MG, Held-Ziolkowska M, Honegger F, Pierchala K. Trunk sway measures of postural stability during clinical balance tests: effects of a unilateral vestibular deficit. Gait Posture. 2001;14(3):227–37.
178. Howcroft J, Kofman J, Lemaire ED. Review of fall risk assessment in geriatric populations using inertial sensors. J Neuroeng Rehabil. 2013;10(1):91.
179. Wittmann F, Lambercy O, Held J, Gonzenbach R, Höver R, Starkey M, et al. Assessment-driven arm therapy at home using an IMU-based virtual reality system. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Singapore. 2015:707–12.
180. Rihar A, Mihelj M, Pasic J, Kolar J, Munih M. Infant trunk posture and arm movement assessment using pressure mattress, inertial and magnetic measurement units (IMUs). J Neuroeng Rehabil. 2014; 11:133.
181. Weiss A, Herman T, Plotnik M, Brozgol M, Maidan I, Giladi N, et al. Can an accelerometer enhance the utility of the Timed Up & Go Test when evaluating patients with Parkinson's disease? Med Eng Phys. 2010;32(2):119–25.
182. Wade E, Parmandi AR, Mataric MJ. Automated administration of the Wolf Motor Function Test for post-stroke assessment. Proceedings of international conference on pervasive computing technologies for healthcare. IEEE, Munich. 2010:1–7.
183. Del Din S, Patel S, Cobelli C, Bonato P. Estimating Fugl-Meyer clinical scores in stroke survivors using wearable sensors. Proceedings of IEEE engineering in medicine and biology conference, Boston. 2011:5839–42.
184. Carpinella I, Cattaneo D, Ferrarin M. Quantitative assessment of upper limb motor function in multiple sclerosis using an instrumented Action Research Arm Test. J Neuroeng Rehabil. 2014;11:67.
185. Leuenberger K, Gassert R. Low-power sensor module for long-term activity monitoring. Proceedings of IEEE engineering in medicine and biology conference, Boston. 2011:2237–41.
186. Leuenberger K, Gonzenbach R, Wiedmer E, Luft A, Gassert R. Classification of stair ascent and descent in stroke patients. Proceedings of international conference on wearable and implantable body sensor networks workshops. IEEE, Zurich. 2014:11–6.
187. Lunenburger L, Oertig M, Brunschwiler A, Colombo G, Riener R, Dietz V. Assessment of spasticity with the robotic gait orthosis Lokomat. Proceedings of 6th world congress on brain injury. ICMS Pty Ltd, Melbourne. 2005.
188. Campolo D, Taffoni F, Formica D, Iverson J, Sparaci L, Keller F, et al. Embedding inertial-magnetic sensors in everyday objects: assessing spatial cognition in children. J Integr Neurosci. 2012;11(1):103–16.
189. Memberg WD, Crago PE. Instrumented objects for quantitative evaluation of hand grasp. J Rehabil Res Dev. 1997;34(1):82–90.

190. Colombo R, Cusmano I, Sterpi I, Mazzone A, Delconte C, Pisano F. Test-retest reliability of robotic assessment measures for the evaluation of upper limb recovery. IEEE Trans Neural Syst Rehabil Eng. 2014;22(5):1020–9.
191. Metzger JC, Lambercy O, Gassert R. Performance comparison of interaction control strategies on a hand rehabilitation robot. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR), Singapore. 2015:846–51.
192. Metzger JC, Lambercy O, Califfi A, Dinacci D, Petrillo C, Rossi P, et al. Assessment-driven selection and adaptation of exercise difficulty in robot-assisted therapy: a pilot study with a hand rehabilitation robot. J Neuroeng Rehabil. 2014;11:154.
193. Colombo R, Sterpi I, Mazzone A, Delconte C, Pisano F. Taking a lesson from patients' recovery strategies to optimize training during robot-aided rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2012;20(3):276–85.
194. Cameirao MS, Badia SB, Oller ED, Verschure PF. Neurorehabilitation using the virtual reality based Rehabilitation Gaming System: methodology, design, psychometrics, usability and validation. J Neuroeng Rehabil. 2010;7:48.
195. Kan P, Huq R, Hoey J, Goetschalckx R, Mihailidis A. The development of an adaptive upper-limb stroke rehabilitation robotic system. J Neuroeng Rehabil. 2011;8:33.

Clinical Aspects for the Application of Robotics in Locomotor Neurorehabilitation

11

Volker Dietz

Abstract

In patients suffering from a movement disorder after a damage of the central nervous system, improvement in walking or hand function can be achieved by providing functional training. After a stroke or a spinal cord injury (SCI), neuronal centers at and below the level of lesion exhibit plasticity that can be exploited by functional training paradigms that include assisting stepping or hand/arm movements of the affected side. Training of locomotor function, the focus of this chapter, requires body-weight support (BWS), while the subjects stand on a moving treadmill. In these individuals, human spinal locomotor centers become activated if an appropriate afferent input is provided. The stroke/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, i.e., more intensive training. In addition, they also offer the ability to standardize training approaches and to obtain objective feedback within training sessions allowing to monitor functional improvements over time. This chapter provides an overview of the clinical aspects for the successful application of robotic devices in the neurorehabilitation of stroke/SCI subjects. First, background information is given for the neural mechanisms of gait recovery after stroke/SCI. Second, the afferent input required for an effective training is discussed and, third, findings from clinical studies are presented covering the feasibility and efficacy of robot-assisted locomotor training.

V. Dietz, MD
Spinal Cord Injury Center, University Hospital
Balgrist, Forchstr. 340, Zurich 8008, Switzerland
e-mail: vdietz@paralab.balgrist.ch

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11.1 Introduction

In typical movement disorders following a damage of the central nervous system (CNS), such as stroke or spinal cord injury (SCI), there is increasing evidence that a defective utilization of afferent input, in combination with secondary compensatory processes, is involved (cf. [1]). The secondary compensatory processes include the development of spastic muscle tone that is required to support the body during stepping movements [2]. The loss of the ability to walk represents a major disability for subjects suffering a SCI or a stroke [3, 4]. Almost two-thirds of all stroke survivors cannot walk without assistance in the acute phase following the incident [5]. In cat (for review, see [6]) and human (for review, see [7, 8]) experiments, neuronal networks underlying the generation of movement patterns show considerable flexibility after a damage of the central or peripheral nervous system. 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.

One major goal of rehabilitation for patients suffering stroke or SCI is to achieve a recovery of 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 [9–14]. 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, first, the neuronal mechanisms of functional movements; second, the basic mechanisms of neuroplasticity underlying behavioral recovery after stroke or an SCI; third, the afferent input that should be provided for an effective training; and, lastly, the functional improvements and limitations to be achieved in response to robot-assisted functional training after a CNS lesion [17]; cf. [18]. This chapter will be focused on the neurorehabilitation of locomotor function.

11.2 Neuroplasticity: Basic Research

There is convincing evidence from research on spinalized animals that a use-dependent plasticity of the spinal cord exists [19, 20]. When stepping is practiced in a spinal cat, this task can be performed more successfully than when it is not practiced [21, 22]. Thus recovery of locomotor function following spinal cord transection can be improved using regular training even in adult animals [9]. In contrast, the cat loses the ability to step spontaneously if it is not regularly performed. During such a locomotor training, the animal is supported. Locomotor movements of the hind limbs are induced by a moving 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 [23]. Furthermore, after hind limb exercise in adult rats, the excitability of spinal reflexes becomes normalized [24]. Stepping movements can also be released in a monkey after transection of the spinal cord, suggesting that also the isolated primate spinal cord is capable of generating hind limb stepping movements [25].

The training of any functional motor task provides sufficient and appropriate proprioceptive input to initiate a reorganization of neural networks within the spinal cord. The same is true for the generation and training of a locomotor pattern after a stroke or SCI. Also in humans with a CNS damage, a greater level of functional recovery might be possible if a use-dependent training approach is applied in both clinical and rehabilitative settings [19]. In contrast, immobilization leads to an undirected, chaotic sprouting after deafferentation from supraspinal input, while a directed sprouting occurs when a rat becomes trained [26]. Similarly the loss of functional capacity following neural injury leads to a neuronal dysfunction below the level of the lesion when locomotor networks are no longer used, for example, following a stroke [19, 27] or a SCI [28].

A considerable degree of locomotor recovery in mammals with SCI can be attributed to a reorganization of spared neural pathways ([29, 30]; for review, see [31]). It has been estimated that if as little as 10–15 % of the descending spinal tracts are spared, some locomotor function can recover [32, 33]. The neuronal networks below an SCI can be activated to generate locomotor activity even in the absence of supraspinal input [18, 32–36]. It can be concluded that assisted training represents an important factor in the recovery of locomotor function.

11.3 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 [37]). Steplike 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 [38], 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 [39] and, nevertheless, also in human spinal interneuronal circuits exist that are involved in the generation of locomotor EMG activity (cf. Fig. 11.1; [41] similar to those described for the cat [23]).

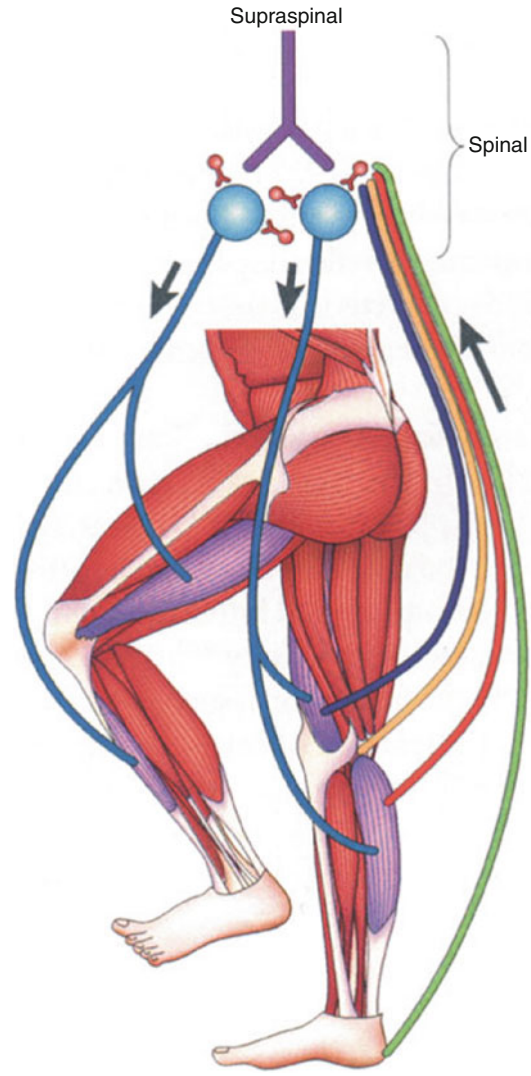

Fig. 11.1 Schematic drawing of the neuronal mechanisms involved in human gait. Leg muscles become activated by a programmed pattern that is generated in spinal neuronal circuits. This pattern is modulated by multisensory afferent input that adapts the pattern to meet existing requirements. Both the programmed 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 [40]

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 assistance) in these patients can improve motor function of the affected limbs [9]. This improvement is based on the neuroplasticity of the CNS at several levels of organization. Neuroplastic effects can partially compensate for the loss in function resulting from lesioned brain or spinal cord areas [8, 42, 43]. In SCI, the supraspinal control over the neural circuitries in the spinal cord is impaired or lost, 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 spontaneously occurring steplike movements [44], myoclonus [7], and the appearance of late flexion reflexes [7] in tetraplegic subjects as well as from locomotor movements induced in body-weight-supported SCI subjects walking on a moving treadmill [10, 45].

A locomotor pattern can even be induced and trained in complete SCI subjects when leg movements are assisted from externally and when an appropriate afferent input to the spinal cord is provided [1, 10, 40, 45–47]. 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 [10]. 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 [5].

When the EMG of antagonistic leg muscles 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 [48]. This indicates that during stepping, 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.

11.3.1 Prerequisites for a Successful Functional Training

In a successful training program for stroke and SCI subjects, first, spastic muscle tone must be present as a partial compensation for paresis [2], and, second, the spinal central pattern generator must be activated by the provision of an appropriate afferent input and proprioceptive feedback to induce plastic neuronal changes [18, 49].

Spastic Muscle Tone For a patient with spasticity, not the physical signs (e.g., exaggerated tendon tap reflexes) assessed during clinical examination but the impaired performance of hand or stepping movements and their treatment are of importance. During locomotor movements a low-amplitude, tonic activation of upper and lower limb muscles takes place, i.e., a normal modulation of EMG activity is lacking while the timing of muscle activity is preserved [50, 51]. The amplitude reduction of leg muscle activity is suggested to be due to a diminished excitatory drive from supraspinal centers and an attenuated activity of polysynaptic (or long-latency) reflexes [40, 52]. Polysynaptic reflexes are known to modulate leg extensor muscle activity [40] and thereby adapt the movement pattern to the environmental requirements. In contrast, short latency reflexes neither in healthy subjects nor in patients with spasticity contribute significantly to muscle activity during natural movements [2]. These observations indicate that the muscle tone required during a movement (e.g., to support the body during the stance phase of stepping) after CNS damage develops on a lower level of organization [2, 53]. The muscle tone required is not achieved by modulated muscle activation as it is the case in healthy subjects. Instead, muscle tone develops with the stretching of the tonically activated muscle. This simple mode of muscle tone generation after a CNS lesion is based on secondarily occurring structural alteration of muscles,

i.e., a loss of sarcomeres [53]. This change in part compensates for the loss of muscle activation and allows support of the body during the stance phase of stepping (Fig. 11.1). However, the performance of fast movements becomes impossible by this mode of muscle tone regulation. Furthermore, patients with spasticity do not only suffer from an impairment of the efferent part of the motor system but also from a defective processing of afferent signals that limits movement performance [52].

Thus in patients with spasticity, in comparison with healthy subjects, muscle activity is enhanced in the passive condition, i.e., the clinical examination, but is reduced during active movements. The physical signs observed during the clinical examination can, therefore, hardly be translated to the movement disorder. Clinically spastic signs are more pronounced after damage of the spinal cord compared to a cerebral lesion. However, pathophysiologically there exist only quantitative but no qualitative differences.

11.3.1.1 Role of Appropriate Afferent Input

Body unloading and reloading are considered crucial to inducing training effects on the spinal 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 [54]. Therefore, a cyclic loading is considered essential for achieving training effects in cats [55] and humans [49, 56]. Overall, observations of healthy subjects [54, 55], small children [57], and patients with paraplegia [48, 58] indicate that afferent input from load receptors essentially contribute to the activation pattern of leg muscles during locomotion. This suggests that proprioceptive input from extensor muscles, and probably also from mechanoreceptors in the foot sole, provides load information [1]. In addition, afferent input of hip joints, coming from muscles that act around the hip, obviously is important for the leg muscle activation during locomotion [49]. The significance of hip joint afferents was also emphasized

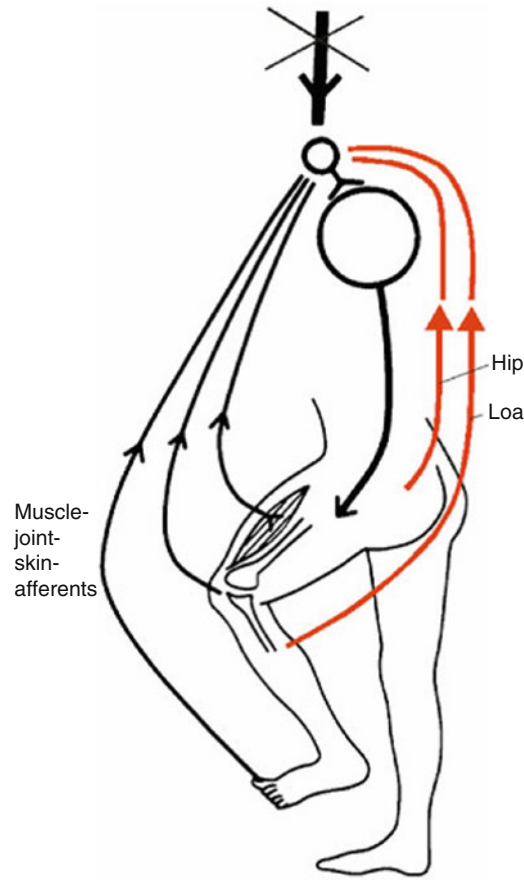

Fig. 11.2 Essential afferent input for the generation of a locomotor pattern. To evoke a locomotor pattern in complete SCI subjects, load and hip joint-related afferent input are suggested to be of crucial importance

for cat locomotion [59]. This afferent activity from load and hip joint receptors is to shape the locomotor pattern, to control phase transitions, and to reinforce ongoing activity (Fig. 11.2). Short-latency stretch and cutaneous reflexes may be involved in the compensation of small 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 the course of a daily locomotor training, the

amplitude of leg extensor EMG activity increases during the stance phase, while an inappropriate tibialis anterior activation decreases [49, 56]. 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 stepping movements on solid ground. Nevertheless, patients with complete paraplegia experience positive effects on the cardiovascular and musculoskeletal systems (e.g., they suffer less from 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 [43, 48] in addition to the spontaneous recovery of spinal cord function that occurs over several months following an SCI [29, 30, 44, 58].

The classification of locomotor ability in SCI subjects [60] shows a relationship between motor scores and locomotor ability only in patients with moderately impaired motor function [61]. Patients with a low motor score undergoing a locomotor training can improve locomotor function without or with little change in motor scores [40, 61, 62]. In these cases, a relatively low voluntary force level in the leg muscles (reflected in the ASIA motor score) is required to achieve the ability to walk. Interestingly, elderly SCI subjects have greater difficulties to translate a gain in motor score into function compared to younger subjects suffering an SCI [63]. This requires specific training programs for elderly subjects focusing on a few rehabilitation goals.

11.4 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 [64] and SCI [13, 43, 47, 65] subjects. Some studies showed stronger improvement in walking ability following BWSTT compared to conventional gait training [64, 66], whereas other groups did not report better functional outcomes [13, 14, 67, 68]. A recent study indicates that most participants achieve an increased functional walking ability by a locomotor training. However this improvement occurs independently from its onset and from the mode of intervention applied [69]. This is unsurprising since, with most approaches, a functional locomotor training is performed, for review cf. [18]. 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, stepping becomes induced by standing on a moving treadmill and with simultaneous unloading of body weight (up to 80 %) (Fig. 11.3a) that facilitates training performance.

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 [70]. This resource constraint limits its 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 training 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

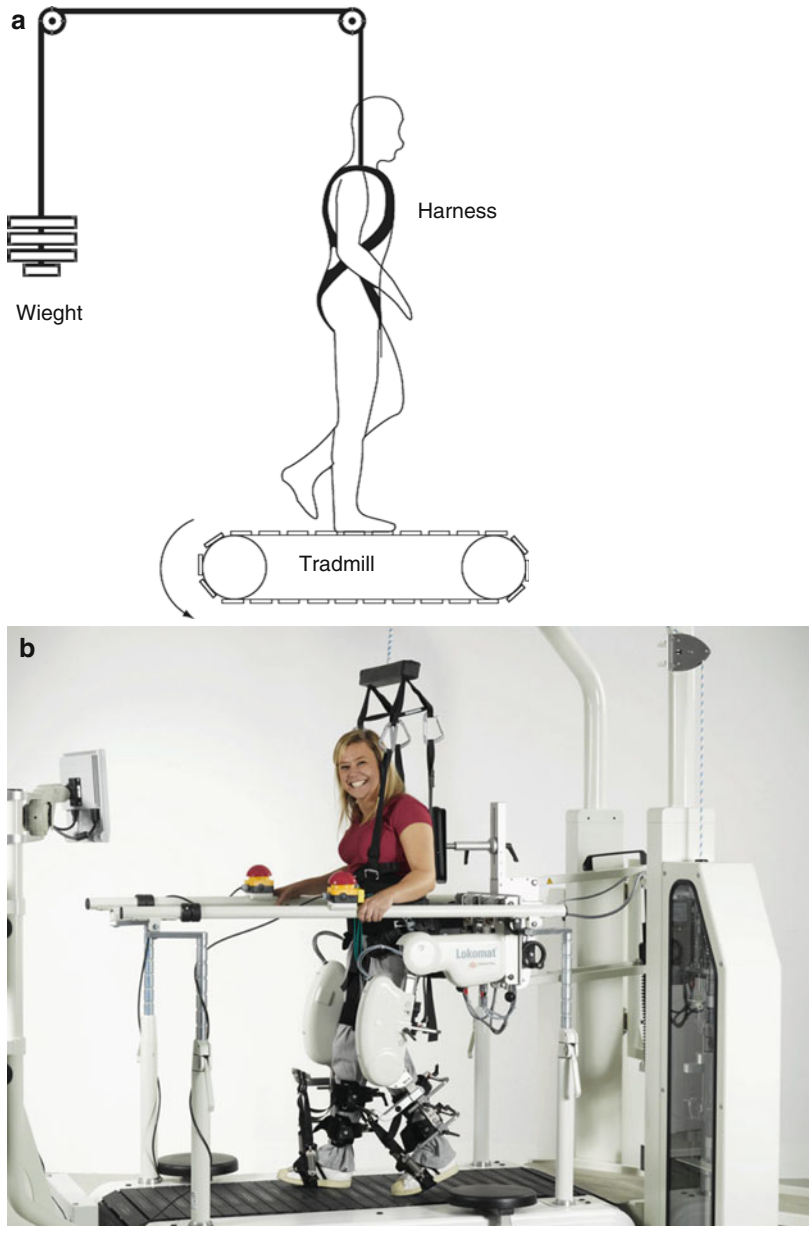

Fig. 11.3 Locomotor training of stroke/SCI subjects. (**a**) Conventional locomotor training using body-weight support and subjects standing on a moving treadmill. (**b**) Version of the Lokomat system in 2007 (Photo **b** – Hocoma AG; courtesy of Hocoma AG, Switzerland)

patient in an adjustable configuration with a body-weight support system (Fig. 11.3b). Later on, this exoskeleton was modified in a way to allow more flexibility in movement performance, and other exoskeletal systems were developed for functional gait training (e.g., [6, 16, 57, 71]).

11.5 Clinical Effects of a Robotic Gait Training

As soon as the concept of plasticity-based functional training became established, the idea of technical assistance of impaired limb movements

was considered [17, 28, 72]. These considerations were fuelled by the notion that longer and intensive training times can best be achieved using a robotic device and that this technology allows for monitoring of changes in movement performance over the course of rehabilitation [1, 73]. Robotic devices can promote recovery by facilitating plasticity [74]. Several studies have investigated the feasibility and benefits of a robotic-assisted treadmill training provided, for example, by the Lokomat system [15, 48, 75–88]. In the past it was difficult to draw general conclusions about effectiveness due to the limited numbers of participants enrolled in the studies and heterogeneous selection criteria (e.g., acute and chronic stroke/SCI subjects, respectively; different pathologies/severities) [89]. Furthermore, robotic training is performed in rather variable terms of training onset, duration, and specific walking conditions (e.g., walking speed, level of body-weight support, amount of assistance), as well as the quality of conventional physiotherapy which the patients frequently receive in parallel with the robotic locomotor training. Today it is obvious that locomotor training is effective in poststroke subjects [90] independently from training approach that is applied [69]. In addition, 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, 48, 81, 91], stroke [79, 80, 82, 84, 87, 88], multiple sclerosis [75, 83], and cerebral palsy [76–78, 85, 86].

Beneficial effects of robot-assisted training are quite diverse, ranging from gains in walking velocity and endurance to an improvement in walking tests [48, 75, 77, 81, 83–86, 88]. Some benefits are associated with changes in gait characteristics [61] such as a better walking quality [82, 92] or a better control of voluntary leg movements [93]. In addition to improvements in walking ability, positive influences on abnormal reflex function [77, 84], respiration [94], and cardiovascular response [95, 96] have also been reported. In addition, a supraspinal plasticity and increased activation of the cerebellum associated with an improvement of function could be demonstrated as a consequence of a robotic-assisted locomotor training [91].

Robotic devices have further been employed to investigate the effects of locomotor training on corticospinal excitability [97, 98], spinal reflex modulation [46, 99], muscle activation patterns in incomplete and complete SCI subjects [49, 96], and spinal neuronal function in chronic complete SCI [100], as well as changes in cardiovascular, metabolic, and autonomic responses [95, 101, 102].

A number of studies were undertaken to compare the efficacy of robot-assisted locomotor training with conventional training [79, 80, 82, 84, 85, 87, 88]. It became apparent that, especially for those with severe neurological deficits, patients benefit from robot-assisted treadmill training [82, 84, 87], 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 [79, 80]. This is reasonable since a robotic device such as the Lokomat is designed to be applied in stroke/SCI subjects suffering severe sensorimotor deficits including a reduced ability to support body weight during stepping and high demands on therapists for physical assistance, e.g., due to high spastic muscle tone.

Consequently, the "Lokomat" was developed to enable longer training periods in severely affected subjects that can lead to better outcomes [103]. An increase in muscle mass associated with cardiovascular training [82] and enhanced oxygen consumption due to the partial body-weight support [104] indicate that in fact locomotor training within a robotic device requires an active movement performance [49]. For an overground walking exercise of severely or completely paralyzed patients with SCI devices, such as ReWalk and Ekso, were constructed (cf. [105]). However, this is associated with a great individual physical expenditure. In addition, the number of stepping cycles and the individual adaptations required for an effective training appear to be quite limited by such devices.

11.6 Future Developments

Robotic assistance for gait training is most effective and appropriate for incomplete SCI patients who are unable to perform stepping movements.

Those with some ability to walk profit from gait training that does not require robotic support. Future technical improvements of robotic devices will allow a training that is challenging with respect to coordination and balance for the individual patient. Some studies report higher inconsistencies in intralimb coordination [106] and reduced EMG activity during robot-assisted therapy compared to therapist-assisted walking [96]. However, stepping quality becomes improved by locomotor training in SCI subjects regardless of training approach [92]. 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 [18, 106]. 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 [46].

In the future, collaborations between clinical and basic researchers are required to further improve robotic functions (e.g., provision of proprioceptive feedback, stepping velocity, virtual reality, and challenge as far as possible for the individual patient). In addition, individual training protocols should be applied 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 [2]. This knowledge has, of course, consequences for therapy and drug applications. 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 the most appropriate training for an individual patient (for review, see [40]).

In the future the most promising approach to improve locomotor function in severely affected patients with an SCI who can only insufficiently profit from training approaches 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 [107] (for review, see [108, 109]). 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 the rodent model of SCI can be applied for this approach to humans with SCI [33].

Conclusion

Functional training represents an established approach for the rehabilitation of stroke and SCI subjects [1]. 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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References

1. Dietz V. Body weight supported gait training: from laboratory to clinical setting. Brain Res Bull. 2008;76(5):459–63.
2. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6(8):725–33 [Research Support, Non-U.S. Gov't Review].
3. Kelly-Hayes M, Robertson JT, Broderick JP, Duncan PW, Hershey LA, et al. The American Heart Association stroke outcome classification: executive summary. Circulation. 1998;97(24):2474–8.
4. Waters RL, Adkins R, Yakura J, Sie I. Donal Munro lecture: functional and neurologic recovery following acute SCI. J Spinal Cord Med. 1998;21(3):195–9.
5. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76(1):27–32.
6. Aoyagi D, Ichinose WE, Harkema SJ, Reinkensmeyer DJ, Bobrow JE. A robot and control algorithm that can synchronously assist in naturalistic motion during body-weight-supported gait training following neurologic injury. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):387–400.
7. Bussel B, Roby-Brami A, Azouvi P, Biraben A, Yakovleff A, et al. Myoclonus in a patient with spinal cord transection. Possible involvement of the spinal stepping generator. Brain. 1988;111(Pt 5):1235–45.
8. Martino G. How the brain repairs itself: new therapeutic strategies in inflammatory and degenerative CNS disorders. Lancet Neurol. 2004;3(6):372–8.
9. Barbeau H, Wainberg M, Finch L. Description and application of a system for locomotor rehabilitation. Med Biol Eng Comput. 1987;25(3):341–4.
10. Dietz V, Colombo G, Jensen L, Baumgartner L. Locomotor capacity of spinal cord in paraplegic patients. Ann Neurol. 1995;37(5):574–82.
11. Hesse S, Werner C. Partial body weight supported treadmill training for gait recovery following stroke. Adv Neurol. 2003;92:423–8.
12. Teasell RW, Bhogal SK, Foley NC, Speechley MR. Gait retraining post stroke. Top Stroke Rehabil. 2003;10(2):34–65.
13. Wernig A, Muller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia. 1992;30(4):229–38.
14. Wernig A, Nanassy A, Muller S. Laufband (treadmill) therapy in incomplete paraplegia and tetraplegia. J Neurotrauma. 1999;16(8):719–26.
15. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37(6):693–700.
16. Hesse S, Uhlenbrock D. A mechanized gait trainer for restoration of gait. J Rehabil Res Dev. 2000;37(6):701–8.
17. Riener R, Lünenburger L, Maier IC, Colombo G, Dietz V. Locomotor training in subjects with sensorimotor deficits: an overview of the robotic gait orthosis lokomat. J Healthc Eng. 2010;1(2):197–216.
18. Dietz V, Fouad K. Restoration of sensorimotor functions after spinal cord injury. Brain. 2014;137:654.
19. Edgerton VR, de Leon RD, Tillakaratne N, Recktenwald MR, Hodgson JA, et al. Use-dependent plasticity in spinal stepping and standing. Adv Neurol. 1997;72:233–47 [Research Support, U.S. Gov't, P.H.S.].
20. Pearson KG. Neural adaptation in the generation of rhythmic behavior. Annu Rev Physiol. 2000;62:723–53.

21. Lovely RG, Gregor RJ, Roy RR, Edgerton VR. Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. Exp Neurol. 1986;92:421–35.
22. Lovely RG, Gregor RJ, Roy RR, Edgerton VR. Weight-bearing hindlimb stepping in treadmill-exercised adult spinal cats. Brain Res. 1990;514:206–18.
23. Barbeau H, Rossignol S. Enhancement of locomotor recovery following spinal cord injury. Curr Opin Neurol. 1994;7(6):517–24.
24. Skinner RD, Houle JD, Reese NB, Berry CL, Garcia-Rill E. Effects of exercise and fetal spinal cord implants on the H-reflex in chronically spinalized adult rats. Brain Res. 1996;729:127–31.
25. Vilensky J, O'Connor B. Stepping in nonhuman primates with a complete spinal cord transection: old and new data, and implications for humans. Ann NY Acad Sci. 1998;860:528–30. Neuronal Mechanisms for Generating Locomotor Activity.
26. Beauparlant J, van den Brand R, Barraud Q, Friedli L, Musienko P, et al. Undirected compensatory plasticity contributes to neuronal dysfunction after severe spinal cord injury. Brain. 2013;136(Pt 11):3347–61 [Research Support, Non-U.S. Gov't].
27. Hubli M, Bolliger M, Limacher E, Luft AR, Dietz V. Spinal neuronal dysfunction after stroke. Exp Neurol. 2012;234(1):153–60 [Research Support, Non-U.S. Gov't].
28. Dietz V. Behavior of spinal neurons deprived of supraspinal input. Nat Rev Neurol. 2010;6(3):167–74.
29. Curt A, Dietz V. Ambulatory capacity in spinal cord injury: significance of somatosensory evoked potentials and ASIA protocol in predicting outcome. Arch Phys Med Rehabil. 1997;78(1):39–43.
30. Curt A, Keck ME, Dietz V. Functional outcome following spinal cord injury: significance of motor-evoked potentials and ASIA scores. Arch Phys Med Rehabil. 1998;79(1):81–6.
31. Curt A, Dietz V. Electrophysiological recordings in patients with spinal cord injury: significance for predicting outcome. Spinal Cord. 1999;37(3):157–65 [Research Support, Non-U.S. Gov't Review].
32. Basso DM. Neuroanatomical substrates of functional recovery after experimental spinal cord injury: implications of basic science research for human spinal cord injury. Phys Ther. 2000;80(8):808–17 [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review].
33. Metz GA, Curt A, van de Meent H, Klusman I, Schwab ME, et al. Validation of the weight-drop contusion model in rats: a comparative study of human spinal cord injury. J Neurotrauma. 2000;17(1):1–17.
34. de Leon RD, Hodgson JA, Roy RR, Edgerton VR. Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats. J Neurophysiol. 1998;79(3):1329–40 [Research Support, U.S. Gov't, P.H.S.].
35. de Leon RD, Hodgson JA, Roy RR, Edgerton VR. Full weight-bearing hindlimb standing following stand training in the adult spinal cat. J Neurophysiol. 1998;80(1):83–91.
36. Wirz M, Colombo G, Dietz V. Long term effects of locomotor training in spinal humans. J Neurol Neurosurg Psychiatry. 2001;71(1):93–6 [Research Support, Non-U.S. Gov't].
37. Dietz V. Do human bipeds use quadrupedal coordination? Trends Neurosci. 2002;25(9):462–7.
38. Fossberg H. Preface. In: Fossberg H, Hirschfeld H, editors. Movement disorders in children: medicine and sport science. Basel: Karger; 1992. p. 7–8.
39. Kuhn RA. Functional capacity of the isolated human spinal cord. Brain. 1950;73(1):1–51.
40. Dietz V. Proprioception and locomotor disorders. Nat Rev Neurosci. 2002;3(10):781–90 [Research Support, Non-U.S. Gov't Review].
41. Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G, et al. Involuntary stepping after chronic spinal cord injury. Evidence for a central rhythm generator for locomotion in man. Brain. 1994;117(Pt 5):1143–59.
42. Cramer SC, Riley JD. Neuroplasticity and brain repair after stroke. Curr Opin Neurol. 2008;21(1):76–82.
43. Dietz V, Harkema SJ. Locomotor activity in spinal cord-injured persons. J Appl Physiol. 2004;96(5):1954–60.
44. Curt A, Dietz V. Traumatic cervical spinal cord injury: relation between somatosensory evoked potentials, neurological deficit, and hand function. Arch Phys Med Rehabil. 1996;77(1):48–53.
45. Dietz V, Colombo G, Jensen L. Locomotor activity in spinal man. Lancet. 1994;344(8932):1260–3 [Clinical Trial Controlled Clinical Trial Research Support, Non-U.S. Gov't].
46. Dietz V, Grillner S, Trepp A, Hubli M, Bolliger M. Changes in spinal reflex and locomotor activity after a complete spinal cord injury: a common mechanism? Brain. 2009;132(Pt 8):2196–205.
47. Dobkin BH, Harkema S, Requejo P, Edgerton VR. Modulation of locomotor-like EMG activity in subjects with complete and incomplete spinal cord injury. J Neurol Rehabil. 1995;9(4):183–90.
48. Wirz M, Zemon DH, Rupp R, Scheel A, Colombo G, et al. Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil. 2005;86(4):672–80.
49. Dietz V, Muller R, Colombo G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. Brain. 2002;125(Pt 12):2626–34 [Comparative Study Research Support, Non-U.S. Gov't].
50. Ibrahim IK, Berger W, Trippel M, Dietz V. Stretch-induced electromyographic activity and torque in spastic elbow muscles. Differential modulation of reflex activity in passive and active motor tasks. Brain. 1993;116(Pt 4):971–89 [Research Support, Non-U.S. Gov't].
51. Dietz V, Quintern J, Berger W. Electrophysiological studies of gait in spasticity and rigidity. Evidence that altered mechanical properties of muscle contribute

to hypertonia. Brain. 1981;104(3):431–49 [Research Support, Non-U.S. Gov't].
52. Kloter E, Wirz M, Dietz V. Locomotion in stroke subjects: interactions between unaffected and affected sides. Brain. 2011;134(Pt 3):721–31 [Research Support, Non-U.S. Gov't].
53. O'Dwyer NJ, Ada L. Reflex hyperexcitability and muscle contracture in relation to spastic hypertonia. Curr Opin Neurol. 1996;9(6):451–5 [Review].
54. Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, et al. Human lumbosacral spinal cord interprets loading during stepping. J Neurophysiol. 1997;77(2):797–811.
55. Pearson KG, Collins DF. Reversal of the influence of group Ib afferents from plantaris on activity in medial gastrocnemius muscle during locomotor activity. J Neurophysiol. 1993;70(3):1009–17.
56. Dietz V. Human neuronal control of automatic functional movements: interaction between central programs and afferent input. Physiol Rev. 1992;72(1):33–69 [Research Support, Non-U.S. Gov't Review].
57. Banala SK, Kim SH, Agrawal SK, Scholz JP. Robot assisted gait training with active leg exoskeleton (ALEX). IEEE Trans Neural Syst Rehabil Eng. 2009;17(1):2–8.
58. Katoh S, el Masry WS. Neurological recovery after conservative treatment of cervical cord injuries. J Bone Joint Surg. 1994;76(2):225–8.
59. Grillner S, Rossignol S. On the initiation of the swing phase of locomotion in chronic spinal cats. Brain Res. 1978;146(2):269–77.
60. Ditunno Jr JF, Ditunno PL, Graziani V, Scivoletto G, Bernardi M, et al. Walking index for spinal cord injury (WISCI): an international multicenter validity and reliability study. Spinal Cord: Off J Int Med Soc Paraplegia. 2000;38(4):234–43 [Clinical Trial Multicenter Study Research Support, Non-U.S. Gov't].
61. Wirz M, van Hedel HJ, Rupp R, Curt A, Dietz V. Muscle force and gait performance: relationships after spinal cord injury. Arch Phys Med Rehabil. 2006;87(9):1218–22 [Multicenter Study Research Support, Non-U.S. Gov't].
62. Maegele M, Muller S, Wernig A, Edgerton VR, Harkema SJ. Recruitment of spinal motor pools during voluntary movements versus stepping after human spinal cord injury. J Neurotrauma. 2002;19(10):1217–29.
63. Wirz M, Dietz V. Recovery of sensorimotor function and activities of daily living after cervical spinal cord injury: the influence of Age. J Neurotrauma. 2014;21.
64. Barbeau H, Visintin M. Optimal outcomes obtained with body-weight support combined with treadmill training in stroke subjects. Arch Phys Med Rehabil. 2003;84(10):1458–65.
65. Dietz V. Locomotor training in paraplegic patients. Ann Neurol. 1995;38(6):965.
66. Visintin M, Barbeau H, Korner-Bitensky N, Mayo NE. A new approach to retrain gait in stroke patients through body weight support and treadmill stimulation. Stroke. 1998;29(6):1122–8.
67. Dobkin B, Barbeau H, Deforge D, Ditunno J, Elashoff R, et al. The evolution of walking-related outcomes over the first 12 weeks of rehabilitation for incomplete traumatic spinal cord injury: the multicenter randomized Spinal Cord Injury Locomotor Trial. Neurorehabil Neural Repair. 2007;21(1):25–35.
68. Moseley AM, Stark A, Cameron ID, Pollock A. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev (Online). 2003(3):CD002840.
69. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, et al. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011;364(21):2026–36 [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.].
70. Morrison SA, Backus D. Locomotor training: is translating evidence into practice financially feasible? J Neurol Phys Ther. 2007;31(2):50–4.
71. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, et al. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379–86.
72. Benito-Penalva J, Edwards DJ, Opisso E, Cortes M, Lopez-Blazquez R, et al. Gait training in human spinal cord injury using electromechanical systems: effect of device type and patient characteristics. Arch Phys Med Rehabil. 2012;93(3):404–12 [Randomized Controlled Trial].
73. Riener R, Lunenburger L, Colombo G. Human-centered robotics applied to gait training and assessment. J Rehabil Res Dev. 2006;43(5):679–94.
74. Everaert DG, Thompson AK, Chong SL, Stein RB. Does functional electrical stimulation for foot drop strengthen corticospinal connections? Neurorehabil Neural Repair. 2010;24(2):168–77 [Clinical Trial Research Support, Non-U.S. Gov't].
75. Beer S, Aschbacher B, Manoglou D, Gamper E, Kool J, et al. Robot-assisted gait training in multiple sclerosis: a pilot randomized trial. Mult Scler. 2008;14(2):231–6.
76. Borggraefe I, Kiwull L, Schaefer JS, Koerte I, Blaschek A, et al. Sustainability of motor performance after robotic-assisted treadmill therapy in children: an open, non-randomized baseline-treatment study. Eur J Phys Rehabil Med. 2010;46:125.
77. Borggraefe I, Meyer-Heim A, Kumar A, Schaefer JS, Berweck S, et al. Improved gait parameters after robotic-assisted locomotor treadmill therapy in a 6-year-old child with cerebral palsy. Mov Disord. 2008;23(2):280–3.
78. Borggraefe I, Schaefer JS, Klaiber M, Dabrowski E, Ammann-Reiffer C, et al. Robotic-assisted treadmill therapy improves walking and standing performance in children and adolescents with cerebral palsy. Eur J Paediatr Neurol. 2010;14:496.

79. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5–13.
80. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, et al. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39(6):1786–92.
81. Hornby TG, Zemon DH, Campbell D. Robotic-assisted, body-weight-supported treadmill training in individuals following motor incomplete spinal cord injury. Phys Ther. 2005;85(1):52–66.
82. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke. 2007;38(2):349–54.
83. Lo AC, Triche EW. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. Neurorehabil Neural Repair. 2008;22(6):661–71.
84. Mayr A, Kofler M, Quirbach E, Matzak H, Frohlich K, et al. Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair. 2007;21(4):307–14.
85. Meyer-Heim A, Ammann-Reiffer C, Schmartz A, Schafer J, Sennhauser FH, et al. Improvement of walking abilities after robotic-assisted locomotion training in children with cerebral palsy. Arch Dis Child. 2009;94(8):615–20.
86. Meyer-Heim A, Borggraefe I, Ammann-Reiffer C, Berweck S, Sennhauser FH, et al. Feasibility of robotic-assisted locomotor training in children with central gait impairment. Dev Med Child Neurol. 2007;49(12):900–6.
87. Schwartz I, Sajin A, Fisher I, Neeb M, Shochina M, et al. The effectiveness of locomotor therapy using robotic-assisted gait training in subacute stroke patients: a randomized controlled trial. PM & R. 2009;1(6):516–23.
88. Westlake KP, Patten C. Pilot study of Lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. J Neuroeng Rehabil. 2009;6:18.
89. Dietz V. Good clinical practice in neurorehabilitation. Lancet Neurol. 2006;5(5):377–8.
90. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2013;(7):CD006185 [Meta-Analysis Research Support, Non-U.S. Gov't Review].
91. Winchester P, McColl R, Querry R, Foreman N, Mosby J, et al. Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury. Neurorehabil Neural Repair. 2005;19(4):313–24 [Clinical Trial, Research Support, N.I.H., Extramural, Research Support, Non-U.S. Gov't].
92. Nooijen CF, Ter Hoeve N, Field-Fote EC. Gait quality is improved by locomotor training in individuals with SCI regardless of training approach. J Neuroeng Rehabil. 2009;6:36.
93. Mirbagheri MM, Tsao C, Pelosin E, Rymer WZ. Therapeutic effects of robotic-assisted locomotor training on neuromuscular properties. Proceedings of the 2005 IEEE 9th international conference on rehabilitation robotics 2005.
94. Sherman MF, Lam T, Sheel AW. Locomotor-respiratory synchronization after body weight supported treadmill training in incomplete tetraplegia: a case report. Spinal Cord. 2009;47(12):896–8.
95. Hunt KJ, Jack A, Pennycott A, Perret C, Baumberger TH, et al. Control of work rate-driven exercise facilitates cardiopulmonary training and assessment during robot-assisted gait in complete spinal cord injury. Biomed Signal Process Control. 2008;3(1):19–28.
96. Israel JF, Campbell DD, Kahn JH, Hornby TG. Metabolic costs and muscle activity patterns during robotic- and therapist-assisted treadmill walking in individuals with incomplete spinal cord injury. Phys Ther. 2006;86(11):1466–78.
97. Blicher JU, Nielsen JF. Cortical and spinal excitability changes after robotic gait training in healthy participants. Neurorehabil Neural Repair. 2009;23(2):143–9.
98. Kamibayashi K, Nakajima T, Takahashi M, Akai M, Nakazawa K. Facilitation of corticospinal excitability in the tibialis anterior muscle during robot-assisted passive stepping in humans. Eur J Neurosci. 2009;30(1):100–9.
99. Querry RG, Pacheco F, Annaswamy T, Goetz L, Winchester PK, et al. Synchronous stimulation and monitoring of soleus H reflex during robotic body weight-supported ambulation in subjects with spinal cord injury. J Rehabil Res Dev. 2008;45(1):175–86.
100. Dietz V, Muller R. Degradation of neuronal function following a spinal cord injury: mechanisms and countermeasures. Brain. 2004;127(Pt 10):2221–31 [Research Support, Non-U.S. Gov't].
101. Magagnin V, Caiani EG, Fusini L, Turiel M, Licari V, et al. Assessment of the cardiovascular regulation during robotic assisted locomotion in normal subjects: autoregressive spectral analysis vs empirical mode decomposition. Conference proceedings of IEEE engineering in medicine and biology society. 2008;2008:3844–7.
102. Magagnin V, Porta A, Fusini L, Licari V, Bo I, et al. Evaluation of the autonomic response in healthy subjects during treadmill training with assistance of a robot-driven gait orthosis. Gait Posture. 2009;29(3):504–8.
103. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. Lancet. 1999;354(9174):191–6.

104. Nash MS, Jacobs PL, Johnson BM, Field-Fote E. Metabolic and cardiac responses to robotic-assisted locomotion in motor-complete tetraplegia: a case report. J Spinal Cord Med. 2004;27(1):78–82.
105. White HSF, Hayes S, White M. The effect of using a powered exoskeleton technology training program on joint range of motion on spinal cord injured individuals: a pilot study. Int J Phys Ther Rehab. 2014;1(102):1–5.
106. Lewek MD, Cruz TH, Moore JL, Roth HR, Dhaher YY, et al. Allowing intralimb kinematic variability during locomotor training poststroke improves kinematic consistency: a subgroup analysis from a randomized clinical trial. Phys Ther. 2009;89(8):829–39.
107. Gonzenbach RR, Gasser P, Zorner B, Hochreutener E, Dietz V, et al. Nogo-A antibodies and training reduce muscle spasms in spinal cord-injured rats. Ann Neurol. 2010;68(1):48–57.
108. Schwab ME. Regeneration of lesioned CNS axons by neutralisation of neurite growth inhibitors: a short review. Paraplegia. 1991;29(5):294–8. [Research Support, Non-U.S. Gov't Review.
109. Schwab ME, Bartholdi D. Degeneration and regeneration of axons in the lesioned spinal cord. Physiol Rev. 1996;76(2):319–70.

Clinical Application of Robotics and Technology in the Restoration of Walking

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Alberto Esquenazi, Irin C. Maier, Tabea Aurich Schuler, Serafin M. Beer, Ingo Borggraefe, Katrin Campen, Andreas R. Luft, Dimitrios Manoglou, Andreas Meyer-Heim, Martina R. Spiess, and Markus Wirz

Abstract

Robots for neurorehabilitation have been designed principally to automate repetitive labor-intensive training and to support therapists and patients during different stages of rehabilitation. Devices designed for body weight-supported treadmill training are promising task-oriented tools intended to assist in the restoration of gait. In early rehabilitation, robots provide a safe environment through the use of a suspension harness and assistance in achieving a more physiological gait pattern while promoting a high number of repetitions. In the later stages of rehabilitation, more sophisticated control strategies, virtual environment scenarios, or the possibility to address specific gait deficits by modulating different parameters extends their application. Scientific and clinical evidence for the effectiveness, safety,

A. Esquenazi, MD (✉)
Department of Physical Medicine and Rehabilitation, MossRehab, Elkins Park, PA, USA
e-mail: aesquena@einstein.edu

I.C. Maier • M.R. Spiess, PhD, PT
Clinical Research and Clinical Application, Hocoma AG, Volketswil, Switzerland

T.A. Schuler, MSc
Pediatric Rehab Research Group, Rehabilitation Center for Children and Adolescents, University Children's Hospital Zürich, Affoltern am Albis, Zürich, Switzerland

S.M. Beer • D. Manoglou
Department of Neurology and Neurorehabilitation, Rehabilitation Centre, Klinik Valens, Valens, Switzerland

I. Borggraefe
Department of Pediatric Neurology and Developmental Medicine, University of Munich, Munich, Germany

K. Campen
Quality Management, arvato CRM Healthcare GmbH, Berlin, Germany

A.R. Luft, MD
Department of Neurology, University Hospital Zurich, Zurich, Switzerland

A. Meyer-Heim
Rehabilitation Center, Children's University Hospital Zurich, Affoltern am Albis, Switzerland

M. Wirz, PT, PhD
Health Department, Institute of Physiotherapy, Zurich University of Applied Sciences, Winterthur, Switzerland

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and tolerability of these devices exists; however documentation of their comparative advantages to conventional therapies is limited.

This might be due to the lack of appropriate selection parameters of locomotor training interventions based on functional impairments. Despite this shortcoming, robotic devices are being integrated into clinical settings with promising results. Appropriate use is dependent on the clinicians' knowledge of different robotic devices as well as the ability to utilize the devices' technical features, thereby allowing patients to benefit from robot-aided gait training throughout the rehabilitation continuum with the ultimate goal of safe and efficient overground walking.

This chapter will provide an overview on the rationales of introducing robots into the clinic and discuss their value in various neurological diagnoses. In addition, recommendations for goal setting and practice of robot-assisted training based on disease-related symptoms and functional impairment are summarized.

Keywords

Robotics • Clinical application • Neurorehabilitation • Locomotor training • Gait rehabilitation

12.1 Introduction

Improving walking function is often a desirable outcome of the rehabilitation program and a primary concern with respect to the aspired social and vocational reintegration for a person diagnosed with a neurological impairment. As such, interventions addressing the recovery of walking function are a major focus of rehabilitation efforts across the continuum of care for patients with a wide range of neurological deficits. Increasing evidence has become available over the past 20 years to support the concept of reorganization of the injured central nervous system (CNS). The potential for reorganization is particularly high within a plastic phase early after CNS injury [1–3] but also possible at later stages [4]. Reorganization in a functionally meaningful way appears to be dependent on motor activity as executed during rehabilitative training and followed by functional improvements [5, 6]. Until recently, little evidence was available favoring any one approach over another [7]. The science behind exercise in neurological disease is not outstanding but does support a "weak but significant dosage effect with conventional therapy" [8]. It was further shown in rodents that timing and order is of upmost importance when combining behavioral with regenerative therapy, such that animals who trained after the end of the regenerative therapy performed better than those who trained simultaneously [9].

Weight-supported treadmill training refers to the use of a harness system that allows unweighing of the patient and permits the use of a motorized treadmill and the assistance of several therapists to support and mobilize the limbs in a walking-like pattern. Robotic-assisted gait training takes advantage of similar features of unweighing the lower limbs and a motorized treadmill and substitutes the manual labor of the therapists with a robotic system that can consistently and reliably position and move the limbs in a walking-like pattern. Conventional physiotherapy is usually not task oriented and focuses on strengthening and range of motion. Task-oriented, high repetition movements based on the principles of motor learning can improve among other things muscular strength, motor control, and movement coordination in patients with impairments due to neurological or orthopedic disorders [10, 11]. Gait training furthermore prevents

Fig. 12.1 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

secondary complications such as muscle atrophy, osteoporosis, joint stiffness, and muscle and soft tissue shortening and promotes reduction of spasticity [12].

Robots for neurorehabilitation were initially designed as a tool for clinicians to automate the labor-intensive repetitive training techniques, especially in the early stage of recovery where patients also require a high amount of support. Because of their programmable force-producing ability, robotic devices can facilitate task-oriented movements during weight bearing, thereby providing correct afferent feedback. Furthermore they can increase the duration and number of training sessions while reducing the number of assisting therapists required. Robots can emulate in a consistent and reproducible manner some features of a therapist's manual assistance and movement guidance, allowing patients to practice their movement training with supervision. Besides enhancing the rehabilitation process and improving therapeutic outcome, robots have the potential to support clinical evaluation, precisely control and measure the therapeutic intervention, implement novel forms of mechanical manipulation impossible for therapists to provide, and supply different forms of feedback, thereby increasing patient's motivation and improving outcomes [13–16].

Depending on the patient's abilities and functional capacity, during gait training up to four therapists may be required in order to secure and stabilize a patient and guide trunk and legs through a normal gait trajectory. Over the past years, several robotic devices have been developed to assist patients participate in gait training and relieve therapists from their labor-intensive work. Exoskeletal systems, like the Lokomat (Fig. 12.1) (Hocoma AG, Switzerland) [17], LOPES (University of Twente, Netherlands) [18], ALEX (University of Delaware, USA) [19], and ReoAmbulator (Motorika, USA) [20], 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,

Fig. 12.2 End-effector-based systems like G-EO systems (Reha Technologies, Olten, Switzerland) work like conventional elliptical trainers, where the subject's feet are strapped to two footplates moving along a gait-like trajectory

Germany) [21], G-EO systems (Fig. 12.2) (Reha Technologies; Olten, Switzerland) [22], HapticWalker [23], LokoHelp [24], or Lyra (Ability; Zurich, Switzerland) all work on the basis of an end-effector system reminiscent of an elliptical trainer: the subject's feet are strapped to two footplates moving along a gait-like trajectory. All these robotic devices offer training conditions supportive of the enhancement of neuroplastic changes in patients with acquired or congenital CNS-related gait impairment as intensity, repetition, task specificity, and engagement are met by these training options.

Within the last 15 years, the number of robotic therapy devices for upper and lower extremity rehabilitation has rapidly increased including devices where limbs are passively stabilized, fixed, assisted, or limited in their range of motion [25]. For walking training four major categories can be described:

- Tethered exoskeletons
- End-effector devices
- Untethered exoskeletons
- Patient-guided suspension systems

Due to space limitations, this chapter will focus only on the first two categories where more scientific data and clinical experience are available.

12.2 Normal Locomotion

It is important, from a clinical standpoint, to understand the events of the walking cycle so that pathological locomotion can then be correlated to the normal cycle.

Under normal conditions walking velocity for adult men is between 1.2 and 1.5 m/s, for adult women it ranges between 1.0 and 1.3 m/s, and for children between 0.8–1.0 m/s. Normal walking is

dependent on unrestricted joint mobility and the precise timing and intensity of muscle action. The result of abnormal biomechanics is reduced walking velocity and increased energy cost [26].

12.3 Robot-assisted Treadmill Training

One example for successful integration of technology into clinical application is robots designed for body weight-supported treadmill training. Mature human gait is a typical cyclical functional movement and locomotor training on a treadmill and supported by a harness has become a promising, task-oriented approach to restoring gait function. Clinical evidence studies indicate that positive therapeutic effects of robot-assisted training are obtained for patients with spinal cord injury (SCI) [27–34], subacute and even chronic hemiparesis [35–41], traumatic brain injury (TBI) [15, 42], and children with cerebral palsy (CP) [43]. Positive therapeutic effects have also been demonstrated in patients with progressive neurological diseases, such as multiple sclerosis (MS) [44–47] and Parkinson's disease (PD) [48–50]. A recent review of the literature that examined the effects of locomotor training with robotic assistance in patients following stroke, SCI, MS, TBI, and PD supports locomotor training with robotic assistance as a beneficial intervention for improving walking function in individuals following a stroke and SCI compared with other training techniques. Limited evidence was available to demonstrate that locomotor training with robotic assistance was beneficial in populations of patients with MS, TBI, or PD. Gait speed and endurance were not found to be significantly different among patients with motor incomplete SCI after various locomotor training approaches [51].

A single published prospective, randomized study in a population of subjects with TBI and gait dysfunction exists; subjects were treated with either robotic-assisted gait training (RAGT) using the Lokomat or manually assisted gait training. Improvement was reported in walking speed for both groups, but improvement of walking symmetry and joint motion was higher in the RAGT group [15].

As kinematic variability, active participation, and motivation and reward are important preconditions of motor learning, rehabilitation robots that constantly repeat a gait pattern as accurately as possible are considered not ideal, especially for patients that have a higher level of function [52]. In order to optimally support patients in their training progression and up to the point where they can safely and efficiently perform overground walking training, different strategies can be applied. Some robotic devices offer patient-moderated control strategies that allow kinematic variability and increase active participation of patients while still guaranteeing successful task execution [18, 53, 54]. Other devices allow training of additional tasks, for example, stair climbing/descent [22]. Patient's active participation can also be encouraged by providing feedback and instructions derived from precise measurements taken by the system [55–57]. 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 motor control toward a more functional gait pattern that will ultimately achieve overground walking. Furthermore combining robots with advanced virtual reality technologies seems to be a promising option for rehabilitation as it allows controlling and manipulating feedback parameters and leads to more challenging and engaging training situations that may increase participation [58–60].

12.4 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 [15, 22, 61–65].

The value and limits of different robot-assisted gait training interventions in comparison to conventional forms of locomotor training however are still under debate [52]. A number of studies aiming to directly compare efficacy of robot-assisted treadmill training with conventional gait therapy resulted in equivocal findings [15, 39, 52, 64, 66–69]. Some of these studies found advantages of robot-assisted treadmill training compared to man-

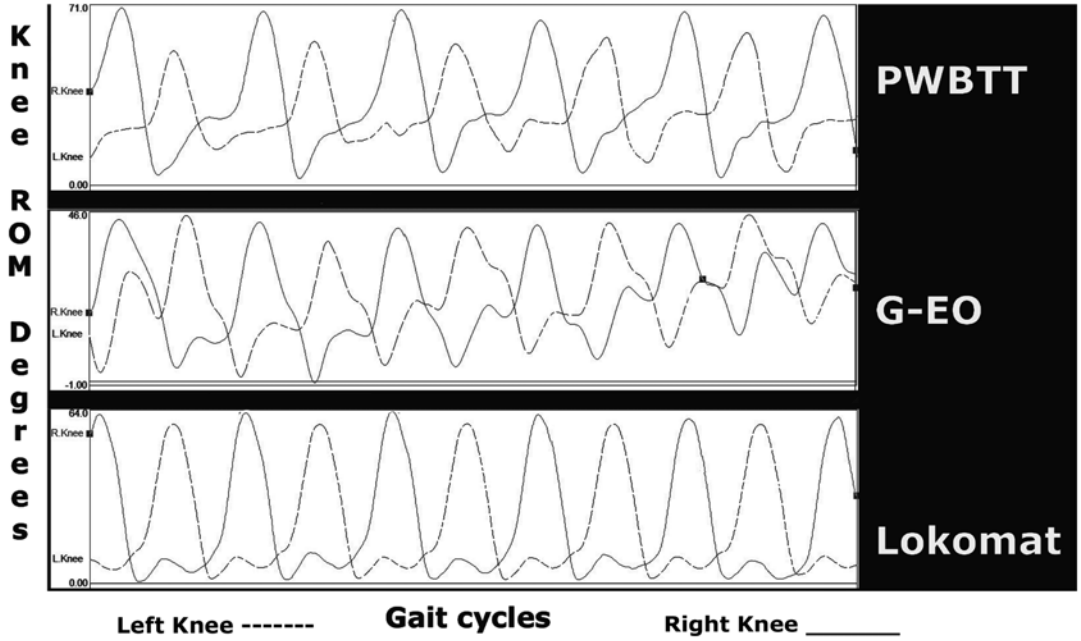

Fig. 12.3 Depiction of a representative data set looking at the knee kinematics in a 32-year-old man with left spastic hemiparesis walking using three different assistance systems in a consecutive fashion. Top manual PWBTT= partial weight-bearing treadmill training, G-EO is an end-effector device and Lokomat a fully robotic device (exoskeleton). *Hash line* = left, *continues line* = right data collected over several walking cycles [66]. Data recoded with CODA CX1 optoelectronic sensors

ual-assisted therapy [15, 39, 64, 67–69]; others found conventional therapy to be more effective [52, 66]. Between studies, considerable variability existed in the diagnosis, time of intervention in relation to the impairment onset, and functional impairment level of patients, ranging from nonambulatory [67–69] to ambulatory patients [52, 64, 66]. The application of robotic intervention was also variable in terms of number of training sessions, training duration, and control techniques implemented. Patients were either trained in the position-control mode where the robot maintains a predefined gait pattern [52] whereas other studies increased the challenge by adapting the parameters over training progression [15, 64, 66, 69].

Conventional training on the other side also varied between studies from stance and balance training with step initiation [68, 69] to manual-assisted treadmill training [15, 52, 64].

Few studies have attempted to directly compare the different robots in a comprehensive manner. At MossRehab, the clinical setup places a Lokomat and a G-EO next to each other. Taking advantage of this, researchers were able to set a 3D kinematic recording system and obtain sequential data from several patients with spinal cord and traumatic brain injury diagnosis using the two systems and comparing that to body weight-supported manual-assisted therapy on a treadmill. The data confirms a more controlled and repetitive gait pattern when using a Lokomat with gait pattern that is most similar to that of overground walking except for pelvic rotation. The G-EO provides a gait pattern that has more variability of motion for the hips and knees with slightly reduced knee motion, and the gait pattern differs slightly from that observed during overground walking. Finally the gait patterns achieved during manual-assisted treadmill body weight-supported therapy were most variable with lack of symmetry of movement and timing. See Fig. 12.3 for a representative data set looking at the knee kinematics in a 32-year-old man with left spastic hemiparesis. Solid lines represent

right, and dotted lines represent left knee over several walking cycles [70]. Data was recoded with CODA CX1 optoelectronic sensors.

The knee kinematic data for Lokomat is more symmetrical and with characteristics that more closely resemble overground normal walking. Recently a repeat data set collected using the newest version of the LokomatPro with FreeD that incorporates pelvic motion has demonstrated improvement in the pelvic rotation during walking training further normalizing the gait pattern.

12.5 Experience Versus Evidence

As the selection of specific training parameters can influence treatment outcomes [11, 39–41, 71, 72], 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 robotic-assisted training effects. Unfortunately, no objective basis for the proper selection of locomotor training parameters currently exists, and the rigid approach required for research does not follow the clinical needs of patients. However a growing number of clinicians and therapists already successfully integrate robotic devices into their clinical setting. Effective integration is dependent on the knowledge and understanding about a patient's level of functional impairment and pathology-specific symptoms related to the time after injury, potential for recovery, and selection of specific training goals that are adjusted over time. Furthermore, the clinician's knowledge about the usefulness and limits of different devices, as well as their ability to utilize the available technical features is crucial in order to optimally support, challenge, and motivate patients. This approach allows the patients to benefit from robot-aided gait training through the different stages of recovery to the point where they can safely and efficiently perform overground walking training.

In the following sections, we provide a brief review on a number of neurological pathologies with resulting functional gait impairments, their specific presentation over time, and the potential for functional improvements where assisted gait training (manual or robot) has been applied. We further provide insight into the training parameters and techniques used during robot-assisted gait training at different stages of the rehabilitation process. The recommendations provided are based both on available published research and clinical experience gained at multiple institutions where multiple robots are currently in use including Lokomat, LokomatPro, G-EO, ReWalk, and Tibion but may also serve to guide robot-assisted gait training with other devices of similar characteristics.

12.6 Pathology-Specific Motor Impairment and Training Goals Over Time

12.6.1 Stroke

Each year around the world, hundreds of thousands of people are affected by a stroke, which affects a person's cognitive, language, perceptual, sensory, and motor function [73]. Stroke causing an ischemic or hemorrhagic brain lesion frequently leads to hemiparesis with weakness, impaired coordination, and other movement disorders that persist in a large proportion of patients so that at 6 months, about half of the surviving patients remain disabled [74–76]. Stroke is the leading cause of long-term disability among adults in the United States, and hemiparesis is the most common impairment after stroke. Recovery is affected by the intensity of motor training and no specific rehabilitation program or therapy technique has so far stood out as being most effective [77]. The brain bears a potential for reorganization through plasticity that compensates for the loss of tissue in motor networks. This potential is enhanced by repetitive and active exercises, the intensity, complexity, and timing of which mainly determines their effectiveness. Intense training with high step repetition and 1 hour a day as part of a rehabilitation program is more effective than no training [78] (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 internal brain repair process that is use independent). Earlier training seems better than late [79] although in the chronic stages of stroke, physical therapy exercises in their widest definition clearly remain effective [80]. The time period in which training is most effective is debated.

Falls or the fear of falling is a noticeable problem of the stroke survivors and their care providers [81] and is further complicated by adverse effects of central acting medications frequently used to control blood pressure and manage spasticity [82, 83].

These problems reduce mobility and increase deconditioning and disuse. Therefore specific interventions that improve mobility and reduce the risk of falling are highly desirable.

Walking is one of the most important and desired activities for patients after stroke as it increases independence and expands their social environment. The primary objective of rehabilitation of gait deficits in this population is to advance their ability to achieve overground walking 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 to promote walking, to avoid learned nonuse of the correct gait pattern, as well as the appearance of more energy-consuming compensatory walking strategies. Motor input provided by the basal ganglia, midbrain, cerebellum, pons, and spinal cord may compensate for diminished motor commands from the cortex and help reestablish the ability for control of bipedal locomotion. In this phase the patient benefits from sensory information during walking, appropriate afferent input of muscle and joint receptors extending to the sole of the feet [84], and possibly rhythmic acoustic input. Treadmill training has proven effective on stroke survivor's mobility [85]. At the same time, there is data reporting no significant differences in walking improvement found between body weight-supported treadmill training (BWSTT), early locomotor training, and home exercise or between BWSTT in a chronic state and home exercise. Many participants had increased functional walking ability at 1 year post training [86].

Robotic gait training appears to be as effective but optimal training protocols are not fully developed [66, 87]. However, to participate in daily life activities, the patient also has to regain household walking abilities, which requires the capacity for multitasking (e.g., walking and scanning the environment, walking and holding something or someone, walking and talking, walking and adapting to environmental changes, etc.).

In later stages opportunities remain to overcome learned nonuse and enable the patient to improve overground walking ability in terms of speed, endurance, the quality and symmetry of gait pattern, and energy efficiency. By providing intensive and repetitive gait training, patients—even those with cognitive deficits—can practice and enhance existing but nonused movements and integrate them in their compensatory gait pattern. Providing a safe training environment enables patients to focus on specific components of their gait training and achieve further improvements.

Patients in the chronic stage after stroke that are nonambulatory however might never regain independent walking ability, and it is therefore important to appropriately set objectives, expectations, and treatment goals. Training goals should match the specific needs and capacities of patients and their caregivers. For this population, prevention of pain, stiffness, and contractures, as well as the regulation of muscle tone, is essential. Another goal is to increase muscle strength in order to stabilize the patient's head and trunk when upright or in an unsupported environment.

12.6.2 Traumatic Brain Injury

Brain injury especially after high velocity trauma often results in a combination of focal and diffuse axonal injury. This may include damage to the corticospinal tract and other critical structures of the central nervous system (CNS). The incidence of traumatic brain injury (TBI) has two peaks, one in the second and third decades and again after the seventh decade of life. In young

individuals, the majority of injuries are the result of trauma from motor vehicle accidents, sports injuries, and assault. Falls account for most of the injuries in the elderly. Men are far more likely to sustain traumatic brain injury with a male to female ratio of 2.4 to 1 [88].

A TBI can interfere with life roles and participation due to limitations in a diverse array of activities, including mobility, cognition, activities of daily living, and communication. The upper motoneuron syndrome (UMNS), with impairment of the patient's ability to produce and regulate voluntary movement due to corticospinal system damage, may be identified as a factor contributing to these deficits. Muscle weakness, impaired selective control, and the emergence of primitive locomotor patterns produce abnormal movement patterns, gait deviations, and compensations commonly seen in patients with TBI [89, 90]. These gait deviations alone or in combination disturb the normal spatiotemporal features of gait typically resulting in a decrease in walking velocity and in the symmetry of gait. For example, after a TBI, the ability to coordinate stance phase-related movements that invoke hip and knee extensor muscles and the ankle plantar flexors to provide stability is impaired. The inability to coordinate flexion and extension of the different lower limb joints appropriately interferes with the motion patterns that allow a smooth transition from swing to stance phases during walking [26]. Furthermore the presence of primitive motor patterns impairs the patient's ability to change the intensity of muscle action that occurs during the different phases of gait compromising the ability to lift and advance the limb during swing. In a prospective, randomized study in a population of subjects with TBI and gait dysfunction, improvement was demonstrated in walking velocity with either RAGT using the Lokomat or manually assisted gait training with greater improvement of walking symmetry and joint motion in the RAGT group [15]. Such an intervention appears to have positive results even in the chronic stage of recovery and had an additional long-term positive impact on the mobility portion of the stroke index scale (SIS) and self-esteem when measured at 6 months post intervention. Aging and osteoarthritis appear to aggravate many of the gait deficits in this population, and periodic gait-retraining interventions using RAGT or BWSTT may reduce the degree of disability and maintain walking capacity.

12.6.3 Spinal Cord Injury

The spinal cord can be compressed, severed, or distorted due to trauma. An accident with an SCI is associated with severe mechanical impact and a loss of the stability of the spine. Often additional injuries of the extremities and the thorax are present [91]. Nontraumatic causes for SCI include degenerative spine disease, tumors, vascular, or infectious processes. Advances in medical care for persons with SCI have resulted in increased rates of survival and a longer life span. Each year, there are approximately 11,000 new SCIs in the United States and approximately 200,000 individuals currently live with a disability related to an SCI in the United States [92].

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 mostly the legs. Based on the clinical examination of motor and sensory function, SCI can be classified using the International Standards for Neurological Classification of SCI (ISNCSCI) of the American Spinal Injury Association (ASIA) [93–96]. It ranges from "motor and sensory complete" (ASIA Impairment scale; AIS A) to a complete recovery of all symptoms (AIS E) (Table 12.1).

In addition there are six special forms of SCI clinical syndromes [97], of which two are important pertaining to the recovery of locomotor function: the central cord syndrome (CCS) and the Brown-Sequard syndrome (BSS) [98]. The CCS describes a lesion of the central matter of the cervical spinal cord. Commonly the arm and hand function are severely impaired whereas leg functions are less affected. The BSS describes a unilateral damage of the spinal cord followed by spinal hemiparesis. These presentations (CCS and the BSS) can be considered as a form of incomplete SCI.

Table 12.1 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 represent the lowest spinal segments of the spinal cord
Muscle grading 3 means active movement through full range of motion, against gravity

Spontaneous neurological recovery can be observed within the first 2 years after injury [91]. Extent of recovery is dependent on several factors including the severity of the lesion, overall health status, prevention of secondary complications, and rehabilitation interventions. Patients with a complete injury (AIS A) might recover function over one or two segments but remain paralyzed below the level of lesion [99, 100], 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 between 50 % for persons with AIS B to over 90 % for AIS D patients [91]. In general both, CCS and BBS also have favorable prognosis pertaining to walking function [97, 98]. In the beginning patients with an incomplete SCI, CCS, or BSS present severe loss of neurological functions which can recover and convert to a less severe ASIA impairment scale level over time [101].

Even though patients classified as having an incomplete injury have a good prognosis to recover walking function, they usually cannot stand or walk in the early stages due to the acute post-traumatic spinal shock with paralysis of the leg muscles. In the early stages of rehabilitation, patients are highly dependent on assistance for almost all of their activities. Routine assistance is provided by specialized nurses or therapists as well as mechanical devices, such as wheelchairs, braces, or other assistive devices including RAGT. The rehabilitation of walking function is designed in response to the patient's status in a manner that they are challenged by the exercises without being overtaxed. 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 and how to transfer safely in case this will be the most effective mode of mobility. With increasing recovery of lower extremity muscle strength and motor control, patients can start to walk without the assistance of a robotic device, either on a treadmill still using body weight support, in a rehabilitation pool, or over ground using a walking aid (e.g., parallel bars, crutches, or overhead support, etc.). At later stages in some patients, the goals may be focused on the development of higher levels of activities like walking on uneven surfaces, carrying objects while negotiating obstacles, and in some cases running, jumping, etc.

12.6.4 Multiple Sclerosis

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) with a variable clinical course (relapsing-remitting, secondary progressive, primary progressive), various pathological features (inflammation, demyelination, axonal loss, and degeneration), and clinical presentation pattern (hemiparesis, paraparesis, or tetraparesis). A major feature of patients with MS is gradual loss of function over time with pathological changes at different sites of the CNS leading to a broad range of symptomatic presentations, functional deficits, and disabilities. Different disease-specific pathophysiological disturbances may influence physical performance in patients with MS. Uhthoff's phenomenon (worsening 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 increase weakness in patients with MS [102, 103]. Together with changes of central recruitment, spasticity, co-contraction, and loss of dexterity, these specific phenomena result in longstanding physical deficits with functional implications frequently affecting gait in this patient population.

Gait disturbances in persons with MS are common and can affect up to 80 % in the long term, typically with a spastic-ataxic gait pattern. Walking impairments produce a negative impact on mobility for personal activities, social participation, and quality of life. Patients with walking disabilities are at high risk for secondary complications (especially falls, osteoporosis, deconditioning, and contractures), and the total costs of the disease management rise steeply after the loss of walking abilities. Therefore, maintaining or improving walking in this population is a key goal of their rehabilitation.

There is good evidence for the beneficial effect of physical training (physical therapy, resistance training, and aerobic training) on mobility in MS [104]. 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 along with spastic-ataxic gait limit the effective treatment duration and expected effects. Thus, reducing physical effort through the use of body weight support or RAGT may be particularly useful in patients with MS, avoiding motor fatigue and increasing treatment effect through a more efficient gait training. There is some evidence that BWSTT and RAGT reduce physical effort, and when provided with body weight support, it might be more beneficial than overground walking training particularly for patients with severe walking disabilities caused by MS.

12.6.5 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, TBI, SCI, stroke, intracranial hemorrhage, brain and spinal cord malignancies, and other degenerative diseases of the CNS (Fig. 12.4). The indication for treatment and the goal of rehabilitation arise from the individual functional impairments rather than from the diagnosis itself. RAGT offers an opportunity for early standing and gait training in patients with acute cerebral lesions. In these patients RAGT should include training for tolerance to positional changes and ideally combined with conventional physiotherapy, trunk stability, and transfer training. The possibility of achieving gait (with or without walking aids) is the main indication for this training. However, other indications should be considered such as the improvement of tone regulation, passive range of motion, alertness, or improving transfer function.

12.7 Recommendations Based on Best Clinical Practice for Robot-assisted Gait Training

12.7.1 Patient Selection

In general RAGT is suitable for both male and female patients. Similar to manual-assisted walking training with a harness and unloading system, special attention should be placed to proper fit of the harness, especially in the perineal area for male patients and for female patients with compression of the breast. Training can be done with patients of almost any age as long as a minimal leg length as well as body weight greater than 15 kg is present. It is preferred to utilize RAGT devices that have pediatric modules adjustable to the smaller anatomy. With aging, osteoporosis and degenerative joint disease need to be considered as a precaution. Patients with recent history of a lower extremity and pelvic fracture should be carefully assessed and medically cleared before training with robotic devices.

Fig. 12.4 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)

RAGT is particularly desirable for patients with more severe walking disabilities; however achieving a realistic goal of overground walking (with or without assistive devices) should be the focus of the rehabilitation process. Patients with acute and post-acute stroke benefit from high-frequency RAGT, which should complement overground gait training when possible. Patients with acute or chronic incomplete SCI (i.e., AIS C or D) benefit greatly from locomotor training movements. Training is also suitable for AIS B patients when assessed within 8 weeks after SCI as well as patients with MS with severe walking disabilities.

RAGT can be used, for example, in patients with limited walking distance of a few steps up to 100 m with and without walking aids with an Expanded Disability Status Scale (EDSS) score of 6.0–7.5. RAGT can also be applied to children with severe motor impairment as classified by the Gross Motor Function Classification System (GMFCS) level IV; however a recent study has shown that patients with GMFCS I–II benefit the most due to their ability to tolerate longer durations of training and greater walking distances [105]. Patients with TBI walking at velocities between 0.2 and 0.6 m/s appear to benefit the most from RAGT.

Even though the possibility of achieving gait (with or without walking aids) is considered the main indication for RAGT, patients with chronic presentation and higher severity with little potential of regaining independent walking ability may also benefit from gait-like repetitive movements. Training can focus on specific goals such as tone regulation, preservation of joint range of motion, and prevention of secondary complications. In adults and children, it offers an alternative therapy method after botulinum toxin, functional orthopedic, or neurosurgical interventions such as tendon lengthening or neurectomies or implantation of intrathecal medication delivery pumps in order to

promote training with newly found biomechanical constraints and help regain muscle strength and endurance. It is recommended that evaluation by a medical rehabilitation team be considered to address the expectations of patients and their caregivers as well as for medical clearance. Also, the time and effort of the therapeutic intervention in comparison to the expected outcome need to be considered carefully and discussed in an open manner before commencing training. In some complex or nonambulatory patients, an initial neurorehabilitation assessment followed by a robotic-assisted training trial may provide information about the feasibility and rationale for this kind of training. In general the indication for robot-assisted gait training should follow the individual goal setting (e.g., improvement of walking ability, mobility, tone regulation, etc.) and may also depend on the financial, social, and other available resources, as well as the organization of the local health system.

Training is suitable for patients in the acute, subacute, or chronic state. Patients with diagnosis of stroke and SCI can be trained very early after injury within a professional setting in the inpatient acute rehabilitation hospital setting. In patients with acquired brain injuries like TBI or stroke and SCI, an early mobilization and verticalization program is also very important to reduce orthostatic hypotension. It is of particular importance to consider the motivation of patients and the ability to use RAGT biofeedback, virtual environment, or gaming capabilities for this.

Besides the device-specific contraindications provided by the manufacturer, other factors that may be diagnostic specific should be taken into account before applying RAGT to patients. To be best suited for training, patients should be able to signal discomfort, enjoyment, fear, and exhaustion. In order to benefit most from training sessions, it is advantageous if patients are cognitively capable of interacting with the treatment staff and able to follow commands, participate, cooperate, and provide feedback during the training. Severe cognitive or psychiatric problems as well as incontinence might be relative contraindications to training with a robotic device.

Patients ideally should be able to be upright for at least 15–20 min without experiencing orthostatic hypotension to participate in RAGT. Training is strenuous and patients must tolerate the cardiopulmonary stress corresponding to exertion. Before each training session, the skin needs to be evaluated for pressure sores or irritation, especially around the area where the harness and the robot interface with the patient (i.e., the pelvis, groin, thigh, shin, and ankles). Pressure sores, as well as acute soft tissue irritation that interferes with harness support, robotic leg cuffs, the use of footwear, or weight bearing, preclude the training. In order to avoid friction and irritation due to fabric creases, it is recommended that the participant wears adequate clothing for the training including running tights, yoga pants or other long snug, tight-fitting athletic clothing. In our clinical experience, a careful fitting of the robotic device by a well-trained and experienced therapist is very important (Fig. 12.5). The time required for patient setup varies with each system and needs to be included in the schedule of the training session [105].

Fig. 12.5 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)

Reduced head control or trunk instability might lead to discontinuation of therapy. In cases of marked leg length asymmetry, correction using insoles or wedges is recommended when feasible, and in patients with asymmetries of more than 4 cm, training might be limited to specific types of robots. Training should also be carefully considered in patients with major lower limb orthopedic deformities, joint contractures, severe spasticity, or sustained clonus. After orthopedic or neurosurgical procedures (i.e., hip reconstructions, osteotomies, or soft tissue surgery, selective dorsal rhizotomy and other neurosurgical procedures), specific training protocols developed in closed cooperation with the surgical team may need to be implemented. At this time there is insufficient literature or clinical experience to support the use of RAGT in patients with progressive neuromuscular disorders such as Duchenne muscular dystrophy, amyotrophic lateral sclerosis, etc.

Passive range of motion of the hips, knees, and ankles must be sufficient to allow kinematics consistent with gait. Marked limitation in range of motion particularly of the knee and hip joints can interfere with the use of RAGT. Severe and fixed contractures of the lower extremities (greater than 20° knee extension and 30° hip extension deficits) interfere with a proper stance phase weight-bearing phase. Joint stability must be present to allow weight bearing.

Abnormal muscular tone expressed by spasticity, hypotonus, or dyskinetic movements needs to be considered carefully and individually before, during, and after the training [106] as they might require specific adjustments and training parameters initially as well as during subsequent training sessions (see below Sect. 12.7.2). Some tone is desirable and necessary to promote CNS plasticity for gait training. For patients with severe spasticity, systemic oral or intrathecal medications or botulinum toxin injections carefully adjusted to the patient's needs might be useful prior to training as long as undesirable weakness is avoided.

12.7.2 Training Initiation and Progression Over Time

12.7.2.1 Training Goals

The objective of the first robotic training session is to fit and familiarize the patients to RAGT. In some cases the challenge might be to reduce patients' hesitance or anxiety toward new technologies; in other patients it might be important to set appropriate treatment expectations. Therapists as well as patients can concentrate on the right setup and selection of adequate training parameters in order to optimize training. The goal is to establish a comfortable and natural walking pattern as permitted by the patient's symptoms and physical presentation. Within the course of therapy, the patient's motor function is likely to improve; accordingly, the training procedures and goals should be adjusted. Initially RAGT provides a safe environment where fear of falling can be reduced, enhancing the patient's ability and motivation to concentrate on specific gait training goals. On the other hand, walking is a cyclical stereotypical pattern that during training should be adapted in accordance with the patient's progress to increase variability of movements and reduce guidance. Today's robotic devices provide a number of possibilities for therapists 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 the use of different devices dependent on the patient goals, equipment technical features, training possibilities, and the introduction of overground gait training.

12.7.2.2 Number of Training Sessions

Early on in rehabilitation, gait training should be performed as often as possible ranging from two up to five training sessions a week, depending on the patient's diagnosis and characteristics, functional abilities, and training goals. Ideally RAGT should always be combined with other physical exercises like aerobic, resistance, and balance training and be applied in addition to therapeutic overground walking training as soon as feasible. In patients with chronic residual gait deficits

Table 12.2 Overview training parameters

	Stroke and MS	SCI	Children
Initial BWS		40–80 %	60 %
Minimal BWS	Limited by deterioration of kinematics	Limited by deterioration of kinematics	Limited by deterioration of kinematics
Initial speed	1.0–1.5 km/h	1.6–2.0 km/h	0.6–1.0 km/h
Target speed	1.5–2.5 km/h	2.5–3.2 km/h	0.8–1.8 km/h
Maximal speed	Limited by deterioration of kinematics	Limited by deterioration of kinematics	1.8 km/h
Initial GF	100 %	100 %	100 %
Minimal GF	Limited by deterioration of kinematics at high speed with low BWS	Limited by deterioration of kinematics at high speed with low BWS	50 %

BWS body weight support, *Km/h* kilometers per hour, *GF* guidance force, *SCI* spinal cord injury, *MS* multiple sclerosis

from acquired brain injury, longer-term training one to two times a week is suggested to maintain functional gains, or episodic more intense therapy can be implemented. This approach may also be beneficial in patients with CP, MS, and SCI in order to maintain walking abilities (see Table 12.2).

12.7.2.3 Setup and Training Duration

For the first training session, 60 min should be scheduled. Initial patient setup may take longer in order to define the proper adjustments of the harness as well as the robot. In severely affected patients with little trunk control, the harness should be adjusted while the patient is in a seated or laying position (Fig. 12.6). Careful adjustment and fitting of the harness as well as the exoskeleton should be done by a well-trained and experienced therapist to avoid complications and assure continued success. To maintain the patients' (in particular children's) cooperation, the phase of total unloading during device attachment should be kept rather short in order to avoid discomfort at the points of interface.

During the first training session, patients have to be carefully observed concerning clinical symptoms of blood pressure, cardiovascular instability, fatigue, exertion, or pain. It is recommended to keep the walking duration short during the first training session; adult patients should not walk longer than 20–30 min and children for 10–20 min. Patients with MS 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 assess the effects. Even if patients seem to tolerate the

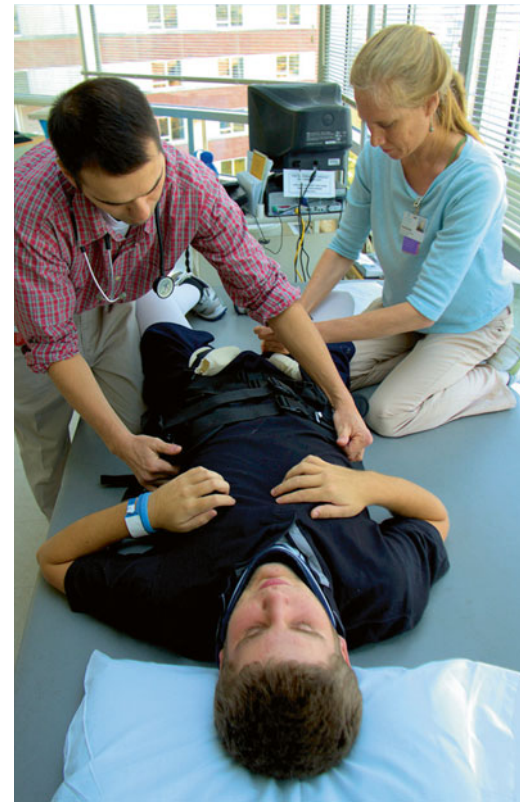

Fig. 12.6 In severely affected patients with little trunk control, the harness should be adjusted while the patient is in a laying position (Photo courtesy of Spaulding Rehabilitation Hospital, USA)

training very well, reactions such as pain and muscle soreness may appear later. Pressure marks due to friction from the harnesses and robot attachment cuffs might become obvious only later due to the reduced sensation in some 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 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 patients with MS up to 30 min and in children 20–45 min are the targeted training duration, but it might be shorter depending on fatigue or motivation. Training sessions should also contain a ramp-up period in order to allow for warm up and prevent over-exhaustion of soft tissue structures like joints or tendons. The last 2–3 min of each training session can be used as a cooldown period, where body weight support can be increased, thereby reducing the effort required from the patient. In general a training session of 60 min should be generally foreseen. In some facilities where multiple units may be available, staggering patients by 20 min within the hour will allow an efficient rehabilitation program where up to three patients can be trained simultaneously with less staff.

12.7.2.4 Body Weight Support

Studies in individuals with SCI have shown that locomotor EMG activity increases with increased loading through the legs [84, 107]. Body weight support should therefore be provided as much as necessary to create a safe and permissive environment and allow for appropriate kinematics but as little as possible to increase loading through the legs [108].

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 posture of the foot and/or knee during walking, which is often affected by paralysis or muscle overactivity. 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 stance phase 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 able to achieve good knee extension during stance; otherwise body weight support should be increased. Based on the literature and available clinical experience, the initial unloading will range from 40 to 80 % of the subject's weight. It might be better to initially provide the patient with 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 support their own body weight. Loading can be increased when proper knee extension during stance phase is evident. The ultimate goal for all patients should be to train with progressively greater weight bearing, eventually carrying their full body weight. Training therefore has to be adapted in accordance with the patient's ability of weight acceptance while keeping control of their movements during the training. Body weight support can be gradually reduced within and over training sessions according to the patient's tolerance. Therapists can use an increasing titration 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 adequate knee extension during stance phase is of great importance to avoid developing undesirable deviations.

12.7.2.5 Walking Speed

During the first training sessions, a slow walking velocity should be attempted approximately 0.6–1.0 km/h (0.2–0.4 m/s) in children, 1.0–1.5 km/h (0.3–0.5 m/s) for stroke and MS patients, and up to 1.6–2.0 km/h (0.4–0.6 m/s) in patients with SCI. Patients should have the opportunity and time to adjust to the new training paradigm and be

allowed to adapt their gait pattern to the new demands imposed by the robotic device and even concentrate on specific gait parameters. Once the patient starts to demonstrate improvements in confidence and comfort walking 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 (0.22–0.5 m/s) in children, 1.5–2.5 km/h (0.42–0.69 m/s) in stroke or MS, and 2.5–3.2 km/h (0.69–0.89 m/s) in SCI patients have been recommended. When patients are training at fast velocity and carrying at least 80 % of their body weight, the therapists should be closely observing the heart rate to ensure aerobic training conditions take place without adverse effects. High-functioning patients from the perspective of walking may be able to tolerate even higher training speeds, but it is important to remember that maximum walking speed is defined by three important parameters: leg length, gender and age, and the importance to maintain episodes of double support as not to resort to running. Another indicator for the correct walking speed might be specific symptoms, i.e., dystonia or marked spasticity. Ataxic patients with stable muscle function can be trained at fast speeds, whereas fatigue or hypertonus may indicate the need for slower gait training.

With an increase in speed, kinematic gait parameters change, and it is required to make the necessary adjustments to the robot controller, e.g., provide higher range of motion for hip extension and flexion or reduce the strapping of the robotic components to the patient in order to provide more range of motion in the hip joint. As variability of gait training is important in terms of motor learning, the therapist can change the speed within one training session. Other parameters that can be adjusted by the therapist include the step length in accordance with changes in speed and the implementation of dual-task training situations like reciprocal arm movements, using the handrails, counting backward, or pretending to kick a ball during walking. A comfortable walking speed, good loading during stance phase, and a harmonic gait pattern are important objectives of training. Undesirable changes in the gait pattern in response to velocity adjustments may reflect the patient's inability to tolerate such an increase in speed and be seen as a need to delay further adjustments.

12.7.2.6 Robotic Guidance

Within the first training session, robotic assistance or guidance (guidance force for Lokomat) should be kept high and not reduced before an individual is able to walk at a higher speed under minimal body weight support. Once the patient demonstrates improvement, the amount of guidance force should be progressively reduced in order to increase the training challenge. In patients diagnosed with MS, this can be the case after two to three training sessions. The amount of assistance or guidance force should be progressively reduced as long as the patient can maintain proper gait kinematics, clear the toes during swing phase, and adequately extend both knees during stance phase, but remains 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 with guidance force less than 50 % is not recommended before the patient can support themselves with minimal body weight support and walk at 0.5 m/s or greater.

12.7.2.7 Biofeedback

Some devices provide a biofeedback system with detailed information for patients and therapist about active participation within the gait cycle, for example, swing and stance phase or pressure applied through the different sections of the foot.

This allows the therapist to provide detailed training instructions in order to achieve specific goals whereas the patient receives immediate feedback on compliance with these instructions (Fig. 12.7). 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 objectives.

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 the therapist's evaluation of patient abilities. For patients with mild

Fig. 12.7 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)

functional impairments, biofeedback values might be a useful training tool, whereas in patients with impairments in alertness, the provision of biofeedback indicators may be too complex.

Due to limitations of alertness and perception in persons with severe brain injuries such as TBI and stroke, training of a single parameter, for example, swing or stance phase of one hip or knee joint, might be recommended in an attempt not to overwhelm the patient. These patients often need manual or verbal feedback in addition to the biofeedback values presented by the device. Depending on device type, the therapist may furthermore have to facilitate knee or foot positioning during walking to provide additional afferent feedback, for instance, support during knee extension or facilitation of plantar flexion in late mid-stance. If the training goal is to change an already established compensatory gait pattern, the patient requires clear instructions by the therapist on what gait parameters should specifically be addressed, for example, achieving proper knee extension or the 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 kept 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 undesirable muscle co-contractions. Increased spasticity might be observed if patients get overexcited or over-motivated during training, and in this case training without displaying biofeedback values might be required for a time.

In young children, patient adaptive control strategies and an adapted biofeedback system are of particular importance to assure maximum participation. 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. More recent versions of some of the robotic devices have included biofeedback through a virtual reality-based environment (Fig. 12.8). Interactive virtual realities like soccer games or other interventions are motivating, especially for young patients, and increase compliance and attention [58]. Children should remain attentive to verbal input provided by their therapist. In some facilities multiple robotic units are set next to each other allowing patients the opportunity to compare their performance and motivate each other.

12.7.3 Specific Training Goals

12.7.3.1 Achievement of Body Alignment and Trunk Control

In some patients, verbal feedback and manual facilitation or a passive support (e.g., neck brace,

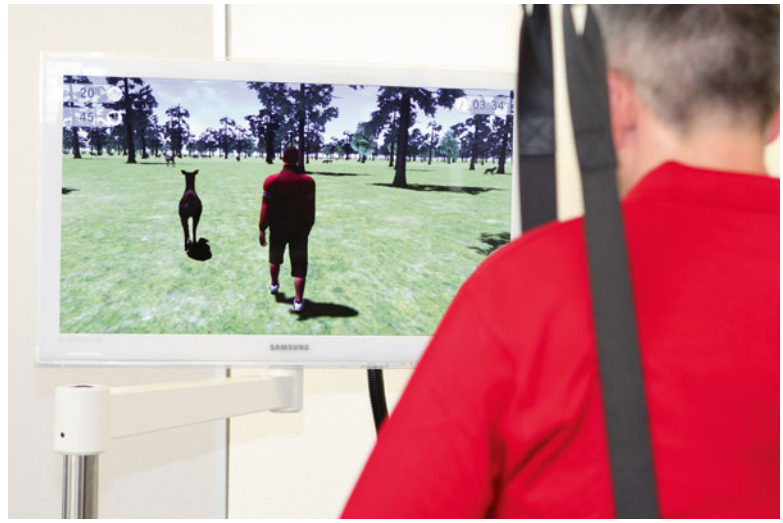

Fig. 12.8 Augmented feedback allows walking in a motivating and patient-friendly virtual reality-based environment and results in good compliance, increased attention, and high muscle activity

soft collar) might be required in order to keep trunk and head in an upright position with symmetric alignment. Some patients may benefit from visual feedback provided by a mirror placed in front of the device during walking training in order to promote self-correction of trunk and head posture. Different items positioned above eyesight, i.e., balloons, bells, or computer screens displaying biofeedback values or augmented feedback, may encourage patients to walk in an upright position.

One more challenge is to integrate paretic or hypertonic arms with correct alignment and motion. Therapists should adjust the arm supports of the device in order to position hands and arms. Special attention is required to support the weak shoulder to prevent subluxation and joint 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.

12.7.3.2 Decreasing Pathological Muscle Tone

Patients with high tone and spasticity affecting the legs may not be able to train in a robotic system as increased forces acting on the robotic drives can trigger the safety mechanisms that result in undesirable frequent stops of the machine, thereby interrupting the training procedure. In order to reduce high muscle tone, training can be started with minimal weight bearing reducing the afferent input and with limited joint range of motion and slow walking speed. Patients with spastic hemiparesis can start walking with a smaller joint range of motion in the affected leg. Once a patient is able to walk without the tone-related interruption and movements are fluid and appropriate, the therapist can increase the weight bearing. If the ankle/foot has clonus, then a heel lift or a brace that limits ankle motion can be used. In more severe cases, botulinum toxin or oral antispasticity agents can be introduced to the rehabilitation process. It is important to remember the potential presence of secondary rheological changes in muscle fiber, collagen tissue, capsule, and tendons resulting in contractures that interfere with functional movements and may need other interventions to restore motion [109, 110].

12.7.3.3 Increasing Range of Motion

Patients in the chronic state may suffer from limitations in the hip or knee joints' range of motion. To obtain a physiological gait pattern, one of the main rehabilitation goals is to increase the joint range of motion and its movement control. Increase in range of motion is achieved initially walking with short steps and slowly encouraging the achievement of a larger range of motion. However in patients with limited range of motion of the hip or in the lower spine and for persons

Fig. 12.9 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)

with SCI with spinal instrumentation, this can cause undesired pain or increase muscle tone. Special attention has to be paid to contractures and the presence of osteoporosis. When present an alternative intervention to regain the lost range should be explored. Optimizing joint range of motion allows an adequate step length and symmetrical gait with adequate stance-to-swing ratio.

12.7.3.4 Improving Ankle Control

Correct positioning of the foot is of special importance in order to obtain a physiological gait pattern and appropriate afferent feedback. The use of elastic foot lifters is strongly recommended in exoskeleton-based robotic devices without footplates or boots due to safety reasons, as sustaining active ankle dorsiflexion for a training session of 35–55 min will be difficult for most patients (Fig. 12.9). Depending on the functional abilities and ROM restrictions (i.e., hypo- or hypertonus, clonus), the foot can be properly adjusted with the foot lifters. Preliminary studies suggest that the muscular activity of ankle dorsiflexors is not affected when wearing foot lifters [111, 112]. As soon as the patient shows an increasing ability to control his/her ankle movements, the therapist can concentrate on further challenging ankle control by slowly and carefully loosening the straps. Walking with lower limb orthotics (e.g., ankle-foot orthoses) is also possible during robot-assisted training. Within a training session, the therapist has to continuously monitor if the orthosis is still needed; otherwise it may be removed. The therapist also has to be aware that this might require additional adaptations of foot lifters or cuffs. When shoes and non-articulated orthoses are used, body weight support, step length, and the amount of knee flexion have to be adjusted in order to permit a comfortable gait pattern.

When training with the use of an end-effector device, foot lifters are not used but the ankle range of motion can be adjusted to achieve the desired kinematic pattern. When using these devices, both articulated and non-articulated orthotics can be used as long as the device is adjusted appropriately and close monitoring of the skin is performed.

12.7.4 Integration into the Clinical Path

Robot-assisted gait training should be integrated as an additional treatment option in a comprehensive rehabilitation program with the specific goal

Fig. 12.10 The G-EO systems (Reha Technologies, Olten, Switzerland) allow training of additional tasks, for example, repetitive practice of stair climbing

to achieve overground walking. 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 verticalization for 20 min 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 participation in activities of daily life (e.g., transfers). In addition patient and therapist can train balance and weight shift from one leg to the other, important tasks for transition to walking. At later stages, technical features of specific devices can be used to keep training at a challenging level (Fig. 12.10) and train specific gait parameters, while integrating proper strength, weight bearing, balance, and gait training during individual therapy sessions. Therapists might decide to gradually integrate or progress from one robotic device to another, thereby offering more degrees of freedom in the hip and knee joints in order to further improve postural stability, strength, and balance. As soon as no further improvements can be observed, robot-assisted training can be discontinued and overground manual-assisted gait training implemented.

Robotic training can then be applied to reduce secondary complications or specifically train certain gait features. To appropriately support the patient at any functional stage, training should remain challenging and motivating and with a focus on training 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 prove their efficacy as well as recommendations of best practice has been increasing. A likely cause of limited gains demonstrated by the use of RAGT may be linked to the complexity of the patient population and its heterogeneous clinical presentation. Achieving significant clinical

relevant results will require large multicenter studies with standardized patient populations and training parameters. Some of these parameters can potentially be based on clinical experience collected over the last 8 years, which have led to a better understanding on how robots can successfully be integrated into clinical care. Robotic devices for gait 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 at an early stage focuses on a large number of repetitions in order to use the plastic potential of the injured CNS, thereby maximizing recovery and minimizing compensation [108], or development of limitation in joint range of motion. 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 change over time. In chronic conditions, robots can support therapist and patient in their 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 ensure a safe and efficient integration of robotic devices into the rehabilitation process, to the patients' benefit.

References

1. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? Neurorehabil Neural Repair. 2012;26(8):923–31.
2. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res. 2008;51(1):S225–39.
3. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci. 2009;10(12):861–72.
4. Dietz V. Neuronal plasticity after a human spinal cord injury: Positive and negative effects." Exp Neurol. 2011;235(1):110–115.
5. Edgerton VR, Tillakaratne NJ, Bigbee AJ, de Leon RD, Roy RR. Plasticity of the spinal neural circuitry after injury. Annu Rev Neurosci. 2004;27:145–67.
6. Maier IC, Schwab ME. Sprouting, regeneration and circuit formation in the injured spinal cord: factors and activity. Philos Trans R Soc Lond B Biol Sci. 2006;361(1473):1611–34.
7. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. Restor Neurol Neurosci. 2004;22(3–5):281–99.
8. Dromerick AW, Lum PS, Hidler J. Activity-based therapies. Neurorx. 2006;3(4):428–38.
9. Wahl AS, Omlor W, Rubio JC, Chen JL, Zheng H, Schroter A, et al. Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat corticospinal tract after stroke. Science. 2014;344(6189):1250–5.
10. Dietz V, Harkema SJ. Locomotor activity in spinal cord-injured persons. J Appl Physiol. 2004;96(5):1954–60.
11. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. Lancet. 1999;354(9174):191–6.
12. Edgerton VR, de Leon RD, Tillakaratne N, Recktenwald MR, Hodgson JA, Roy RR. Use-dependent plasticity in spinal stepping and standing. Adv Neurol. 1997;72:233–47.
13. Kahn LE, Lum PS, Rymer WZ, Reinkensmeyer DJ. Robot-assisted movement training for the stroke-impaired arm: does it matter what the robot does? J Rehabil Res Dev. 2006;43(5):619–30.
14. Reinkensmeyer DJ, Emken JL, Cramer SC. Robotics, motor learning, and neurologic recovery. Annu Rev Biomed Eng. 2004;6:497–525.
15. Esquenazi A, Lee S, Packel AT, Braitman L. A randomized comparative study of manually assisted versus robotic-assisted body weight supported treadmill training in persons with a traumatic brain injury. PMR. 2013;5(4):280–90.
16. Esquenazi A, Packel A. Robotic-assisted gait training and restoration. Am J Phys Med Rehabil. 2012;91(11 Suppl 3):S217–27; quiz S28–31.
17. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37(6):693–700.
18. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379–86.

19. Banala SK, Agrawal SK, Scholz JP, editors. Active Leg Exoskeleton (ALEX) for gait rehabilitation of motor-impaired patients. IEEE 10th international conference on rehabilitation robotics; 12–15 June 2007, Noordwjik, 2007.
20. Mantone J. Getting a leg up? Rehab patients get an assist from devices such as HealthSouth's AutoAmbulator, but the robots' clinical benefits are still in doubt. Mod Healthc. 2006;36(7):58–60.
21. Hesse S, Uhlenbrock D. A mechanized gait trainer for restoration of gait. J Rehabil Res Dev. 2000;37(6):701–8.
22. Hesse S, Waldner A, Tomelleri C. Innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients. J Neuroeng Rehabil. 2010;7:30.
23. Schmidt H, Hesse S, Bernhardt R, Krüger J. HapticWalker. A novel haptic foot device. ACM Trans Appl Percept. 2005;2(2):166–80.
24. Freivogel S, Mehrholz J, Husak-Sotomayor T, Schmalohr D. Gait training with the newly developed 'LokoHelp'-system is feasible for non-ambulatory patients after stroke, spinal cord and brain injury. A feasibility study. Brain Inj. 2008; 22(7–8):625–32.
25. Riener R. Robot-aided rehabilitation of neural function in the upper extremities. Acta Neurochir Suppl. 2007;97(Pt 1):465–71.
26. Esquenazi A, Talaty M. Gait analysis: technology and clinical application. In: Braddom RL, editor. Physical medicine and rehabilitation. 4th ed. Philadelphia: Saunders, Elsevier; 2011. p. 99–116.
27. Barbeau H, Ladouceur M, Norman KE, Pepin A, Leroux A. Walking after spinal cord injury: evaluation, treatment, and functional recovery. Arch Phys Med Rehabil. 1999;80(2):225–35.
28. Barbeau H, Rossignol S. Enhancement of locomotor recovery following spinal cord injury. Curr Opin Neurol. 1994;7(6):517–24.
29. Behrman AL, Harkema SJ. Locomotor training after human spinal cord injury: a series of case studies. Phys Ther. 2000;80(7):688–700.
30. Dietz V, Colombo G, Jensen L. Locomotor-activity in spinal man. Lancet. 1994;344(8932):1260–3.
31. Dietz V, Colombo G, Jensen L, Baumgartner L. Locomotor capacity of spinal cord in paraplegic patients. Ann Neurol. 1995;37(5):574–82.
32. Field-Fote EC. Spinal cord control of movement: implications for locomotor rehabilitation following spinal cord injury. Phys Ther. 2000;80(5):477–84.
33. Finch L, Barbeau H, Arsenault B. Influence of body weight support on normal human gait: development of a gait retraining strategy. Phys Ther. 1991; 71(11):842–55.
34. Wernig A, Müller S. Laufband locomotion with body-weight support improved walking in persons with severe spinal-cord injuries. Paraplegia. 1992; 30(4):229–38.
35. Teixeira da Cunha Filho I, Lim PAC, Qureshy H, Henson H, Monga T, Protas EJ. A comparison of regular rehabilitation and regular rehabilitation with supported treadmill ambulation training for acute stroke patients. J Rehabil Res Dev. 2001;38: 245–55.
36. JR Teixeira da Cunha I, Lim PA, Qureshy H, Henson H, Monga T, Protas EJ. Gait outcomes after acute stroke rehabilitation with supported treadmill ambulation training: a randomized controlled pilot study. Arch Phys Med Rehabil. 2002;83(9):1258–65.
37. Hesse S, Bertelt C, Jahnke MT, Schaffrin A, Baake P, Malezic M, et al. Treadmill training with partial body weight support compared with physiotherapy in nonambulatory hemiparetic patients. Stroke J Cereb Circ. 1995;26(6):976–81.
38. Laufer Y, Dickstein R, Chefez Y, Marcovitz E. The effect of treadmill training on the ambulation of stroke survivors in the early stages of rehabilitation: a randomized study. J Rehabil Res Dev. 2001; 38(1):69–78.
39. Pohl M, Mehrholz J, Ritschel C, Ruckriem S. Speed-dependent treadmill training in ambulatory hemiparetic stroke patients: a randomized controlled trial. Stroke J Cereb Circ. 2002;33(2):553–8.
40. Sullivan KJ, Knowlton BJ, Dobkin BH. Step training with body weight support: effect of treadmill speed and practice paradigms on poststroke locomotor recovery. Arch Phys Med Rehabil. 2002;83(5):683–91.
41. Visintin M, Barbeau H, Korner-Bitensky N, Mayo NE. A new approach to retrain gait in stroke patients through body weight support and treadmill stimulation. Stroke J Cereb Circ. 1998;29(6):1122–8.
42. Freund JE, Stetts DM. Use of trunk stabilization and locomotor training in an adult with cerebellar ataxia: a single system design. Physiother Theory Pract. 2010;26(7):447–58.
43. Willoughby KL, Dodd KJ, Shields N. A systematic review of the effectiveness of treadmill training for children with cerebral palsy. Disabil Rehabil. 2009;31(24):1971–9.
44. Benedetti MG, Gasparroni V, Stecchi S, Zilioli R, Straudi R, Piperno R. Treadmill exercise in early multiple sclerosis: a case series study. Eur J Phys Rehabil Med. 2009;45(1):53–9.
45. Giesser B, Beres-Jones J, Budovitch A, Herlihy E, Harkema S. Locomotor training using body weight support on a treadmill improves mobility in persons with multiple sclerosis: a pilot study. Mult Scler. 2007;13(2):224–31.
46. Newman MA, Dawes H, van den Berg M, Wade DT, Burridge J, Izadi H. Can aerobic treadmill training reduce the effort of walking and fatigue in people with multiple sclerosis: a pilot study. Mult Scler. 2007;13(1):113–9.
47. van den Berg M, Dawes H, Wade DT, Newman M, Burridge J, Izadi H, et al. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. J Neurol Neurosurg Psychiatry. 2006;77(4):531–3.
48. Miyai I, Fujimoto Y, Yamamoto H, Ueda Y, Saito T, Nozaki S, et al. Long-term effect of body weight-supported treadmill training in Parkinson's disease:

a randomized controlled trial. Arch Phys Med Rehabil. 2002;83(10):1370–3.
49. Miyai I, Fujimoto Y, Ueda Y, Yamamoto H, Nozaki S, Saito T, et al. Treadmill training with body weight support: its effect on Parkinson's disease. Arch Phys Med Rehabil. 2000;81(7):849–52.
50. Pohl M, Rockstroh G, Ruckriem S, Mrass G, Mehrholz J. Immediate effects of speed-dependent treadmill training on gait parameters in early Parkinson's disease. Arch Phys Med Rehabil. 2003;84(12):1760–6.
51. Tefertiller C, Pharo B, Evans N, Winchester P. Efficacy of rehabilitation robotics for walking training in neurological disorders: a review. J Rehabil Res Dev. 2011;48(4):387–416.
52. Hornby TG, Reinkensmeyer DJ, Chen D. Manually-assisted versus robotic-assisted body weight-supported treadmill training in spinal cord injury: what is the role of each? PM R. 2010;2(3):214–21.
53. Riener R, Lunenburger L, Jezernik S, Anderschitz M, Colombo G, Dietz V. Patient-cooperative strategies for robot-aided treadmill training: first experimental results. IEEE Trans Neural Syst Rehabil Eng. 2005;13(3):380–94.
54. Duschau-Wicke A, Caprez A, Riener R. Patient-cooperative control increases active participation of individuals with SCI during robot-aided gait training. J Neuroeng Rehabil. 2010;7:43.
55. Banz R, Bolliger M, Muller S, Santelli C, Riener R. A method of estimating the degree of active participation during stepping in a driven gait orthosis based on actuator force profile matching. IEEE Trans Neural Syst Rehabil Eng. 2009;17(1):15–22.
56. Lunenburger L, Colombo G, Riener R. Biofeedback for robotic gait rehabilitation. J Neuroeng Rehabil. 2007;4:1.
57. Lunenburger L, Colombo G, Riener R, Dietz V. Biofeedback in gait training with the robotic orthosis Lokomat. Conference proceedings of IEEE engineering in medicine and biology society. San Francisco, CA, USA; September 1st–5th 2004;7:4888–91
58. Brutsch K, Schuler T, Koenig A, Zimmerli L, Koeneke SM, Lunenburger L, et al. Influence of virtual reality soccer game on walking performance in robotic assisted gait training for children. J Neuroeng Rehabil. 2010;7:15.
59. Koenig A, Wellner M, Koneke S, Meyer-Heim A, Lunenburger L, Riener R. Virtual gait training for children with cerebral palsy using the Lokomat gait orthosis. Stud Health Technol Inform. 2008;132:204–9.
60. Lunenburger L, Wellner M, Banz R, Colombo G, Riener R. Combining immersive virtual environments with robot-aided gait training. 10th International Conference on Rehabilitation Robotics (ICORR), 13–15 June 2007, Noordwijk, 2007.
61. Borggraefe I, Meyer-Heim A, Kumar A, Schaefer JS, Berweck S, Heinen F. Improved gait parameters after robotic-assisted locomotor treadmill therapy in a 6-year-old child with cerebral palsy. Mov Disord. 2008;23(2):280–3.
62. Hesse S, Werner C, von Frankenberg S, Bardeleben A. Treadmill training with partial body weight support after stroke. Phys Med Rehabil Clin N Am. 2003;14(1 Suppl):S111–23.
63. Lo AC, Triche EW. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. Neurorehabil Neural Repair. 2008;22(6):661–71.
64. Westlake KP, Patten C. Pilot study of lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. J Neuroeng Rehabil. 2009;6(1):18.
65. Wirz M, Zemon DH, Rupp R, Scheel A, Colombo G, Dietz V, et al. Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil. 2005;86(4):672–80.
66. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5–13.
67. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke J Cereb Circ. 2007;38(2):349–54.
68. Mayr A, Kofler M, Quirbach E, Matzak H, Frohlich K, Saltuari L. Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair. 2007;21(4):307–14.
69. Schwartz I, Sajin A, Fisher I, Neeb M, Shochina M, Katz-Leurer M, et al. The effectiveness of locomotor therapy using robotic-assisted gait training in subacute stroke patients: a randomized controlled trial. PMR. 2009;1(6):516–23.
70. Esquenazi A. Kinematic differences during pathological walking with three rehabilitation interventions. International neurorehabilitation symposium, Zurich, 2013.
71. Kwakkel G, Kollen BJ, Wagenaar RC. Long term effects of intensity of upper and lower limb training after stroke: a randomised trial. J Neurol Neurosurg Psychiatry. 2002;72(4):473–9.
72. Sunderland A, Tinson DJ, Bradley EL, Fletcher D, Langton Hewer R, Wade DT. Enhanced physical therapy improves recovery of arm function after stroke. A randomised controlled trial. J Neurol Neurosurg Psychiatry. 1992;55(7):530–5.
73. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2–220.
74. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, et al. Long-term functional recovery after first ischemic stroke: the Northern Manhattan Study. Stroke J Cereb Circ. 2009;40(8):2805–11.

75. Johnston M, Pollard B, Morrison V, MacWalter R. Functional limitations and survival following stroke: psychological and clinical predictors of 3-year outcome. Int J Behav Med. 2004;11(4):187–96.
76. Jorgensen HS, Reith J, Nakayama H, Kammersgaard LP, Raaschou HO, Olsen TS. What determines good recovery in patients with the most severe strokes? The Copenhagen Stroke Study. Stroke J Cereb Circ. 1999;30(10):2008–12.
77. Kollen BJ, Lennon S, Lyons B, Wheatley-Smith L, Scheper M, Buurke JH, et al. The effectiveness of the Bobath concept in stroke rehabilitation: what is the evidence? Stroke J Cereb Circ. 2009;40(4):e89–97.
78. Pollock A, Baer G, Langhorne P, Pomeroy V. Physiotherapy treatment approaches for the recovery of postural control and lower limb function following stroke: a systematic review. Clin Rehabil. 2007;21(5):395–410.
79. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. Stroke J Cereb Circ. 2008;39(2):390–6.
80. Ferrarello F, Baccini M, Rinaldi LA, Cavallini MC, Mossello E, Masotti G, et al. Efficacy of physiotherapy interventions late after stroke: a meta-analysis. J Neurol Neurosurg Psychiatry. 2011;82(2):136–43.
81. Divani AA, Vazquez G, Barrett AM, Asadollahi M, Luft AR. Risk factors associated with injury attributable to falling among elderly population with history of stroke. Stroke J Cereb Circ. 2009;40(10):3286–92.
82. Esquenazi A. Falls and fractures in older post-stroke patients with spasticity: consequences and drug treatment considerations. Clin Geriatr. 2004;12(8):27–35.
83. Nichol MB, Shi SG, Knight TK, Esquenazi A, Barron R. Risk of hip or vertebral fracture in stroke survivors using antispasticity medications: a case-control study. J Outcome Res. 2006;10:1–11.
84. Dietz V, Muller R, Colombo G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. Brain. 2002;125(Pt 12):2626–34.
85. Globas C, Macko RF, Luft AR. Role of walking-exercise therapy after stroke. Expert Rev Cardiovasc Ther. 2009;7(8):905–10.
86. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, et al. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011;364(21):2026–36.
87. Forrester LW, Wheaton LA, Luft AR. Exercise-mediated locomotor recovery and lower-limb neuroplasticity after stroke. J Rehabil Res Dev. 2008;45(2):205–20.
88. Elovic E, Antoinette T. Epidemiology and primary prevention of traumatic brain injury. In: Horn LJ, Zasler ND, editors. Medical rehabilitation of traumatic brain injury. Philadelphia: Hanley & Belfus; 1996.
89. Williams G, Morris ME, Schache A, McCrory PR. Incidence of gait abnormalities after traumatic brain injury. Arch Phys Med Rehabil. 2009;90(4):587–93.
90. Perry J, Burnfield JM. Pathological mechanisms. In: Perry J, editor. Gait analysis: normal and pathological function; Thorofare, New Jersey, USA. 2010.
91. Consortium_for_Spinal_Cord_Medicine. Outcomes following traumatic spinal cord injury: clinical practice guidelines for health-care professionals. J Spinal Cord Med. 2000;23(4):289–316.
92. Model_Systems_Knowledge_Translation_Center. Spinal Cord Injury Factsheets [cited 2015 August]. Available from: http://www.msktc.org/sci/factsheets.
93. Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, et al. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med. 2011;34(6):535–46.
94. Kirshblum SC, Waring W, Biering-Sorensen F, Burns SP, Johansen M, Schmidt-Read M, et al. Reference for the 2011 revision of the international standards for neurological classification of spinal cord injury. J Spinal Cord Med. 2011;34(6):547–54.
95. Schuld C, Wiese J, Hug A, Putz C, Hedel HJ, Spiess MR, et al. Computer implementation of the international standards for neurological classification of spinal cord injury for consistent and efficient derivation of its subscores including handling of data from not testable segments. J Neurotrauma. 2011;29(3):453–61.
96. Furlan JC, Fehlings MG, Tator CH, Davis AM. Motor and sensory assessment of patients in clinical trials for pharmacological therapy of acute spinal cord injury: psychometric properties of the ASIA Standards. J Neurotrauma. 2008;25(11):1273–301.
97. McKinley W, Santos K, Meade M, Brooke K. Incidence and outcomes of spinal cord injury clinical syndromes. J Spinal Cord Med. 2007;30(3):215–24.
98. Wirz M, Zorner B, Rupp R, Dietz V. Outcome after incomplete spinal cord injury: central cord versus Brown-Sequard syndrome. Spinal Cord. 2009;48(5):407–14.
99. Steeves JD, Kramer JK, Fawcett JW, Cragg J, Lammertse DP, Blight AR, et al. Extent of spontaneous motor recovery after traumatic cervical sensorimotor complete spinal cord injury. Spinal Cord. 2011;49(2):257–65.
100. Wirz M, van Hedel HJ, Rupp R, Curt A, Dietz V. Muscle force and gait performance: relationships after spinal cord injury. Arch Phys Med Rehabil. 2006;87(9):1218–22.
101. Spiess MR, Muller RM, Rupp R, Schuld C, van Hedel HJ. Conversion in ASIA impairment scale during the first year after traumatic spinal cord injury. J Neurotrauma. 2009;26(11):2027–36.
102. Uhthoff W. Untersuchungen über die bei der multiplen Herdsklerose vorkommenden Augenstörungen. Arch Psychiatr Nervenkrankheiten Berlin. 1890;21:55–116 and 303–410.
103. Rae-Grant AD. Unusual symptoms and syndromes in multiple sclerosis. Continuum (Minneap Minn). 2013;19(4 Multiple Sclerosis):992–1006.

104. Doring A, Pfueller CF, Paul F, Dorr J. Exercise in multiple sclerosis—an integral component of disease management. EPMA J. 2011;3(1):2.
105. Borggraefe I, Schaefer JS, Klaiber M, Dabrowski E, Ammann-Reiffer C, Knecht B, et al. Robotic-assisted treadmill therapy improves walking and standing performance in children and adolescents with cerebral palsy. Eur J Paediatr Neurol. 2010;14(6):496–502.
106. Schmartz AC, Meyer-Heim AD, Muller R, Bolliger M. Measurement of muscle stiffness using robotic assisted gait orthosis in children with cerebral palsy: a proof of concept. Disabil Rehabil Assist Technol. 2011;6(1):29–37.
107. Visintin M, Barbeau H. The effects of body weight support on the locomotor pattern of spastic paretic patients. Can J Neurol Sci. 1989;16(3):315–25.
108. Harkema SJ, Behrman AL, Barbeau H. Locomotor training: principles and practice. 1st ed. New York: Oxford University Press; 2011.
109. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6(8):725–33.
110. Esquenazi A, Mayer NH. Instrumented assessment of muscle overactivity and spasticity with dynamic polyelectromyographic and motion analysis for treatment planning. Am J Phys Med Rehabil. 2004;83(10 Suppl):S19–29.
111. Schuler T, Brutsch K, Muller R, Hvan Hedel UJ, Meyer-Heim A. Virtual realities as motivational tools for robotic assisted gait training in children: a surface electromyography study. NeuroRehabilitation. 2011; 28(4):401–11.
112. Aurich Schuler T, Muller R, van Hedel HJ. Leg surface electromyography patterns in children with neuro-orthopedic disorders walking on a treadmill unassisted and assisted by a robot with and without encouragement. J Neuroeng Rehabil. 2013;10:78.

Standards and Safety Aspects for Medical Devices in the Field of Neurorehabilitation

13

Burkhard Zimmermann

Abstract

An overview of standards and safety aspects for medical devices in the field of neurorehabilitation is given as a snapshot in time. Common basic safety principles for medical devices and international applicable standards for medical devices, especially in the context of neurorehabilitation, are summarized. Trends and ongoing international activities in standardization and regulatory framework are described. This chapter could help start-up companies for medical devices or researchers which think about the commercialization of their results for a better understanding of the actual situation of Standards and Safety Aspects for Medical Devices in the Field of Neurorehabilitation and how these standards should be integrated in a process of medical devices development.

Keywords

First fault • Medical devices • Hazards • Risk • Regulatory • Safety aspects • Software requirements • Standards • Usability engineering • Risk management • Biocompatibility

13.1 Introduction

The requirements for technical appliances within neurorehabilitation in its various phases are as varied as the individual patterns of disease of patients affected in the medical discipline of neurorehabilitation. Furthermore the 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

B. Zimmermann (✉)
Department of Quality Management, Hocoma AG, Industriestrasse 4, 8604 Volketswil, Switzerland

IISART, Zürich, Zürich, Switzerland
e-mail: burkhard.zimmermann@hocoma.com; standards@iisartonline.org

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relearn the functions of extremities that have been completely or partially lost.

This whole chapter focuses on medical devices which are electrically powered. Definitions about medical devices have been proposed by different organizations and standards, unfortunately not always synonymously. Medical devices which transfer to or from the patient or detect such energy transfer to or from the patient are named "medical electrical equipment" or "medical electrical system" according to the IEC 60601–1 standard family.

At present, it does not matter whether these medical devices are simple or complex in structure or whether they offer active or passive support. The essential common ground—expressed very simply—is they support 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 and essential performances, which is a defined term in IEC 60601–1. However, the technical appliances being considered here are always in very close contact with patients, who differ from one another in many ways. A few factors are listed here, but they are not exhaustive:

- Age of the patients (from child to advanced old age)
- Low/medium serious impairment by, for example, the limited freedom of movement of 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 trained in the use of the devices
- From the application in special clinical situations such as intensive care and monitoring rooms up to application in the patient's home healthcare environment
- From early rehabilitation immediately following the occurrence of the neurological lesion to late or long-term rehabilitation

All these aspects should be noted at the conception and design phase of the medical devices. Since the therapy of the patient is at the forefront when utilizing technical appliances, we are dealing with medical devices which should be safe and effective. Only after that, the company can specify the following in a certified quality management system:

- The design of such products is safe and effective, taking into consideration the purpose and intended use: indications, contraindications, and essential performances based on the clinical functions of the medical device.
- The patient population.
- The surroundings of the application.
- The usability for the user and/or the patient.
- The product risk management and usability engineering.
- Clinical evaluation or trials.
- Software life cycle management.
- Biocompatibility where required.

The state of the art for the development of a medical device is based on a design process. Good development practices differentiate the whole process in different phases with milestones. It could be helpful to define for each milestone a checklist summarizing all aspects which should be fulfilled to pass from one phase to the next. From experience, it is very helpful to integrate also the necessary steps for fulfilling the applicable standards. In an early phase of development, the applicable standards should be defined. The risk management process should be started in parallel with the first steps of soft- and hardware development. As soon as applied parts and the material is defined, biocompatibility could start with first steps like material data analyses. First usability engineering topics could also start in parallel with the first drafts of the (graphic) user interface and/or available prototypes. This approach helps to start and finalize the evidence of applicable standard in accordance with the whole project management for devolving a medical device. It is obvious that final decision for the release of the new or changed medical device is based on the result of completed evidence of the applicable standards (and other aspects).

More detailed information about the controlling of the design of medical devices could be found in the FDA guidance document "Design Control Guidance For Medical Device Manufacturers."

All of these considerations must meet the cost demands of today's, nationally very varying, health system. Thus, not only investment and maintenance costs, 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.

Requirements on medical devices are regulated in national laws and regulations and are to be fulfilled 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. Medical device regulatory systems often classify "medical devices" on the basis of their risk potential in several classes.

At the same time, the concept of "medical devices" is defined in different ways on a national regulative level. One international organization, the International Medical Device Regulators Forum (IMDRF), former known as Global Harmonization Task Force (GHTF), which is aiming at a national legislative body, becomes increasingly important, when it is a question of "medical devices" and their regulations. The IMDRF (http://www.imdrf.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):
- 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 may be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach:
- 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 in achieving its intended purpose, should be subject to the same IMDRF 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 having a different classification for the accessory than for the "parent" device.

Note 4: Components to medical devices are generally controlled by 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 of the medical device 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. Also the term "manufacturer" is not defined in a coherent sense worldwide. Important to understand is the fact that the manufacturer is responsible not only for the design and manufacture process. Medical device registration and all the aspects of product life cycle and quality management processes are also his responsibilities.

Actual 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 the individual patient situation requires. For this purpose, sensory and associated control systems, which can control the essential ability to detect and adapt in a given situation, are necessary.

Such systems are also used outside medical devices area since several decades. Under the catchword "robots," there are very diverse products on the market, which have been in industrial use for a long time, but recently are also becoming established in the "service and personal care sector." All application sectors have their own standards and safety mechanisms, which will be briefly addressed in the following sections. The big difference between the industrial , service and person care robots and medical devices which are using robotic technologies is the involvement of patients. Only medical devices are treating patients with all their limitations.

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 for an optimized patient outcome.

Technical standards and safety packages do only insufficiently take into consideration some of the above-listed basic conditions in the conflicting priorities of cost-effective, highly effective, and safe "medical devices."

13.2 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/growth/single-market/european-standards/harmonised-standards/medical-devices/index_en.htm.

These harmonized standards could be used to show the evidence of MDD Annex I Essential Requirements.

Besides the Medical Device Directive, manufacturers should be aware that they should have to fulfill all applicable European directives. It should be mentioned that medical devices very often fulfill the definition of a "machine" which is given in the European Machinery Directive 2006/42/EC [2]. According to this directive, there is also a list of harmonized standards regularly published. It is the obligation of the manufacturer of medical devices to provide the evidence of applicable standards.

In the USA, the Food and Drug Administration (FDA; http://www.fda.gov/MedicalDevices) is responsible for regulation framework of medical devices.

Besides these official directives and regulations, it should be mentioned that there are a lot of other documents available to help and guide manufactures of medical devices but also the national regulators in the field of medical device technology.

Appendix I shows available guidance documents from IMDRF and GHTF; Appendix II shows published MEDDEV documents.

Additional standards may become relevant in order to provide evidence for fulfillment of certain requirements of the regulations, e.g., Annex I of MDD 93/42/EEC [1]. In particular, the product standards contain details for safety aspects, which can either be of a general or high specific nature. These coherences will be outlined roughly subsequently.

13.2.1 Standards for Medical Devices

International standards are published from different organizations. In the area of medical devices, the most important international organizations are IEC and ISO. Each of these organizations has national members, typically only one member per country. These members play an important role for the release of new or changed standards, for new work proposals and the global strategy of the whole umbrella organization. Both organizations are independent from each other. Both create standards in the area of medical devices; there is no clear borderline between their responsibilities. For all users of their standards, it is important that there are neither conflicts nor contrary requirements for the same topic. Both organizations try to take care about that. Nowadays, both organizations work together for projects in so-called joint working groups (JWG).

Types and scopes of standards for medical devices are described on high-level documents in ISO/IEC Guide 63 [3] and ISO/IEC Guide 51 [4]. According to these documents, international standards for medical devices can be classified into the following listed groups.

13.2.1.1 Product Standards

These standards are related to a specific product or group of products. These include:

- Standards that state safety or performance parameters and include reference test methods that can be used to demonstrate conformance to those parameters (e.g., IEC 60601–1 [5] and the associated supplementary standards and special specifications for medical electrical devices).
- IEC 60601–1 [5] Medical electrical equipment Part 1: "General requirements for basic safety and essential performance" is the key standard for all medical devices which are medical *electrical* equipment's or systems. In the IEC 60601–1 [5] series are other specific collateral standards included which have a specific focus like usability engineering for all medical *electrical* equipment's or systems. Details are shown in Sect. 13.2.2.
- In some cases international standard organizations write additional technical reports for specific standards to give the user of standards more background information and a guidance how to use a specific standard. Since several months IEC publishes their technical reports regarding the IEC 60601 series in the IEC 60601–4-"x" [6] format:
- Disclosure and test method standards where adherence to declare pass/fail criteria is necessary for safety and performance of medical devices

13.2.1.2 Process Standards

A series of types of standard falls in this category, including:

- Quality management system standards that establish a framework within which the manufacturer is able to design, develop, and produce medical devices that consistently meet specifications (e.g., standards for "good manufacturing practice" (GMP)). Quality management standards like ISO13485 [7] cover the whole life cycle for a medical device (ISO 9001 is normally not accepted as an adequate standard for medical device manufacturers). The design and development phase, production, and purchasing of parts; storage; transporting; servicing; document management; and other aspects are covered and should be followed. Where a registration procedure for medical device is required, normally the conformity to (national) quality management system standards (ISO 13485 [7]) is a part of the process.

- The ISO standards for quality management are currently (2014; Dec.) under revision. ISO 9001 changed in the meantime the whole structure and will include aspects from risk management. ISO 13485 [7] (new version was published in 2016) is not anymore following the structure from ISO 9001
- Standards for processes used for the design, development, or production of safe and effective medical devices (e.g., sterilization, biological evaluation, clinical investigation; sterility, biocompatibility, or risk management and usability engineering)

13.2.1.3 Installation and Environmental Standards

The standards for installation are generally applicable for medical devices which must be installed (putting into operation is not equal to installation). These can be:

- Construction and installation standards
- System standards (addresses the proper precautions and procedures for interconnection of multiple devices into a single system (medical electrical system))
- Commissioning standards (addresses the proper testing and inspection procedures applying to permanent installed equipment and systems prior to initial use)
- Environmental standards (addresses precautions and testing to ensure that a medical device does not negatively affect its environment and the environment does not degrade or otherwise impair the performance of a medical device (e.g., electromagnetic compatibility standards))

Parts of IEC 62353 [8] Medical electrical equipment—Recurrent test and test after repair of medical electrical equipment give specific advice which tests could be applicable after installation.

13.2.1.4 In-Process Standards

These can be:

- Routine in-service testing standards to ensure that the safety of medical devices is maintained over the useful life of the medical device
- Quality assurance and calibration standards to ensure the continued proper function and accuracy of medical devices, where relevant to safety

13.2.1.5 Safety Standards

Scopes of safety standards will ensure that each standard is restricted to specific aspects and makes reference to standards of wider application for all other relevant aspects. Such a hierarchy is built on:

- *Basic safety standards* include fundamental concepts, principles, and requirements with regard to general safety aspects, applicable to all kinds or a wide range of products, processes, and services (basic safety standards are sometimes referred as horizontal standards too). (Note: ISO uses the term "horizontal" in the same way like IEC the term "collateral.")
- *Group safety standards* include safety aspects, applicable to several or a family of similar products, processes, or services dealt with by two or more technical committees or subcommittees, making reference, as far as possible, to basic safety standards.
- *Product safety standards* include all necessary safety aspects of a specific or a family of product(s), process(es), or service(s) within the scope of a single technical committee or subcommittee, making reference, as far as possible, to basic safety standards and group safety standards (product safety standards are sometimes referred to as vertical standards).

13.2.2 Standards for Medical Electrical Devices for Neurorehabilitation

Each medical device in this category should fulfill the IEC 60601 standards series as product standard, and this is supplemented by the ISO 80601 standards, where applicable.

13.2.2.1 IEC 60601 Standards Series

The IEC 60601 standards series essentially defines safety requirements and essential performances for medical electrical devices and medical electrical systems.

IEC 60601–1 [5] covers the basic safety and the essential performance characteristics of medical electrical devices and medical electrical systems. For the user of this standard, it is important to know which version is accepted and in which country. The last published version is IEC 60601–1 Edition 3 with amendment 1 from 2012 to 2008 (IEC 60601–1:2005+A1:2012) [5]. A couple of countries still require and accept only the previous edition; other countries have a longer transitory period for the new one. In addition to this situation, the user of standards should be aware of national deviations which are quite normal. In the second half of 2016 IEC TC 62 will decide if an amendment A2 of IEC 60601-1 should be created. The second approach would be to go directly to work on a fourth edition of IEC 60601-1.

This standard is accompanied by a series of further requirements of a general nature (coded as IEC 60601–*1-x* and named collateral standards) as well as by requirements for certain types of specific medical devices (coded as IEC 60601–*2-x* and *ISO 80601–2-x*) and named particular standards.

Standards from the IEC 60601–*2-x* (series), which could related directly and partiually to the subject of medical devices in neurorehabilitation should be carefully evaluated. Standards that could be used (in part) are, for example:

- Medical electrical equipment—Part 2–10: Particular requirements for the safety of nerve and muscle stimulators
- Amendment 1, Medical electrical equipment—Part 2–10: Particular requirements for the safety of nerve and muscle stimulators

Appendix III offers an overview of the currently published IEC 60601–1-*x* standards among other standards from IEC SC 62 A and SC D which are the relevant subgroups for this topic contain basic requirements for all medical devices, provided they are electrically operated and used for all cases described.

All standards from the IEC 60601 family are dealing with basic safety and essential performance. Therefore, it is important to understand the meaning of these defined terms in IEC 60601–1 [5]:

- Basic safety is a defined term: "freedom from unacceptable risk directly caused by physical hazards when medical electrical equipment is used under normal conditions and single fault condition." More details are given in Sects. 13.2.4 and 13.2.5.
- Essential performance is a defined term: "performance of a clinical function, other than that related to basic safety, where loss or degradation beyond the limits specified by the manufacturer results in an unacceptable risk." NOTE essential performance is most easily understood by considering whether its absence or degradation would result in an unacceptable RISK.

Medical electrical equipment or a medical electrical system that does not perform properly could result in unacceptable risk for patients, operators, or others. In order to achieve its intended use, medical electrical equipment or the medical electrical system needs to perform within certain limits. These limits are usually specified by the manufacturer, collateral or particular standards of the IEC 60601 series.

Examples of essential performance from medical devices are:

- Correct administration of a drug by a syringe pump where inaccuracy/incorrect administration would cause an unacceptable risk to the patient
- The ability of an electrocardiograph/monitor to recover from the effects of the discharge of a defibrillator where the failure to recover could lead to an incorrect response by the medical staff that would present an unacceptable risk to the patient
- Correct operation of an alarm system in an intensive care or operating room monitoring system where an incorrect/missing alarm signal could lead to an incorrect response by the medical staff that would present an unacceptable risk to the patient

- Correct output of diagnostic information from medical electrical equipment that is likely to be relied upon to determine treatment, where incorrect information could lead to an inappropriate treatment that would present an unacceptable risk to the patient

For purposes of IEC 60601 standards, performance related to basic safety aspects of the medical electrical equipment, such as the performance of basic insulation, is not considered to be essential performances.

Committee unpublished draft version of IEC 60601–4-1 [6] gives a little bit more explanation regarding essential performance:

> All medical electrical equipment must perform as per their intended use. It must be noted essential performances are not related to all the performance of the ME Equipment. Not all these performances can be called essential! Essential performances are related to the clinical functions that must be preserved in normal condition and in single fault condition. If the risk of degradation of performances is found to be unacceptable, then they will be considered as essential performances. For a more complete understanding of what essential performances means, the reader should read clause 4.3 and the sub-clause (informative rational section) of the IEC 60601–1: [5]

During risk analysis, the manufacturer shall identify the performance of the clinical function(s) of the medical electrical equipment or medical electrical system, other than that related to basic safety, that is necessary to achieve its intended use or that could affect the safety of the medical electrical equipment or medical electrical system.

The manufacturer shall then specify performance limits between fully functional and total loss of the identified performance in both normal conditions and single fault conditions.

The manufacturer shall then evaluate the risk from the loss or degradation of the identified performance beyond the limits specified by the manufacturer. If the resulting risk is unacceptable, then the identified performance constitutes an essential performance of the medical electrical equipment or medical electrical system.

The manufacturer shall implement risk-control measures to reduce the risk from the loss or degradation of the identified performance to an acceptable level.

If a manufacturer of a medical device claimed to have no essential performances, the result of risk management process according to ISO 14971 [9] should show evidence.

Unfortunately, the term clinical function is not defined in the standards at the moment; therefore, each manufacturer defines the clinical functions for its specific medical devices individually, during risk management process to identify the essential performance of the specific medical devices.

Essential performances generally relate to medical device operating as intended without creating an unacceptable risk. A failure of essential performance can be either a lack of performance (such as life-supporting performance) or incorrect performance (such as delivering an incorrect dose to the patient).

Summary Essential performance is based on a risk management process related to performance of clinical functions.

Applicable product standards for medical devices 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 or as mentioned above in the area of machines. International standards about treadmills, stationary training equipment, or body weight support systems, for example, can be used additionally if medical device standards are not available in a specify area.

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.

13.2.2.2 Quality Management System Standards

Quality management system standards are ranked among the process standards. ISO 13485 [7] Medical Devices Quality Management System

for International Applications should normally be fulfilled. For the American market, the Food and Drug Administration (FDA) regulations according to 21 CFR § 820 aspects from "good manufacturing praxis" (GMP) are mandatory. Here, it should be noted that the requirements from FDA are not standards but regulations having a legislative character.

13.2.2.3 Programmable Electrical Medical Systems

For medical devices that are categorized as PEMS (programmable electrical medical systems), apart from the requirements which IEC 60601–1 sets, those of IEC 62304 [10] concerning the life cycle requirements for medical device software must also be complied with.

This standard defines the life cycle requirements for medical device software. The set of processes, activities, and tasks described in this standard establishes a common framework for medical device software life cycle processes. This standard applies to the development and maintenance of processes.

This standard applies to the development and maintenance of processes when software is itself a medical device or when software is an embedded or integral part of the final medical device. This standard does not cover validation and final release of the medical device, even when the medical device consists entirely of software.

13.2.2.4 Biocompatibility

For medical devices intended to have direct or indirect contact with biological tissues, cells, or body fluids, manufactures should proceed according to the instructions and principles of the ISO 10993 standard family, in order to verify the biocompatibility of the materials utilized, where this is necessary.

ISO 10993 series is a risk management-based approach. ISO 10993–1 [11] gives an overview and explanation which additional standards of the whole series are applicable, based on the intended use of the medical device and nature and duration of body contacting material, either direct or indirect.

ISO 10993 series does not cover testing of materials and devices which do not come into direct or indirect contact with the patient's body nor does it cover biological hazards arising from any mechanical failure.

13.2.2.5 Usability Engineering

Usability engineering requirements which are given in IEC 60601–1-6 (Appendix I) standard and the IEC 62366 [12] standard "Application of Usability Engineering to Medical Devices" should be consulted.

The reason why usability is important is explained in the standard:

> Medical practice is increasingly using medical devices for observation and treatment of patients. Use errors caused by inadequate medical device usability have become an increasing cause for concern. Many of the medical devices developed without applying a usability engineering process are non-intuitive, difficult to learn and to use. As healthcare evolves, less skilled users including patients themselves are now using medical devices and medical devices are becoming more complicated. In simpler times, the user of medical device might be able to cope with an ambiguous, difficult-to-use user interface. The design of a usable medical device is a challenging endeavor, yet many organizations treat it as if it were just "common sense". The design of the user interface to achieve adequate (safe) usability requires a very different skill set than that of the technical implementation of the interface.
>
> The usability engineering process is intended to achieve reasonable usability, which in turn is intended to minimize use errors and to minimize use-associated risks. Some, but not all, forms of incorrect use are amenable to control by the manufacturer.

Figure 13.1 shows the relationship between the risk management process according ISO 14971 [9] and the usability engineering process according IEC 62366–1 [12].

13.2.2.6 Recurrent Test and Test After Repair

Concerning construction and environmental standards, the standards IEC 62353 [8] for periodic tests should be considered.

This international standard applies to testing of medical electrical equipment and medical electrical system before putting into service;

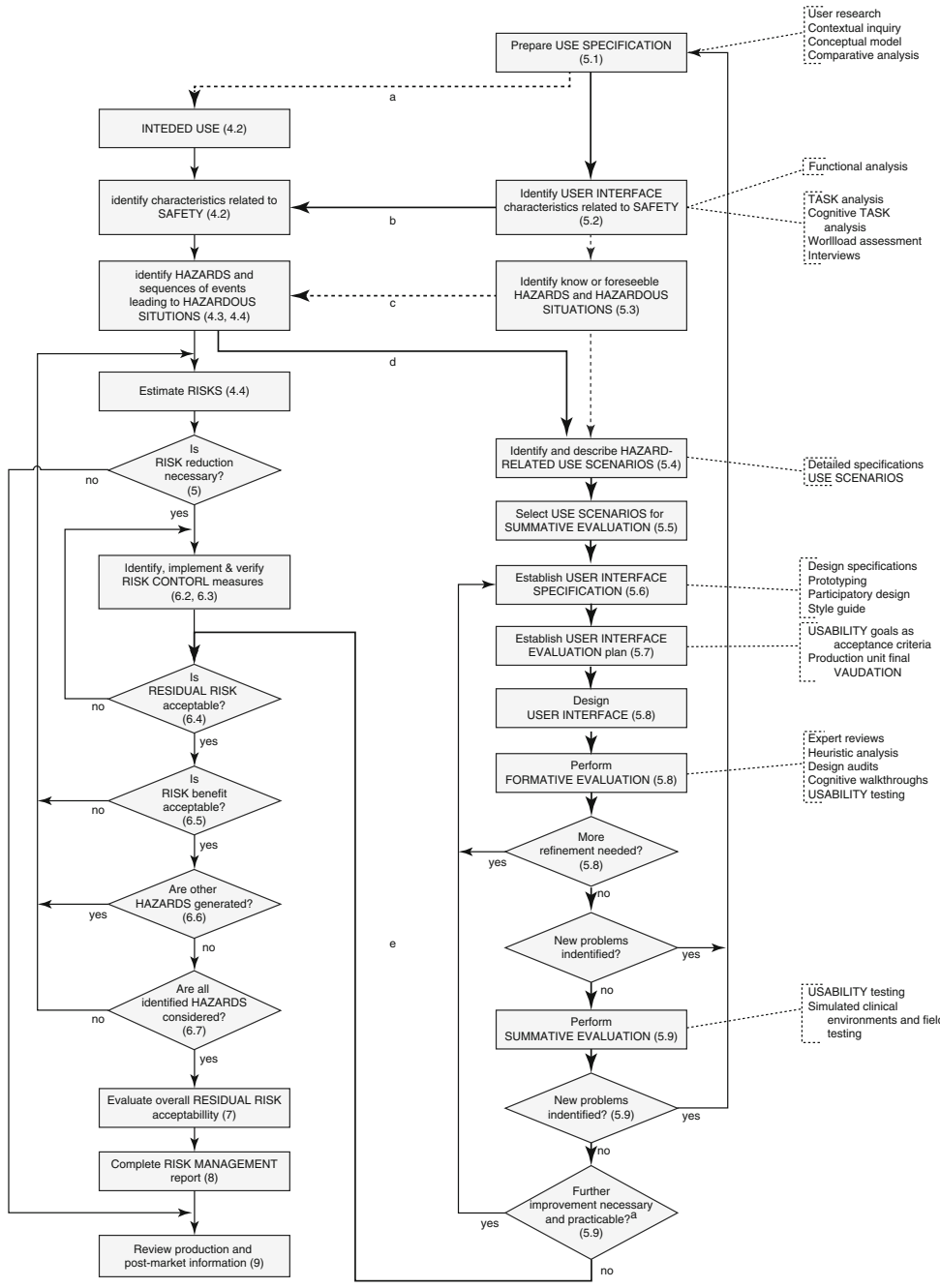

Fig. 13.1 The relationship between the risk management process (ISO 14971) and the usability engineering process (IEC 62366–1). (**a**–**e**) Represent information flow between the two processes. The heavy *solid lines* (**b**, **d**, **e**) represent information flow required by usability engineering process. If new problems are identified these should be interpreted to mean new hazards, hazardous situations, or hazard-related use scenarios discovered or implemented risk control is ineffective. Key: (**a**) Use Specification is an input to ISO 14971:4.2; (**b**) identified user interface characteristics related to safety (see 5.2); (**c**) identified foreseeable HAZARD and HAZARDOUS SITUATIONS (see 5.3); (**d**) identified sequences of events leading to HAZARDOUS SITUATIONS from ISO 14971:2007, 4.4, are an input to determining HAZARD-RELATED USE SCENARIOS (see 5.4); (**e**) evaluate RESIDUAL RISK. IEC 62366-1 ed. 1.0 (Copyright© 2015 IEC Geneva, Switzerland. www.iec.ch; used with permission)

during maintenance, inspection, and servicing; and after repair or on occasion of recurrent tests to assess the safety of such medical electrical equipment or medical electrical system or parts thereof.

This standard contains tables with allowable values relating to different editions of IEC 60601–1 [5]. For the purpose of this standard, the application of measuring methods is independent of the edition, according to which the medical electrical equipment or medical electrical system is designed.

This standard contains:

- "General requirements," which contain clauses of general concern.
- "Particular requirements," further clauses handling special types of medical electrical equipment or medical electrical systems and applying in connection with the "general requirements."
- This standard is also applicable to tests after repair [8].

This standard is not applicable to the assembly medical electrical system. For assembling medical electrical system, see Clause 16 of IEC 60601–1 [5]. IEC 62353 [8] does not define requirements for repair, exchange of components, and modification of medical electrical equipment or medical electrical system.

13.2.2.7 Electromagnetic Disturbances

IEC 60601–1–2 [13] concerning electromagnetic compatibility, in particular, are to be included, which are to be taken into account for the case under consideration. IEC 61000 series gives much more details about the whole topic of electromagnetic compatibility (EMC).

13.2.2.8 Home Healthcare Environment

Medical devices which are designed for usage at patients home should also fulfill the IEC 60601–1-11 [14] "Medical electrical equipment—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."

The definition of home healthcare environment is given as:

> dwelling place in which a patient lives or other places where patients are present, excluding professional healthcare facility environments, where operators with medical training are continually available, when patients are present.
> **NOTE 1** Professional healthcare facilities include hospitals, physician offices, freestanding surgical centers, dental offices, freestanding birthing centers, limited care facilities, multiple treatment facilities and emergency medical services.

According to that standard, the manufacturer decides if a medical device is intended to be used in the home healthcare environment.

13.2.3 Future Standards for Medical Electrical Devices for Neurorehabilitation

It should be mentioned that, recently, the ISO (International Organization for Standardization) has addressed the subject of "medical robots" within ISO/TC 299/JWG 05 "Joint ISO/TC 299 - IEC/SC 62A—IEC/SC 62D; Medical robot safety" Functions and started deliberations about creating together with IEC TC 62A a technical report "IEC/TR 60601–4-1 [6]: Medical electrical equipment—Part 4–1: Guidance and interpretation—Medical electrical equipment and medical electrical systems employing a degree of autonomy." Such medical devices with a degree of autonomy are already used in neurorehabilitation, and these medical devices will be affected by such a technical report.

Also under the lead of IEC, new relevant standardization activities (since 2015, March) are in the pipeline. A first standardization project about rehabilitation robots which could be applicable for medical devices in the area of neurorehabilitation will be created under the roof IEC SC62 D. The draft title is "Particular requirements for the basic safety and essential performance of medical robots for rehabilitation, compensation or alleviation of disease, injury or disability."

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.

On the other side, 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 medical devices. Something between medical application and industrial use are robots, which are so-called service robots; they are intended to fulfill their purpose in the environment of humans, but not as medical devices. Nevertheless, standards from the responsible ISO TC 299 WG2 (personal care robot safety subcommittee could be helpful to understand safety principles.

13.2.4 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 basic or first failure safety, what is a hazard, and what is accepted for a specific medical device? 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." ISO/IEC documents explain some terms which are essential for further understanding of safety aspects.

> basic safety (IEC 60601–1; [5])
> Freedom from unacceptable risk directly caused by physical hazards, when medical electrical equipment is used under normal condition and single fault condition.

Additional explanations given in Annex A of IEC 60601–1 [5]:

> Basic safety relates to a device not resulting in harm incidental to its operation. Basic safety is often a passive form of protection (such as radiation shielding or electrical grounding).

Essential performances generally relate to medical electrical equipment or medical electrical system operating as intended without creating a hazards. A failure of essential performances can be either a lack of performance (such as life-supporting performance) or incorrect performance (such as delivering an incorrect dose to the patient).

In general, basic safety relates to product properties that are not device specific, and essential performances relate to a class of products (such as a defibrillators being able to deliver the correct electrical shock).

While the terms basic safety and essential performances are generally considered to be mutually exclusive, there are some hazards directly caused by physical hazards, when medical electrical equipment is used under normal condition and single fault conditions:

- *Harm* [4]: "injury or damage to the health of people or damage to property or the environment"
- *Hazard* [4]: "potential source of harm"
- *Hazardous Situation* [4]: "circumstance in which people, property or the environment is/are exposed to one or more hazards"
- *Inherently Safe Design* [4]: "measures taken to eliminate hazards and/or to reduce risks by changing the design or operating characteristics of the product or system"
- *Intended Use* [4]: "use in accordance with information provided with a product or system, or, in the absence of such information, by generally understood patterns of usage"
- *Patient* [4]: "living being (person or animal) undergoing a medical, surgical, or dental procedure"
  - NOTE: A PATIENT can be an OPERATOR.
  - Additional NOTE from the author: An elderly person is not a patient. Age is not a disease, injury, or disability.
- *Residual Risk* [4]: "risk remaining after risk reduction measures have been implemented"
- *Risk* [4]: "combination of the probability of occurrence of harm and the severity of that harm"
- *Safety* [4]: "freedom from risk which is not tolerable"

The term "safe" is often understood by the general public as the state of being protected

from all hazards. However, this is a misunderstanding; "safe" is rather the state of being protected from recognized hazards that are likely to cause harm. Some level of risk is inherent in products or systems.

Note: these defined terms of ISO/IEC Guide 53 [4] and IEC 60601–1 [5] are not used in all standards for medical devises in the absolutely same way. The same term could be defined in different ways from one standard to the next.

The risk associated with a particular hazardous situation depends on the elements shown in Fig. 13.2.

Besides the (fundamental) requirements for safety of a medical device, nearly 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. These should be considered during the risk management process to identify the clinical functions of a specific medical device. Similarly, the medical device should render the specified services in the form of defined physical properties, 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 health 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 the patient, user, and third parties that can lead to a life-threatening situation or even death in case of the wrong indication.

It becomes 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 (see Sect. 13.3.2).

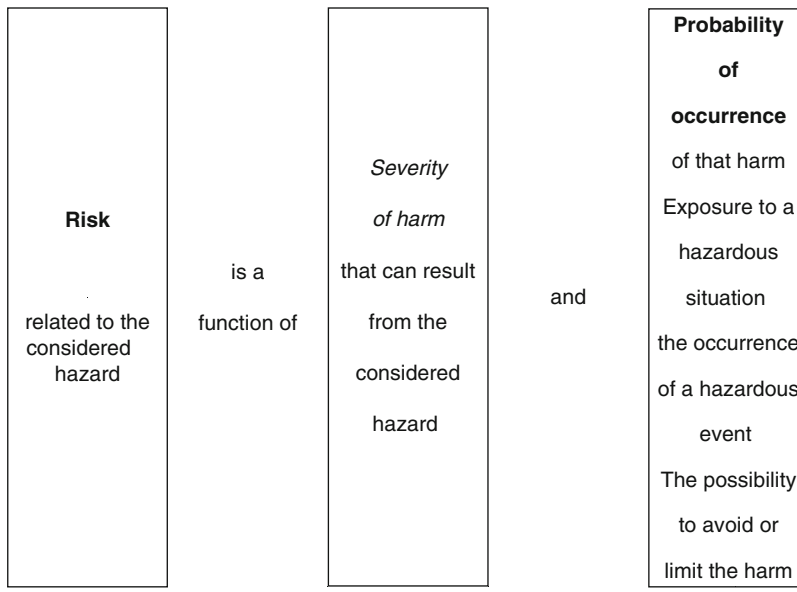

Fig. 13.2 Relationship between risk and a particular hazardous situation

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.

All medical devices must perform as per their intended use. It must be noted that essential performances are not related to all the performance of the medical device. Not all these performances can be called essential! Essential performance is related to the clinical functions that must be preserved in normal condition and in single fault condition. If the risk of degradation of performances is found to be unacceptable then they will be considered as essential performances. Essential performances generally relates to medical devices operating as intended without creating an unacceptable risk. A failure of essential performances can be either a lack of performance (such as life-supporting performance) or incorrect performance (such as delivering an incorrect dose to the patient).

It has long been recognized that medical electrical equipment or a medical electrical system that does not perform properly could result in unacceptable risk for patients, operators (users), and others.

Summary Essential performance is based on a risk management process related to performance of clinical functions.

Tests that could applied 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 rank, being conscious of the benefits that results, taking the costs of any further reduction of risk into account.

Risks must be reduced to a level as low as reasonably practicable (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.

Since complex medical electrical systems or equipment cannot be exhaustively assessed by tests, their correctness (functionality) and reliability must be assessed in other ways. IEC 62304 requires that the manufacturer shall develop and document an architecture for the interfaces between the software items and the components external to the software items (both software and hardware), and between the software items. Different risk classes (A – C) gives a much more clear view which software items are essential to risk control and the standard give advice how these could be handled. 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 IS0 14971 [9].

IEC 60601–1 [5] and IEC 60601–2-x 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 multifault 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. 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 measurement 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.

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

13.2.5 Safety Aspects of Medical Electrical Devices for Neurorehabilitation

Medical devices in the neurorehabilitation sector have to take into consideration 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 the patient's lesions and their 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 combined with the usability engineering 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 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 engineering.

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 not familiar in any case with the application of modern medical technology, should be given enough information in the form of indication, contraindication, and possible side effects, residual risks, and advice in handling of the medical device 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 and usability management and must be systematically implemented. The user of a medical device 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 of the medical device. It is recommended to adapt the duration of training to the prior medical and technology 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. For medical devices with a higher degree of autonym, the role of the user changes more in the direction of supervision of the treatment. He should always be aware of unforeseeable situation where his spontaneously intervention could be needed.

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 should be possible at any time. This inherent autonomy of medical device 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 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.

Chapter 14 of the cited standard (IEC 60601–1 [5]) describes the requirements of such a programmable electrical medical system (PEMS). More guidelines for a corresponding development life cycle are given in IEC 62304 [10] in which, among other things, again draws upon ISO 14971 [10].

Software architecture is mandatorily prescribed 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, programmable electronics subsystem (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 [10] 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 [5]
- 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 which 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

More information about PEMS structure, PEMS development life cycle management, and documentation is given in IEC 60601–1; Annex H. [5]. Also Appendix IV listed additional Guidelines about Software and Software Development Cycle.

Conclusion

Medical device technology used in 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 "rehabilitation devices (robots)" and medical devices with a degree of autonomy. 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. Additionally the standard organizations and their member organizations push more and more to actualize existing standards in shorter periods. These organizations are also under the pressure from national regulators for medical devices to create additional standards which sometimes have a more political than safety background.

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 complex 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, significant efforts have to be placed 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, and pressure from the healthcare system regarding cost is worldwide increasing. The world of medical device technology used in 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 inflated their sets of rules such 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 national and international regulation demands, expressed in increasing constraints, with the ability to promptly introduce innovative treatment alternatives in an acceptable cost frame.

13.3 Appendix I: Overview of the Currently Published IMDRF/ (GHTF) Documents [June 2016]

IMDRF/MDSAP WG/N3 FINAL:2016 (Edition 2) Requirements for Medical Device Auditing Organizations for Regulatory Authority Recognition

IMDRF/RPS WG/N19 FINAL:2016 Common Data Elements for Medical Device Identification

IMDRF/MDSAP WG/N8 FINAL:2015 Guidance for Regulatory Authority Assessors on the Method of Assessment for MDSAP Auditing Organizations

IMDRF/MDSAP WG/N24 FINAL:2015 Medical Device Regulatory Audit Reports

IMDRF/SaMD WG/N23 FINAL:2015 Software as a Medical Device (SaMD): Application of Quality Management System

IMDRF/NCAR WG/N14 FINAL:2015 Medical Devices: Post-Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form

IMDRF/SaMD WG/N12 FINAL:2014 Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations

IMDRF/MDSAP WG/N11 FINAL:2014 MDSAP Assessment and Decision Process for the Recognition of an Auditing Organization

IMDRF/RPS WG/N13 FINAL:2014 In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC)

IMDRF/RPS WG/N9 FINAL:2014 Non-In Vitro Diagnostic Device Market Authorization Table of Contents (nIVD MA ToC)

IMDRF/MDSAP WG/N3 FINAL:2013—See also Edition 2
Requirements for Medical Device Auditing Organizations for Regulatory Authority Recognition

IMDRF/MDSAP WG/N4 FINAL:2013 Competence and Training Requirements for Auditing Organizations

IMDRF/MDSAP WG/N5 FINAL:2013 Regulatory Authority Assessment Method for the Recognition and Monitoring of Medical Device Auditing Organizations

IMDRF/MDSAP WG/N6 FINAL:2013 Regulatory Authority Assessor Competence and Training Requirements

IMDRF/UDI WG/N7 FINAL:2013 UDI Guidance: Unique Device Identification (UDI) of Medical Devices

IMDRF/SaMD WG/N10 FINAL:2013 Software as a Medical Device (SaMD): Key Definitions

IMDRF/MC/N39 FINAL:2015 IMDRF Strategic Plan 2020

IMDRF/MC/N16 FINAL:2014 IMDRF Document Format and Style Guide

IMDRF/MC/N17 FINAL:2014 IMDRF Document Template

IMDRF/MC/N18 FINAL:2014 IMDRF Presentation Template

IMDRF/MC/N2 FINAL:2014 (Edition 2) MDRF Standard Operating Procedure

IMDRF/MC/N1 FINAL:2014 (Edition 3) IMDRF Terms of Reference

IMDRF/MDSAP WG/N29 FINAL:2015 Clarification of the Term "Legal Entity" for MDSAP Recognition Purposes

IMDRF/NCAR WG/N30 FINAL:2015 Medical Devices: Post-Market Surveillance - IMDRF National Competent Authority Report (NCAR) Pilot Plan

IMDRF/NCAR WG/N31 FINAL:2015 Medical Devices: Post Market Surveillance: National Competent Authority Report (NCAR) Pilot Plan; Implementing Material

IMDRF/RPS WG/N32 FINAL:2015 Strategic Assessment of Electronic Submission Messaging Formats

IMDRF/MC/N34 FINAL:2015 Statement regarding Use of ISO 14971:2007 "Medical devices - Application of risk management to medical devices"

IMDRF/MC/N35 FINAL:2015 Statement regarding Use of IEC 62304:2006 "Medical device software—Software life cycle processes"

IMDRF/MC/N36 FINAL:2015 Statement regarding Use of IEC 60601-1 "Medical electrical equipment—Part 1: General requirements for basic safety and essential performance"

IMDRF/MC/N37 FINAL:2015 Statement regarding Use of ISO 10993-1:2009 "Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process"
IMDRF/MC/N38 FINAL:2015 Statement regarding Use of ISO 11137-1:2006 "Sterilization of health care products—Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices"
IMDRF/RPS WG/N26 FINAL:2015 (Edition 2) IMDRF Table of Contents (ToC) Pilot Plan
IMDRF/MC/N25 FINAL:2015 Statement regarding Use of ISO 14155:2011 "Clinical investigation of medical devices for human subjects – Good clinical practice"
IMDRF/Standards WG/N15 FINAL:2014 Standards WG: Final Report: 'List of international standards recognized by IMDRF management committee members' Current as of: March 2014
IMDRF/MDSAP WG/N22 FINAL:2014 MDSAP: Overview of Auditing Organization Assessment and Recognition Decision Related Processes
IMDRF/RPS WG/N20 FINAL:2014 Points to consider in the use of the IMDRF Table of Content for Medical Device Submissions pre-RPS
IMDRF/RPS WG/N21 FINAL:2014 RPS Beta Testing Document

13.4 Appendix II: Overview of the Currently Published MEDDEV Documents [March 2015]

	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 Treatment of Computers Used to Program Implantable Pulse Generators	February 1998
	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
	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
	MEDDEV 2.1/6 Qualification and Classification of stand alone software	January 2012
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
	MEDDEV 2.2/4 Conformity assessment of *In Vitro* Fertilisation (IVF) and Assisted Reproduction Technologies (ART) products	January 2012
2.4 Classification of MD	MEDDEV 2.4/1 rev.9 Classification of medical devices	June 2010

	Title	Date
2.5 Conformity assessment procedure	General rules Quality assurance Regulatory auditing of quality systems of medical device manufacturers (See document in the GHTF-Global Harmonization Task Force)	June 2016
	MEDDEV 2.5/3 rev.2 Subcontracting quality systems related	June 1998
	MEDDEV 2.5/5 rev.3 Translation procedure	February 1998
	MEDDEV 2.5/6 rev.1 Homogenous batches (verification of manufacturers' products)	February 1998
Conformity assessment for particular groups of products	MEDDEV 2.5/7 rev.1 Conformity assessment of breast implants	July 1998
	MEDDEV 2.5/9 rev.1 Evaluation of medical devices incorporating products containing natural rubber latex	February 2004
	MEDDEV 2.5/10 Guideline for Authorised Representatives	January 2012
2.7 Clinical investigation, clinical evaluation	MEDDEV 2.7/1 rev.3 Clinical evaluation: Guide for manufacturers and notified bodies Appendix 1: clinical evaluation on coronary stents	December 2009 December 2008
	MEDDEV 2.7/2 rev. 2 Guidelines for Competent Authorities for making a validation/assessment of a clinical investigation application under directives 90/385/EEC and 93/42/EC	September 2015
	MEDDEV 2.7/3 rev. 3 Clinical investigations: serious adverse reporting under directives 90/385/EEC and 93/42/EC - SAE reporting form	May 2015
	The new SAE reporting form will be taken in use 1 September 2016 at the latest.	
	MEDDEV 2.7/4 Guidelines on Clinical investigations: a guide for manufacturers and notified bodies	December 2010
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 Annex 1, Annex 2, Annex 3, Annex 4	April 2001
2.12 Market surveillance	MEDDEV 2.12/1 rev.8 Guidelines on a Medical Devices Vigilance System January 2013 I. MEDDEV 2.12/1 rev.8 – Latest Version Forms *MEDDEV 2.12/1 rev. 7 MIR and FSCA are still valid* Active PDF forms How to use FSCA and MIR forms Manufacturer Incident Report – MIR Field Safety Corrective Action – FSCA MIR and FSCA xml files *Please note: Some browser plugins are not compatible with PDF forms. If you have problems opening these forms, please save them to your computer and open them from there.* Other forms and templates Field Safety Notice Template Trend Report Periodic Summary Report EU Vigilance Pilot on Trending – Additional MIR Form EU Vigilance Pilot MIR form EU Vigilance Pilot MIR Step-by-Step Guide EU Vigilance Pilot Toolkit for Users II. Device Specific Vigilance Guidance DSVG 00 Introduction to Device Specific Vigilance Guidance DSVG 01 Cardiac Ablation Vigilance Reporting Guidance	
	MEDDEV 2.12/2 rev.2 Post Market Clinical Follow-up studies	January 2012

	Title	Date
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	
2.14 IVD	MEDDEV 2.14/1 rev.2 Borderline and Classification issues. A guide for manufacturers and notified bodies	January 2012
	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 DeviceDirective, Article 10	January 2007
	MEDDEV 2.14/4 CE marking of blood based in vitro diagnostic medical devices for vCJD based on detection of abnormal PrP	January 2012
2.15 Other guidances	MEDDEV 2.15 rev.3 Committees/Working Groups contributing to the implementation of the medical device directives	December 2008

- Guidance Notes for Manufacturers of Class I Medical Devices endorsed by the MDEG on December 2009
- Guidance Notes for Manufacturers of Custom-Made Medical Devices endorsed by the MDEG on June 2010
- Guidance document on Dir. 2005/50/EC endorsed by the MDEG on December 2006
- Informative document of the Commission’s services on placing on the market of medical devices (16 November 2010)
- Information on the relation between the revised Directives 90/385/EEC and 93/42/EEC concerning (active implantable) medical devices and Directive 2006/42/EC on machinery (21 August 2009)
- Information on the relation between the revised Directive 93/42/EEC concerning medical devices and Directive 89/686/EEC on personal protective equipment (21 August 2009)
- Informative document of the Commission’s services on implementation of directive 2007/47/EC amending directives 90/385/EEC, 9342/EEC and 98/8/EC (5 June 2009)
- Information on the Medical Devices Directives in relation to medical device own brand labellers (4 February 2008)

13.5 Appendix III: Overview of the Currently Published IEC TC 62 (SC 62A and SC 62D) [June 2016]

IEC TR 60513:1994
Edition 2.0
Fundamental aspects of safety standards for medical electrical equipment

IEC 60601-1:2015 SER
Edition 1.0
Medical electrical equipment - ALL PARTS

IEC 60601-1:2005+AMD1:2012 CSV
Edition 3.1
Medical electrical equipment—Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005+AMD1:2012 CSV/COR1:2012
Edition 3.1
Corrigendum 1—Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005
Edition 3.0
Medical electrical equipment—Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005/ISH1:2008
Edition 3.0
Interpretation sheet 1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005/ISH2:2009
Edition 3.0
Interpretation sheet 2 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005/ISH3:2013
Edition 3.0
Interpretation sheet 3 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005/COR1:2006
Edition 3.0
Corrigendum 1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005/COR2:2007
Edition 3.0
Corrigendum 2 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005/AMD1:2012
Edition 3.0
Amendment 1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

IEC 60601-1:2005/AMD1:2012/COR1:2014
Edition 3.0
Corrigendum 1 - Amendment 1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance

IEC 60601-1-2:2014
Edition 4.0
Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests

IEC 60601-1-6:2010+AMD1:2013 CSV
Edition 3.1
Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability

IEC 60601-1-6:2010
Edition 3.0
Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability

IEC 60601-1-6:2010/AMD1:2013
Edition 3.0
Amendment 1 - Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability

IEC 60601-1-8:2006+AMD1:2012 CSV
Edition 2.1
Medical electrical equipment - Part 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
Edition 2.0
Medical electrical equipment - Part 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/AMD1:2012
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 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 60601-1-9:2007+AMD1:2013 CSV
Edition 1.1
Medical electrical equipment - Part 1-9: General requirements for basic safety and essential performance - Collateral Standard: Requirements for environmentally conscious design

IEC 60601-1-9:2007
Edition 1.0
Medical electrical equipment - Part 1-9: General requirements for basic safety and essential performance - Collateral Standard: Requirements for environmentally conscious design

IEC 60601-1-9:2007/AMD1:2013
Edition 1.0
Amendment 1 - Medical electrical equipment - Part 1-9: General requirements for basic safety and essential performance - Collateral Standard: Requirements for environmentally conscious design

IEC 60601-1-10:2007+AMD1:2013 CSV
Edition 1.1
Medical electrical equipment - Part 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
Edition 1.0
Medical electrical equipment - Part 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/AMD1:2013
Edition 1.0
Amendment 1 - Medical electrical equipment - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers

IEC 60601-1-11:2015
Edition 2.0
Medical electrical equipment - Part 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 60601-1-11:2015 RLV
Edition 2.0
Medical electrical equipment – Part 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 60601-1-12:2014
Edition 1.0
Medical electrical equipment - Part 1-12: General requirements for basic safety and essential per-

formance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems intended for use in the emergency medical services environment

IEC TR 60601-4-2:2016
Edition 1.0
Medical electrical equipment - Part 4-2: Guidance and interpretation - Electromagnetic immunity: performance of medical electrical equipment and medical electrical systems

IEC TR 60601-4-3:2015
Edition 1.0
Medical electrical equipment - Part 4-3: Guidance and interpretation - Considerations of unaddressed safety aspects in the third edition of IEC 60601-1 and proposals for new requirements

IEC TR 60878:2015
Edition 3.0
Graphical symbols for electrical equipment in medical practice

IEC TR 60930:2008
Edition 2.0
Guidelines for administrative, medical and nursing staff concerned with the safe use of medical electrical equipment and medical electrical systems

IEC TR 61258:2008
Edition 2.0
Guidelines for the development and use of medical electrical equipment educational materials

IEC TR 62296:2009
Edition 2.0
Considerations of unaddressed safety aspects in the second edition of IEC 60601-1 and proposals for new requirements

IEC 62304:2006+AMD1:2015 CSV
Edition 1.1
Medical device software - Software life cycle processes

IEC 62304:2006
Edition 1.0
Medical device software - Software life cycle processes

IEC 62304:2006/AMD1:2015
Edition 1.0
Amendment 1 - Medical device software - Software life cycle processes

IEC TR 62348:2012
Edition 2.0
Assessment of the impact of the most significant changes in Amendment 1 to IEC 60601-1:2005 and mapping of the clauses of IEC 60601-1:2005 to the previous edition

IEC 60601-2-2:2009
Edition 5.0
Medical electrical equipment - Part 2-2: Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories

IEC 60601-2-2:2009/COR1:2014
Edition 5.0
Corrigendum 1 - Medical electrical equipment - Part 2-2: Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories

IEC 60601-2-3:2012+AMD1:2016 CSV
Edition 3.1
Medical electrical equipment - Part 2-3: Particular requirements for the basic safety and essential performance of short-wave therapy equipment

IEC 60601-2-3:2012
Edition 3.0
Medical electrical equipment - Part 2-3: Particular requirements for the basic safety and essential performance of short-wave therapy equipment

IEC 60601-2-3:2012/AMD1:2016
Edition 3.0
Amendment 1 - Medical electrical equipment - Part 2-3: Particular requirements for the basic safety and essential performance of short-wave therapy equipment

IEC 60601-2-4:2010
Edition 3.0
Medical electrical equipment - Part 2-4: Particular requirements for the basic safety and essential performance of cardiac defibrillators

IEC 60601-2-5:2009
Edition 3.0
Medical electrical equipment - Part 2-5: Particular requirements for the basic safety and essential performance of ultrasonic physiotherapy equipment

IEC 60601-2-6:2012+AMD1:2016 CSV
Edition 2.1
Medical electrical equipment - Part 2-6: Particular requirements for the basic safety and essential performance of microwave therapy equipment

IEC 60601-2-6:2012
Edition 2.0
Medical electrical equipment - Part 2-6: Particular requirements for the basic safety and essential performance of microwave therapy equipment

IEC 60601-2-6:2012/AMD1:2016
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-6: Particular requirements for the basic safety and essential performance of micro-wave therapy equipment

IEC 60601-2-10:2012+AMD1:2016 CSV
Edition 2.1
Medical electrical equipment - Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators

IEC 60601-2-10:2012
Edition 2.0
Medical electrical equipment - Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators

IEC 60601-2-10:2012/AMD1:2016
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators

IEC 60601-2-16:2012
Edition 4.0
Medical electrical equipment - Part 2-16: Particular requirements for basic safety and essential performance of hemodialysis, hemodiafiltration and hemofiltration equipment

IEC 60601-2-18:2009
Edition 3.0
Medical electrical equipment - Part 2-18: Particular requirements for the basic safety and essential performance of endoscopic equipment

IEC 60601-2-19:2009+AMD1:2016 CSV
Edition 2.1
Medical electrical equipment - Part 2-19: Particular requirements for the basic safety and essential performance of infant incubators

IEC 60601-2-19:2009
Edition 2.0
Medical electrical equipment - Part 2-19: Particular requirements for the basic safety and essential performance of infant incubators

IEC 60601-2-19:2009/COR1:2012
Edition 2.0
Corrigendum 1 - Medical electrical equipment - Part 2-19: Particular requirements for the basic safety and essential performance of infant incubators

IEC 60601-2-19:2009/AMD1:2016
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-19: Particular requirements for the basic safety and essential performance of infant incubators

IEC 60601-2-20:2009+AMD1:2016 CSV
Edition 2.1
Medical electrical equipment - Part 2-20: Particular requirements for the basic safety and essential performance of infant transport incubators

IEC 60601-2-20:2009
Edition 2.0
Medical electrical equipment - Part 2-20: Particular requirements for the basic safety and essential performance of infant transport incubators

IEC 60601-2-20:2009/COR1:2012
Edition 2.0
Corrigendum 1 - Medical electrical equipment - Part 2-20: Particular requirements for the basic safety and essential performance of infant transport incubators

IEC 60601-2-20:2009/COR2:2013
Edition 2.0
Corrigendum 2 - Medical electrical equipment - Part 2-20: Particular requirements for the basic safety and essential performance of infant transport incubators

IEC 60601-2-20:2009/AMD1:2016
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-20: Particular requirements for the basic safety and essential performance of infant transport incubators

IEC 60601-2-21:2009+AMD1:2016 CSV
Edition 2.1
Medical electrical equipment - Part 2-21: Particular requirements for the basic safety and essential performance of infant radiant warmers

IEC 60601-2-21:2009
Edition 2.0
Medical electrical equipment - Part 2-21: Particular requirements for the basic safety and essential performance of infant radiant warmers

IEC 60601-2-21:2009/COR1:2013
Edition 2.0
Corrigendum 1 - Medical electrical equipment - Part 2-21: Particular requirements for the basic safety and essential performance of infant radiant warmers

IEC 60601-2-21:2009/AMD1:2016
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-21: Particular requirements for the basic safety and essential performance of infant radiant warmers

IEC 60601-2-23:2011
Edition 3.0
Medical electrical equipment - Part 2-23: Particular requirements for the basic safety and essential performance of transcutaneous partial pressure monitoring equipment

IEC 60601-2-24:2012
Edition 2.0
Medical electrical equipment - Part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers

IEC 60601-2-25:2011
Edition 2.0
Medical electrical equipment - Part 2-25: Particular requirements for the basic safety and essential performance of electrocardiographs

IEC 60601-2-26:2012
Edition 3.0
Medical electrical equipment - Part 2-26: Particular requirements for the basic safety and essential performance of electroencephalographs

IEC 60601-2-27:2011
Edition 3.0
Medical electrical equipment - Part 2-27: Particular requirements for the basic safety and essential performance of electrocardiographic monitoring equipment

IEC 60601-2-27:2011/COR1:2012
Edition 3.0
Corrigendum 1 - Medical electrical equipment - Part 2-27: Particular requirements for the basic safety and essential performance of electrocardiographic monitoring equipment

IEC 60601-2-31:2008+AMD1:2011 CSV
Edition 2.1
Medical electrical equipment - Part 2-31: Particular requirements for the basic safety and essential performance of external cardiac pacemakers with internal power source

IEC 60601-2-31:2008
Edition 2.0
Medical electrical equipment - Part 2-31: Particular requirements for the basic safety and essential performance of external cardiac pacemakers with internal power source

IEC 60601-2-31:2008/AMD1:2011
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-31: Particular requirements for the basic safety and essential performance of external cardiac pacemakers with internal power source

IEC 60601-2-34:2011
Edition 3.0
Medical electrical equipment - Part 2-34: Particular requirements for the basic safety and essential performance of invasive blood pressure monitoring equipment

IEC 60601-2-36:2014
Edition 2.0
Medical electrical equipment - Part 2-36: Particular requirements for the basic safety and essential performance of equipment for extracorporeally induced lithotripsy

IEC 60601-2-39:2007
Edition 2.0
Medical electrical equipment - Part 2-39: Particular requirements for basic safety and essential performance of peritoneal dialysis equipment

IEC 60601-2-40:1998
Edition 1.0
Medical electrical equipment - Part 2-40: Particular requirements for the safety of electromyography and evoked response equipment

IEC 60601-2-41:2009+AMD1:2013 CSV
Edition 2.1
Medical electrical equipment - Part 2-41: Particular requirements for the basic safety and essential performance of surgical luminaires and luminaires for diagnosis

IEC 60601-2-41:2009
Edition 2.0
Medical electrical equipment - Part 2-41: Particular requirements for the basic safety and essential performance of surgical luminaires and luminaires for diagnosis

IEC 60601-2-41:2009/AMD1:2013
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-41: Particular requirements for the basic safety and essential performance of surgical luminaires and luminaires for diagnosis

IEC 60601-2-46:2010
Edition 2.0
Medical electrical equipment - Part 2-46: Particular requirements for basic safety and essential performance of operating tables

IEC 60601-2-47:2012
Edition 2.0
Medical electrical equipment - Part 2-47: Particular requirements for the basic safety and essential performance of ambulatory electrocardiographic systems

IEC 60601-2-49:2011
Edition 2.0
Medical electrical equipment - Part 2-49: Particular requirements for the basic safety and essential performance of multifunction patient monitoring equipment

IEC 60601-2-50:2009+AMD1:2016 CSV
Edition 2.1
Medical electrical equipment - Part 2-50: Particular requirements for the basic safety and essential performance of infant phototherapy equipment

IEC 60601-2-50:2009
Edition 2.0
Medical electrical equipment - Part 2-50: Particular requirements for the basic safety and essential performance of infant phototherapy equipment

IEC 60601-2-50:2009/COR1:2010
Edition 2.0
Corrigendum 1 - Medical electrical equipment - Part 2-50: Particular requirements for the basic safety and essential performance of infant phototherapy equipment

IEC 60601-2-50:2009/AMD1:2016
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-50: Particular requirements for the basic safety and essential performance of infant phototherapy equipment

IEC 60601-2-52:2009+AMD1:2015 CSV
Edition 1.1
Medical electrical equipment - Part 2-52: Particular requirements for the basic safety and essential performance of medical beds

IEC 60601-2-52:2009
Edition 1.0
Medical electrical equipment - Part 2-52: Particular requirements for the basic safety and essential performance of medical beds

IEC 60601-2-52:2009/COR1:2010
Edition 1.0
Corrigendum 1 - Medical electrical equipment - Part 2-52: Particular requirements for the basic safety and essential performance of medical beds

IEC 60601-2-52:2009/AMD1:2015
Edition 1.0
Amendment 1 - Medical electrical equipment - Part 2-52: Particular requirements for the basic safety and essential performance of medical beds

IEC 60601-2-62:2013
Edition 1.0
Medical electrical equipment - Part 2-62: Particular requirements for the basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment

IEC TR 61289:2011
Edition 1.0
High frequency surgical equipment - Operation and maintenance

IEC TR 62653:2012
Edition 1.0
Guideline for safe operation of medical equipment used for haemodialysis treatments

IEC PAS 63023:2016
Edition 1.0
Medical electrical system - Input interface for haemodialysis equipment for use of external alarming device

IEC 80369-5:2016
Edition 1.0
Small-bore connectors for liquids and gases in healthcare applications - Part 5: Connectors for limb cuff inflation applications

IEC 80601-2-30:2009+AMD1:2013 CSV
Edition 1.1
Medical electrical equipment - Part 2-30: Particular requirements for the basic safety

and essential performance of automated non-invasive sphygmomanometers

IEC 80601-2-30:2009
Edition 1.0
Medical electrical equipment - Part 2-30: Particular requirements for the basic safety and essential performance of automated non-invasive sphygmomanometers

IEC 80601-2-30:2009/COR1:2010
Edition 1.0
Corrigendum 1 - Medical electrical equipment - Part 2-30: Particular requirements for the basic safety and essential performance of automated non-invasive sphygmomanometers

IEC 80601-2-30:2009/AMD1:2013
Edition 1.0
Amendment 1 - Medical electrical equipment - Part 2-30: Particular requirements for the basic safety and essential performance of automated type non-invasive sphygmomanometers

IEC 80601-2-35:2009+AMD1:2016 CSV
Edition 2.1
Medical electrical equipment - Part 2-35: Particular requirements for the basic safety and essential performance of heating devices using blankets, pads and mattresses and intended for heating in medical use

IEC 80601-2-35:2009
Edition 2.0
Medical electrical equipment - Part 2-35: Particular requirements for the basic safety and essential performance of heating devices using blankets, pads and mattresses and intended for heating in medical use

IEC 80601-2-35:2009/COR1:2012
Edition 2.0
Corrigendum 1 - Medical electrical equipment - Part 2-35: Particular requirements for the basic safety and essential performance of heating devices using blankets, pads or mattresses and intended for heating in medical use

IEC 80601-2-35:2009/COR2:2015
Edition 2.0
Corrigendum 2 - Medical electrical equipment - Part 2-35: Particular requirements for the basic safety and essential performance of heating devices using blankets, pads or mattresses and intended for heating in medical use

IEC 80601-2-35:2009/AMD1:2016
Edition 2.0
Amendment 1 - Medical electrical equipment - Part 2-35: Particular requirements for the basic safety and essential performance of heating devices using blankets, pads or mattresses and intended for heating in medical use

IEC 80601-2-58:2014
Edition 2.0
Medical electrical equipment - Part 2-58: Particular requirements for the basic safety and essential performance of lens removal devices and vitrectomy devices for ophthalmic surgery

IEC 80601-2-59:2008
Edition 1.0
Medical electrical equipment - Part 2-59: Particular requirements for the basic safety and essential performance of screening thermographs for human febrile temperature screening

IEC 80601-2-59:2008/COR1:2009
Edition 1.0
Corrigendum 1 - Medical electrical equipment - Part 2-59: Particular requirements for the basic safety and essential performance of screening thermographs for human febrile temperature screening

IEC 80601-2-60:2012
Edition 1.0
Medical electrical equipment - Part 2-60: Particular requirements for the basic safety

and essential performance of dental equipment

IEC 80601-2-71:2015
Edition 1.0
Medical electrical equipment - Part 2-71: Particular requirements for the basic safety and essential performance of functional near-infrared spectroscopy (NIRS) equipment

ISO 80369-1:2010
Edition 1.0
Small-bore connectors for liquids and gases in healthcare applications—Part 1: General requirements

ISO 80369-6:2016
Edition 1.0
Small bore connectors for liquids and gases in healthcare applications - Part 6: Connectors for neuraxial applications

ISO 80369-20:2015
Edition 1.0
Small-bore connectors for liquids and gases in healthcare applications—Part 20: Common test methods

ISO 80601-2-12:2011
Edition 1.0
Medical electrical equipment - Part 2-12: Particular requirements for basic safety and essential performance of critical care ventilators

ISO 80601-2-13:2011
Edition 1.0
Medical electrical equipment - Part 2-13: Particular requirements for basic safety and essential performance of an anaesthetic workstation

ISO 80601-2-13:2011/AMD1:2015
Edition 1.0
Amendment 1 - Medical electrical equipment -- Part 2-13: Particular requirements for basic safety and essential performance of an anaesthetic workstation

ISO 80601-2-55:2011
Edition 1.0
Medical electrical equipment - Part 2-55: Particular requirements for the basic safety and essential performance of respiratory gas monitors

ISO 80601-2-56:2009
Edition 1.0
Medical electrical equipment - Part 2-56: Particular requirements for basic safety and essential performance of clinical thermometers for body temperature measurement

ISO 80601-2-61:2011
Edition 1.0
Medical electrical equipment—Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment

ISO 80601-2-67:2014
Edition 1.0
Medical electrical equipment—Part 2-67: Particular requirements for basic safety and essential performance of oxygen-conserving equipment

ISO 80601-2-69:2014
Edition 1.0
Medical electrical equipment—Part 2-69: Particular requirements for basic safety and essential performance of oxygen concentrator equipment

ISO 80601-2-70:2015
Edition 1.0
Medical Electrical Equipment–Part 2-70: Particular requirements for basic safety and essential performance of sleep apnoea breathing therapy equipment

ISO 80601-2-72:2015
Edition 1.0
Medical electrical equipment—Part 2-72: Particular requirements for basic safety and essential performance of home healthcare environment ventilators for ventilator-dependent patients

ISO 81060-1:2011
Edition 1.0
Non-invasive sphygmomanometers—Part 1: Requirements and test methods for non-automated measurement type

ISO 81060-2:2013
Edition 2.0
Non-invasive sphygmomanometers—Part 2: Clinical investigation of automated measurement type

13.6 Appendix IV: 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 Radio logical 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

13.7 Appendix V: Additional Documents Published by IEEE

- 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

References

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 harmonized standards under the directive 2010/C 183/03. Amended by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007.
2. Directive 2006/42/EC of the European Parliament and of the Council of 17 May 2006 on machinery, and amending Directive 95/16/EC.
3. ISO Guide 63.
4. ISO Guide 51.
5. IEC 60601-1:2005+AMD1:2012 CSV; Medical electrical equipment—Part 1: general requirement for basic safety and essential performance.
6. IEC/TR 60601–4-1: Medical electrical equipment—Part 4–1: guidance and interpretation—Medical electrical equipment and medical electrical systems employing a degree of autonomy second committee draft status.

7. ISO 13485:2016; Medical devices—quality management systems—Requirements for regulatory purposes.
8. IEC 62353:2014; Medical electrical equipment—recurrent test and test after repair of medical electrical equipment.
9. ISO 14971:2007; Medical devices—application of risk management to medical devices.
10. IEC 62304:2006; Medical device software—software life cycle processes.
11. ISO 10993-1:2009/Cor 1:2010 Biological evaluation of medical devices—Part 1: evaluation and testing within a risk management system and additional parts.
12. IEC 62366: with AMMENDMENT 1: 2014–01; Medical devices—application of usability engineering to medical devices.
13. IEC 60601-1-2:2014; Medical electrical equipment—Part 1–2: general requirements for basic safety and essential performance—collateral standard: electromagnetic compatibility- requirements and tests.
14. IEC 60601-1-11:2015 RLV; Medical electrical equipment; 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.

14 Clinical Application of Rehabilitation Technologies in Children Undergoing Neurorehabilitation

Hubertus J.A. van Hedel
and Tabea Aurich (-Schuler)

Abstract

The application of rehabilitation technologies in children with neurological impairments appears promising as these systems can induce repetitive goal-directed movements to complement conventional treatments. Characteristics of robotic-supported and computer-assisted training are in line with principles of motor learning and include high numbers of repetitions, prolonged training durations, and online feedback about the patient's active participation. When experienced therapists apply these technologies, they can be considered a rather safe and in combination with virtual realities a motivating supplementary approach. Therapists might have to take into account that there might be some factors that are different when applying such technologies to children with congenital versus acquired neurological lesions. Currently, clinical guidelines on how to apply such technologies are missing, and clinical evidence considering the effectiveness of such technologies has just started to commence in pediatric neurorehabilitation. Experienced therapists formulated recommendations that might be useful to those with less experience on how to apply some of these systems to train the lower and upper extremity intensively and playfully. Finally, suggestions are made on how these technologies could be integrated into the clinical path.

Keywords

Adolescents • Robot-assisted therapy • Computer-assisted systems • ICF-CY • Virtual reality • Pediatric neurorehabilitation • Habilitation • Rehabilitation • Inclusion and exclusion criteria • Training intensity • Clinical evidence

H.J.A. van Hedel, PhD, PT (✉)
T. Aurich (-Schuler), MSc
Pediatric Rehab Research Group,
Rehabilitation Center for Children and Adolescents,
University Children's Hospital Zurich,
Mühlebergstrasse 104,
CH-8910 Affoltern am Albis, Switzerland
e-mail: hubertus.vanhedel@kispi.uzh.ch

14.1 Introduction

The treatment of upper and lower extremity functions and activities in children with neurological disorders presents a high challenge as the

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developmental status interferes with the additional complexity of neurological, functional, cognitive, and motivational aspects. Symptoms that affect overall functioning are among others spasticity, muscle weakness, impaired balance, contractures, and joint and bone deformities. In young patients with congenital or acquired brain lesions, comorbidities such as epilepsy, learning difficulties, behavioral challenges, or sensory impairments can be of similar complexity to treat as the motor disabilities, and this will affect both therapy planning and execution (see, e.g., [1]).

The motor symptoms can worsen during growth, especially during the pubertal growth spurt. Neurodevelopmental treatment concepts adapted their principles over time, and their focus switched from passive inhibition techniques to self-activity of the child [2, 3]. Besides the conventional physical and occupational therapy, multidisciplinary rehabilitation programs include now also approaches such as sports, strength training [4], or functional task-orientated training [5].

In line with this change in therapeutic focus, rehabilitation goals become nowadays more and more defined at the domain of activities and participation (according to the International Classification of Functioning, Disability and Health – Child and Youth version, ICF-CY) [6]. Also in children with neurological impairments, the goal of rehabilitation is to improve the independence in daily life activities. Improved independence will reduce the burden of care for the whole family and positively affect the quality of life both for the young patient and his family. Currently, it is agreed that this can only be achieved by a multidisciplinary approach.

In this chapter, we will focus on the treatment of motor impairments of the lower and upper extremities with new technologies such as robot-assisted and computer-based rehabilitation systems that complement conventional rehabilitation interventions in children.

14.2 Potential Advantages of Rehabilitation Technologies

Independent from whether a therapeutic program consists of conventional interventions or new rehabilitation technologies, children with congenital or acquired neurological lesions profit from periods of intensive physiotherapeutic interventions. These interventions are necessary for enhancing motor development in childhood, especially during intense growth periods. Furthermore, intense rehabilitation is also required in children after surgical interventions. Such interventions aim to improve biomechanics (like multilevel surgery) or reduce spasticity (like intrathecal baclofen administration or selective dorsal rhizotomy) [7, 8]. The intensity of therapy, repetition, and a goal-oriented and task-specific training program are nowadays considered essential to achieve successful functional outcome [5, 9]. Rehabilitation programs tailored to the special needs of an individual child are personnel intensive and, therefore, costly. Often limited resources hinder the achievement of optimal therapy conditions and limit the dosages of rehabilitation measures.

Robotic therapies could contribute considerably to the motor learning concept in rehabilitation. Robots can deliver high-dosage (i.e., number of practice movements) and high-intensive (i.e., number of movements per unit time) training interventions, have accurate movement controllability, and can provide immediate and precise feedback. These points are all considered important for successful neurorehabilitation [10]. Motivation appears important, especially in children and adolescents. Nowadays, most rehabilitation robots are equipped with virtual reality games to provide feedback and enhance motivation. Child-friendly games with strong, immersive qualities could distract children from monotonous, repetitive exercises. These games can be adapted to the developmental and functional status of the child, which can lead to more challenging training situations thereby increasing active participation (see, e.g., [11–15]). Feedback has been extensively investigated, and there is general agreement that it facilitates learning [16] and can be considered one of the most important variables, besides practice. The repeated practice must be linked to incremental success at a trained task, and this is usually achieved by trial and error practice, with multisensory feedback about performance success [10]. Regarding robotic therapies, feedback should result in changes in muscle activity, induced by the patient, toward a more physiological and functional movement pattern.

Nevertheless, we also account for some critical points in applying robot-supported rehabilitation. For the upper extremity, studies in adult patients after stroke reported significant improvements in impairments, but failed to find improvements in the performance of activities of daily living (ADL) [17, 18]. This could be due to a lack of transfer from the functional to the activity performance domain as described by the ICF-CY or to an insufficient sensitivity of ADL outcome measures. Measures of ADL could be too unspecific to distinguish between true recovery and compensation. The difference between recovery and compensation is important, also with respect to motor learning. True recovery means that undamaged brain and spinal regions are recruited, which generate commands to the same muscles as were used before the injury [19]. This requires a certain structural redundancy around the affected region [20]. Compensation, however, refers to the use of a different movement strategy involving different muscles to accomplish the same task. Motor learning is a prerequisite for both, but it seems as if true recovery improves performance across a range of tasks, whereas improvement through compensation is limited to the task itself. Huang and Krakauer [21] therefore speculated "that what is needed to see improvement in ADL measures is subsequent intense training in everyday tasks once impairment has been reduced to a specific level. This serial approach (i.e., focus on impairment first and then on function) might address the apparent paradox of a parallel dissociation between impairment and functional measures after a particular rehabilitative treatment" [21]. Compensation can, of course, be a successful strategy to solve ADL-relevant problems; however, compensatory strategies might hinder further progress and should not become routine. Instead, the aim should be to change the training and the goals in such a way that alternative motor solutions can be used.

Repetition of identical movements is not desirable, as kinematic variability is an important prerequisite for motor learning. Rehabilitation robots that just play back a preprogrammed gait pattern are not considered optimal, especially in functionally better patients [22]. The consolidation of a learned task over time also seems better if kinematic variability is introduced [23] (the "repetition without repetition" principle according to Bernstein [24]). Finally, variable practice might facilitate translation of the skill into everyday life [19]. Several innovative control strategies have been developed over the last years to allow certain movement variability. Some studies suggest the superiority of assist as needed compared to fully assisted control strategies [25–30].

Nevertheless, despite these advantages of rehabilitation technologies, therapists and physicians should keep in mind that especially in pediatric neurorehabilitation, parents could have excessive expectations and hopes when therapists apply such expensive, high-tech rehabilitation devices. Realistic goals should be defined early in the rehabilitation process and communicated clearly to the parents.

14.3 Applying Rehabilitation Technologies: Children Versus Adults

From clinical experience, it appears that the acceptability of rehabilitation technologies in combination with games appears to be much higher in children compared to adults. Younger patients can immerse easily in games and identify themselves quickly with the avatar. Especially attractive high-quality graphics increase immersion, which is advantageous with respect to motivation and duration of training and number of repetitions. During training, game scores can motivate them to continue with the training. Many executive functions, e.g., short-term memory, selective or divided attention, and alertness, can be partially affected after a congenital or acquired brain injury and become automatically trained when playing such games. Therapists should take impairments in one or more of these executive functions into consideration when selecting appropriate games (i.e., concerning the level of difficulty, required reaction time, etc.). Additionally important in deciding what games can be played is the frustration tolerance of the children.

Nowadays, young patients are often experienced in playing computer games. This also causes some problems because these "game users" are used to attractive graphics of excellent quality.

Unfortunately, many of the games delivered with rehabilitation technologies are on a qualitative lower level. Over time, this will likely reduce the compliance of the users. Systems that are more open, i.e., on which other available games can be installed and played as well, have a great advantage therefore. Therapists can select additional games with good graphics that could be used to induce meaningful and physiological movements when applied correctly. This would increase the acceptance of the system by the patients considerably.

The high-immersive capacity of children undergoing rehabilitation also has some disadvantages. Occupational and physical therapists experienced in applying rehabilitation technologies for years report that the increased immersion also lets children forget that they should perform therapeutically desired movements consisting of physiological rather than compensatory movement strategies. Some children show increased muscular tonus when playing games in such devices. For some games, the young patients might find out how they can "trick" the system, i.e., they find out how they can increase their game score while performing less active, undesirable compensatory movements. The presence of a trained therapist who can guide the child or adolescent in performing the movements correctly is, therefore, inevitable, especially when movement quality is the primary therapeutic goal or compensatory movements lead to malalignment of joint axes, which could result in damaging forces on body structures.

Another disadvantage when applying such systems in children is that they show less patience when technological system errors delay the training. Repetitive stops often result in decreased motivation and compliance and, as a result, a preliminary termination of the training session. If this situation occurs in several subsequent sessions, long-term compliance might be compromised.

14.4 Habilitation Versus Rehabilitation

Although therapists apply the same therapeutical techniques, including rehabilitation technologies, they face differences when treating patients with either congenital or acquired brain lesions. First, when taking into account factors such as age, size and location of the brain lesion, or severity of functional and cognitive impairment, it is likely that children with congenital brain lesions might show less functional improvements compared to children with acquired lesions, because these latter might show additional spontaneous neurological recovery. Second, children with congenital brain lesions might have developed functional compensatory strategies (potentially accompanied by joint contractures) over (many) years. Children with acquired brain lesions, however, might have better chances of restoring physiological selective voluntary movements to a certain extent. If the therapist and patient decide to minimize the use of compensatory movements and train selective movements, patients and parents should be informed that initially this might result in a decrease in independence, as functionally useful compensatory movements would be restricted. It remains difficult to predict how successful such an intervention would be, as it is difficult to estimate whether part of the limitations in selective movements might be caused by so-called learned nonuse of the upper or lower extremity (for a nice review see [31]). If the chance of improving physiological movements is small and compensatory movements appear the best option, then one must say that current rehabilitation technologies do not include exercises to practice a simple supportive function of a leg or assisting functions of the affected arm and hand (e.g., to use the affected hand for supporting tasks).

Third, often the rehabilitation goal of children with congenital lesions is, especially for those who are more severely affected, to maintain (rather than improve) the current level of functionality. It appears that it is often easier for children with acquired lesions (and their parents) to define specific treatment goals, because they are aware of the previous capabilities of the child. As such a reference is missing for children with congenital lesions, our therapists report that these children and their parents often have more difficulties in defining specific treatment goals. Other therapists though report that parents of

children with congenital lesions formulate more qualitative goals (e.g., with respect to walking, better knee extension, improved initial contact with the heel) rather than goals related to performance or participation. Besides, children with acquired lesions appear sometimes more motivated compared to those with congenital lesions. This would be in line with literature showing that some children with developmental disorders appear less motivated and more passive in their playing behavior (less complex and less challenging) despite equal curiosity and pleasure [32, 33]. Furthermore, the motivation appears to differ between different fields. Some children with cerebral palsy (CP) appear less motivated for cognitive or motor tasks. It appears that children with CP with higher IQ, better motor skills, and fewer restrictions in self-care, communication, and social skill lessons have higher motivation than those who do not [34].

14.5 General Practical Considerations

Lower and upper extremity rehabilitation technologies should complement conventional therapies well. Especially in pediatrics, the systems should be robust (with respect to both hardware and software), and donning and doffing should require little time. Due to the relatively large age span (5–21 years old children and youths) and consecutive wide range of anthropometrics, especially exoskeleton devices might have the disadvantage that it might take time to adjust the device optimally to the patient. When planning therapies, it might make sense to plan sufficient time before the patient arrives so the therapist can prepare the device or needed materials (e.g., gloves) and software settings to the patient. An adequate room, quiet and with a pleasant atmosphere, can assist in improving the compliance of children who might initially have a fear of too much technology. The young patients will less and less accept devices that are repeatedly uncomfortable. Furthermore, little time should be spent on performing calibrations, starting up the game, or changing from one game to another. For patients who have difficulties in keeping concentrated for a longer time, it is proved useful when therapists can pause the game in between when needed. Importantly, in case of technical difficulties, companies should provide fast and adequate support. In this respect, it is also important to mention that costs occur not only when buying the devices but also when the guarantee has passed or yearly services are needed.

Importantly, therapists should also be given time and support in getting used to these technologies. A poor instruction will likely result in uncertainties with applying the devices, and it is unlikely that such therapists might achieve exploiting all the possibilities that some of the devices have. It is advantageous when collaborations with technically well-versed people exist, and from the onset on, it should be determined what standardized assessments might be useful to determine the effectiveness of these interventions.

Good therapeutic quality can only be achieved if therapists apply such systems regularly. It should be noted that especially when starting to introduce such technologies into the clinic, therapists should be given sufficient time to get familiarized to such devices. Similar to working with conventional techniques, therapists should first get a "feeling" what patient requirements are needed to train with and profit from such an intervention. This is very important because evidence-based guidelines on patient selection are currently not available (see, e.g., Aurich et al. [35] for the application of the Lokomat). Furthermore, we recommend selecting a small team of therapists who would apply the technologies repetitively on a daily basis rather than have each team member performing such training once in a while. From our experience, we work in a relative small pediatric rehabilitation center, it should *not* be recommended to build teams of therapists who *only* apply such technologies. We would rather recommend building teams of therapists who work part of their time with the technologies and part of their time with conventional therapeutic techniques. This increases the flexibility of the therapists and allows therapists to have full programs, also in times when only a few patients have been referred to train with rehabilitation technologies.

Having therapists working both with conventional and traditional techniques might also improve the transfer from improved body functions to activities for the patient.

14.6 Technology-Supported Lower Extremity Rehabilitation in Children

14.6.1 Introduction

In general, robot-assisted gait training (RAGT) can be placed on a continuum from training first stepping movements on a dynamic tilt table over manual bodyweight-supported treadmill therapy (BWSTT) and overground training in a therapeutic environment to community gait training (Fig. 14.1). Please note, however, that we consider such systems complementary to conventional interventions. By no means, we would recommend performing RAGT solely, as improvements in physiological leg movements still need to be translated in improved overground walking. Depending on strength and coordination of the legs, it might be advantageous to use an exoskeleton robot to guide the leg movements in a physiological pattern. When patients become somewhat better, an end-effector device might induce higher muscle activity and a more variable walking pattern. Basics like trunk stability and generating stepping movements are required for manual BWSTT, where therapists assist to achieve appropriate lower limb kinematics and inter-limb coordination during partial bodyweight unloading. Overground and community-related gait training require considerable physical and cognitive capacities to ambulate with little or no assistance or walking aids, especially when covering uneven terrains, environmental disturbances, and stair walking.

In general, RAGT is indicated for patients with limited leg muscle strength and self-initiation of stepping while having some head and trunk control and being cardiovascularly stable (Fig. 14.1). Possible therapy goals during RAGT could be increase of body alignment, trunk control, ankle control and range of motion, muscle tone regulation, decrease of bodyweight support and biomechanical/ kinematical guidance, improvement of speed, walked distance and gait symmetry, etc. Overall, most of these goals are also training parameters that can be adjusted to personalize the intensity of the training.

14.6.2 Overview of Pediatric Lower Extremity Systems

There are nowadays many commercial systems available, so a complete overview cannot be given here. A dynamic tilt table (Erigo, Hocoma AG, Volketswil, Switzerland) is one option to train adolescents in a minimal conscious state or a very early state after severe brain injury, respectively. Goals can be related to locomotion (release step initiation), but mostly involve functions such as circulation, verticalization, perception, or muscle tone regulation (see also Fig. 14.1).

Devices aiming at inducing repetitive step movements reach from rather simple constructed end-effector equipment that can be placed on a treadmill so the existing bodyweight support system can be used (Lokohelp Pedago, Lokohelp Group, Weil am Rhein, Germany) to more complex complete end-effector systems like the LYRA (Ability AG, Zurich, Switzerland, Fig. 14.2), in which repetitive physiological leg movements can be trained. The RT600 FES step and stance (Restorative Therapies, Baltimore, USA) allows a combination with functional electrical stimulation, while the G-EO System (Reha Technology AG, Olten, Switzerland, Fig. 14.3) allows to practice even climbing-stair-like movements. These systems use footplates as already integrated with the Gait Trainer (GT I, Reha-Stim, Berlin, Germany). In general, the end-effector technology allows efficient setup times.

The first commercially widely distributed exoskeleton gait trainer was the Lokomat (Hocoma AG, Volketswil, Switzerland, see Fig. 14.4). This system allows a full biomechanical guidance of hip and knee joints. Many other exoskeleton devices have been developed in the meantime (e.g., ReoAmbulator or AutoAmbulator,

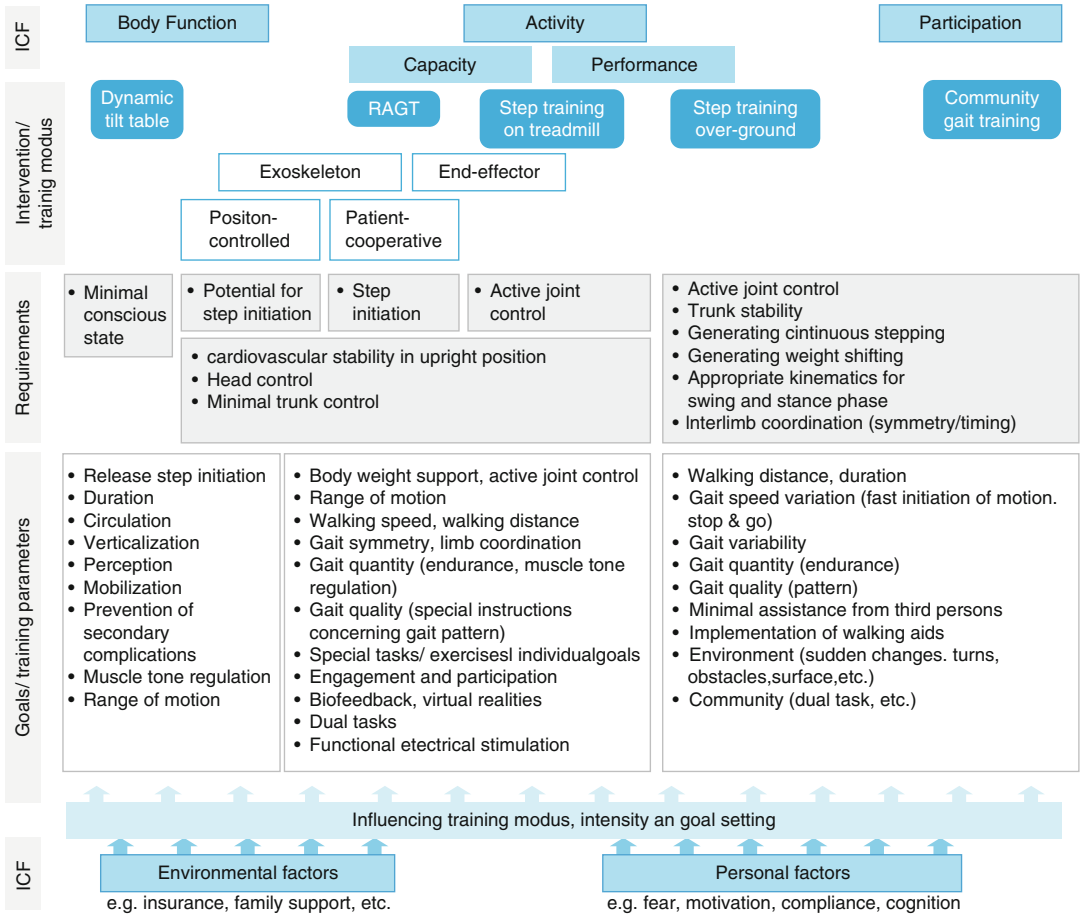

Fig. 14.1 Robot-assisted gait training (*RAGT*) can be positioned on a continuum from initiating stepping movements on a dynamic tilt table over exoskeleton and end-effector robot-supported systems and manually assisted bodyweight-supported treadmill training to community ambulation. When changing from training body functions to activities and, finally, participation, according to the domains of the International Classification of Functioning, Disability and Health (*ICF*), the requirements change as well. Please note that both environmental and personal factors can play a role in determining the individual goals and adjusting the training parameters for each session

Motorika Medical Ltd., New Jersey, USA; Walkbot K for children, P&S Mechanics, Seoul, Korea; Guangzhou Yikang Medical Equipment Industrial Co., Ltd, Guangzhou City, China; Robogait, BAMA Technology, Ankara, Turkey). Then, there are also some motorized medical devices intended to experience assisted, guided, repetitive leg movements in an upright position. Examples are the Innowalk and Innowalk Pro (Made for Movement (global), Skien, Norway), where children of 80–150 cm height and maximally 50 kg weight can already train in the small version.

14.6.3 Clinical Evidence

Most literature on children and youths undergoing RAGT involved the application of the Lokomat. A first study about RAGT in 26 young patients (mean age 10.1 years) with congenital and acquired neurological movement disorders showed that RAGT could be well integrated with rehabilitation routines and was well accepted by patients, parents, and therapists [36]. Gait speed and the Gross Motor Function Measure (GMFM) improved significantly after RAGT and conventional physical therapy. In a follow-up study, the

Fig. 14.2 The end-effector gait trainer LYRA (Ability AG, Zurich, Switzerland) allows to train children and youths with body heights varying between 1.00 and 1.95 m and a bodyweight up to 150 kg. The patient is positioned on footplates, and step lengths can easily be adjusted from 39 to 67 cm according to the patient's need. Foot-bindings are interchangeable taking into account different shoe sizes and different step widths. Pediatric handrails can be mounted onto the handrails supporting the younger patients, and additional hip stabilization is available in various sizes (Picture with kind permission from Ability AG)

maximum short-distance gait speed and dimension D (standing) of the GMFM could be significantly improved after 3–5 sessions/week of 45–60 min of RAGT for 3–5 weeks, in combination with conventional therapy in children with CP [37]. Furthermore, the dimensions D and E (walking) of the GMFM changed for the better in 20 outpatients with CP [38], especially in mildly affected children (Gross Motor Function Classification System (GMFCS) levels I and II). In comparison, patients with GMFCS levels III and IV improved less in motor function over time. A sustainability study of the same group showed that improvements in gait capacity (GMFM dimensions D, E, and gait speed) induced by 12 sessions of RAGT during 3 weeks were maintained at 6 months after baseline in 14 children with CP [39]. Arellano-Martinez and

Fig. 14.3 The G-EO System (Reha Technology AG, Olten, Switzerland) is a high-tech end-effector device that allows children and adults to execute a repetitive walking pattern in either a passive, an adaptive-assisted, or adaptive way. Moreover, it can be set to simulate walking up or down the stairs (in the G-EO Evolution). The end-effector technology allows a rotating pelvis for a physiological gait pattern and a distinguished weight shift from one leg to the other. The pediatric module is intended for children with body heights varying between 0.90 and 1.60 m and a maximum weight of 50 kg (Picture with kind permission from Reha Technology AG)

colleagues [40] investigated two groups of children with spastic hemiplegic CP, randomly assigned to either training with the Lokomat or along a rail inside a hydrotherapy tank. Significant changes in quantitative measurements of gait could be observed in both groups, but they sustained only in the Lokomat group after a 1-year follow-up. While these studies provide some insight into the long-term effects of RAGT, all mentioned studies lacked a control group.

A bi-center survey showed that RAGT appears safe [41]. Of 47 adverse events in 89 patients, 85 % were insignificant and not affecting therapy continuation. Only five adverse events (joint pain, open skin lesions, tendinopathy) were considered mild or moderate and interfered with further

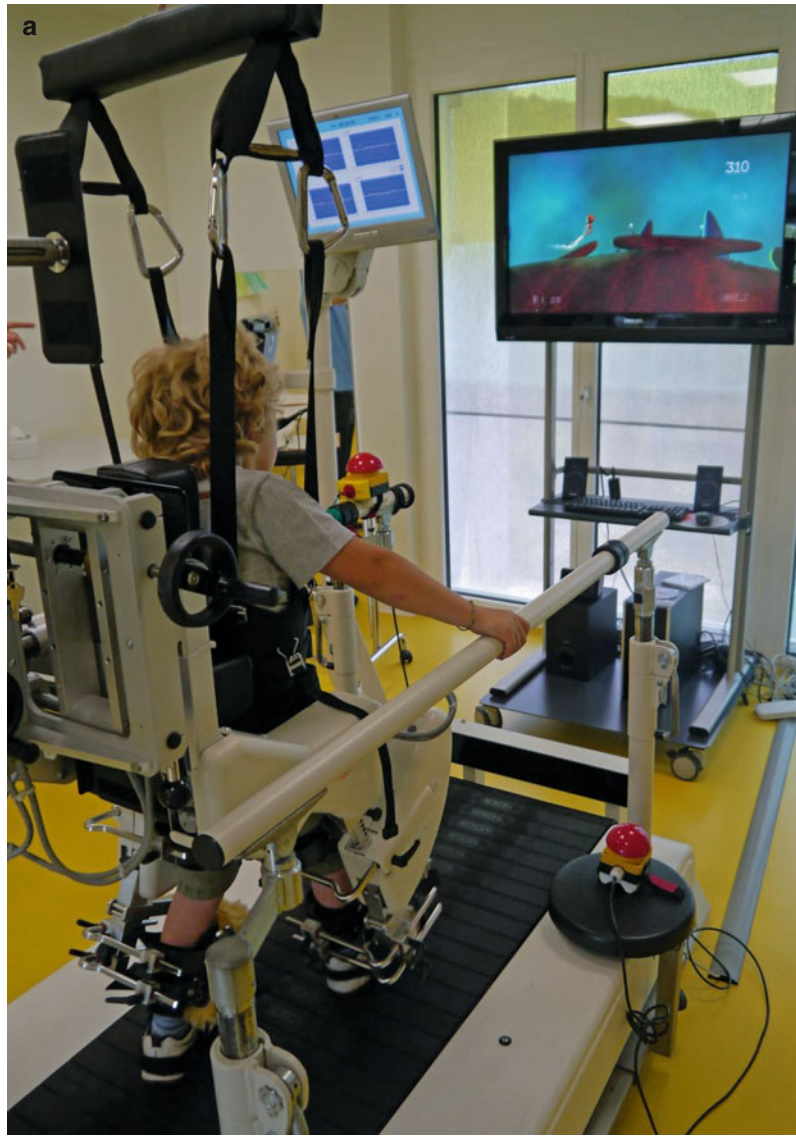

Fig. 14.4 The exoskeleton Lokomat system comprises a treadmill belt, a weight support system, and the driven gait orthosis itself. Depending on the size of the patient, specific leg orthoses are used: (**a**) pediatric leg orthosis for children with a femur length between 21 and 35 cm or (**b**) adult leg orthoses intended for patients with a femur length between 35 and 47 cm. The patient is fixated with three cuffs per leg to the legs of the orthosis. The hip and knee joint of the device are actuated. Until now, the device is position controlled, meaning that the relationship between hip and knee movements is fixed. Stumbling is prevented by elastic straps that keep the feet in dorsiflexion. The Lokomat system can be adjusted to get the best possible fit for each patient. Especially young patients become motivated by the game scenarios (in **a** the Gabarello game is shown) that provide an online feedback about the patient's active participation. Recent developments, currently under investigation, include a free D modus (moveable pelvis and leg cuffs), new control mechanisms (i.e., path control rather than position control), and innovative virtual scenarios (With kind permission from the University Children's Hospital Zurich)

Fig. 14.4 (continued)

training. It has been criticized that fixation during RAGT might be too strong to improve balance. Results of Druzbicki et al. [42] were therefore somewhat unexpected, as they showed improvements in balance after RAGT in children with CP. Improvements in hip and knee stiffness were observed after a single session of RAGT, especially in children with higher levels of spastic hypertonia [43].

An advantage of RAGT is that additional virtual reality scenarios can motivate the children while simultaneously providing feedback about the active participation of the child. Patritti et al. [44] suggested that augmented feedback techniques appear to be associated with better motor outcomes. Brütsch et al. [12] showed that RAGT with virtual reality could lead to more challenging situations during training. In subsequent studies, active participation of healthy children and children with neurological gait disorders could be increased with instructions of the therapist, virtual reality, or a combination of the two. Children showed higher biofeedback values (more activity) [11] and increased leg muscle activation [15] during RAGT with virtual reality compared to other interventions. Even within one single session of RAGT with virtual reality, children can modify their participation, according to the challenging situations within the game [14]. Higher levels of muscle activity and heart rate during demanding parts of a virtual reality game were observed. Furthermore, game performances correlated moderately with the cognitive capacity of patients. Electromyographic data of children with neuro-orthopedic disorders could confirm that virtual reality or verbal encouragement from therapists increased leg muscle activity, while the pattern of activation remained physiological [45]. Additionally, these results suggest that RAGT with the Lokomat in general exploits restorative rather than compensatory walking patterns [45].

Who might profit most from RAGT? Patritti et al. [44] indicated that less severely affected patients (GMFCS level II against GMFCS level III patients) improved significantly more in clinical outcomes as well as gait biomechanics. This contradicts recent findings from van Hedel et al. [46]. Improvements in walking activity were larger and correlated better with the number of Lokomat trainings in more severely affected patients with CP (i.e., GMFCS levels III and IV) compared to the less affected patients (GMFCS level II), whose changes corresponded better with the number of conventional physical therapy sessions.

A recent study of Schroeder et al. [47] could show with a prospective controlled cohort of 18 children with bilateral spastic CP that significant improvements in the ICF-CY domains of activity and participation occur after 12 sessions of RAGT. Clinically meaningful changes could be observed when including all children and youths (GMFCS levels I–III). However, the authors found a tendency that younger patients responded better than older patients, as did less severely impaired patients and patients who absolved RAGT for the first time. This teaches us that age and previous training have to be considered as relevant variables when trying to induce gross motor improvements. Furthermore, maintaining gross motor performances over time might be a more realistic goal especially for more severely affected patients [47]. Another recently published study of Schroeder et al. [48] detected that gross motor abilities at baseline as well as age were relevant patient-specific determinants of responsiveness to RAGT in children. No association could be found for the changes in gross motor performances and the variables sex, diagnosis, and botulinum toxin injection prior to the therapy block. Overall, a high interindividual variability in treatment response was found for the 83 included children with CP [48].

To our knowledge, there are currently only two randomized controlled trials performed. A randomized controlled trial evaluated the effectiveness of repetitive locomotor training with the Gait Trainer GT I versus conventional training in 18 ambulatory children with diplegic and tetraplegic CP [49]. Gait velocity and endurance in children absolving RAGT were significantly improved and maintained at 1 month after the treatment had finished. No significant changes in the parameters were observed in the control group, and a between-group comparison showed that the effects of the experimental and the control

treatments were significantly different in all primary outcome measures. These results appear very promising for the field of pediatric RAGT, but, unfortunately, the inclusion criteria and patient characteristics are sometimes unclear. A better description could have helped to determine potential responders and nonresponders an important issue in rehabilitation research. The first randomized controlled trial for RAGT with the pediatric Lokomat was performed by Druzbicki et al. [50]. They concluded that children with spastic diplegic CP slightly improved their walking speed, but without significant differences between the intervention or control group. Unfortunately, also this study comprises many methodological limitations; the effectiveness and efficacy in children and youths are still inconclusive.

Therefore, we consider algorithms and recommendations (as partly presented in this book chapter or as proposed for children with CP by Aurich-Schuler et al. [35]) as a valuable contribution to the development of standardized training approaches. Such recommendations should take into account patient-specific impairments and therapy goals. In our experience, besides biomechanical and pure motor control reasoning, we propose that additional factors play an important role in pediatrics, i.e., personal factors such as fear or motivation. For example, consider a child with rather good walking ability but problems in dual-task performance during overground walking due to fear of falling. Within the safe environment of robotic therapies, the child could first exercise dual tasks (with or without motivating virtual reality scenarios), before changing to treadmil training and finally overground walking while simultaneously performing more daily life-related dual-task exercises.

14.6.4 Clinical Application Based on Best Practice

14.6.4.1 The Lokomat System

Most of the RAGT devices provide bodyweight support or at least support for vertical postural control. In the following paragraphs of this chapter, we will focus on the Lokomat (Fig. 14.4). The Lokomat is one of the most widely distributed robotic systems (>550 adult and >200 pediatric devices worldwide). It is also by far the most studied system, and we gained considerable clinical experience in its application.

14.6.4.2 Patient Selection

In general, rehabilitation physicians together with physical therapists and human movement scientists estimate the potential risks and therapeutic benefits of RAGT for each patient. Feasibility of RAGT for a particular patient is determined during a trial session subsequent to the initial medical consultation. Feasibility is given if the robotic device can be well adjusted to the patient. It should not cause discomfort, and necessary prerequisites for applying a physiological gait pattern should be achieved (e.g., sufficient knee extension during stance, ample knee and hip flexion during swing). Other important guidelines are the inclusion and exclusion criteria, as defined by the manufacturer or recently published experience-based recommendations [35]. Particularly important are the allowed anthropometrics and therapy compliance. Rather than relying on a minimum age (e.g., 4 or 5 years), we recommend evaluating the cognitive state, especially of very young patients and for intensive therapy programs. The patient should have a certain understanding of the treatment situation and should be able to respond adequately to demands that arise during RAGT. For patients who underwent orthopedic or neurosurgical procedures, clinical pathways were developed to standardize the process of gait rehabilitation and to find the best onset for RAGT [35]. Abnormal muscle tone expressed as spasticity, hypotonus, or dyskinetic movements needs to be considered carefully before, during, and after the training, as they might influence the training parameters. Training might be improved in patients with severe spasticity when the dosage of antispastic medication is optimized or botulinum toxin injections are applied several weeks prior to the onset of the training period.

14.6.4.3 Initial Assessment and Training Over Time

The integration of RAGT in the overall therapeutic setting and therapy frequency depend on patient-related, infrastructural, and economic aspects as well as the organization of the particular health-care system. Two or three, up to five sessions per week have been suggested. However, best therapy intensity, duration, and frequency are topics of ongoing clinical research and still to some extent controversial [47]. The therapy intensity depends on the current individual treatment priorities and whether they can be supported with RAGT. To encompass the various needs of young patients, different intensity programs may be useful to cover specific rehabilitation targets:

I. A *low-intensity* program for patients who have little potential for regaining independent walking. The main goal is to initiate some stepping or to improve other functions, such as verticalization or muscle tonus regulation. This intensity could also be applied to patients where the goal is to maintain the current level of walking ability.
II. A *moderate-intensity* program to train gait-related aspects/parameters for patients who are capable of ambulating overground or for nonambulating patients who are very motivated to improve their function.
III. A *high-intensity* program to achieve or maintain overground walking ability, with or without assistive devices, during rehabilitation, re-rehabilitation, or also after orthopedic or neurological surgery or after muscle tone-reducing botulinum toxin injections.

Like any other training devices, rehabilitation robots should be operated from experienced therapists in a flexible manner, with well-defined therapy goals and in combination with additional exercises [35]. Therapeutic procedures and objectives should change in agreement with motor function progression. Therapists should combine different devices or technical features to implement new challenges, or they have to decide when and how to replace RAGT gradually by other interventions.

We recommend that the first training session should be scheduled for 60 min and conducted by two experienced therapists (ideally a physiotherapist who knows the patient and a therapist who is experienced with the robotic device). We advise a ramp-up period with a gradual increase of training duration (e.g., 20–30–35 min) depending on the patient's fatigability and compliance. Training periods of more than 45 min are difficult, because children are often not able to keep motivation and concentration up for so long, and appropriate activity cannot be assured anymore.

Initially, about 50–60 % bodyweight support should be provided. Already in the first sessions, this can be gradually decreased in patients who are familiar with walking and loading and who can extend their knees during stance. Bodyweight support should be gradually decreased according to the patient's capacity while assuring a tolerable loading response with adequate knee extension during stance. Taking over bodyweight also reduces the pulling of the harness and alleviates soft-tissue pain.

Guidance force should initially be set to 100 % for safety reasons, except when the cuffs cause painful pressure, for example, in the case of contractures. Training with reduced guidance force can increase the interaction of the patient with the robot allowing a diversification of training possibilities and a more independent gait pattern. Nevertheless, we do not recommend training below 60 % of guidance force in children. Unpublished data from our group showed surprisingly that leg muscle activity levels did not increase when reducing the guidance force. Therefore, if patients should increase in leg muscle activation, we recommend to use other strategies than reducing guidance force (e.g., walking faster or have therapists verbally encouraging the children to remain active).

If knee and ankle joint control is a main focus of the therapy, we suggest training with minimal bodyweight support combined with a reduced guidance force. The focus should be made on controlling the knee positioning during heel strike and loading phase and performing an optimal knee extension during stance phase. New robot control strategies (patient-cooperative

assist-as-needed) and new technical developments with more kinematical freedom are in focus to allow a more active, variable natural walking (see outlook).

Experienced-based data display that walking velocity in children and adolescents is usually set between 1.0 and 1.8 km/h for the pediatric module and between 1.6 and 2.4 km/h for adolescents in the adult module. The walking speed should not be too fast (pediatric module ≤2.0 km/h; adult module ≤2.5 km/h) to allow the child to concentrate on a physiological walking pattern or specific tasks. Having mentioned that, unpublished data from our group show that muscle activities increase in a physiological manner when walking at higher velocities. In patients with severe spasticity, a lower speed is recommended to prevent an increasing muscle tone.

The Lokomat lacks a driven ankle joint. The use of elastic foot lifters is strongly recommended to avoid stumbling, especially for patients with difficulties to control their ankle dorsiflexion actively during swing. Recent studies could show that the muscular activity of the shank is not largely affected when wearing foot lifters, provided that they are not tied up too strong [15, 45].

The patient's participation can be visualized by the Lokomat's biofeedback line charts. The therapist should read the data carefully to not overinterpret the patient's activity because both biofeedback and virtual reality scenarios that use these data are strongly affected by spasm or compensatory movements. The complexity of this feedback modus requires the therapist to translate these graphs into easy-to-understand patient instructions. However, to participate in daily life, patients also have to relearn indoor and outdoor walking abilities. Walking in daily life consists mostly of a dual-task or multitask activities, such as walking and looking around, walking and talking, walking and handling something, adapt walking to changes of the ground, or negotiating obstacles.

14.6.5 Outlook

Despite the fact that most studies report improvement in walking capacity, there is currently no conclusive evidence about the efficacy of RAGT in young patients with neurological movement disorders. Various smaller studies should be performed to develop evidence-based guidelines on the application of RAGT, followed by well-designed large-scale controlled studies. RAGT could play an important role in future directions for rehabilitation research. It allows excellent documentation of training (duration, the number of steps, bodyweight support, guidance force, etc.), which could be useful in investigating dose-response relationships. Furthermore, RAGT allows the documentation of (changes in) body functions and walking-related outcome that are currently difficult to assess with clinical assessments (e.g., joint torques, active participation during RAGT). This also applies to patients who are still not able to walk overground. The future success of RAGT and its impact on the advancement of neurorehabilitation might be dependent on the input of the clinical users on the further development of this concept and a close translational cooperation between clinicians and rehab engineering.

Besides randomized controlled trials, we could also learn from collecting large amounts of data from various centers that apply the same technology worldwide, but with variations in dosage, patient's characteristics, or application protocols. One of these endeavors has recently started. In the Advanced Rehabilitation Technology Integrated Centers (ARTIC) network, several centers in the USA, Asia, and Europe agreed on applying a basic dataset of patient characteristics, assessments, and data that can be directly imported from each Lokomat training. Despite that this network has started only recently, several hundreds of cases have already been documented in the database.

Finally, it remains questionable how much of the improved functions during RAGT can be translated to overground ambulation. We think that one of the factors limiting a good transfer might be the reduced complexity of walking movements during RAGT. The patient can focus solely on performing nice physiological leg movements, and this does not take into consideration the large complexity of overground ambulation,

Fig. 14.5 Innovative movement therapy in childhood. Screenshot taken from the serious game *Magic Castle*. In an effort to perform a dual-task training early during rehabilitation, several games were developed by serious game designers from the Zurich University of the Arts. In *Magic Castle*, the avatar of the young patient is a little wizard who travels on the back of an animal. If the child is a little active in the Lokomat system, this animal is a snail. If the child becomes more active, the animal switches from the snail to a turtle or a sheep. The dual task consists of pointing the magic wand of the therapist on objects that are displayed in the game. When the wizard points sufficiently long at an object (i.e., accurate and prolonged pointing task), the object becomes alive, and the child playing the game gets additional points (Picture with kind permission of the Zurich University of the Arts/Specialization in Game Design)

where dual-task performance is a prerequisite for successful, safe ambulation. We have therefore started with collaborators from the technical university and serious game designers to modify Lokomat training. A new software allows to train an additional task (with the upper extremity) within the Lokomat. In the newly developed games (Fig. 14.5), the focus is still on performing active stepping movements in the Lokomat, but the additional voluntary upper extremity tasks should force the patient to divide his attention. This dual-task approach should resemble the cognitive load experienced during overground ambulation. We hypothesize that such a training incorporated in an early phase of rehabilitation might slow down the initial skill acquisition, but will improve the generalizability from RAGT to overground walking.

14.7 Technology-Supported Upper Extremity Rehabilitation in Children

Parents of children undergoing neurorehabilitation often communicate that they prioritize improvements in gait above changes in upper extremity function. However, it should not be forgotten that arm and hand functions are important prerequisites for many activities of daily living and therewith independence. As conventional training performed by occupational or physical therapists of the arm and hand is very labor-intensive, more and more systems to train the upper extremity have entered the field of rehabilitation in the past years. More recently, therapists have started to apply these systems to children with neurological diagnoses. Not all systems

Fig. 14.6 The upper extremity end-effector device InMotion2 (Interactive Motion Technologies, Watertown, MA, USA) allows to train planar movements in a two-dimensional workspace. This device is nowadays probably the best investigated upper extremity rehabilitation robot in pediatrics (Picture with kind permission from Interactive Motion Technologies)

were specifically modified to be applied to young patients. While the anthropometrics were changed for some exoskeleton systems, it was often forgotten to adjust the games to the requirements of a younger target group, and children had to play games initially developed for senior patients after stroke.

Compared to the lower extremity, it seemed to have taken longer to develop and introduce rehabilitation technologies aiming at improving upper extremity functions in the clinical field. It is likely that the relative few degrees of freedom of the lower extremity and the cyclical rhythmic walking pattern encouraged engineers in an earlier phase to develop assisting technologies. However, despite the higher complexity, new technologies were introduced during the last years to train arm and hand function. Due to these late developments, evidence is still very scarce, and the best application is therefore still largely based on clinical experience.

14.7.1 Overview of Pediatric Upper Extremity Systems

This paragraph is intended to provide a short, most likely incomplete, list of commercially available devices that would enable to train arm and hand function in children and youths. Please note that some of these devices are discussed later in greater detail.

The pediatric Armeo Spring (Hocoma AG, Volketswil, Switzerland) is a weight-supporting exoskeleton device with integrated springs. The tension of the springs can be adjusted to support the weight of the arm against gravity and enables to train movements in three dimensions. Its anthropometrics were adjusted to enable children from age 5 and higher to train into the device.

The InMotion2 (Fig. 14.6) is the commercially available version of the MIT-Manus (Interactive Motion Technologies, Watertown, MA, USA). It is an end-effector robot assisting planar two-dimensional pointing movements of the shoulder and elbow. It appears to be currently the most frequently investigated upper extremity device in children and youths.

The Bi-Manu-Track allows active and passive training, including pronation and supination of the forearm, extension and flexion of the wrist, and extension in the metacarpophalangeal joints (Reha-Stim Medtec GmbH, Berlin, Germany).

Another device that can be used to train active, assistive, or passive is the Amadeo (Tyromotion GmbH, Graz, Austria). This device focuses on hand and finger movements. Several games can be played by performing adequate finger or hand

Fig. 14.7 Training elbow and shoulder movements with the Pablo sensor system (Tyromotion GmbH, Graz, Austria). Besides enabling a playful training, the Pablo system is also intended to perform standardized assessments of the upper extremity (Picture with kind permission from Tyromotion)

movements. The first version of the device was not specifically developed for children, and it was difficult to fixate smaller hands to the sledges that move the fingers and thumb in flexion and extension movements. A new version has been released that takes into account the anthropometrics of smaller children and includes more games to allow a more variable training program. The same company also distributes the Pablo (Fig. 14.7). This system allows assessing strength or training playfully various movements, including pronation and supination or flexion and extension of the wrist. However, due to the size of the handlebars, it seems that it will be difficult to use for children aged below about 12 years.

A glove-based system with no support but with games to train arm and grasping movements is the YouGrabber system (YouRehab Ltd., Schlieren, Switzerland). It contains two data gloves, an infrared camera, and display. It enables an interactive training, and games can be selected and set to train specific single-joint movements, more complex multi-joint movements, including bilateral movements, or, for example, mirror training.

When rehabilitation specialists and management have to make a decision on what system to purchase, several questions appear relevant: the patient group with its specific impairments and severity (e.g., age groups, more proximal or distal impairments, cognitive capacity), the costs (purchase and annual recurring), practicability (e.g., time needed for donning and doffing, but also how easy it is to use for patients and therapists), and the available space. It might make sense to convince the supplier to deliver a system and test it first for a couple of months before deciding to buy.

14.7.2 Clinical Evidence

In adults with stroke, a meta-analysis concluded that adult patients after stroke who received electromechanical or robot-assisted arm training were more likely to improve their generic activities of daily living. The paretic arm function improved also, but not arm muscle strength [51]. Considerably less literature (and of less methodological quality) is available on the application and effectiveness of upper extremity devices in children and adolescents with congenital or acquired brain lesions (for an overview see also, e.g., Meyer-Heim and van Hedel [52]). The end-effector robot InMotion2 (Interactive Motion Technologies Inc., Watertown, MA, USA) was first applied to 12 children aged between 4 and 12 years with upper limb hemiplegia caused by congenital or acquired brain injury [53]. These children continued with their community-based

therapy while they received 1 h of robotic training, twice a week for 8 weeks. Per session, they performed 640 repetitive, goal-directed planar reaching movements with their paretic arm (mainly shoulder and elbow movements). The Quality of Upper Extremity Skills Test (QUEST) and the Fugl-Meyer upper limb subtest improved, while the parents reported improvements in "how much" and "how well" the paretic arm was used in daily life tasks [53]. The InMotion2 system was also evaluated by Frascarelli et al. [54] in a similar patient group. After 18 sessions, the Melbourne Scale, the Fugl-Meyer upper limb subtest, the Modified Ashworth Scale, the Reaching Performance Scale, smoothness and velocity of movement derived from the robotic system improved. Compared to the previously mentioned study by Fasoli et al. [53], patients had now no additional therapies (but a control group was still lacking). A later study showed further that children with CP had more difficulties than typically developing children in learning to adapt to a novel dynamic environment [55]. Nevertheless, in 12 children with CP aged 5–12 years, it was shown that robot-based evaluations improved significantly in trained movements. Improvements were sustained at follow-up, and children improved their performance in untrained movements indicating generalization [56].

The New Jersey Institute of Technology Robot-Assisted Virtual Rehabilitation system (NJIT-RAVR, see [57]) comprises a HapticMaster (Moog, the Netherlands) in combination with a custom-made gimbal ring. The system has 6 degrees of freedom and is force controlled. In the first study, only two children with CP were tested who performed several "games" in a virtual reality environment. Therapeutic goals were improving speed and accuracy of shoulder and elbow movements, general upper extremity strength, or improving forearm pronation and supination. In a subsequent study, nine children with CP performed 9, 60-min, training sessions, which included this system [58]. Overall, the young patients improved in the Melbourne Assessment of Unilateral Upper Limb Function test, a composite of three timed upper extremity tasks and several measurements of reaching kinematics.

In our opinion, it is important to combine such systems with games that playfully motivate the children to perform many movement repetitions. Indeed, a previous review evaluated the effectiveness of virtual reality alone (i.e., without robotic or mechanical supporting system) to improve upper limb function in children with neurological impairments [59]. Children with CP participated in four out of five studies, but for most studies the number of participants was very small. Only in the randomized controlled trial from Reid and Campbell, who evaluated the GestureTek Extreme IREX VR, 19 children with CP were in the experimental group, while 12 received conventional care [60]. Also included was a study that evaluated the glove-based virtual reality system nowadays known as YouGrabber (see previous paragraph) in five children with congenital and acquired central and peripheral neurological lesions [61]. After 3 weeks of training, some improvements were observed, and patient motivation remained high throughout this period. The YouGrabber system was later evaluated in a small randomized controlled pilot trial [62]. Changes in hand and key-pinch strength and manual dexterity, quantified by the Box and Block Test (BBT) and the Nine-Hole Peg Test (NHPT), were examined. Ten children with CP were in the experimental group and received 12 therapy sessions (each lasting 45 min). The seven children in the control group performed computer games for a similar amount of time, which required no large hand and arm movements. The BBT tended to improve more, and effect sizes for most measures were larger in the experimental group suggesting that children with CP might profit from such an intervention [62].

It seems that the development of new systems is growing rapidly now, and despite the rather small field of pediatric neurorehabilitation, many groups are developing new systems to train arm and hand function (see, e.g., the new Handreha haptic device developed for children aged 7–14 years with hemiplegia [63] or the pediatric robotic thumb exoskeleton for at-home rehabilitation [64]). Unfortunately though, as presented in this overview, well-designed randomized controlled studies evaluating the effectiveness of

these systems are merely lacking. Recently, Gilliaux et al. [65] performed a first randomized controlled trial investigating the effectiveness of robot-assisted therapy in children with CP. Sixteen children were divided in two groups and received five therapies (each lasting 45 min) per week for 8 weeks. One group received five conventional therapies per week, while the other group received two robotic and three conventional interventions. The robotic device was an end-effector robotic prototype called REAplan. Per session, participants performed on average 744 movements with the robot. The smoothness of movement and the Box and Block test improved significantly more in the patients who received the combination of conventional and robotic training compared to those who received solely conventional training. It seems therefore justified to conclude that despite that well-designed sufficiently powered studies are lacking in this field, the application of such technologies complementing conventional interventions seems promising for children undergoing neurorehabilitation.

14.7.3 Clinical Application Based on Best Practice

14.7.3.1 Upper Extremity Systems

In our center, occupational therapists apply since several years the YouGrabber, pediatric Armeo Spring, and Amadeo. We selected these devices because, in our opinion, they provide different levels of support therewith covering a range of patients with various levels of impairments (see blue triangles in Fig. 14.8).

The YouGrabber system has no active or passive structures that support the patient, so the patient has to be fully active to train with the device. Some alleviation of the intensity can be performed by having the patient placing his hands on the table (e.g., on a cloth) while performing movements. The YouGrabber consists of two data gloves (sizes xs to xl) that contain three bending sensors for the thumb, index, and middle finger and a sensor positioned on the back of the glove. Also, it is combined with an infrared camera that tracks the position of the hand in space. While the sensors hardly limit movements of the hand and arm, the bending sensors for the thumb, index, and middle finger are nowadays unfortunately only available in one size. This makes it more difficult to adjust it to children with smaller hands. On a monitor in front of the patient, games can be displayed that should motivate the young patient to perform many repetitive movements. As the system has no means to support or assist movements, patients should be able to initiate and perform at least some movements (of elbow or shoulder) against gravity. In specific cases, it can also be used to train finger movements specifically. The system has several advantages compared to other systems. For example, it allows besides a unilateral training also a bilateral training, and it can be used to perform virtual mirror movement training. Also, the workspace of the games can be adjusted to the individual active range of motion of the patient. The therapeutic goals that can be achieved with the system are described in Fig. 14.8.

Figure 14.8 also shows the pediatric Armeo Spring. This exoskeleton device is officially not a robot, as it does not contain any actuators, but it has springs that support the weight of the upper and lower arm, thereby alleviating arm movements against gravity. Single joints of the device can be set to move freely or fixated (e.g., to train single-joint movements in other joints). It also contains a pressure-sensitive hand module that allows training arm movements with grasping hand movements. It is the commercial version based on the T-WREX system, which was initially developed for adult patients by Reinkensmeyer and colleagues [66]. In our center, the pediatric version is applied especially to patients who have at least a minimal function of the elbow or shoulder. Besides that it can be used to train the initiation of movements, it can be used to maintain or improve reach, grasp, and transfer movements, as well as active range of motion and force regulation. For many games, the therapists can select whether active grasping movements should be performed or not. As the device can be well adjusted to different body sizes, strength, and range of motion of the patient, it can offer an individually optimized support of the patient. A monitor is placed in front of the patient, which allows an online feedback on the patient's movement performance, while the games should encourage the patient to continue with the training.

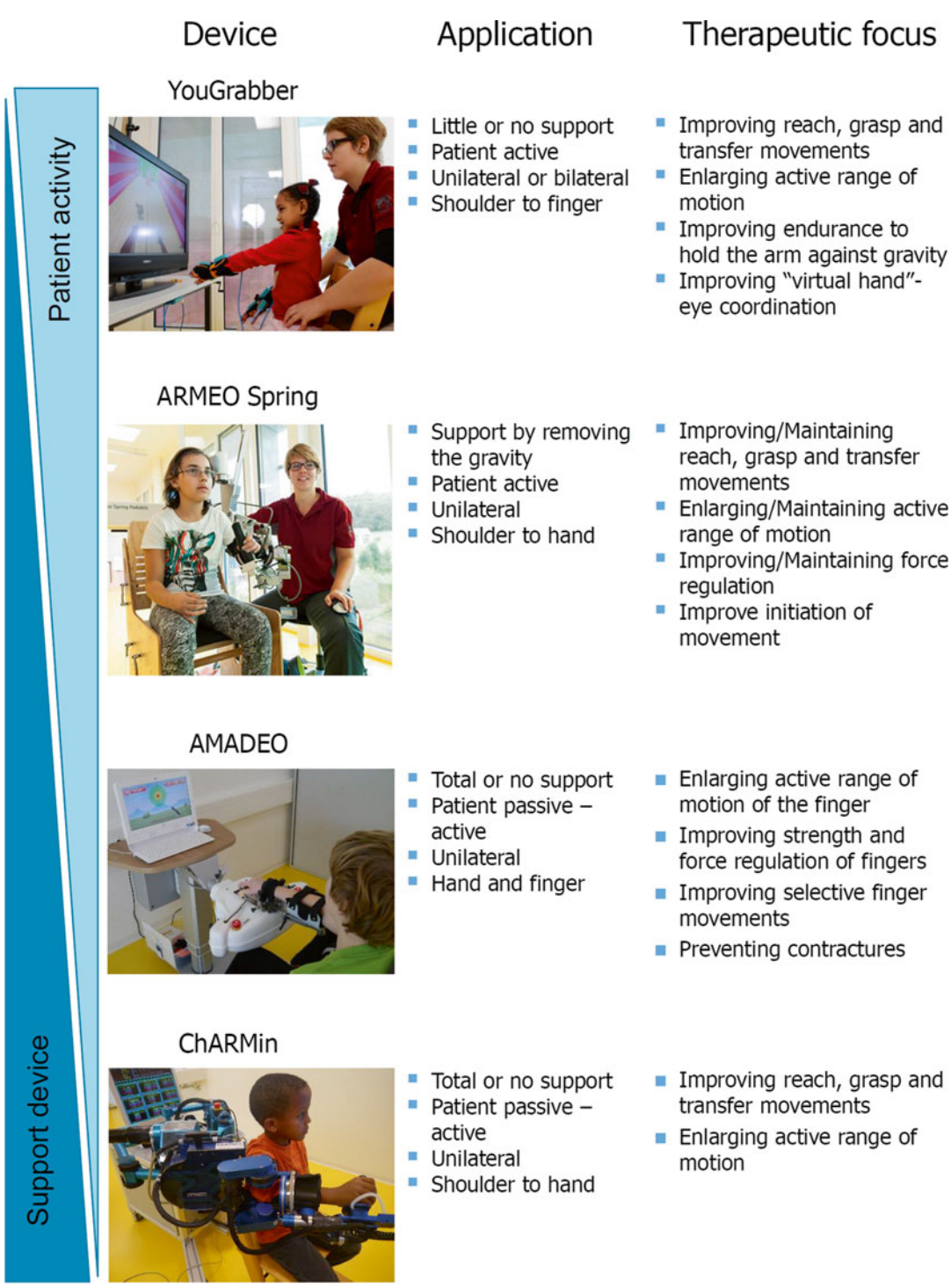

Fig. 14.8 These systems (YouGrabber, YouRehab GmbH, Schlieren, Switzerland; Armeo Spring, Hocoma AG, Volketswil, Switzerland; Amadeo, Tyromotion GmbH, Graz, Austria; and the ChARMin, Sensory-Motor Systems Lab of the ETH Zurich and the Rehabilitation Center of the University Children's Hospital Zurich, Affoltern am Albis, Switzerland) allow different levels of support and can cover a continuum from severely affected young patients to patients with few impairments. The *light blue triangle* reflects differences in impairment and activity of the patient. The more affected a patient is and the less active he or she can be, the more support from the system (*dark blue triangle*) is required. Furthermore presented are the main characteristics of the device and the therapeutic goals that might be achieved with the device (With kind permission from the University Children's Hospital Zurich)

The Amadeo (Fig. 14.8) was specifically developed to train hand and finger opening and closing. Fingers and thumb are fixated with special adhesive patches and small magnets to sledges of the device that bend and extend the fingers and thumb. The device can be unilaterally applied, while fingers and thumb can be trained in an active, assistive, or passive modus. In the active modus, various games can be played that train strength or active range of motion. In the assistive and passive modes, mobilizing movements are induced by the device, while the patient is encouraged to move with the device and take over if possible. In the first version of the Amadeo, games could not be performed in these modes. The Amadeo depicts on the screen how much activity the patient provides. In the passive modus, the device completely takes over the fingers and thumb according to the predefined range of motion and movement velocity set by the therapist.

Prior to the training, the therapist can calibrate the range of motion of each finger separately. This allows an optimal range of motion throughout the training, but would also allow the therapist to block several fingers to enable a patient to focus on and train one specific finger if therapeutically meaningful. Training with the Amadeo is especially indicated for children and adolescents who experience reduced selective voluntary motor control or limited range of motion of the fingers or reduced strength (control) of the hand. Depending on the functional impairments, the therapist decides what the best modus of the device would be to train the child. As the Amadeo was initially developed for adult patients, the sledges of the device are positioned relatively far from each other, also including the sledge for the thumb. This makes it difficult for children and young adolescents with small hands to perform physiological movements of fingers and thumb simultaneously. The company constructed the new version of the device differently. Now also children with smaller hands should be able to train physiological hand movements.

The Children's Arm Rehabilitation Mechatronic Interface or ChARMin (Fig. 14.8) is a newly developed exoskeleton upper extremity robot with actuated joints. It is intended to train shoulder, elbow, wrist, and hand grasping movements of more severely affected children and adolescents. The development and technical aspects of ChARMin are described in Chap. 17 (Riener 3D Arm Robot ARMin). The feasibility of the device will be tested in children and youths undergoing neurorehabilitation as soon as the ethical committee and the Swiss authorities approve the device.

14.7.3.2 Patient Selection

There are some general inclusion criteria for applying upper limb rehabilitation devices in children undergoing neurorehabilitation. Particularly important appear the anthropometrics (device dependent) and therapy compliance. A minimum age of 5 is recommended because of the anthropometrics and from clinical experience. Children aged 5 years and older can understand the therapy situation and should be able to respond adequately to the demands of the training. Children with various diagnoses are trained with such technologies, including children with congenital (CP) or acquired brain lesions (e.g., stroke, traumatic brain injury, encephalitis). Other diagnoses are spinal cord injury, degenerative diseases of the upper extremity joints, muscle weakness caused by immobilization, or muscle atrophy. There are many contraindications, although most are relative. Contraindications depend on the device that will be applied and should always be discussed with the responsible physician. Examples of such contraindications are severe adipositas (e.g., the arm cannot be fitted into the orthosis), severe joint contractures, joint instabilities, fractures, osteoporosis, allergic against material that is in contact with the skin, or open skin lesions. Depending how well the device can be disinfected, patients with contagious infections should not train with such technologies. Relative contraindications can be lesions of nerves, pain in the upper extremity (e.g., shoulder), or strong spontaneous movements such as seen in children with ataxia, dystonia, or with myoclonic twitches. Also instable vital functions (e.g., pulmonary or cardiovascular), apraxia, strong visual impairments, strong spasticity (Modified Ashworth 4), or severe epilepsy can be

relative contraindications. Besides, severe cognitive deficits, uncooperative or aggressive behavior, and insufficient trunk and head stability or the inability to position the patient well in the device can cause that such interventions cannot take place. In general, several of these issues can be cleared if an initial test training is performed.

14.7.3.3 Initial Assessment and Training and Course of Training Over Time

Prior to the first training, a physician sees the young patient and evaluates the indication and potential contraindications for upper extremity robotic-supported or computer-assisted interventions. Furthermore, in a first session, therapists perform several assessments to evaluate the functional abilities and limitations of the patient. These assessments include evaluating grasping, transferring and releasing objects (e.g., with the Box and Block Test; gross motor functioning), collecting coins and performing the Nine-Hole Peg Test (fine motor functioning), opening and closing a bottle, and manipulating small objects to investigate bimanual tasks. Also, therapists test muscle strength (Jamar dynamometry of hand and finger strength and manual muscle tests of more proximal muscle groups). They evaluate sensory function and might perform Modified Ashworth tests to score the severity of spasticity. We are still in a process of optimizing the assessments. We recently started to introduce the Goal Attainment Scaling, to evaluate whether goals defined by patients and their parents on the ICF activity domain can be achieved at the end of the rehabilitation period. Also, in some children we apply the Assisting Hand Assessment or the Melbourne Assessment of Unilateral Upper Limb Function.

After the assessments, one or more devices are tested with the patient to see what might be the best device with respect to the functional and cognitive abilities of the patient and the therapeutic goals that are defined together with the parents. Information concerning this test session is communicated to the physician, and together the decision is made whether the child should receive such training in addition to conventional occupational and physiotherapeutic therapy. A training session lasts 45 min and includes the donning and doffing of the system. The effective training time amounts therefore to about 30–35 min. A selection of the therapeutic games is based on the individual requirements of the patient and the therapeutic goals. We recommend that training takes place three to five times per week. Based on unpublished data from our group, at least 12 training sessions are recommended, as this can result in significant functional improvements [62]. Training is complemented with high-intensive conventional occupational therapy, as well as strength training or sports.

The intensity of training with rehabilitation devices can be increased over time. Besides a prolongation of the training duration or the number of repetitions, therapists can reduce the hands-on support that they might provide at the onset of the training. More difficult, complex, or faster games can be selected, or the child can switch from one system with considerable arm support to another system with less or no support.

With some systems such as the YouGrabber, other difficulty levels can be achieved. The child can be placed on an unstable surface (trunk balance in combination with upper extremity movements) or increase the strength component by playing the game while a Thera-Band is attached to the arm. Indeed, it is not uncommon when a system like the YouGrabber is used at a certain point to improve trunk stability rather than upper extremity function. Sometimes, rather than reducing the support of the system, the therapist might increase the difficulty level by choosing a more complex game to keep the motivation of the child higher. Therapists should develop the confidence and creativity to play around with such rehabilitation technologies to find solutions that fit best to the requirements of the patient. At the end, it is the difficult task of the therapist to get a feeling to what approach the child might respond best to.

14.7.4 Outlook

The systems that are currently applied allow still possibilities for improvements (e.g., graphics, practicability, the robustness of hard- and

software, costs). Currently, the knowledge and flexibility of the therapist are often required to solve problems when patients train with these devices. On the short term, research is needed toward evidence-based guidelines on how to apply these technologies and who might profit from them. In the future, it would be desirable that upper (but also lower) extremity rehabilitation systems could detect nonphysiological movements and apply corrected physiological ones to assist the therapist. Likely, these systems would be especially driven exoskeleton devices that could detect such deviations and apply corrected movements. Only then, it might become possible that in the field of pediatric neurorehabilitation, a single therapist could treat several patients simultaneously. This could reduce health-care costs while keeping the quality of the intervention to an acceptable level.

Conclusion

As a general conclusion, it should be mentioned that the application of rehabilitation technologies in pediatric neurorehabilitation is emerging. More work has been done on the lower extremity compared to the upper extremity. Still, the level of evidence of the effectiveness of the various applications appears inconclusive. The number of studies and the number of participants included in these studies are generally small, and most studies lack a control group. The pediatric field should work to substantiate the evidence in the next years. We should identify responsive patient groups, come up with objective and responsive functional outcome measures, and initiate collaborations with other centers to recruit appropriate sample sizes.

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References

1. O'Shea TM. Diagnosis, treatment, and prevention of cerebral palsy. Clin Obstet Gynecol. 2008;51:816–28.
2. Mayston M. Evidence-based physical therapy for the management of children with cerebral palsy. Dev Med Child Neurol. 2005;47:795.
3. Mayston MJ. People with cerebral palsy: effects of and perspectives for therapy. Neural Plast. 2001;8:51–69.
4. Verschuren O, Ada L, Maltais DB, Gorter JW, Scianni A, Ketelaar M. Muscle strengthening in children and adolescents with spastic cerebral palsy: considerations for future resistance training protocols. Phys Ther. 2011;91:1130–9.
5. Salem Y, Godwin EM. Effects of task-oriented training on mobility function in children with cerebral palsy. NeuroRehabilitation. 2009;24:307–13.
6. World Health Organisation ICoF. Disability and health, child & youth version: ICF-CY. Geneva: WHO; 2007.
7. Berker AN, Yalcin MS. Cerebral palsy: orthopedic aspects and rehabilitation. Pediatr Clin North Am. 2008;55:1209–25. ix.
8. Damiano DL, Alter KE, Chambers H. New clinical and research trends in lower extremity management for ambulatory children with cerebral palsy. Phys Med Rehabil Clin N Am. 2009;20:469–91.
9. Damiano DL. Activity, activity, activity: rethinking our physical therapy approach to cerebral palsy. Phys Ther. 2006;86:1534–40.
10. Holden MK. Virtual environments for motor rehabilitation: review. Cyberpsychol Behav. 2005;8:187–211, discussion 212–9.
11. Brutsch K, Koenig A, Zimmerli L, Merillat-Koeneke S, Riener R, Jancke L, et al. Virtual reality for enhancement of robot-assisted gait training in children with central gait disorders. J Rehabil Med. 2011;43:493–9.
12. Brutsch K, Schuler T, Koenig A, Zimmerli L, Koeneke SM, Lunenburger L, et al. Influence of virtual reality soccer game on walking performance in robotic assisted gait training for children. J Neuroeng Rehabil. 2010;7:15.
13. Koenig A, Wellner M, Koneke S, Meyer-Heim A, Lunenburger L, Riener R. Virtual gait training for children with cerebral palsy using the Lokomat gait orthosis. Stud Health Technol Inform. 2008;132:204–9.
14. Labruyere R, Gerber CN, Birrer-Brutsch K, Meyer-Heim A, van Hedel HJ. Requirements for and impact of a serious game for neuro-pediatric robot-assisted gait training. Res Dev Disabil. 2013;34:3906–15.
15. Schuler T, Brutsch K, Muller R, van Hedel HJ, Meyer-Heim A. Virtual realities as motivational tools for

robotic assisted gait training in children: a surface electromyography study. NeuroRehabilitation. 2011; 28:401–11.
16. Bilodeau EA, Bilodeau IM. Motor-skills learning. Annu Rev Psychol. 1961;12:243–80.
17. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabil Neural Repair. 2008;22:111–21.
18. Prange GB, Jannink MJ, Groothuis-Oudshoorn CG, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev. 2006; 43:171–84.
19. Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. Curr Opin Neurol. 2006;19:84–90.
20. Jacobs KM, Donoghue JP. Reshaping the cortical motor map by unmasking latent intracortical connections. Science. 1991;251:944–7.
21. Huang VS, Krakauer JW. Robotic neurorehabilitation: a computational motor learning perspective. J Neuroeng Rehabil. 2009;6:5.
22. Hornby TG, Reinkensmeyer DJ, Chen D. Manually-assisted versus robotic-assisted body weight-supported treadmill training in spinal cord injury: what is the role of each? PM R. 2010;2:214–21.
23. Winstein C, Wing AM, Whitall J. Motor control and learning principles for rehabilitation of upper limb movements after brain injury. In: Grafman J, Robertson IH, editors. Handbook of neuropsychology. 2nd ed. Philadelphia: Elsevier; 2003.
24. Bernstein N. The coordination and regulation of movements. New York: Pergamon; 1967.
25. Cai LL, Fong AJ, Otoshi CK, Liang Y, Burdick JW, Roy RR, et al. Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. J Neurosci. 2006;26:10564–8.
26. Duschau-Wicke A, Caprez A, Riener R. Patient-cooperative control increases active participation of individuals with SCI during robot-aided gait training. J Neuroeng Rehabil. 2010;7:43.
27. Duschau-Wicke A, von Zitzewitz J, Caprez A, Lunenburger L, Riener R. Path control: a method for patient-cooperative robot-aided gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2010;18:38–48.
28. Krishnan C, Kotsapouikis D, Dhaher YY, Rymer WZ. Reducing robotic guidance during robot-assisted gait training improves gait function: a case report on a stroke survivor. Arch Phys Med Rehabil. 2013;94:1202–6.
29. Lee C, Won D, Cantoria MJ, Hamlin M, de Leon RD. Robotic assistance that encourages the generation of stepping rather than fully assisting movements is best for learning to step in spinally contused rats. J Neurophysiol. 2011;105:2764–71.
30. Schuck A, Labruyere R, Vallery H, Riener R, Duschau-Wicke A. Feasibility and effects of patient-cooperative robot-aided gait training applied in a 4-week pilot trial. J Neuroeng Rehabil. 2012;9:31.
31. Taub E, Uswatte G, Elbert T. New treatments in neurorehabilitation founded on basic research. Nat Rev Neurosci. 2002;3:228–36.
32. Jennings KD, Connors RE, Stegman CE. Does a physical handicap alter the development of mastery motivation during the preschool years? J Am Acad Child Adolesc Psychiatry. 1988;27:312–7.
33. Messier J, Ferland F, Majnemer A. Play behavior of school age children with intellectual disability: their capacities, interests and attitude. J Dev Phys Disabil. 2008;20:193–207.
34. Majnemer A, Shevell M, Law M, Poulin C, Rosenbaum P. Level of motivation in mastering challenging tasks in children with cerebral palsy. Dev Med Child Neurol. 2010;52:1120–6.
35. Aurich (-Schuler) T, Warken B, Graser JV, Ulrich T, Borggraefe I, Heinen F, et al. Practical recommendations for robot-assisted treadmill therapy (Lokomat®) in children with cerebral palsy: indications, goal setting, and clinical implementation within the WHO-ICF framework. Neuropediatrics. 2015;46:248–60.
36. Meyer-Heim A, Borggraefe I, Ammann-Reiffer C, Berweck S, Sennhauser FH, Colombo G, et al. Feasibility of robotic-assisted locomotor training in children with central gait impairment. Dev Med Child Neurol. 2007;49:900–6.
37. Meyer-Heim A, Ammann-Reiffer C, Schmartz A, Schafer J, Sennhauser FH, Heinen F, et al. Improvement of walking abilities after robotic-assisted locomotion training in children with cerebral palsy. Arch Dis Child. 2009;94:615–20.
38. Borggraefe I, Schaefer JS, Klaiber M, Dabrowski E, Ammann-Reiffer C, Knecht B, et al. Robotic-assisted treadmill therapy improves walking and standing performance in children and adolescents with cerebral palsy. Eur J Paediatr Neurol. 2010;14:496–502.
39. Borggraefe I, Kiwull L, Schaefer JS, Koerte I, Blaschek A, Meyer-Heim A, et al. Sustainability of motor performance after robotic-assisted treadmill therapy in children: an open, non-randomized baseline-treatment study. Eur J Phys Rehabil Med. 2010;46:125–31.
40. Arellano-Martinez IT, Rodriguez-Reyes G, Quinones-Uriostegui I, Arellano-Saldana ME. Spatial-temporal analysis and clinical findings of gait: comparison of two modalities of treatment in children with cerebral palsy-spastic hemiplegia. Preliminary report. Cir Cir. 2013;81:14–20.
41. Borggraefe I, Klaiber M, Schuler T, Warken B, Schroeder SA, Heinen F, et al. Safety of robotic-assisted treadmill therapy in children and adolescents with gait impairment: a bi-centre survey. Dev Neurorehabil. 2010;13:114–9.
42. Druzbicki M, Rusek W, Szczepanik M, Dudek J, Snela S. Assessment of the impact of orthotic gait training on balance in children with cerebral palsy. Acta Bioeng Biomech. 2010;12:53–8.
43. Schmartz AC, Meyer-Heim AD, Muller R, Bolliger M. Measurement of muscle stiffness using robotic assisted gait orthosis in children with cerebral palsy: a

proof of concept. Disabil Rehabil Assist Technol. 2011;6:29–37.
44. Patritti B, Sicari M, Deming L, Romaguera F, Pelliccio M, Benedetti MG, et al. Enhancing robotic gait training via augmented feedback. Conf Proc IEEE Eng Med Biol Soc. 2010;2010:2271–4.
45. Aurich Schuler T, Muller R, van Hedel HJ. Leg surface electromyography patterns in children with neuro-orthopedic disorders walking on a treadmill unassisted and assisted by a robot with and without encouragement. J Neuroeng Rehabil. 2013;10:78.
46. Van Hedel HJ, Meyer-Heim A, Rüsch-Bohtz C. Robot-assisted gait training might be beneficial for more severely affected children with cerebral palsy: brief report. Dev Neurorehabil. 2015.
47. Schroeder AS, Homburg M, Warken B, Auffermann H, Koerte I, Berweck S, et al. Prospective controlled cohort study to evaluate changes of function, activity and participation in patients with bilateral spastic cerebral palsy after Robot-enhanced repetitive treadmill therapy. Eur J Paediatr Neurol. 2014;18:502–10.
48. Schroeder AS, Von Kries R, Riedel C, Homburg M, Auffermann H, Blaschek A, et al. Patient-specific determinants of responsiveness to robot-enhanced treadmill therapy in children and adolescents with cerebral palsy. Dev Med Child Neurol. 2014;56:1172–9.
49. Smania N, Bonetti P, Gandolfi M, Cosentino A, Waldner A, Hesse S, et al. Improved gait after repetitive locomotor training in children with cerebral palsy. Am J Phys Med Rehabil. 2011;90:137–49.
50. Druzbicki M, Rusek W, Snela S, Dudek J, Szczepanik M, Zak E, et al. Functional effects of robotic-assisted locomotor treadmill therapy in children with cerebral palsy. J Rehabil Med. 2013;45:358–63.
51. Mehrholz J, Hadrich A, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev. 2012;6:CD006876.
52. Meyer-Heim A, van Hedel HJ. Robot-assisted and computer-enhanced therapies for children with cerebral palsy: current state and clinical implementation. Semin Pediatr Neurol. 2013;20:139–45.
53. Fasoli SE, Fragala-Pinkham M, Hughes R, Hogan N, Krebs HI, Stein J. Upper limb robotic therapy for children with hemiplegia. Am J Phys Med Rehabil/Assoc Acad Physiatrists. 2008;87:929–36.
54. Frascarelli F, Masia L, Di Rosa G, Cappa P, Petrarca M, Castelli E, et al. The impact of robotic rehabilitation in children with acquired or congenital movement disorders. Eur J Phys Rehabil Med. 2009;45:135–41.
55. Masia L, Frascarelli F, Morasso P, Di Rosa G, Petrarca M, Castelli E, et al. Reduced short term adaptation to robot generated dynamic environment in children affected by cerebral palsy. J Neuroeng Rehabil. 2011;8:28.
56. Krebs HI, Fasoli SE, Dipietro L, Fragala-Pinkham M, Hughes R, Stein J, et al. Motor learning characterizes habilitation of children with hemiplegic cerebral palsy. Neurorehabil Neural Repair. 2012;26:855–60.
57. Qiu Q, Ramirez DA, Saleh S, Fluet GG, Parikh HD, Kelly D, et al. The New Jersey Institute of Technology Robot-Assisted Virtual Rehabilitation (NJIT-RAVR) system for children with cerebral palsy: a feasibility study. J Neuroeng Rehabil. 2009;6:40.
58. Fluet GG, Qiu Q, Kelly D, Parikh HD, Ramirez D, Saleh S, et al. Interfacing a haptic robotic system with complex virtual environments to treat impaired upper extremity motor function in children with cerebral palsy. Dev Neurorehabil. 2010;13:335–45.
59. Galvin J, McDonald R, Catroppa C, Anderson V. Does intervention using virtual reality improve upper limb function in children with neurological impairment: a systematic review of the evidence. Brain Inj. 2011;25:435–42.
60. Reid D, Campbell K. The use of virtual reality with children with cerebral palsy: a pilot randomized trial. Ther Recreation J. 2006;40:255–68.
61. Wille D, Eng K, Holper L, Chevrier E, Hauser Y, Kiper D, et al. Virtual reality-based paediatric interactive therapy system (PITS) for improvement of arm and hand function in children with motor impairment – a pilot study. Dev Neurorehabil. 2009;12: 44–52.
62. Van Hedel H, Wick K, Eng K, Meyer-Heim A. Improving dexterity in children with cerebral palsy – preliminary results of a randomized trial evaluating a glove based VR-system. Int Conf Virtual Rehabil. 2011:127–32.
63. Bouri M, Baur C, Clavel R, Newman CJ, Zedka M. "Handreha": a new hand and wrist haptic device for hemiplegic children. The Sixth International Conference on Advances in Computer-Human Interactions, Nice, France; 2013. p. 286–92.
64. Aubin PM, Sallum H, Walsh C, Stirling L, Correia A. A pediatric robotic thumb exoskeleton for at-home rehabilitation: the isolated orthosis for thumb actuation (IOTA). IEEE Int Conf Rehabil Robot. 2013; 2013:6650500.
65. Gilliaux M, Renders A, Dispa D, Holvoet D, Sapin J, Dehez B, et al. Upper limb robot-assisted therapy in cerebral palsy: a single-blind randomized controlled trial. Neurorehabil Neural Repair. 2015;29:183–92.
66. Sanchez RJ, Liu J, Rao S, Shah P, Smith R, Rahman T, et al. Automating arm movement training following severe stroke: functional exercises with quantitative feedback in a gravity-reduced environment. IEEE Trans Neural Syst Rehabil Eng. 2006;14:378–89.

Part III

Robots for Upper Extremity Recovery

Restoration of Hand Function in Stroke and Spinal Cord Injury

15

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 profoundly impact quality of life. In the past 25 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, actuated assistance has largely consisted of robotic arms and hands which perform a task for the user. A number of individuals, however, could benefit from actuated hand exoskeletons which make use of residual arm function to position and stabilize the user's own hand. These devices would be much smaller and could exploit residual sensory information to provide feedback to the user. Recently, therapeutic devices for the hand have begun to utilize increasing knowledge of stroke to target specific impairment mechanisms. While, traditionally, assistive devices have been developed for individuals with spinal cord injury and therapeutic devices have been developed for stroke survivors, individuals with incomplete spinal cord injury may benefit from hand therapy, while stroke survivors with severe hand impairment may see functional benefits from using assistive devices.

D.G. Kamper, PhD
Department of Biomedical Engineering,
Illinois Institute of Technology,
Wishnick Hall 314, 3255 S. Dearborn St., Chicago,
IL 60616, USA
e-mail: kamper@iit.edu

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

15.1 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. Our hands constitute our primary means of interacting with our environment. Human evolution is closely linked with evolution of the hand. Indeed, one of the earliest species within our genus *Homo* was labeled *Homo habilis*, the "handy man," for the presumed use of stone tools [1]. Features of the hand have facilitated this tool use which is so intertwined with human existence and development. In modern humans, the thumb is longer, compared to the other digits, than in any other primates [2, 3]. Increased thumb length, coupled with the saddle shape that has evolved for the carpometacarpal (CMC) joint [4], affords the human thumb the greatest range of motion among all animals, thereby facilitating opposition with the fingers for grasping objects.

The neuromechanical complexity of the hand drives its dexterity. The hand, distal to the wrist, is comprised of 19 bones connected through joints which provide more than 21 degrees-of-freedom (DOF) or more than three times the total of the effective DOF for the rest of the upper limb. The thumb contains five DOF, and each finger has another four, in addition to the DOF at the finger CMC joints. Rotation at the CMC joints of the ring and little fingers can be significant and enables formation of the palmar arch [5]. 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 [6].

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. These and the other extrinsic muscles, which provide most of the power to the hand in accordance with their size, originate proximal to the wrist. This arrangement minimizes mass and bulk in the hand, thereby minimizing weight and inertia. This minimization is important as the hand, the most distal portion of the upper extremity, can have the greatest moment arm and linear acceleration with respect to the shoulder.

The intrinsic muscles, such as the lumbricals and interossei, have both their origins and insertions within the hand. The muscle bellies for all the hand musculature, however, reside proximal to the metacarpophalangeal (MCP) joints in the digits. This maximizes the range of motion of the digits. Unlike the situation at the elbow or knee, where the contracting muscles (e.g., biceps brachii or biceps femoris) limit joint rotation, the fingers can curl completely such that maximum MCP rotation approaches and PIP rotation exceeds 90°. Additionally, with the abduction/adduction DOF, digits can actually overlap each other in a functional manner. Current robotic hands are not capable of such a rich repertoire of movements. The large active range of motion is achieved without sacrificing power. 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.

While hand biomechanics affords considerable flexibility, it does increase motor control complexity. Each musculotendon unit influences multiple DOF simultaneously, and most tendons cross multiple joints. Many tendons 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. These interactions impact the map-

ping of musculotendon force to force at the digit tip. The mappings also change substantially with joint posture.

Thus, substantial cortical resources are devoted to the hand. Disproportionately large regions of the motor and sensory cortices and the corticospinal and dorsal column pathways are devoted to the hand [7]. Monosynaptic corticomotoneuronal pathways project predominantly to hand muscles [8]. Significant activation of all seven muscles which actuate the index finger is needed to create even an isometric flexion force at the fingertip [9]. Individuated finger movement can be performed to a remarkable extent in humans. Indeed, seemingly similar muscles for the same digit, such as EDC and extensor indicis, may be selectivity excited for different movements [10], and different compartments of even the same muscle may be activated independently [11].

15.2 Pathophysiology

With its heavy reliance on cortical projections for both motor commands and sensory feedback, hand function is especially impacted by injuries to the central nervous system, such as those produced by stroke or spinal cord injury. Diminished capacity to control the hand greatly reduces functionality of the entire upper extremity. As a testament of its importance, loss of the hand, such as through amputation, is considered to result in a 90 % reduction in the functionality of the entire upper extremity [12]. The resulting loss of motor control can have a profound impact on self-care, employment, and leisure activities. Hand impairment can even impact mobility in individuals with combined lower and upper extremity deficits by reducing the ability to use mobility aids. Thus, potential ambulators may become largely nonambulatory because of hand impairment.

15.2.1 Stroke

Stroke, produced by either hemorrhage or occlusion of blood vessels in the brain, is the leading cause of major long-term disability within the United States. Almost 800,000 Americans will incur a stroke each year, thereby leading to a population of seven million stroke survivors [13]. Worldwide, an estimated 15 million strokes occur each year according to the World Health Organization. In fact, the World Stroke Organization reports that one in six individuals will experience a stroke during their lifetime. Thus, the long-term management of people with stroke-related problems is a major therapeutic, rehabilitation, and social challenge. While stroke is often considered a problem of the elderly, approximately 28 % of strokes in the United States occur in people under the age of 65 and about 4–5 % occur in individuals younger than 45 [14]. The Greater Cincinnati/Northern Kentucky Stroke Study showed that within 10 years, the proportion of all strokes occurring in those under 55 years old rose from 13 % to 19 % [15]. Unfortunately, recent evidence suggests that the rate of stroke even among adolescents and young adults has been increasing [16]. Thus, a growing number of adults experience a stroke that will affect their prime working years, which contributes substantially to the enormous financial impact of stroke, with associated medical and disability costs estimated at $73.7 billion in 2010 [17].

Stroke potentially impacts a number of bodily functions, from speech to vision to sensorimotor control of the limbs. Hemiparesis affecting both the upper and lower extremities is typical. Roughly 30–50 % of stroke survivors will have chronic hemiparesis, involving the hand in particular [18]. Deficits in voluntary digit extension are especially common [19].

The severity of hand impairment in stroke survivors can range widely, from a flaccid paralysis to trouble with finger individuation. A typical presentation has the wrist and fingers flexed with preferential weakness of extension. The deficits arise from a variety of sources, including somatosensory loss, flexor hypertonicity, reduced and aberrant muscle activation, and loss of individuation, which are covered in detail in Sect. 15.3.2.

15.2.2 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 [20]. 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, primarily in the elderly, 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 [20].

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 [21]. Fifty percent or more of new SCI cases involve incomplete injury [22].

Tetraplegia typically involves the hands. Loss of descending drive can lead to flaccidity in the hand muscles, especially for high tetraplegia (C1–C4), although some muscle tone may be present, especially for low tetraplegia (C5–C8). Extensor muscle tone, however, seems to be as prevalent as flexor muscle tone, unlike the situation in stroke survivors. Abnormal interlimb reflexes, in which stimulation of lower limb nerves can produce excitation of hand muscles, may be present [23].

Hand function can be adversely impacted by a variety of means. As motoneurons and nerve roots are often damaged at the spinal level of injury, and even multiple segments below the level of the injury, flaccid paresis and muscle atrophy are common [24]. This greatly limits functional recovery. Up to 70 % of the paresis observed for C5–C7 lesions can be attributed to destruction of the nerve roots and motoneurons [25]. One study observed up to a 90 % loss of motor units in the thenar muscles of the thumb in subjects at the C4–C5 levels [26]. Joint movement can be restricted by edema resulting from limited venous return, contracture arising from muscle shortening, and connective tissue formation around tendons and joint capsules.

Hand impairment mechanisms in individuals with incomplete SCI warrant further study. Substantial atrophy in more proximal muscles has been reported [27], as have reductions in nerve conduction velocities, diminished tetanic force production, and elongated twitch times [28].

15.3 Rehabilitation Technology

Technology has been developed in an effort to restore functional capabilities lost due to stroke or SCI. For individuals with incomplete SCI or stroke survivors with some residual voluntary motor excitation, a number of devices have been created to facilitate rehabilitation. Research has shown 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. While neurogenesis is rare, synaptogenesis is constantly occurring. 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 [29, 30] or to harmful changes, such as in focal dystonia [31].

Experimental evidence suggests that intensive repetitive training of new motor tasks is required to induce long-term brain plasticity [32]. 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 [33–35]. Similarly, in humans, repetitive practice has been shown to lead to functional improvement following stroke

[36–38]. Devices which encourage and direct this therapeutic practice would be seemingly beneficial, as long as they address specific impairment mechanisms.

For individuals with complete SCI and stroke survivors with more severe impairment, it may not be possible to improve voluntary sensorimotor control. For these individuals, assistive devices, which are intended to improve functional capabilities rather than sensorimotor control, have been developed.

15.3.1 Assistive Devices

For individuals with higher-level SCI, assistive devices have traditionally been comprised of external equipment programmed to perform specific tasks. For example, powered wheelchairs can restore mobility to individuals with tetraplegia, while robots can be used to perform upper extremity tasks. These robotic arms have been located at workstations (DeVAR [39]), mounted to the user's wheelchair (iARM, Assistive Innovations), and placed atop a mobile platform (thereby permitting autonomous movement) (Baxter, Rethink Robotics).

One of the first successful assistive robots was the Handy 1 [40], a robot workstation that could be used for eating, drinking, grooming, and even art projects (Fig. 15.1). The Handy 1 employed a Cyber 310 robotic arm, which had five DOF in addition to a gripper end effector. 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 [41] 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).

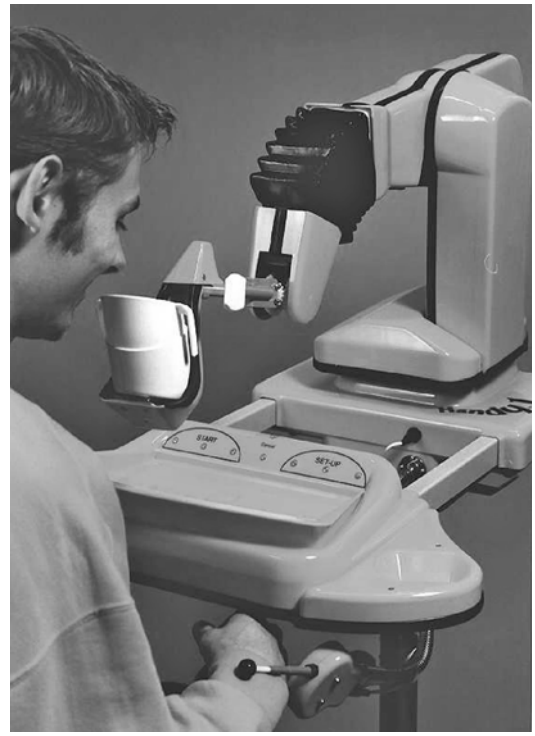


Fig. 15.1 The Handy 1 workstation, intended to help users with eating, drinking, and grooming. First developed by Mike Topping at Staffordshire University (Reprinted with permission from Topping [94]. © Emerald Group Publishing Limited; all rights reserved)

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 [42]. KARES could perform tasks such as grasping objects and turning off and on light switches under the direction of the user. Its successor, KARES II, had a mobile platform, which could extend the workspace of the robot, and compliant control which facilitated interactions with the environment [43]. The Raptor wheelchair robot system was developed by the Rehabilitation Technologies Division of Applied Resources Corporation expressly as an assistive device. It received US Food and Drug Administration (FDA) approval and was sold commercially beginning in 2000 [44]. 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 iARM (Assistive Innovations, Didam, the Netherlands). The iARM provides six DOF and a gripper end effector and can be powered from a wheelchair battery [45]. It is designed for close interaction with the user (see Fig. 15.2a). A wide variety of control options are available dependent upon the capabilities and preferences of the user. The JAC02 robotic arm (Kinova Robotics) is a lightweight 6-axis robotic arm with three fingers for gripping (Fig. 15.2b). It can be mounted to a wheelchair or a tabletop. Considerable federal funding has led to the development of increasingly sophisticated prosthetic

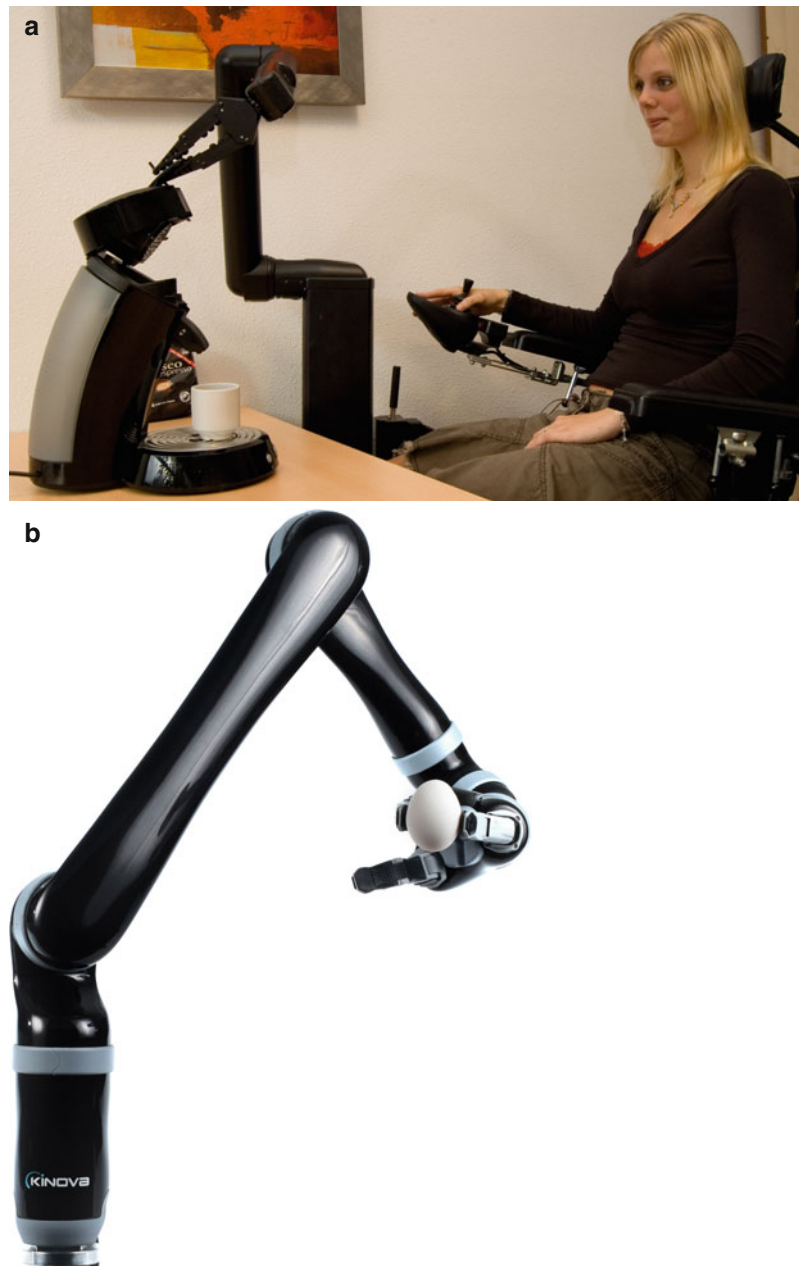


Fig. 15.2 Wheelchair-mounted assistive robots. (**a**) The iARM wheelchair-mounted assistive robot, seen here assisting a user to make a cup of coffee (Photo courtesy of Assistive Innovations, Didam, the Netherlands) (**b**) The JAC02 robotic arm has three fingers for grasping objects such as a cup of water (Photo courtesy of Kinova Robotics, Boisbriand, Canada)

arms and hands, such as those from DEKA and from the Applied Physiology Laboratory at Johns Hopkins.

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, consists of a PUMA robot arm affixed to a powered omnidirectional base [46]. 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 4 (Fraunhofer IPA) has the potential to benefit those with tetraplegia or severe stroke by retrieving and transporting objects. The Home Exploring Robot Butler (HERB) has been developed at Carnegie Mellon University for assisting individuals with household tasks (Fig. 15.3a) [47]. Additionally, the Baxter robot (Rethink Robotics, Inc.) has been proposed as an assistant to individuals with disability (Fig. 15.3b).

One of the primary limitations in using assistive devices is controlling the robot based on user

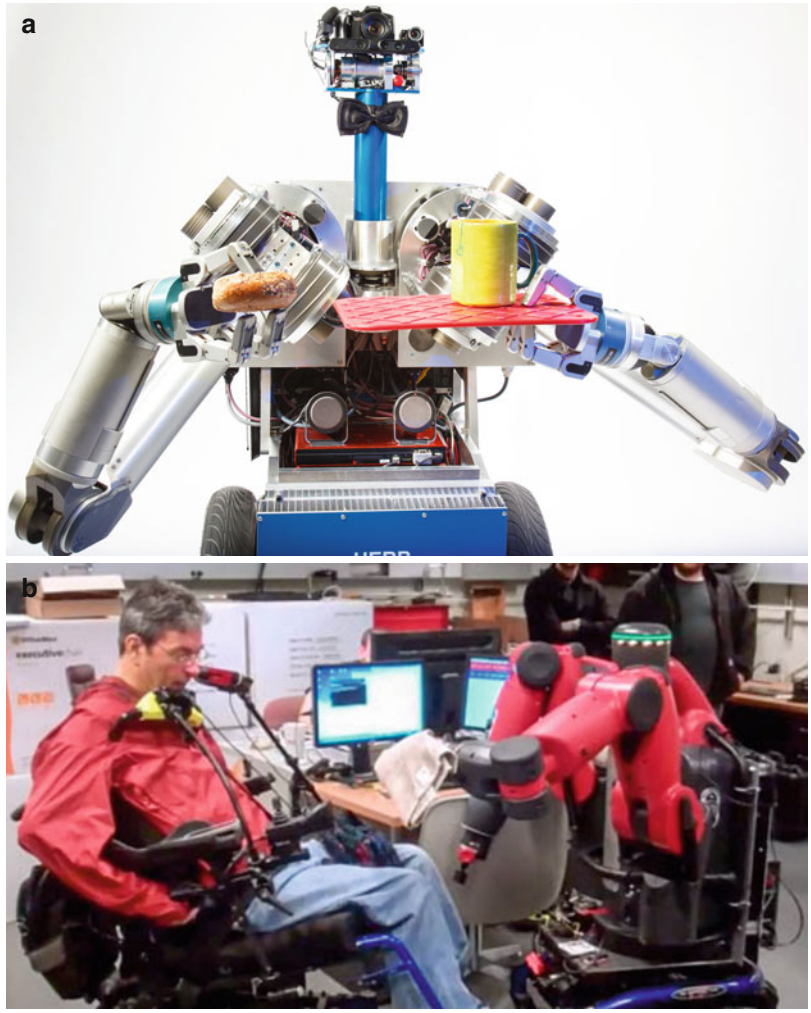


Fig. 15.3 Mobile robotic assistants. (**a**) HERB (Carnegie Mellon University) carrying coffee and a doughnut (Photo courtesy of Dr. Siddhartha Srinivasa, Carnegie Mellon University) (**b**) Baxter (Rethink Robotics, Inc.) employed as an assistant to an individual with paralysis (Photo courtesy of Rethink Robotics, Inc.)

intent. 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. This intent must first be discerned and then conveyed to the device in a translatable manner. Brain-machine interfaces (BMI) are one means for providing facile control of multiple DOF robotic devices. Electrical signals from the brain can be decoded to determine which task the user wants to perform and even details (e.g., velocity) of the intended movement. While electroencephalograms have been used to control devices [48], finer control has been achieved using indwelling electrodes such as intracortical arrays or the less invasive electrocorticographic electrodes. The electrode arrays, such as the Utah array, consist of up to 100 electrodes implanted into motor or premotor cortices. For example, recordings from motor cortex have been successfully used in monkeys to drive a robot to move to specific locations in space [49]. Human participants have successfully controlled a DLR Lightweight Robot III arm (German Aerospace Center, Oberpfaffenhofen, Germany) [50] and a modular prosthetic limb from the Johns Hopkins Applied Physics Laboratory to grasp and retrieve objects (Fig. 15.4) [51].

These BMI-controlled robots restore motor function, but do not provide any sensation to the user. Researchers are investigating how to provide sensory information, such as cutaneous sensation and proprioception, to the user. Techniques involve stimulation of peripheral nerves [52] or somatosensory cortex [53].

For a number of stroke survivors and individuals with SCI, control of arm may be relatively spared in relation to the hand. These individuals could benefit from a device which assists hand tasks but allows free arm movement. Sets 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 different tasks.

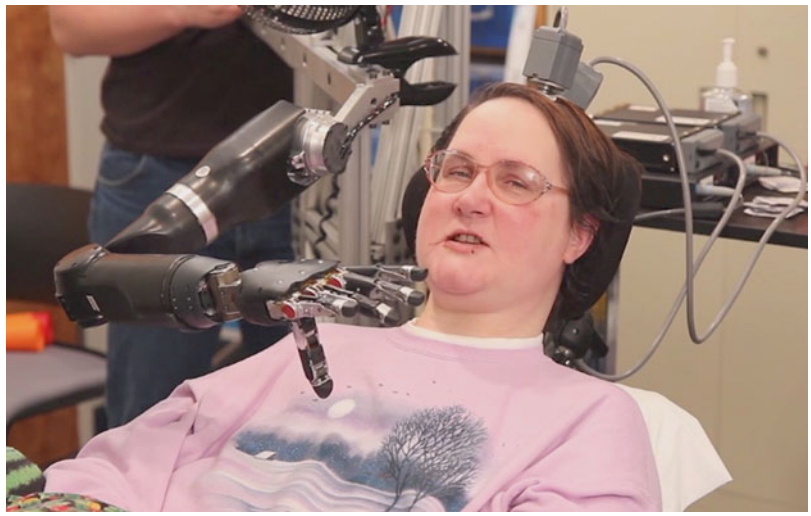


Fig. 15.4 BMI-controlled robotic limbs. Woman with tetraplegia uses modular prosthetic arm to grasp and manipulate objects (Photo courtesy of Motorlab, University of Pittsburgh)

Recently, some assistive devices have been developed expressly for the hand to facilitate grasp and release [54]. The Soft Extra Muscle (SEM) Glove (Bioservo Technologies, Isafjordsgatan, Sweden) could help individuals with incomplete tetraplegia by amplifying their grasping force [55]. Other laboratories are also working to develop an assistive glove [56, 57].

15.3.2 Therapeutic Devices

For therapy, passive movement of the limb is not the goal. Active participation is key to improving motor control and has been shown to lead to better results [58]. Very sophisticated devices have been developed which can move the limb through desired trajectories, but if these devices allow the user to be passive, they may be limited in effectiveness.

Rather than focusing exclusively on moving the extremity, as assistive exoskeletons might, therapeutic devices need to directly consider the underlying impairment mechanisms in the hopes of facilitating recovery. In the stroke hand, deficits arise especially from somatosensory loss, flexor hypertonicity, reduced and aberrant muscle activation, and loss of individuation.

15.3.2.1 Reduced Somatosensation

Somatosensory data is integral to proper hand function. Coordinated motor control 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 [59]. Proprioceptive acuity, especially in the thumb, is superior to other body segments, such as the toes [60]. To support this sensory precision, a disproportionately large portion of somatosensory cortex is devoted to the hand [61].

Despite the importance of sensory information to task execution, relatively few researchers have directly targeted somatosensation for rehabilitation following stroke or SCI. One group at ETH Zürich has been developing robotic technology both to quantify sensory capabilities and to treat sensory deficits [62]. Index finger and thumb motion are coupled on a linear slide. Through admittance control, compliance can be carefully modulated to create haptic boundaries simulating contact with real objects. In this manner, the user actively explores their environment to train sensing characteristics of external objects, such as object size through proprioception (Fig. 15.5).

15.3.2.2 Flexor Hypertonicity

One of the primary contributors to hand impairment after stroke is hypertonicity of the long finger flexor muscles. This manifests as spasticity, excessive coactivation, and prolonged relaxation time.

Spasticity is defined as a velocity-dependent reflex response to impose stretch under conditions which would not produce a reflex response in non-spastic muscles [63]. In the hand, spasticity is predominantly observed in the finger flexors, such as FDS and FDP (see Fig. 15.6a). Interestingly, spasticity is largely absent in the long thumb flexor (flexor pollicis longus), even in individuals with spasticity in the finger flexor muscles [64].

A variety of factors, such as decreased reciprocal inhibition, afferent disinhibition, and altered postactivation depression [65], may contribute to the spastic reflex. Additionally, the motoneurons of a spastic muscle may have an elevated resting potential, increasing firing probability. Indeed, spontaneous discharge of motor units is much more frequent in spastic muscle [66], and the spastic reflex response is dependent upon absolute muscle fiber length in addition to stretch velocity and magnitude [67]. It should be emphasized, however, that the degree to which spasticity impacts voluntary movement is open to question [65].

Hypertonicity may manifest in different ways 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 (Fig. 15.6b). Thus, the first phase of grasp, opening the hand to position it around the object, may be substantially impaired.

Fig. 15.5 Sample training exercise with a robot designed to provide therapy for sensation. User picks the length corresponding to the virtual object represented by the haptic trainer (Photo courtesy of Dr. Roger Gassert, ETH Zürich)

Object release may also be affected as deactivation of the finger flexors may be abnormal (Fig. 15.6c). Stroke survivors have been shown to have prolonged relaxation time in FDS following a grasp, both for the impaired and less impaired sides [68]. 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.

In my laboratory, we have observed that stretching can reduce hyperexcitability in stroke survivors [68], in agreement with findings by other groups [69]. Thus, we created an actuated glove orthosis, the X-Glove (Fig. 15.7), to perform cyclical stretching. The X-Glove uses cables running across the dorsal side of the digits to pull the digits into extension and then allows the digits to relax back into flexion. Single stretching sessions led to at least transient improvement of hand motor control in stroke survivors [70]. In stroke survivors in the subacute phase of recovery, 30-min stretching sessions repeated over 3 days showed a cumulative effect, with greater improvement each day as well as from before to after stretching [71].

The flexor hypertonicity biases the hand toward a flexed posture. We have shown that applied constant extension joint torque can increase the active workspace [72] for the finger and reduce error in point-to-point finger movements. Thus, several devices have been designed to overcome this bias by providing extension force. The SaeboFlex

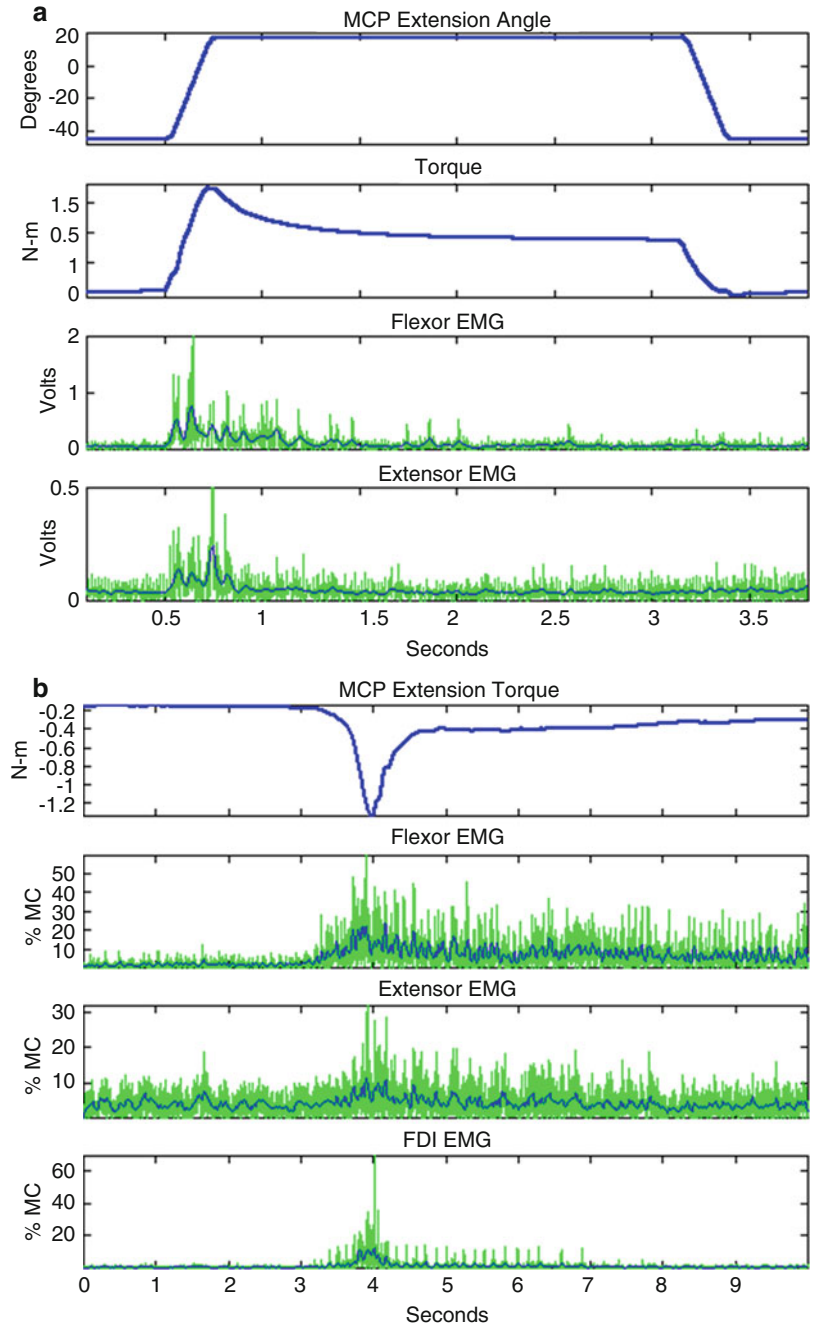
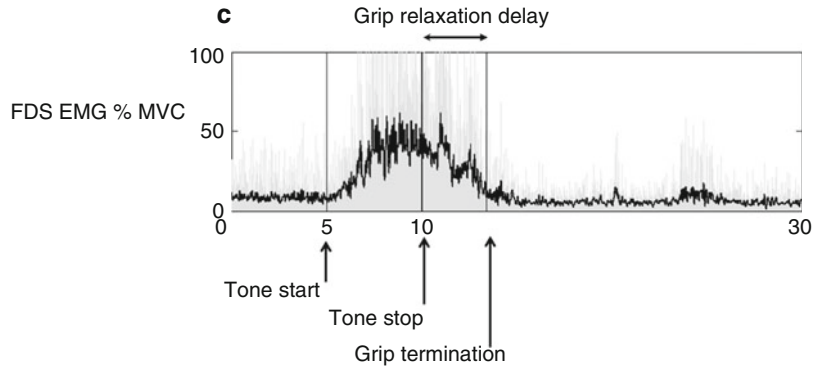


Fig. 15.6 Examples of hypertonicity in long finger flexors in stroke survivors. (**a**) Spastic stretch reflex evoked by rapid extension rotation (300°/s) of the MCP joints stretches. Note increases in flexor EMG and torque (From Kamper and Rymer [95]; used with permission). (**b**) Excessive flexor coactivation results in net flexion torque during attempted production of voluntary extension torque about MCP joints (From Kamper et al. [96]; used with permission). (**c**) Prolonged relaxation of long finger flexor (*FDS*) following generation of voluntary grasp force cued by audible tone

Fig. 15.6 (continued)



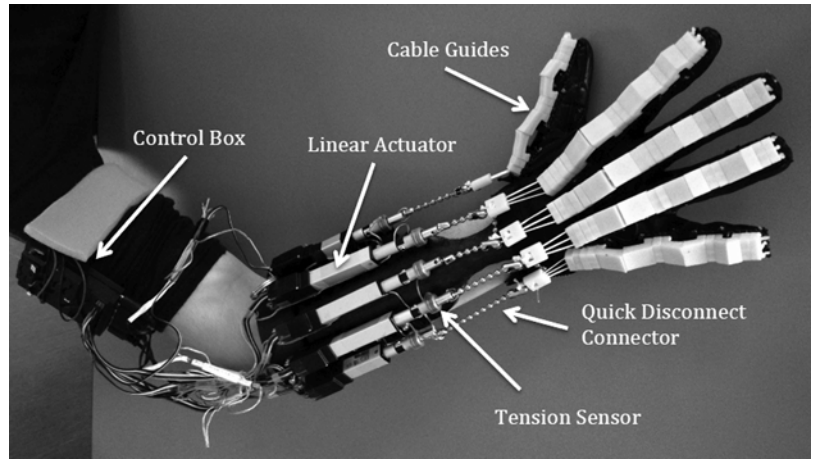


Fig. 15.7 The eXtension-Glove (Rehabilitation Institute of Chicago, Chicago, IL, USA), which can perform cyclical stretching of the long finger flexors. Cables run through guides on the back of each digit to a linear motor driven by a microcontroller. The X-Glove can also actively assist extension during voluntary movement

(Saebo Inc., Charlotte, NC), for example, uses passive springs to apply extension torque to the more proximal joints of the digits. We created a control mode in the X-Glove which applies a constant extension force, set equivalent to measure flexion force at full passive extension, for each digit. The user can flex the digits by creating sufficient flexion force to overcome the extension force, but the bias assists in digit extension for hand opening prior to grasp and for object release. Additionally, Dr. Peter Lum's group at Catholic University has incorporated extension compensation into the HandSOME device with passive springs [73] (Fig. 15.8a) and into the HEXORR hand exoskeleton through electric motors [74] (Fig. 15.8b).

15.3.2.3 Impaired Voluntary Neuromuscular Activation

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 individuals with severe hand impairment. A group of study participants with severe impairment created maximum index finger extension force equal only to 9 % of the normal peak value, while generating finger flexion forces only 27 % of normal levels [75].

This weakness arises primarily from an inability to fully activate the muscle voluntarily. We found that even in individuals who could voluntarily produce no more than 20 % of the forces neurologically intact participants created, external electrical stimulation could generate force levels close to normal (Fig. 15.9a). Additionally, stroke survivors may have great difficulty modulating muscle activity with task. A study from my laboratory showed dramatically reduced ranges of activation levels for given muscles as the stroke survivor attempted

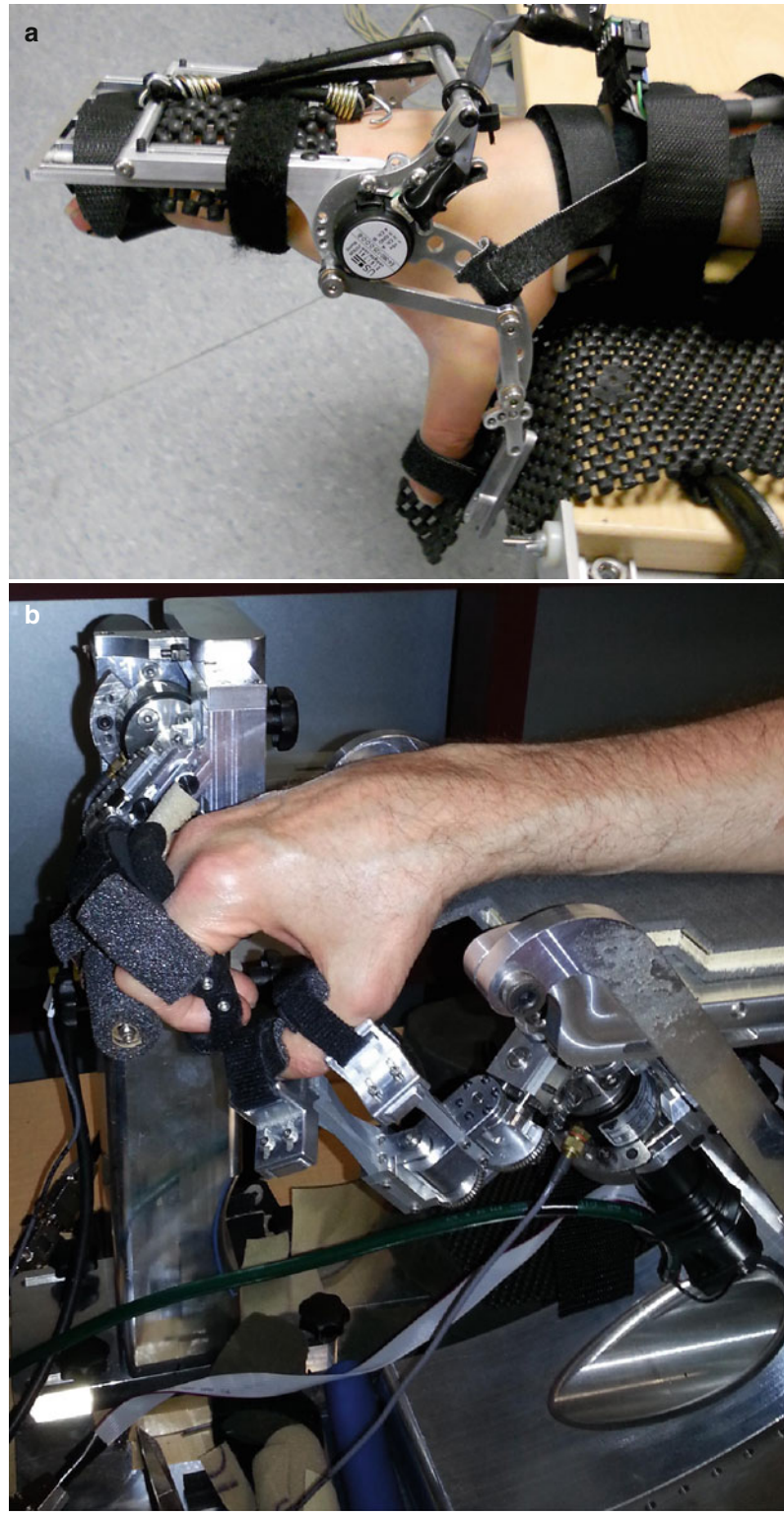


Fig. 15.8 (**a**) The HandSOME exoskeleton (Catholic University, Washington, D.C.). Passive springs provide nonlinear extension compensation (From Brokaw et al. [73]; used with permission). (**b**) HEXORR (Catholic University, Washington, D.C.). The motors actuating the MCP-PIP joints in the fingers and MCP joint in the thumb can be programmed to provide compensation for flexion torques (Photos courtesy of Dr. Peter Lum, Catholic University)

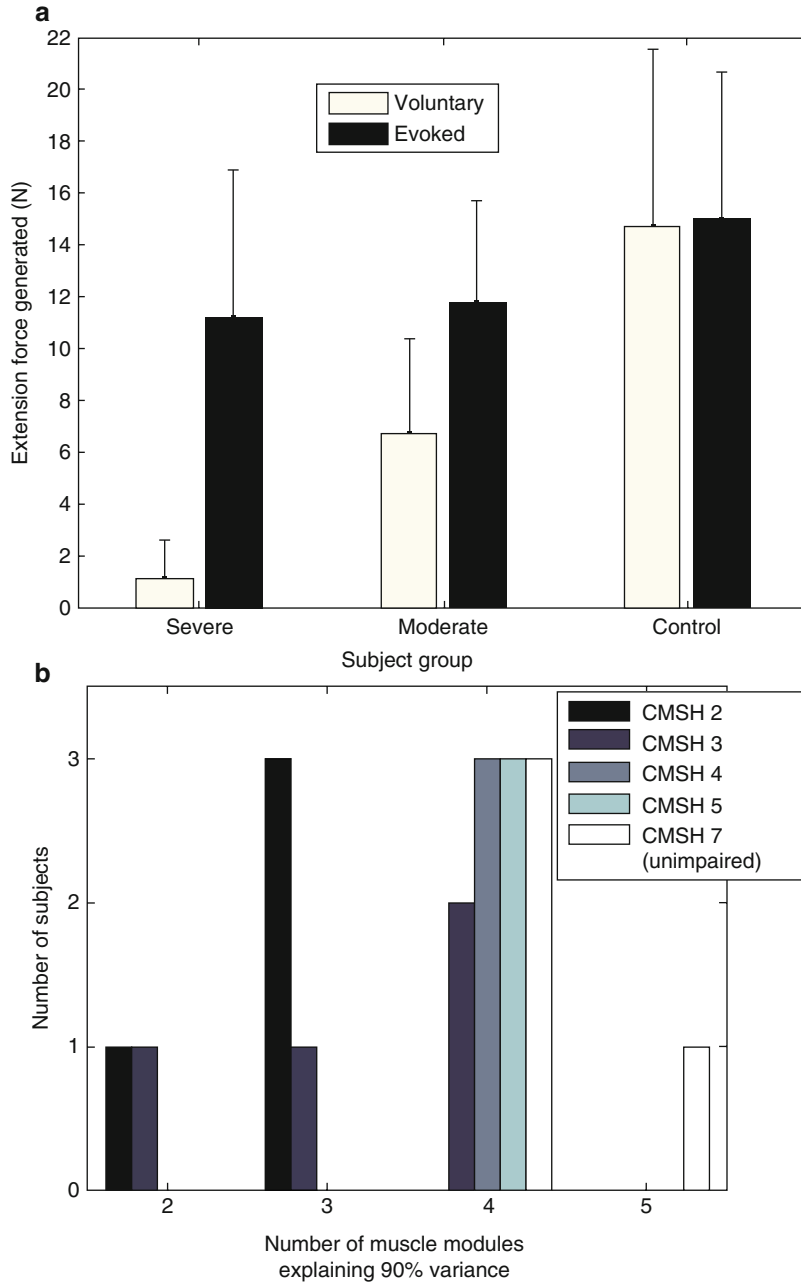


Fig. 15.9 Activation deficits following stroke. (**a**) Maximum extension force created either entirely voluntarily (*white bars*) or with the addition of external stimulation (*black bars*) or at the tip of the middle finger. Activation deficits are readily apparent in stroke survivors (from Hoffmann et al. [97]; used with permission). (**b**) Number of muscle modules needed to explain the variance in activation patterns across six different tasks. *CMSH* Chedoke-McMaster Stroke Assessment for Stage of Hand (From Lee et al. [77]; used with permission)

to create thumb forces in different directions [76]. For example, while neurologically intact subjects varied activation from 10 % to 60 % of maximum voluntary contraction (MVC) across force directions, activation of the same muscle in stroke survivors with severe hand impairment

ranged only from 30 % to 40 %. The ability to span regions in the activation workspace is also curtailed following stroke. Stroke survivors tend to produce fewer distinct activation patterns across tasks than neurologically intact individuals [77] (Fig. 15.9b).

One technique for directly addressing activation patterns in therapy involves the utilization of electromyographically (EMG) driven devices. We have developed the Voice and EMG-Driven Actuated (VAEDA) Glove in order to incorporate practice of generating activation patterns into clinical therapy (Fig. 15.10a). Cables traversing the dorsal side of the hand are connected to a motor located remotely through a Bowden cable. Extension assistance is provided only when EMG signals recorded from FDS and EDC fall within specified ranges. Similarly, the device only permits the user to close her hand when EMG signals fall within the proper ranges. As EMG patterns for opening and closing can be indistinguishable in some stroke survivors, a voice recognition chipset is used to determine state (open, close, hold), while EMG controls movement within that state.

An EMG-controlled exoskeleton has also been developed by Dr. Raymond Tong's group in Hong Kong. The glove employs linear actuators to drive coupled rotation of the MCP and PIP joints for each finger in both flexion and extension [78]. Electrodes placed over APB and EDC were used to initiate hand closing and opening, respectively (Fig. 15.10b).

Drs. Sang Wook Lee and Hyung-Soon Park have been developing a glove in which cables are routed in order to mimic the pathways of individual tendons in the hand [79]. Hence, assistance can be provided to individual muscles. Activation patterns can thus be trained directly with this device (Fig. 15.10c).

15.3.2.4 Loss of Individuation

One of the hallmarks of human motor control is the capability for highly independent movement of each digit, especially the thumb and index finger. Humans are not born with this ability; however, it develops over the first years after birth. Individuation requires the development of monosynaptic corticomotoneuronal pathways to hand muscles [80]. These pathways develop months after birth [81]. Unfortunately, stroke or SCI may degrade the ability to independently manipulate the digits [82].

Recently, some devices have been developed with the intent to facilitate rehabilitation of digit individuation. Amadeo System (Tyromotion, GmbH, Graz, Austria) uses an approach in which the fingertips are attached to linear tracks which directly control fingertip location. Each digit is attached to a separate track and can therefore be moved independently (Fig. 15.11a). One drawback is that the hand position and orientation are fixed as the Amadeo is externally grounded.

Alternatively, the MusicGlove is unactuated but encourages practice of thumb-finger opposition movements [83]. Sensors are embedded in the tips of the glove such that contact between the thumb and any finger can be detected and distinguished (Fig. 15.11b). The user must make the appropriate opposition movement in order to play the key specified by a video game similar to Guitar Hero. The FINGER robot can independently actuate the index and middle fingers through sets of eight-bar linkages to help those with more impairment to use the game for training [84].

In my laboratory, we have created a pneumatically driven glove, the PneuGlove [85], which we have coupled to a virtual keyboard. The user must flex and extend specified digits in order to "play" the virtual keys dictated by the computer program (Fig. 15.11c). The PneuGlove can be used to assist or resist performance of the task, with the level of assistance/resistance specified by the therapist [86].

15.4 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 MANUS (iARM) and the JAC02 sold are in the hundreds

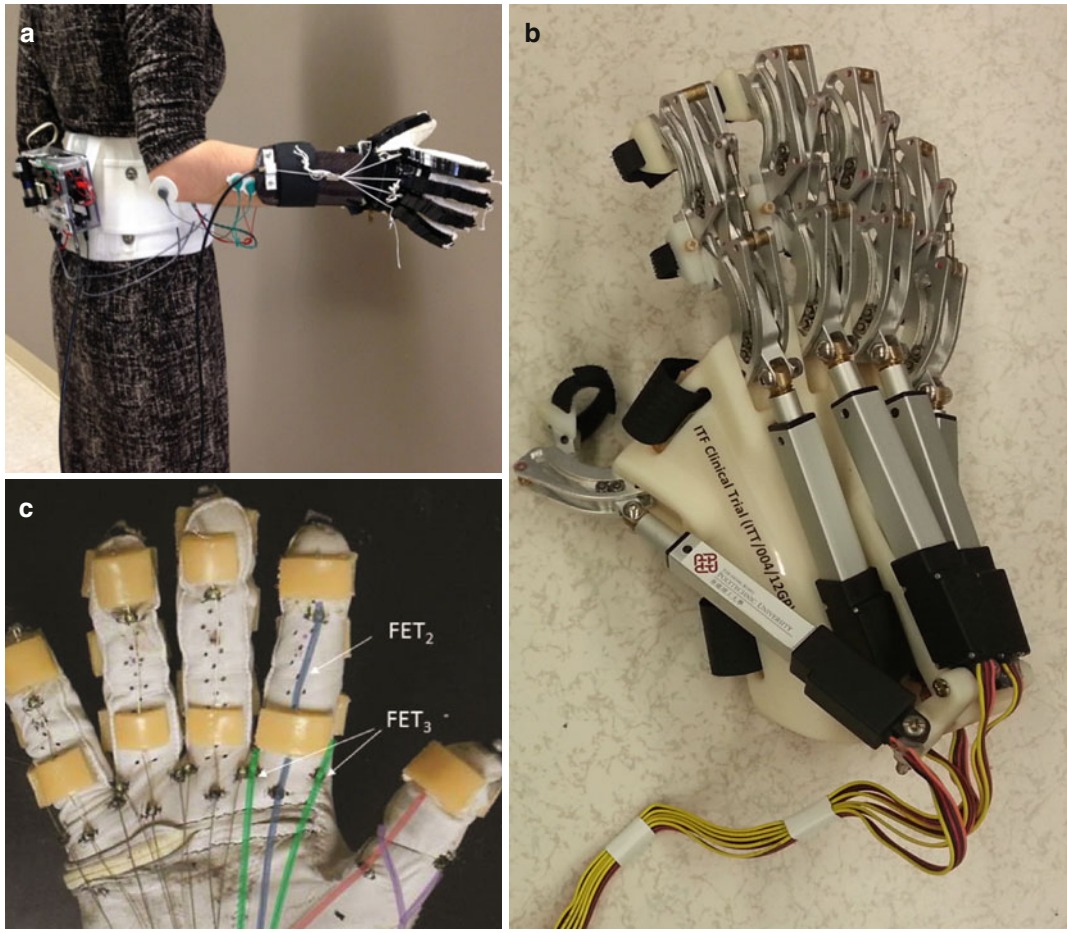


Fig. 15.10 Actuated hand orthoses for promoting neuromuscular activation patterns. (**a**) VAEDA Glove employs EMG control of hand opening and closing (Rehabilitation Institute of Chicago/Illinois Institute of Technology, Chicago, IL). (**b**) Exoskeleton uses linear actuators to control MCP and PIP flexion and extension. Hand opening and closing can be triggered by EMG activity (Hong Kong Polytechnic University, Hong Kong, China) (Photo courtesy of Dr. Evan Susanto, Hong Kong Polytechnic) (**c**) Individual cables mimic the actions of physiological tendons to facilitate practice of muscle activation patterns (Photo courtesy of Dr. Sang Wook Lee, Catholic University)

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.

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. Many countries are now facing an altered population model in which older generations comprise the largest percentage of the populace. Mobile assistants created to aid older individuals who have restricted movement and strength could also prove beneficial to individuals with tetraplegia or severe stroke. Additionally, powered exoskeletons intended to augment the capabilities of the wearer (whether an elderly individual or a soldier) may also be applicable for individuals with neuromuscular disabilities.

Fig. 15.11 Devices used to train finger individuation. (**a**) Amadeo (Tyromotion, Inc.) has a separate actuated linear slide for each digit (Photo courtesy of Tyromotion, Inc.). (**b**) MusicGlove (Flint Rehabilitation) employs sensor in the tips of the digits to detect proper thumb-finger opposition (Photo courtesy of Flint Rehabilitation). (**c**) The actuated virtual keypad (*AVK*) employs the PneuGlove with its pneumatically driven air chambers to facilitate practice playing the virtual keypad (From Thielbar et al. [86]; used with permission)

Assistive technology targeting low tetraplegia, such as C7–T1, or severe stroke 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. In addition to providing hand actuation, they would also be able to exploit the exquisite sensory capabilities of the hand in those individuals with motor impairment but sensory sparing. A number of researchers are currently working on assistive gloves, but the primary complication of interfacing with the hand remains a challenge. The device should be easily donnable and doffable, while minimally interacting with the palmar surface of the hand. It should also be very low profile, both for aesthetics and function (e.g., inserting the hand into a confined space), and lightweight while still possessing sufficient power both for grasping and for opening the digits against flexor tone. The need for such assistive devices is underscored by medical procedures being performed in an attempt to improve hand function. Three individuals with brachial plexus injuries underwent hand amputation in Austria in order to be fitted with myoelectric prostheses [87]. Seemingly, the existing skeletal structure could be exploited with an

assistive device to create a more satisfying outcome for the user.

In the last 10 years, a number of devices have been developed expressly to facilitate hand therapy after neuromuscular injury. Clinical studies performed with these devices are still somewhat rare, but the ones that have been performed have shown some promise. Merians et al. saw improvement in the Jebsen-Taylor Hand Function Test (JTHFT) [88] and in finger fractionation following arm-finger training [89]. Godfrey et al. reported statistically significant gains in active range of motion and grip strength in stroke survivors with chronic impairment after completion of a training regimen with HEXORR [90]. Susanto et al. reported gains in the Action Research Arm Test and Wolf Motor Function Test following 20 training sessions with their hand exoskeleton [91]. A pilot study with the MusicGlove led to improved performance on the Box and Block Test and the Nine-Hole Peg Test [83]. We were able to show significant gains in the Fugl-Meyer Upper Extremity Stroke Assessment and palmar pinch after training with the PneuGlove [85] and in JTHFT and finger individuation with the PneuGlove incorporated into the AVK system [86]. Larger trials with control groups and blinded raters, however, are needed to truly assess efficacy. Inevitably, other interventions will need to be combined with the rehabilitative devices if substantial clinical benefit is to be obtained.

Conclusions

The neuromechanical complexity of the hand makes it a challenging target for rehabilitation after stroke or SCI. Rigid control of the many DOF in the digits, however, may not be necessary to restore at least partial function. Principles from soft robotics may be utilized to exploit the existing skeletal structure of the hand (e.g., Polygerinos et al. [92]) and thus minimize the mass and bulk on the hand of devices actuating the digits.

The soft robotics design concept is especially appropriate for therapeutic devices, which should be designed to maximize effort of the user. An increasing number of therapy devices are being created for the hand (see Balasubramanian et al. [93] for a review), with a number of recent commercial ventures such as Gloreha (Idrogenet, Lumezzane, Italy), the IpsiHand Bravo (Neurolutions, St. Louis, MO), and RAPAEL (Neofect, Yongin, Korea). While the number of clinical studies which have been run are limited, preliminary results have given some encouragement. Results may be improved by the targeting of specific impairment mechanisms. For example, we are attempting to treat flexor hyperexcitability with a pharmacological agent while simultaneously addressing trouble with creating activation patterns by employing an EMG-controlled glove. Application to treatment of incomplete SCI would seemingly benefit from more complete identification of impairment mechanisms.

Inevitably, for some stroke survivors and individuals with SCI, capacity for restoration of hand motor control will be limited. For them, assistive mechatronic devices hold the best hope for improving function. Developments in decoding of human intent are leading to more natural control of assistive robots, which could consist either of external machines with robotic grippers or exoskeletons/gloves incorporating the user's hand in the task. Growing research in the area of wearable exoskeletons and personal assistants to aid the geriatric population should also benefit those with neuromuscular injury, including stroke survivors and individuals with SCI.

References

1. Dunsworth H. Origin of the genus Homo. Evo Edu Outreach. 2010;3:353–66.
2. Napier JR. Studies of the hands of living primates. Proc Zool Soc Lond. 1960;134:647–57.
3. Young RW. Evolution of the human hand: the role of throwing and clubbing. J Anat. 2003;202:165–74.
4. Marzke MW, Marzke RF. Evolution of the human hand: approaches to acquiring, analysing and interpreting the anatomical evidence. J Anat. 2000;197(Pt 1):121–40.
5. Buffi JH, Crisco JJ, Murray WM. A method for defining carpometacarpal joint kinematics from

three-dimensional rotations of the metacarpal bones captured in vivo using computed tomography. J Biomech. 2014;46:2104–8.
6. Brand PW, Hollister AM. Clinical mechanics of the hand. 3rd ed. St. Louis: Mosby; 1999.
7. Penfield W, Rasmussen T. The cerebral cortex of man: a clinical study of localization of function. New York: The Macmillan Company; 1950.
8. Rathelot JA, Strick PL. Subdivisions of primary motor cortex based on cortico-motoneuronal cells. Proc Natl Acad Sci U S A. 2009;106:918–23.
9. Valero-Cuevas FJ, Zajac FE, Burgar CG. Large index-fingertip forces are produced by subject-independent patterns of muscle excitation. J Biomech. 1998;31:693–703.
10. Darling WG, Cole KJ, Miller GF. Coordination of index finger movements. J Biomech. 1994;27:479–91.
11. Keen DA, Fuglevand AJ. Common input to motor neurons innervating the same and different compartments of the human extensor digitorum muscle. J Neurophysiol. 2004;91:57–62.
12. Association AM. Guides to the evaluation of permanent impairment. Chicago: American Medical Association; 1990.
13. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129: e28–92.
14. Roth EJ, Lovell L. Employment after stroke: report of a state of the science symposium. Top Stroke Rehabil. 2014;21 Suppl 1:S75–86.
15. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79:1781–7.
16. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995–2008. Ann Neurol. 2011;70:713–21.
17. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation. 2010;121:e46–215.
18. Xie J, George MG, Ayala C, et al. Outpatient rehabilitation among stroke survivors—21 states and the district of Columbia, 2005. MMWR: Morb Mortal Wkly Rep. 2007;56:504–7.
19. Trombly CA. Stroke. In: Trombly CA, editor. Occupational therapy for physical dysfunction. Baltimore: Williams & Wilkins; 1989. p. 454–71.
20. National Spinal Cord Injury Statistical Center, University of Alabama at Birmingham Department of Physical Medicine and Rehabilitation, at www.nscisc.uab.edu.
21. Waters RL, Adkins RH, Yakura JS. Definition of complete spinal cord injury. Paraplegia. 1991;29:573–81.
22. Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? Spinal Cord. 2006;44:523–9.
23. Calancie B, Molano MR, Broton JG. Interlimb reflexes and synaptic plasticity become evident months after human spinal cord injury. Brain: J Neurol. 2002;125:1150–61.
24. Dietz V, Curt A. Neurological aspects of spinal-cord repair: promises and challenges. Lancet Neurol. 2006;5:688–94.
25. Dietz V, Fouad K. Restoration of sensorimotor functions after spinal cord injury. Brain: J Neurol. 2014;137:654–67.
26. Yang JF, Stein RB, Jhamandas J, Gordon T. Motor unit numbers and contractile properties after spinal cord injury. Ann Neurol. 1990;28:496–502.
27. Thomas CK, Zaidner EY, Calancie B, Broton JG, Bigland-Ritchie BR. Muscle weakness, paralysis, and atrophy after human cervical spinal cord injury. Exp Neurol. 1997;148:414–23.
28. Hager-Ross CK, Klein CS, Thomas CK. Twitch and tetanic properties of human thenar motor units paralyzed by chronic spinal cord injury. J Neurophysiol. 2006;96:165–74.
29. Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science. 1995;270:305–7.
30. Gaser C, Schlaug G. Brain structures differ between musicians and non-musicians. J Neurosci: Off J Soc Neurosci. 2003;23:9240–5.
31. Altenmuller E, Jabusch HC. Focal dystonia in musicians: phenomenology, pathophysiology and triggering factors. Eur J Neurol. 2010;17 Suppl 1:31–6.
32. Plautz EJ, Milliken GW, Nudo RJ. Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. Neurobiol Learn Mem. 2000;74:27–55.
33. Jones TA, Chu CJ, Grande LA, Gregory AD. Motor skills training enhances lesion-induced structural plasticity in the motor cortex of adult rats. J Neurosci Off J Soc Neurosci. 1999;19:10153–63.
34. Kleim JA, Jones TA, Schallert T. Motor enrichment and the induction of plasticity before or after brain injury. Neurochem Res. 2003;28:1757–69.
35. Jones TA, Schallert T. Use-dependent growth of pyramidal neurons after neocortical damage. J Neurosci: Off J Soc Neurosci. 1994;14:2140–52.
36. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006; 296:2095–104.
37. Liepert J, Miltner WH, Bauder H, et al. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. Neurosci Lett. 1998; 250:5–8.
38. Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. Stroke; J Cereb Circ. 2000;31:1210–6.

39. Hammel J, Hall K, Lees D, et al. Clinical evaluation of a desktop robotic assistant. J Rehabil Res Dev. 1989;26:1–16.
40. Topping M. An overview of the development of handy 1, a rehabilitation robot to assist the severely disabled. J Intell Robot Syst. 2002;34:253–63.
41. Song W, Kim J, An K, Lee I, Song W, Lee B, Hwang S, Son M, Lee E. Design of novel feeding robot for Korean food. International conference on smart homes and health telematics. Seoul; 2010.
42. Jung J, Song W, Lee H, Kim J, Bien Z. A study on the enhancement of manipulation performance of wheelchair-mounted rehabilitation service robot. International conference on rehabilitation robotics. Stanford; 1999.
43. Bien Z, Park K, Chung MJ. Mobile platform-based assistive robot systems. In: Helal A, Mokhtari M, Abdulrazak B, editors. The engineering handbook of smart technology for aging, disability and independence. Hoboken: Wiley; 2008.
44. Mahoney RM. The raptor wheelchair robot system. In: Mokhtari M editor. Integration of assistive technology in the information age. Amsterdam, The Netherlands: IOS Press; 2001. p. 135–41.
45. Driessen BJF, Evers HG, Woerden JA. MANUS—a wheelchair-mounted rehabilitation robot. Proc Inst Mech Eng H J Eng Med. 2001;215:285–90.
46. Van der Loos M, Michalowski S, Leifer L. Design of an omnidirectional mobile robot as a manipulation aid for the severely disabled. New York: World Rehabilitation Fund; 1986.
47. Srinivasa S, Ferguson D, Helfrich C, et al. HERB: a home exploring robotic butler. Auton Robot. 2010; 28:5–20.
48. Pfurtscheller G, Guger C, Muller G, Krausz G, Neuper C. Brain oscillations control hand orthosis in a tetraplegic. Neurosci Lett. 2000;292:211–4.
49. Taylor DM, Tillery SI, Schwartz AB. Information conveyed through brain-control: cursor versus robot. IEEE Trans Neural Syst Rehabil Eng. 2003; 11:195–9.
50. Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature. 2012;485:372–5.
51. Collinger JL, Wodlinger B, Downey JE, et al. High-performance neuroprosthetic control by an individual with tetraplegia. Lancet (London, England). 2013; 381:557–64.
52. Tan DW, Schiefer MA, Keith MW, Anderson JR, Tyler J, Tyler DJ. A neural interface provides long-term stable natural touch perception. Sci Transl Med. 2014;6:257ra138.
53. Tabot GA, Dammann JF, Berg JA, et al. Restoring the sense of touch with a prosthetic hand through a brain interface. Proc Natl Acad Sci U S A. 2013;110: 18279–84.
54. Lucas L, DiCicco M, Matsuoka Y. An EMG-controlled hand exoskeleton for natural pinching. J Robot Mechatron. 2004;16:1–7.
55. Nilsson M, Ingvast J, Wikander J, von Holst H. The soft extra muscle system for improving the grasping capability in neurological rehabilitation. IEEE Engineering in Medicine and Biology. San Diego: IEEE; 2012. p. 412–7.
56. Polygerinos P, Wang Z, Galloway KC, Wood RJ, Walsh CJ. Soft robotic glove for combined assistance and at-home rehabilitation. Robot Auton Syst. 2015;73:135–43.
57. In H, Kang BB, Sin M, Cho K. Exo-glove: a wearable robot for the hand with a soft tendon routing system. IEEE Robot Autom Mag. 2015;22:97–105.
58. Hu XL, Tong KY, Song R, Zheng XJ, Leung WW. A comparison between electromyography-driven robot and passive motion device on wrist rehabilitation for chronic stroke. Neurorehabil Neural Repair. 2009; 23:837–46.
59. Johansson RS, Vallbo AB. Tactile sensibility in the human hand: relative and absolute densities of four types of mechanoreceptive units in glabrous skin. J Physiol. 1979;286:283–300.
60. Refshauge KM, Kilbreath SL, Gandevia SC. Movement detection at the distal joint of the human thumb and fingers. Exp Brain Res. 1998;122:85–92.
61. Nakamura A, Yamada T, Goto A, et al. Somatosensory homunculus as drawn by MEG. Neuroimage. 1998;7:377–86.
62. Metzger J-C, Lambercy O, Califfi A, Conti FM, Gassert R. Neurocognitive robot-assisted therapy of hand function. IEEE Trans Haptics. 2013;7:140–9.
63. Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koella WP, editors. Spasticity: disordered motor control. Chicago: Year Book Medical Publishers; 1980. p. 485–95.
64. Towles JD, Kamper DG, Rymer WZ. Lack of hypertonia in thumb muscles after stroke. J Neurophysiol. 2010;104:2139–46.
65. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6:725–33.
66. Mottram CJ, Suresh NL, Heckman CJ, Gorassini MA, Rymer WZ. Origins of abnormal excitability in biceps brachii motoneurons of spastic-paretic stroke survivors. J Neurophysiol. 2009;102: 2026–38.
67. Kamper DG, Schmit BS, Rymer WZ. Effect of muscle biomechanics on the quantification of spasticity. Ann Biomed Eng. 2001;29:1122–34.
68. Seo NJ, Rymer WZ, Kamper DG. Delays in grip initiation and termination in persons with stroke: effects of arm support and active muscle stretch exercise. J Neurophysiol. 2009;101:3108–15.
69. Selles RW, Li X, Lin F, Chung SG, Roth EJ, Zhang LQ. Feedback-controlled and programmed stretching of the ankle plantarflexors and dorsiflexors in stroke: effects of a 4-week intervention program. Arch Phys Med Rehabil. 2005;86:2330–6.
70. Triandafilou KM, Ochoa J, Kang X, Fischer HC, Stoykov ME, Kamper DG. Transient impact of

prolonged versus repetitive stretch on hand motor control in chronic stroke. Top Stroke Rehabil. 2011;18:316–24.
71. Triandafilou KM, Kamper DG. Carryover effects of cyclical stretching of the digits on hand function in stroke survivors. Arch Phys Med Rehabil. 2014;95:1571–6.
72. Cruz EG, Kamper DG. Use of a novel robotic interface to study finger motor control. Ann Biomed Eng. 2006;38:259–68.
73. Brokaw EB, Black I, Holley RJ, Lum PS. Hand Spring Operated Movement Enhancer (HandSOME): a portable, passive hand exoskeleton for stroke rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2011;19:391–9.
74. Godfrey SB, Holley RJ, Lum PS. Clinical effects of using HEXORR (Hand Exoskeleton Rehabilitation Robot) for movement therapy in stroke rehabilitation. Am J Phys Med Rehabil/Assoc Acad Physiatrists. 2013;92:947–58.
75. Cruz EG, Waldinger HC, Kamper DG. Kinetic and kinematic workspaces of the index finger following stroke. Brain: J Neurol. 2005;128:1112–21.
76. Triandafilou KM, Fischer HC, Towles JD, Kamper DG, Rymer WZ. Diminished capacity to modulate motor activation patterns according to task contributes to thumb deficits following stroke. J Neurophysiol. 2011;106:1644–51.
77. Lee SW, Triandafilou K, Lock BA, Kamper DG. Impairment in task-specific modulation of muscle coordination correlates with the severity of hand impairment following stroke. PLoS One. 2013; 8:e68745.
78. Hu XL, Tong KY, Wei XJ, Rong W, Susanto EA, Ho SK. The effects of post-stroke upper-limb training with an electromyography (EMG)-driven hand robot. J Electromyogr Kinesiol: Off J Int Soc Electrophysiol Kinesiol. 2013;23:1065–74.
79. Lee SW, Landers KA, Park HS. Development of a biomimetic hand exotendon device (BiomHED) for restoration of functional hand movement post-stroke. IEEE Trans Neural Syst Rehabil Eng: Publ IEEE Eng Med Biol Soc. 2014;22:886–98.
80. Lemon RN. The G. L. Brown prize lecture. Cortical control of the primate hand. Exp Physiol. 1993;78:263–301.
81. Olivier E, Edgley SA, Armand J, Lemon RN. An electrophysiological study of the postnatal development of the corticospinal system in the macaque monkey. J Neurosci: Off J Soc Neurosci. 1997;17:267–76.
82. Lang CE, Schieber MH. Reduced muscle selectivity during individuated finger movements in humans after damage to the motor cortex or corticospinal tract. J Neurophysiol. 2004;91:1722–33.
83. Friedman N, Chan V, Reinkensmeyer AN, et al. Retraining and assessing hand movement after stroke using the MusicGlove: comparison with conventional hand therapy and isometric grip training. J Neuroeng Rehabil. 2014;11:76.
84. Taheri H, Rowe JB, Gardner D, et al. Design and preliminary evaluation of the FINGER rehabilitation robot: controlling challenge and quantifying finger individuation during musical computer game play. J Neuroeng Rehabil. 2014;11:10.
85. Connelly L, Jia Y, Toro ML, Stoykov ME, Kenyon RV, Kamper DG. A pneumatic glove and immersive virtual reality environment for hand rehabilitative training after stroke. IEEE Trans Neural Syst Rehabil Eng: Publ IEEE Eng Med Biol Soc. 2010;18:551–9.
86. Thielbar KO, Lord TJ, Fischer HC, et al. Training finger individuation with a mechatronic-virtual reality system leads to improved fine motor control post-stroke. J Neuroeng Rehabil. 2014;11:171.
87. Aszmann OC, Roche AD, Salminger S, et al. Bionic reconstruction to restore hand function after brachial plexus injury: a case series of three patients. Lancet. 2015;385:2183–9.
88. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. Arch Phys Med Rehabil. 1969;50:311–9.
89. Merians AS, Fluet GG, Qiu Q, et al. Robotically facilitated virtual rehabilitation of arm transport integrated with finger movement in persons with hemiparesis. J Neuroeng Rehabil. 2011;8:27.
90. Godfrey SB, Holley RJ, Lum PS. Clinical effects of using HEXORR (Hand Exoskeleton Rehabilitation Robot) for movement therapy in stroke rehabilitation. Am J Phys Med Rehabil/Assoc Acad Physiatrists. 2013;92:947–58.
91. Susanto EA, Tong RK, Ockenfeld C, Ho NS. Efficacy of robot-assisted fingers training in chronic stroke survivors: a pilot randomized-controlled trial. J Neuroeng Rehabil. 2015;12:42.
92. Polygerinos P, Galloway KC, Savage E, Herman M, O'Donnell K, Walsh CJ. Soft robotic glove for hand rehabilitation and task specific training. International conference on robotics and automation. Seatlle: IEEE; 2015. p. 2913–9.
93. Balasubramanian S, Klein J, Burdet E. Robot-assisted rehabilitation of hand function. Curr Opin Neurol. 2010;23:661–70.
94. Topping M. Flexibot—a multi-functional general purpose service robot. Ind Robot. 2001;28:395–401.
95. Kamper DG, Rymer WZ. Quantitative features of the stretch response of extrinsic finger muscles in hemiparetic stroke. Muscle Nerve. 2000;23:954–61.
96. Kamper DG, Harvey RL, Suresh S, Rymer WZ. Relative contributions of neural mechanisms versus muscle mechanics in promoting finger extension deficits following stroke. Muscle Nerve. 2003;28:309–18.
97. Hoffmann G, Conrad MO, Qiu D, Kamper DG. Contributions of voluntary activation deficits to hand weakness after stroke. Top Stroke Rehabil. 2016;15:1–9 [Epub ahead of print].

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

16

Hermano Igo Krebs, Dylan Edwards, and Neville Hogan

Abstract

MIT's motto is "Mens et Manus" (Mind and Hand), and we have adopted it as the guiding rule (principle) for our line of research: using robotics and information technology to reconnect the brain to the hand. Nurture allows a patient to reduce impairment, increase function, and improve the quality of life beyond natural recovery. This chapter describes our efforts toward this goal since the initial development of the MIT-Manus in 1989. Numerous clinical trials involving thousands of patients (subjects) working with (receiving therapy using) the commercial version of the MIT-Manus have been conducted since then, and we have created a complete robotic gym for the upper extremity. Recently, the American Heart Association and the Veterans Affairs/Department of Defense endorsed the use of robot-assisted therapy in stroke rehabilitation for upper extremity, and we have been focusing on how to tailor therapy to a particular patient's need and in determining who is a responder (and no-responder) to this kind of intervention.

H.I. Krebs, PhD (✉)
Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA

Department of Neurology, University of Maryland, School of Medicine, Baltimore, MD, USA

Department of Rehabilitation Medicine I, Fujita Health University, School of Medicine, Nagoya, Japan

Institute of Neuroscience, Newcastle University, Newcastle Upon Tyne, UK

Department of Mechanical Science and Bioengineering, Osaka University, Osaka, Japan
e-mail: hikrebs@mit.edu

D. Edwards, PT, PhD
Laboratory for Non-Invasive Brain Stimulation and Human Motor Control, Department of Neurology, Weill Cornell Medical College, Burk-Cornell Medical Research Institute, White Plains, NY, USA

N. Hogan, PhD
Department of Mechanical Engineering, Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA

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16.1 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 a 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 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.

16.1.1 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 guidelines for stroke care came to the same conclusion endorsing the use of rehabilitation robots for the upper 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." 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" [2].

These endorsements came on the 21st anniversary of our initial efforts begun in 1989 that led to what became known as "MIT-Manus." It would be difficult to deny the impact of this work on neuro-rehabilitation, described by our clinical colleagues as "perhaps one of the most important developments in neuro-recovery in the last 75 years" (Dr. Bruce Volpe, Feinstein Institute for Medical Research). 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. The central challenge of rehabilitation robotics is to provide tools to manage and harness positive plastic changes. 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. The message seems clear: we must study the process of neuro-recovery as well as the technologies that might augment this process.

16.1.2 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. 16.1).

16.1.2.1 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 DOFs of the human skeleton was technically feasible, it would have been large, complex, and—most importantly—difficult to revise or modify. With a modular approach, individual modules could be refined and optimized without redesign of other modules.

16.1.2.2 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 degrees of freedom (DOF) and one passive DOF. It consisted of a semi-direct-drive, five-bar-linkage SCARA mechanism (Selective Compliance Assembly Robot Arm) driven by brushless motors [3, 4]. Since then several variants were deployed under the commercial name of InMotion2 robot (Interactive Motion Technologies, Watertown, MA, USA—see Fig. 16.2).

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

Based on their mechanical interface with a human, robots can be classified as end-effector or exoskeletal designs. End-effector robots interact with the human via a handshake, i.e., the interaction takes place through a single point of contact. In other words, there is power exchange only at the tip of the robot. Exoskeletal robots are mounted on distinct human limb segments with more than one

Fig. 16.1 A gym of upper-extremity robots. *Top row*, *left* shows a person with chronic stroke working with the anti-gravity shoulder-and-elbow robot. The *top row*, *middle panel* shows a person working with the planar shoulder-and-elbow robot. The *top row*, *right panel* shows the wrist robot during therapy at the Burke Rehabilitation Hospital. The *middle row*, *left panel* shows the hand module for grasp and release. The *middle row*, *middle panel* shows reconfigurable robots. The robotic therapy shoulder-and-elbow and wrist modules can operate in standalone mode or be integrated into a coordinated functional unit. The *middle row*, *right panel* shows the shoulder-and-elbow and hand module integrated into a coordinated functional unit. The *bottom row* shows an exoskeletal robot with three active DOFs designed for psychophysical studies of 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, psychophysical experiments can assist or selectively apply perturbation force fields to shoulder, elbow, and wrist (either flexion/extension or abduction/adduction)

point of contact. End-effector robot designs like the MIT-Manus are simpler, afford significantly faster "don" and "doff" (set-up 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, end-effector 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

Fig. 16.2 The MIT-Manus evolution. The figure shows the original MIT-Manus and several of its commercial variants

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. Hence, we designed a highly backdriveable, 3-active DOF, gravity-compensated shoulder-elbow-and-wrist exoskeletal robot. A variant was deployed under the commercial name of InMotion-Exos robot, which adds to MIT-Manus' shoulder-and-elbow capability either wrist flexion/extension or wrist abduction/adduction as shown in Fig. 16.1 (Interactive Motion Technologies, Watertown, MA, USA). Two InMotion-Exos can be configured for bimanual use.

16.1.2.4 Gravity Non-compensated 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 450–650 range of shoulder abduction and from 300 to 900 of shoulder elevation or flexion [5]. 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.

16.1.2.5 Wrist Robot

To extend treatment beyond the shoulder and elbow, we designed and built a wrist module for robotic therapy [6]. The device accommodates the range of motion of a normal wrist in everyday tasks, i.e., flexion/extension 60°/60°, abduction/adduction 30°/45°, and 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 degrees of freedom 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 [7]. If robot and human had the same number of degrees of freedom but these were not coaligned, motion might evoke excessive forces or torques. By allowing the human joint more degrees of freedom 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.

16.1.2.6 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 [8]. 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. 16.1). 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 (see Fig. 16.3).

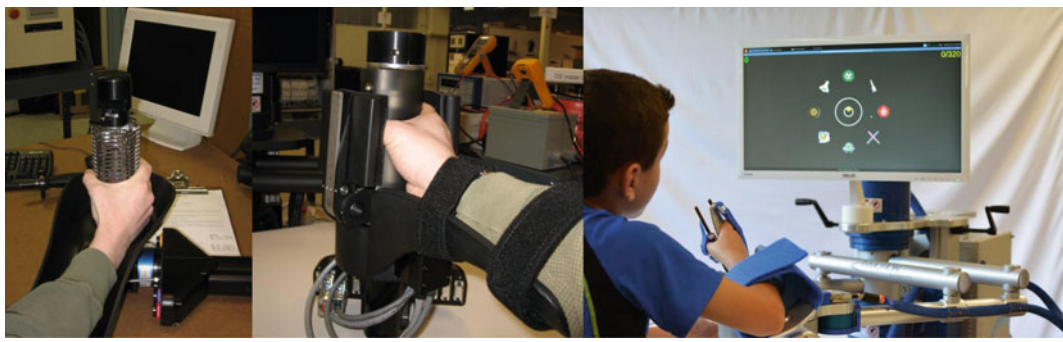

Fig. 16.3 The hand-module evolution. The figure shows the original hand module and several of its commercial variants

16.2 Harnessing Plasticity to Augment Recovery

16.2.1 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 [9]. 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.

Placement of subjects in an experimental (robot-trained) or control (robot-exposure) group was done in random fashion. Individuals in the experimental group received no less than 25 sessions of sensorimotor robotic therapy for the paretic arm (1-h session daily every weekday). Patients were asked to perform goal-directed, visually guided and evoked reaching movements with their paretic arm. MIT-Manus' low impedance and low friction assured that the robot would not suppress patient's attempts to move. The robot afforded gentle guidance and assistance only when a patient could not move or deviated from the desired path [10]. We named this intervention "sensorimotor" therapy, and it was similar to the "hand-over-hand" assistance that a therapist often provides during usual care. It is interesting to note that this form of "assistance as needed," which has been a central feature of our approach from the outset, has been adopted by other groups [11–13].

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) [14–16]. 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 F-M and has met standards for inter-rater reliability, significant intra-class correlation coefficients, and internal item consistency for inpatients [17].

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-S/E and MP scores (see Table 16.1). In fact, the robot-trained group improved twice as much 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.

Table 16.1 Burke inpatient studies

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			
Function Independence Measure (FIM)	32.0 ± 5	25.5 ± 6.5	NS

($n=96$) Mean interval change in impairment and disability (significance $p<0.05$)

16.2.2 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 [18]. Complete motor recovery, when it occurs, will unfold rapidly in hours or days. The more commonly observed partial recovery, with broad variability in final motor outcomes, unfolds over longer periods [19, 20]. At the time of our initial studies, the state of knowledge regarding motor recovery post stroke indicated that the majority of gains in motor abilities occurred within the first 3 months after stroke onset and that over 90 % of motor recovery was complete within the first 5 months [21]. However, 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 suggested 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) [22].

The VA-ROBOTICS study vanquished for good the old dogma 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. 16.2). 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 which corresponds to the MCID threshold—Minimum Clinically Important Difference [23]).

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.

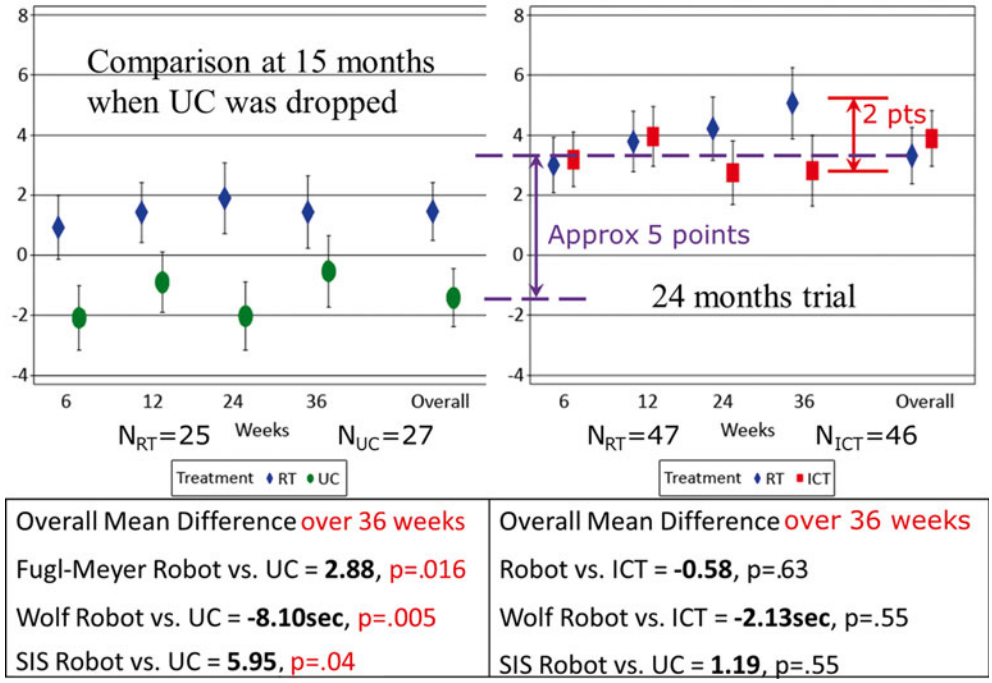

Fig. 16.4 Changes over time in the VA-ROBOTICS. Training lasted for 12 weeks with an additional 6-month follow-up after completion of the intervention. The *left panel* shows the comparison of the first half of the robot group with the usual care (first half as therapists learned how to employ the system). 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

In this era of cost containment, cost-benefit analysis is essential, and in this case, it provided an important result [24]. As expected, active interventions added cost beyond the usual care offered in the VA; for example, the extra expenditure of the robotic equipment and an additional therapist cost the VA $5,152 per patient. However, when we compared the total cost, which included the clinical care needed to take care of these Veterans, there were no significant differences between active intervention and usual care. In fact, the robotic group costs less to the VA. The total healthcare utilization cost of the usual-care group was $19,098 per patient, compared to $17,831 total healthcare cost for the robotic group (including the additional cost of robotic therapy). To check the possibility that a Hawthorne-like effect may have biased the cost analysis, we requested the VA to examine whether the total healthcare costs increased for the robotic therapy group after the cessation of the intervention. It did not. In fact, the total healthcare cost for the robotic group went down further, perhaps because patients continued to improve even without intervention (see Fig. 16.4) [24]. This suggests better care for the same or lower total cost.

This exciting result led the UK National Health Service (NHS) and its Health Technology Assessment (HTA) Programme to embark on the largest ever randomized clinical trial in robotic therapy. RATULS will enroll over 720 stroke patients. The goal of this research is to determine whether the same cost advantage can be observed in the British healthcare system. Of note here is the fact that enrollment is ahead of schedule, potentially leading to a total enrollment of 800 stroke patients (see https://research.ncl.ac.uk/ratuls/).

Summarizing briefly, there is now objective evidence that in the "real" therapy world away from the 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 equivalent or better results in acute/subacute stroke.

16.2.3 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 was never more evident than when we tested a common perception among 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 [22], 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 non-compensated 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) [25]. 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 of the duration used in 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' compliant and backdrivable behavior allowed for expression of movement outside a rigid trajectory and provided assistance with a performance-based algorithm, adapting forces as needed to challenge or assist movement. This algorithm, introduced in 2002 and described further below, 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 controller updates its characteristics after each group of five games; the better the patient performs, the less guidance is provided and the more she/he is challenged to move quickly [10]. 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.

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 it improved less. In fact, the planar (gravity-compensated) robot training subjects showed the greatest change.

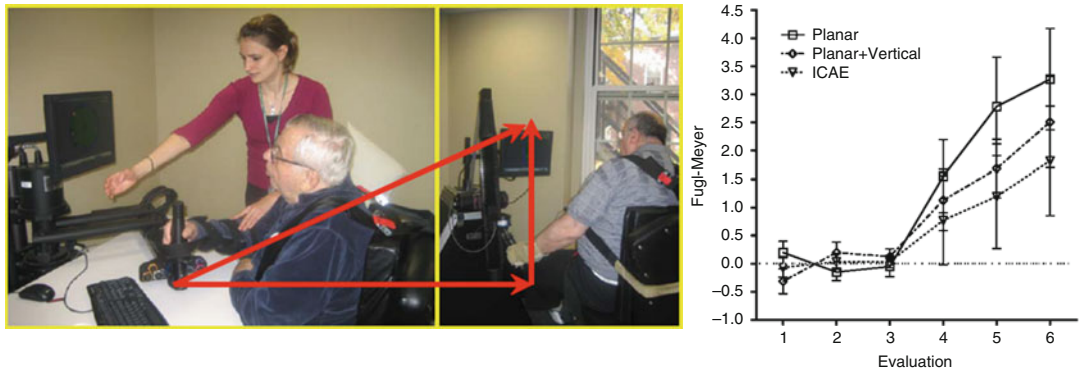

Fig. 16.5 Component training and spatial composition. The FMA change at each point (mean, STD) with ICAE standing for intensive conventional arm exercise. Baseline demonstrates stability and no difference among groups. Changes from baseline to final and follow-up showed a significant benefit for both robotic groups

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 non-compensated) 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 modules for whole arm antigravity reaching and gravity-compensated planar reaching, and the training with block of each movement type in close succession interfered with motor consolidation [26, 27]. This interpretation is supported by a prior robotic study which found that non-gravity-compensated 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 [5]. Whether motor memories require an interval to consolidate [28, 29] 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 (Fig. 16.5).

16.2.4 Augmenting Robotic-Mediated Therapy: Neuromodulation

We have been investigating modes to increase the impact of robotic therapy. In particular, we have been investigating the potential of combining robotic-mediated therapy with transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) [31, 32]. Of the latter, we have been focusing particularly on anodal tDCS that can transiently increase corticomotor

excitability of intrinsic hand muscles and improve upper limb function in patients with chronic stroke.

We tested whether the increased corticomotor excitability might extend to muscles acting about the wrist in patients with residual motor deficit due to chronic stroke and remain present during robotic training involving active wrist movements. We employed TMS and measured the motor-evoked potentials (MEPs) in the flexor carpi radialis (FCR). In particular, we measured corticomotor excitability and short-interval cortical inhibition (SICI) before and immediately after a period of tDCS (1 mA, 20 min, anode, and TMS on same affected hemicranium) and robotic wrist training (1 h). We observed following tDCS an escalation in MEP amplitude increase (mean 168±22%SEM; $p<0.05$), which remained increased after robot training (163±25%; $p<0.05$). Conditioned MEPs were of significantly higher amplitude after tDCS or robotic training (62±6% pre-TDCS, $p<0.05$; 89±14% post-tDCS, $p=0.40$; 91±8% post-robot; $p<0.28$), suggesting that the increased corticomotor excitability is associated with reduced intracortical inhibition [31]. These effects continued during an expanded period of robotic motor training, demonstrating that a motor learning and retraining program can coexist with tDCS-induced changes in cortical motor excitability. This result supports the concept of employing brain stimulation to potentially augment robotic therapy outcomes (Fig. 16.6).

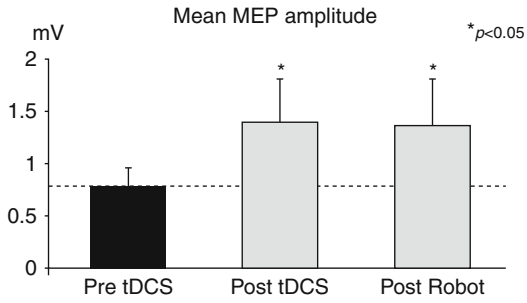

Fig. 16.6 Mean (± SEM) MEP amplitude from across subjects. MEPs were recorded from the FCR muscle during a low-level isometric wrist flexion, before and immediately following 20 min anodal brain stimulation (tDCS), then again after 1 h of robotic wrist therapy. Following tDCS, MEP amplitude was significantly elevated and remained significantly elevated after robotic therapy

16.2.5 Which Processes Underlie Neuro-recovery?

A common assumption is that sensorimotor therapy works by helping patients to "relearn" motor control [33]. 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 sensorimotor 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 sensorimotor 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 [10]. 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 2 s, 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 towards 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 indicators reflecting patient's performance in the last batch of five repetitions [34]. 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 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

Table 16.2 Motor impairment outcomes of performance-based progressive robotic therapy

Severity	Impairment measure (Mean±Sem)	F-M 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[a]	32	45.4 ± 1.7[a]	22
CNS >4; NIHSS <15	Follow-up (3 months)	24.5 ± 0.9[a]	44	46.5 ± 1.9[a]	25
Severe	Before treatment	8.2 ± 0.7		17.3 ± 1.8	
N = 16	After treatment	10.9 ± 0.9[a]	33	23.7 ± 2.0[a]	52
CNS <4	Follow-up (3 months)	12.5 ± 0.9[a]	37	26.3 ± 2.2[a]	52
NIHSS >15					

F-M SEC Fugl-Meyer, shoulder-elbow component, *MP* Motor Power, *CNS* Canadian Neurological Scale, *NIHSS* National Institutes of Health Stroke Scale
[a]Denotes significant change, $P < 0.001$

do more of the movement. Finally, smoothness and aiming (deviation from a straight path) quantify the tradeoff 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 [35]. 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 16.2). More important for our understanding of recovery, the magnitude of the improvement achieved with this adaptive algorithm was 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 that is adapted to the patient in order to present a continuous challenge substantially enhanced recovery.

An important and informative detail is that like others we found that this enhancement of recovery was achieved with fewer repetitions [36]. 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 sensorimotor 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.

16.2.6 Robot-Mediated Assay

First proposed over 25 years ago, robot-aided neuro-rehabilitation is increasingly being incorporated into every day clinical practices. In addition to delivering high-intensity, reproducible sensorimotor therapy, these devices are precise and reliable "measuring" tools. These measurements are

objective and repeatable. Reducing the time to evaluate a patient's movement ability may offer new opportunities for designing therapeutic programs and for providing superior biomarkers [37]. Clinical scales and robotic devices were used at two clinical sites on 208 patients with moderate to severe acute ischemic stroke to measure (determine) range of arm movement 7, 14, 21, 30, and 90 days after the event.

Kinematic and kinetic parameters were compared to clinical assessments. Robot measures accurately forecast the clinical outcomes (cross-validated R^2 of modified Rankin scale = 0.60; NIH Stroke Scale = 0.63; Fugl-Meyer = 0.73; Motor Power = 0.75). The robotic measures revealed greater sensitivity in measuring the recovery of patients (increased standardized effect = 1.47) demonstrating that robotic measures will more than adequately capture outcome and the altered effect size will reduce noticeably the required sample size by close to 70%. Reducing sample size will substantially improve study efficiency [38].

The reliability of human-administered clinical scales has often been questioned; for example, Sanford reported an inter-rater variability of ±18 points (95% confidence interval) for the total Fugl-Meyer scale, pointing out that small patient improvements will not be identified by this score [39, 40]. Krebs found up to a 15% discrepancy between therapists when evaluating the same patient for the upper extremity FMA scale [41, 42], Gregson estimated an inter-rater agreement of 59% for the Modified Ashworth Scale (MAS) [43]. The MAS is considered a reliable clinical scale by some [44], but totally unreliable by others [45, 46]. 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 can not only greatly reduce the amount of time required to evaluate patients' motor progress, 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 [10, 47] (Fig. 16.7).

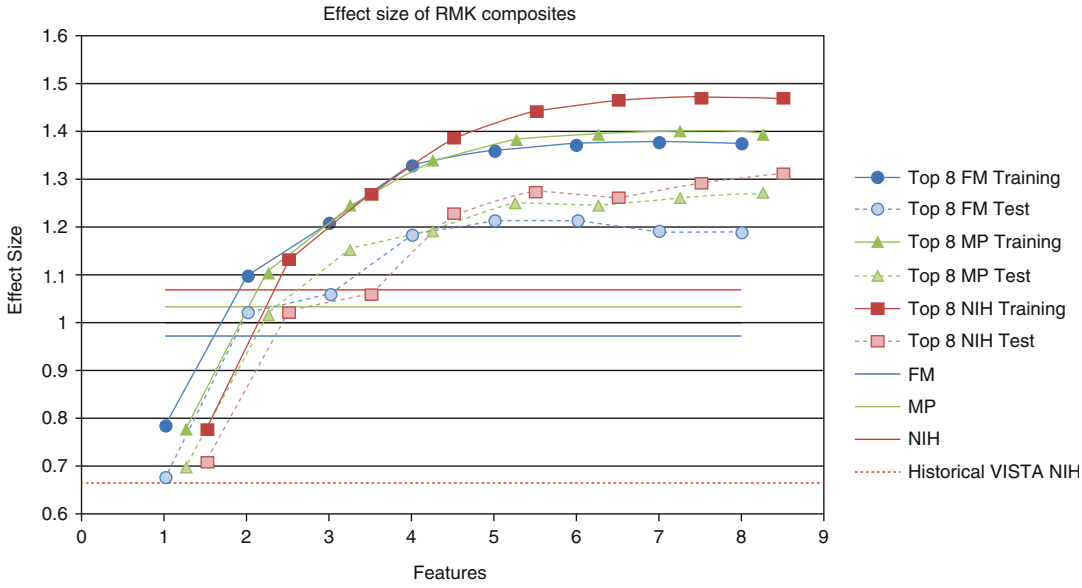

Fig. 16.7 Optimization of effect size for robot-derived robot-assisted measurement of kinematic and kinetic (RMK2) metrics. The *horizontal lines* show the day 7 to day 90 effect size for comparable patients of the historical Virtual International Stroke Trials Archive (VISTA) data for the NIHSS, as well as the effect sizes for the NIHSS, FM, and MP assessment scales for our completers' cohort. The figure also shows the performance of the robot-derived RMK2 composites optimized for effect size for the trained (*solid lines*) and cross-validated sets (*dashed lines*). Note the increase of over 20% in cross-validated effect size for the RMK2 composites over the clinical scales with four-features for this study (and over 70%; over the historical data)

16.3 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 as compared to usual care, even for patients many years post stroke. At the same time, other forms of robotic therapy have been singularly ineffective as compared to usual care. The contrast is starkest when we contrast upper-extremity and lower-extremity therapy. For example, the 2010 American Heart Association (AHA) and the 2010 Veterans Administration/Department of Defense guidelines for stroke care endorses the use of rehabilitation robots for the upper extremity but not for the lower extremity [1, 2]. While the AHA and VA recommendations compared robotic outcomes to usual care as practiced in the USA, results are only marginally better when considering a mixture of usual-care practices around the world with the latest Cochrane report stating that while robotics alone was not superior to a mixture of usual care, robotic walking training plus usual care leads to better outcomes than equal time in usual care alone [48].

Of course, these differences might arise from the contrasting neuromechanical complexity of upper-extremity reaching and grasping vs. 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 doesn't 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 rhythmic training but ultimately doing the wrong thing. The technology we have deployed to date for upper-extremity therapy is straightforward, though non-trivial, 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-engined 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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References

1. Miller EL, Murray L, Richards L, Zorowitz RD, Bakas T, Clark P, Billinger SA, N. American Heart Association Council on Cardiovascular, and C. the Stroke. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association. Stroke. 2010;41:2402–48.
2. G. Management of Stroke Rehabilitation Working. VA/DOD clinical practice guideline for the management of stroke rehabilitation. J Rehabil Res Dev. 2010;47:1–43.

3. Hogan N, Krebs HI, Charnnarong J, Srikrishna P, Sharon A. MIT-MANUS: a workstation for manual therapy and training. I, In Robot and human communication, 1992. Proceedings, IEEE International Workshop on; 1992. p. 161–5.
4. Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neurorehabilitation. IEEE Trans Rehabil Eng. 1998;6:75–87.
5. Krebs HI, Ferraro M, Buerger SP, Newbery MJ, Makiyama A, Sandmann M, Lynch D, Volpe BT, Hogan N. Rehabilitation robotics: pilot trial of a spatial extension for MIT-Manus. J Neuroeng Rehabil. 2004;1:5.
6. Krebs HI, Volpe BT, Williams D, Celestino J, Charles SK, Lynch D, Hogan N. Robot-aided neurorehabilitation: a robot for wrist rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15:327–35.
7. Charles SK, Hogan N. Dynamics of wrist rotations. J Biomech. 2011;44:614–21.
8. Masia L, Krebs HI, Cappa P, Hogan N. Design and characterization of hand module for whole-arm rehabilitation following stroke. IEEE ASME Trans Mechatron. 2007;12:399–407.
9. Volpe BT, Krebs HI, Hogan N. Is robot-aided sensorimotor training in stroke rehabilitation a realistic option? Curr Opin Neurol. 2001;14:745–52.
10. Krebs HI, Palazzolo JJ, Dipietro L, Ferraro M, Krol J, Rannekleiv K, Volpe BT, Hogan N. Rehabilitation robotics: performance-based progressive robot-assisted therapy. Auton Robot. 2003;15:7–20.
11. Riener R, Lunenburger L, Jezernik S, Anderschitz M, Colombo G, Dietz V. Patient-cooperative strategies for robot-aided treadmill training: first experimental results. IEEE Trans Neural Syst Rehabil Eng. 2005;13:380–94.
12. Emken JL, Benitez R, Sideris A, Bobrow JE, Reinkensmeyer DJ. Motor adaptation as a greedy optimization of error and effort. J Neurophysiol. 2007;97:3997–4006.
13. Wolbrecht ET, Chan V, Reinkensmeyer DJ, Bobrow JE. Optimizing compliant, model-based robotic assistance to promote neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2008;16:286–97.
14. Aisen ML, Krebs HI, Hogan N, McDowell F, Volpe BT. The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. Arch Neurol. 1997;54:443–6.
15. Krebs HI, Volpe BT, Aisen ML, Hogan N. Increasing productivity and quality of care: robot-aided neurorehabilitation. J Rehabil Res Dev. 2000;37:639–52.
16. Volpe BT, Krebs HI, Hogan N, Edelsteinn L, Diels CM, Aisen ML. Robot training enhanced motor outcome in patients with stroke maintained over 3 years. Neurology. 1999;53:1874–6.
17. Ferraro M, Demaio JH, Krol J, Trudell C, Rannekleiv K, Edelstein L, Christos P, Aisen M, England J, Fasoli S, Krebs HI, Hogan N, Volpe BT. Assessing the motor status score: a scale for the evaluation of upper limb motor outcomes in patients after stroke. Neurorehabil Neural Repair. 2002;16:283–9.
18. Twitchell TE. The restoration of motor function following hemiplegia in man. Brain. 1951;74:443–80.
19. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1994;75:394–8.
20. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part I: outcome. The Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76:399–405.
21. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: time course of recovery. The Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76:406–12.
22. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, Ringer RJ, Wagner TH, Krebs HI, Volpe BT, Bever Jr CT, Bravata DM, Duncan PW, Corn BH, Maffucci AD, Nadeau SE, Conroy SS, Powell JM, Huang GD, Peduzzi P. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362:1772–83.
23. Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. Phys Ther. 2012;92:791–8.
24. Wagner TH, Lo AC, Peduzzi P, Bravata DM, Huang GD, Krebs HI, Ringer RJ, Federman DG, Richards LG, Haselkorn JK, Wittenberg GF, Volpe BT, Bever CT, Duncan PW, Siroka A, Guarino PD. An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. Stroke. 2011;42(9):2630–2.
25. Conroy SS, Whitall J, Dipietro L, Jones-Lush LM, Zhan M, Finley MA, Wittenberg GF, Krebs HI, Bever CT. Effect of gravity on robot-assisted motor training after chronic stroke: a randomized trial. Arch Phys Med Rehabil. 2011;92(11):1754–61.
26. Brashers-Krug T, Shadmehr R, Bizzi E. Consolidation in human motor memory. Nature. 1996;382:252–5.
27. Shadmehr R. Generalization as a behavioral window to the neural mechanisms of learning internal models. Hum Mov Sci. 2004;23:543–68.
28. Caithness G, Osu R, Bays P, Chase H, Klassen J, Kawato M, Wolpert DM, Flanagan JR. Failure to consolidate the consolidation theory of learning for sensorimotor adaptation tasks. J Neurosci. 2004;24:8662–71.
29. Stickgold R. Sleep-dependent memory consolidation. Nature. 2005;437:1272–8.
30. Overduin SA, Richardson AG, Lane CE, Bizzi E, Press DZ. Intermittent practice facilitates stable motor memories. J Neurosci. 2006;26:11888–92.
31. Edwards DJ, Krebs HI, Rykman A, Zipse J, Thickbroom GW, Mastaglia FL, Pascual-Leone A, Volpe BT. Raised corticomotor excitability of M1 forearm area following anodal tDCS is sustained during robotic wrist therapy in chronic stroke. Restor Neurol Neurosci. 2009;27:199–207.

32. Volpe BT, Huerta PT, Zipse JL, Rykman A, Edwards D, Dipietro L, Hogan N, Krebs HI. Robotic devices as therapeutic and diagnostic tools for stroke recovery. Arch Neurol. 2009;66:1086–90.
33. Hogan N, Krebs HI, Rohrer B, Palazzolo JJ, Dipietro L, Fasoli SE, Stein J, Hughes R, Frontera WR, Lynch D, Volpe BT. Motions or muscles? Some behavioral factors underlying robotic assistance of motor recovery. J Rehabil Res Dev. 2006;43:605–18.
34. Schmidt R, Lee T. Motor Control and learning: a behavioral emphasis. Champaign: Human Kinetics; 2005.
35. Ferraro M, Palazzolo JJ, Krol J, Krebs HI, Hogan N, Volpe BT. Robot-aided sensorimotor arm training improves outcome in patients with chronic stroke. Neurology. 2003;61:1604–7.
36. Duarte JE, Gebrekristos B, Perez S, Rowe JB, Sharp K, Reinkensmeyer DJ. Effort, performance, and motivation: insights from robot-assisted training of human golf putting and rat grip strength. IEEE Int Conf Rehabil Robot. 2013;2013:1–6.
37. Bosecker C, Dipietro L, Volpe B, Krebs HI. Kinematic robot-based evaluation scales and clinical counterparts to measure upper limb motor performance in patients with chronic stroke. Neurorehabil Neural Repair. 2010;24:62–9.
38. Krebs HI, Krams M, Agrafiotis DK, Dibernardo A, Chavez JC, Littman GS, Yang E, Byttebier G, Dipietro L, Rykman A, McArthur K, Hajjar K, Lees KR, Volpe BT. Robotic measurement of arm movements after stroke establishes biomarkers of motor recovery. Stroke. 2014;45:200–4.
39. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med. 1975;7:13–31.
40. Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. Phys Ther. 1983;63:1606–10.
41. Krebs HI, Volpe BT, Ferraro M, Fasoli S, Palazzolo J, Rohrer B, Edelstein L, Hogan N. Robot-aided neurorehabilitation: from evidence-based to science-based rehabilitation. Top Stroke Rehabil. 2002;8:54–70.
42. See J, Dodakian L, Chou C, Chan V, McKenzie A, Reinkensmeyer DJ, Cramer SC. A standardized approach to the Fugl-Meyer assessment and its implications for clinical trials. Neurorehabil Neural Repair. 2013;27:732–41.
43. Gregson JM, Leathley MJ, Moore AP, Smith TL, Sharma AK, Watkins CL. Reliability of measurements of muscle tone and muscle power in stroke patients. Age Ageing. 2000;29:223–8.
44. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67:206–7.
45. Gregson JM, Leathley MJ, Moore AP, Smith TL, Sharma AK, Watkins CL. Clinical measures: reliable or not? Age Ageing. 2001;30:86–7.
46. Pomeroy VM, Dean D, Sykes L, Faragher EB, Yates M, Tyrrell PJ, Moss S, Tallis RC. The unreliability of clinical measures of muscle tone: implications for stroke therapy. Age Ageing. 2000;29:229–33.
47. Michmizos K, Rossi S, Castelli E, Cappa P, Krebs H. Robot-aided neurorehabilitation: a pediatric robot for ankle rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2015;23(6):1056–67.
48. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2013;7:CD006185.

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

17

Tobias Nef, Verena Klamroth-Marganska, Urs Keller, 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, with more frequent, more numerous, and longer repetitions. 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

T. Nef, PhD (✉)
Gerontechnologoy and Rehabilitation Group, ARTORG Center for Biomedical Engineering Research, University of Bern, Murtenstrasse 50, Bern 3010, Switzerland
e-mail: tobias.nef@artorg.unibe.ch

V. Klamroth-Marganska, MD • R. Riener, PhD
Sensory-Motor Systems Lab, Department of Health Sciences and Technology, Institute of Robotics and Intelligent Systems, ETH Zurich, Tannenstrasse 1, Zurich 8092, Switzerland

Spinal Cord Injury Center, Balgrist Campus, Lenghalde 5, Zurich 8008, Switzerland

U. Keller
Sensory-Motor Systems Lab, Department of Health Sciences and Technology, Institute of Robotics and Intelligent Systems, Tannenstrasse 1, Zurich 8092, Switzerland

Rehabilitation Centre, University Children's Hospital Zurich, Affoltern a. A., Mühlebergstrasse 104, Affoltern a. A. 8910, Switzerland

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17.1 State of the Art

17.1.1 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 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 are training intensity [10–12] including frequency, 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 they support the objective observation and evaluation of the rehabilitation progress.

17.1.2 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. 17.1). In most applications, the patient looks at a graphical display—either a large, immersive 3D projection or a 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.

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

End-effector-based robots are connected to the patient's hand or forearm at a single point (Fig. 17.2). Depending on the number of links of

Fig. 17.1 Typical setup for a robot-supported arm therapy system

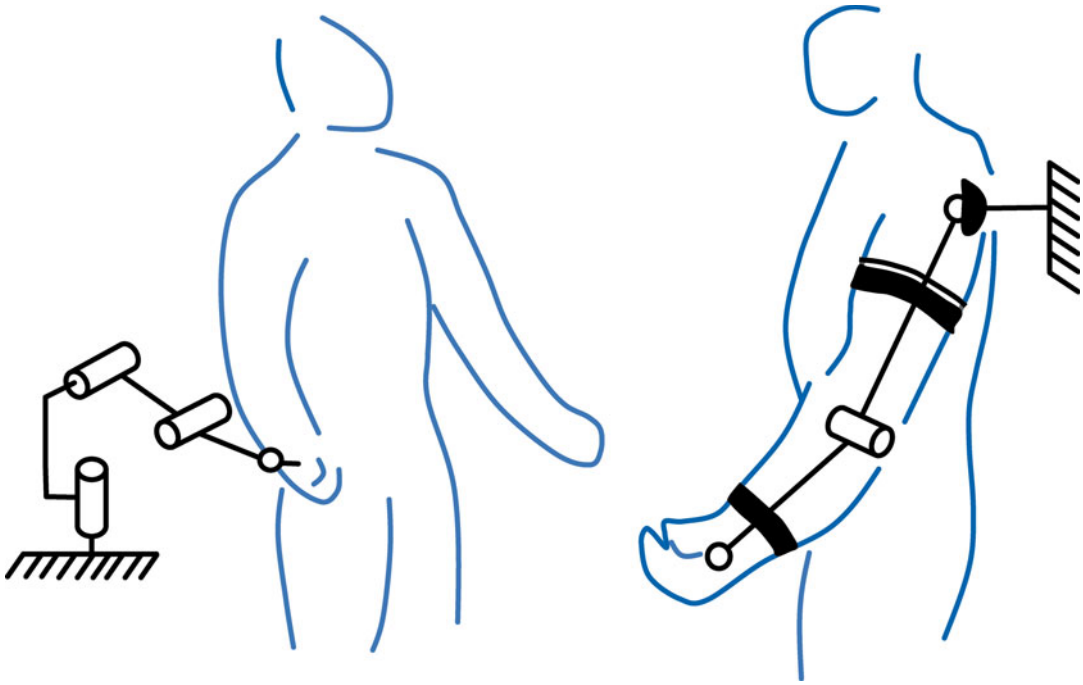

Fig. 17.2 Schematic view of end-effector-based (*left*) and exoskeleton (*right*) robots

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 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 on the lower arm and another cuff affixed to the upper arm. Some examples of arm-rehabilitation exoskeletons include the Dampace [25], the

ArmeoSpring (former T-Wrex) [26], the MGA-Exoskeleton [27], the L-Exos [28], the Caden-7 [29], the Intelligent Robotic Arm [30], as well as 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.

17.1.2.2 Number and Type of Actuated Joints

Apart from the mechanical structure, 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 ArmeoSpring, 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. Interventional 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 proximal to 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].

An interesting research question is whether robotic training should focus on whole-arm/hand functional movements, simply in distal fashion or by combining distal and proximal modes. There is evidence from Krebs et al. [44] that training both the transport of the arm and manipulation of an object did not confer any advantage over solely training transport of the arm. This calls for further investigation with other robotic devices—especially with whole-arm exoskeletons.

17.1.2.3 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 or her 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 [45, 46]. 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 ArmeoSpring device is based on the former T-Wrex device [47] 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 or her 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 [47].

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

17.2.1 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, 48]. This version is characterized by four degrees of freedom (DOF) actuating the shoulder in 3D and flex/extend the elbow (Fig. 17.3). 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 additional DOF (six altogether) allowing also pronation/supination of the lower arm and wrist flexion/extension (Fig. 17.1). 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 [49, 50]. 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. 17.4) 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.

17.2.2 Mechanical Setup of the ARMin III Robot

The ARMin III robot (Fig. 17.4) 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. 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 which is an important requirement for sensorless force-control [50] 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 varying body plans, 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 accommo-

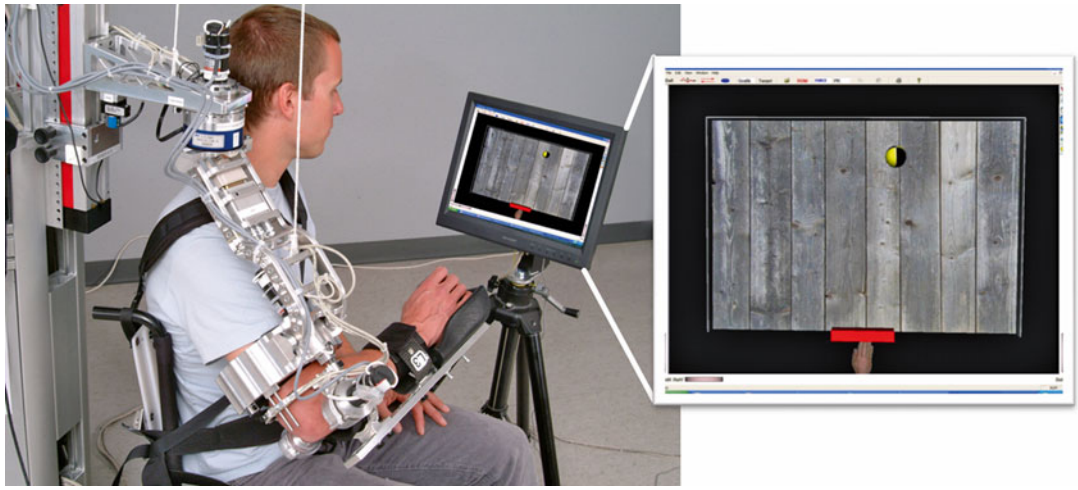

Fig. 17.3 ARMin I robot with a healthy test person (*left*). The person is looking at a computer monitor showing the movement task (*right*)

Fig. 17.4 ARMin III setup

date 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].

17.2.3 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 spasms and "loosened" the arm and hand. After 10–15 min of passive mobilization, active training followed, including games, reaching exercises, and ADL training scenarios [51, 52].

17.2.3.1 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 recorded 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 [46]. 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.

17.2.3.2 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. 17.5). 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 or her 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 on his or her own, 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 both 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 needs. 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 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 needs.

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 or her 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. 17.5). Here, the patient holds a virtual ping-pong racket and

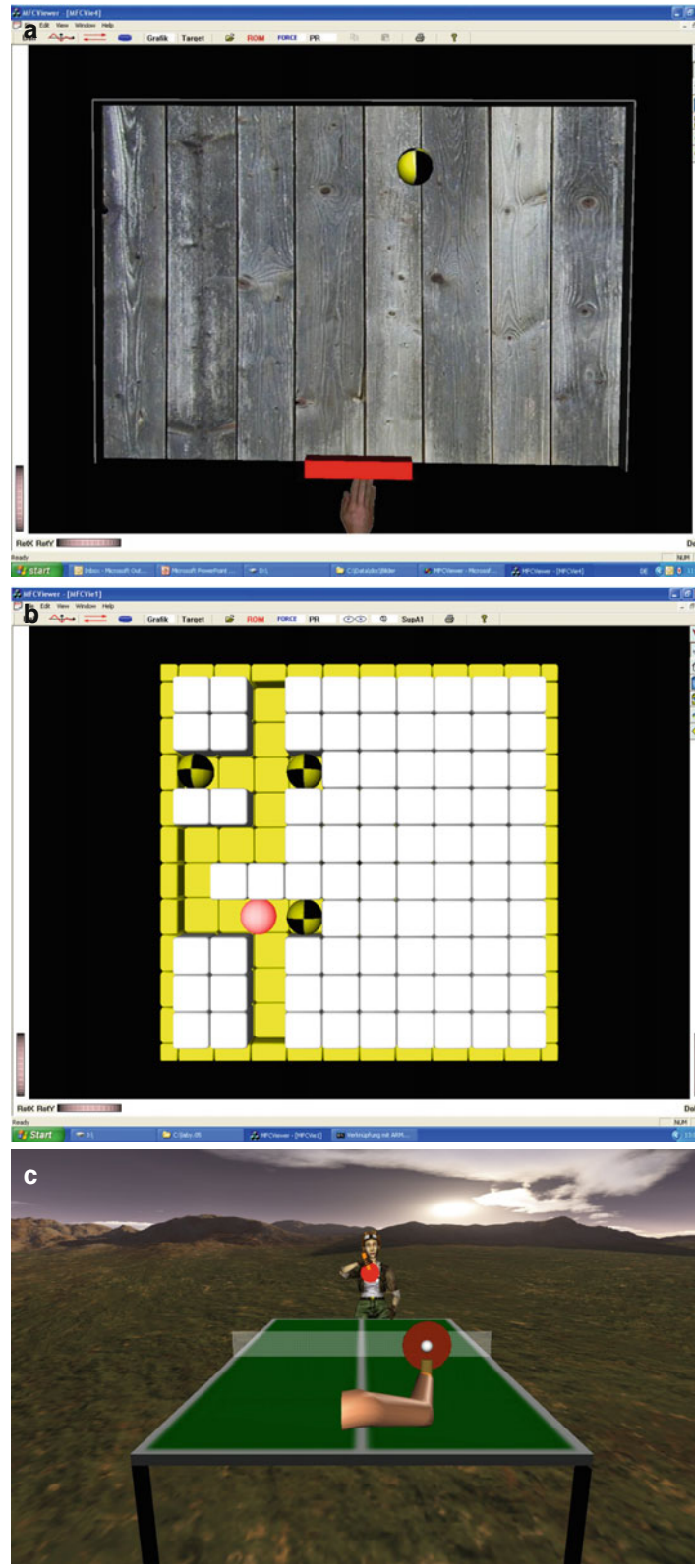

Fig. 17.5 Virtual reality scenarios for arm training. Ball game (**a**), labyrinth (**b**), and ping-pong game (**c**)

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 ping-pong game.

Another therapeutic computer game is the labyrinth game, where the patient navigates his or her 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 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 or her 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 [52]. 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 or her 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 floats somewhat, and it is very easy for the patient to lift his or her arm. In the second supporting scheme, the robot allows upward arm movements but resists downward movements. With this strategy, the patient must lift his or her arm by him- or herself, but whenever he or she gets tired, he or she can rest, and the arm will stay at the current position without any effort. Both strategies can also be combined. 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.

17.2.3.3 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. As with 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. 17.6), 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 dip-

per. 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 or her hand and put them into the pan, wait until he or she 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 or her own movement trajectory, and the patient always sees feedback on how much he or she is currently supported by the robotic device. This is technically challenging because the cooking scenario involves several different movements [54, 55]. 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].

17.2.4 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 or her 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 or her 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 or her 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 veloci-

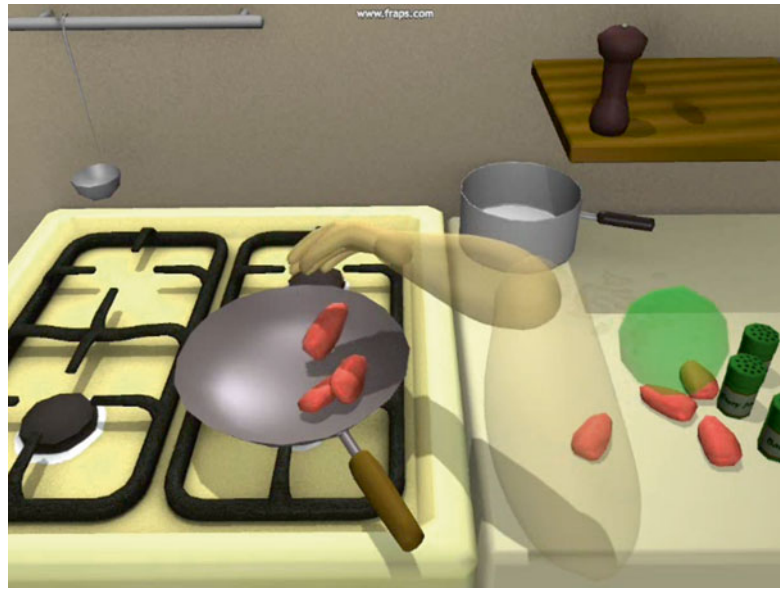

Fig. 17.6 Kitchen scenario

ties and measures the required force. This technique has been implemented and evaluated for the lower limb within the Lokomat gait training robot [57].

17.2.5 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.

17.2.5.1 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 17.1 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 plans, changing from left-arm use to right-arm use, and comfort evaluation.
- Functional testing of the software. The questions were whether the test subject understood the instructions, whether he or she could

Table 17.1 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]	$F_{max}=(451\text{ N}, 804\text{ N}, 706\text{ N})^T$ 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

successfully perform the exercises, and whether he or she 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.

17.2.5.2 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].

17.2.5.3 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 [52]. 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 measurements 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 motor portion of the Fugl-Meyer Assessment (FMA). It showed moderate but significant improvements in all three subjects ($p<0.05$): Starting with 14, 26, and 15 out of a maximum score of 66 points, the gains were 3.1, 3.0, and 4.2 points, respectively. 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 [51]. 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 again 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. Starting with 21, 24, 11, and 10 out of a maximum score of 66 points, the gains at the end of therapy were 17.6, 3.1, 6.8, and 2.1, and at 6 month follow-up 29, 5, 8, and 3 points, respectively. 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.

17.2.5.4 Randomized Clinical Trial with Stroke Patients

In order to investigate the effectiveness of arm treatment with ARMin, a clinical study with subjects in the chronic phase post stroke was performed [58]. It was the first large-scale clinical study to offer neurorehabilitative therapy of the arm with an exoskeleton robot. A key aspect was to investigate the effects of ADL training based on reaching and grasping movements. ARMin III provides the required functions: audiovisual ADL tasks, large movement ranges in the three-dimensional space, actuation of proximal and distal joints including hand opening and closing, and a patient-responsive control.

Four hospitals participated in the trial. Seventy-seven patients in the chronic phase (i.e., more than 6 months) post stroke with moderate to severe impairment of an arm (as tested with FMA: 8–38/max 66 points) were randomly assigned to either ARMin training or conventional, physical, or occupational therapy. During therapy with ARMin, each of the three therapy modes (mobilization, games, and ADL training) had to be performed for at least 10 min. Conventional therapy resembled the regular therapy given in outpatient clinics. Both groups were trained for 8 weeks, three times per week, with 1 h for each training session (total of 24 sessions). Outcome measures were obtained at five time points: prior to, during (after 4 weeks), directly after, and 2 and 6 months after the training phase. The primary outcome measure was the FMA, a well-established clinical test that measures impairment of the arm. Further outcome measures were performed to evaluate task-oriented function (by means of the Wolf Motor Function Test and the Motor Activity Log). Furthermore, participation in life was assessed (with the Stroke Impact Scale). With ARMin, isometric strength in the arm (i.e., of shoulder abduction, adduction, anteversion, and retroversion and of elbow flexion and extension) was measured.

Results confirmed the hypothesis: after 8 weeks of training, ARMin therapy was not only as successful as conventional therapy but the improvements in motor function significantly exceeded those of conventional therapy (FMA, mean difference: 0.78 points, 95 % CI 0.03–1.53). Especially the most severely affected profited from robotic therapy (mean difference 1.91 points, 95 % CI 1.00–2·82). Of note, the robotic group gained significantly less strength than the conventional group. We speculate that the variables for the path assistance chosen during ARMin therapy might have been too supportive, tempting patients to diminish their own effort and therefore restricting strength training. A future focus for chronic patients would be to integrate specific strength training tasks in the robot. The other tests showed no significant difference between the two groups.

The higher motor functional gains in the ARMin group were still too small to be clinically meaningful for the single subject, but promising taking into consideration that the patients were in the chronic phase when a plateau of recovery is approached and gains in most cases are only limited.

A multitude of robotic systems, from simple manipulandum to exoskeletons with different control strategies, are under development and increasingly tested in clinical settings. A meta-analysis including 19 trials showed that, compared to conventional therapy, electromechanical and robot-assisted arm training does improve arm function but not arm muscle strength. Results with ARMin are in accordance with this result. Looking only at exoskeletons, few clinical studies are available. Training with ARAMIS, either bilateral or unilateral, was compared to conventional physical therapy. Each training group significantly improved in FMA scores and range of motion without significant group differences [59].

Similar to ARMin training, a 3D movement training with the 4 DOF robot Pneu-Wrex resulted in better impairment reduction than conventional tabletop training ($p=0.07$) in patients with chronic stroke and moderate to severe deficits [60].

In a crossover study, multi-joint and single-joint functional trainings with the 6-DOF exoskeleton robot BONES were compared. While in the single-joint group one joint after the other was trained within a session, the multi-joint group combined task-oriented training (e.g., multi-joint) with single-joint training within a session. Patients showed similar significant, although not significantly different, improvements after 4 weeks training with a mean 3-point gain in the FMA in both training programs [61]. Authors concluded that task-specific training is not the key factor for successful robotic training.

We believe that future studies on patients should be performed in the first days to weeks after stroke, when the potential for real recovery rather than compensation is highest. Here, an exoskeleton robot should be the ideal tool as it enables to train purposeful movements with control of the whole arm from the shoulder to the hand. It is thus capable of guiding the arm in a—close to—physiological manner during task training. Different learning strategies that have been proven to be successful can be implemented in the software. Through the measurement functionality of ARMin, the VR tasks can be adapted continuously to the subjects' abilities in order to achieve a patient-tailored, intensified therapy.

17.3 Current Developments and Ongoing Testing

17.3.1 From ARMin for Adults to CHARMin for Children

As mentioned above, an intensive, task-oriented rehabilitation training with active participation is crucial for recovery of arm motor functions in adult stroke patients. These key features can be addressed using robotic support during arm training. That is why robots are increasingly used to complement rehabilitation training in stroke (e.g., ARMin III) and SCI patients (e.g., ARMin IV) or patients suffering from other neurological or motor impairments.

For children who suffer from cerebral palsy (CP) and other motor deficits, it is also known that an intensive training [62] with active participation [63] is important to maintain and improve arm motor function. A small number of robots are available that were tested with young patients (i.e., InMotion2 [64], NJIT-RAVR [65], REAPlan [66], and ArmeoSpring Pediatric [67]). First results suggest that children profit from the intense training provided by the robot.

Based on the knowledge acquired with the adult arm robot ARMin and in close collaboration with the Rehabilitation Center for Children and Adolescents, Affoltern a. A., Switzerland, a new prototype—ChARMin—was developed for the use for children with neurological diagnoses including congenital or acquired brain lesions [68]. To the best of our knowledge, ChARMin is the first active robotic platform able to support single-joint and spatial movements and which was built specifically for the needs of the pediatric target group.

Multiple aspects had to be changed in the new pediatric robot to achieve a design that covers the requirements of children. The robot needs to cover the target group of 5- to 18-year-old children and adolescents. The anthropometric ranges that need to be covered are too large to have it realized in a single system. Therefore, a modular design was chosen for ChARMin consisting of a proximal module that covers the entire range from 5- to 18-year-old children and a distal module that covers children aged 5–13 years and 13–18 years (Fig. 17.7). With this modular design and adjustable length settings for the shoulder height, the upper arm, the forearm, and the hand length, the robot is applicable to all the children within the target group.

The kinematic shoulder structure of ARMin could not be transferred to the ChARMin concept as a miniaturization would lead to robotic parts very close to the patient's head. The new mechanical structure uses a parallel remote center of rotation mechanism (Fig. 17.7, proximal module)

to actuate the horizontal shoulder rotation and another parallel structure for the shoulder internal/external rotation. This combination of serial and parallel kinematics provides the safety distance needed between the robot and the child. The two robotic concepts for ARMin and ChARMin are shown in Fig. 17.8.

Similar to the adult ARMin version, the pediatric version has six DOF (three DOF for the shoulder and a single DOF for elbow, pro-/supination, and wrist). Instead of an actuated hand module, ChARMin has an instrumented rubber bulb that detects the grip pressure, which can be used as an input for the software. The robot can be used for the right- and left-arm side and is mobile for transportation and positioning according to the patient. A passive gravity compensation mechanism and backdrivable joints allow for safe conditions even in the case of power loss.

An audiovisual interface with game-like scenarios is used to motivate the child to actively participate during the therapy session (Fig. 17.9).

While the passive mobilization and parts of the active game-supported arm therapy were transferred to the ChARMin robot, the ADL tasks were replaced with more child-friendly gaming scenarios. Different game scenarios were implemented that allow for a diversified training (Fig. 17.10). While some games are played with single joints (joint-based), others allow to perform multi-joint movements (end-effector based) in a workspace that is previously defined by the therapist (Fig. 17.11).

Different support strategies are used to support the patient when needed. The support can be changed continuously from free nonsupported movements to completely guided movements, where the patient can stay passive. Between these extreme conditions, the support can be changed to optimally support the patient such that he or she is challenged but not bored or over-challenged.

Moreover, the interface supports robot-assisted assessments. Five different assessment packages, which were previously evaluated in SCI patients with ARMin IV [69], can be used to assess the active and passive joint range of motion, the cubic workspace of the hand, the quality of point-to-point movements, the resistance to passive movements, and the isometric joint torques for the six different joints.

The first ChARMin feasibility study is planned in the Rehabilitation Center for Children and Adolescents, Affoltern a. A., Switzerland, after receiving ethical approval. The study will investigate the applicability of the robot to children with cerebral palsy or other neurological diagnoses. Furthermore, the different support modes will be evaluated and the psychometric properties of the robot-assisted assessments determined.

17.3.2 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

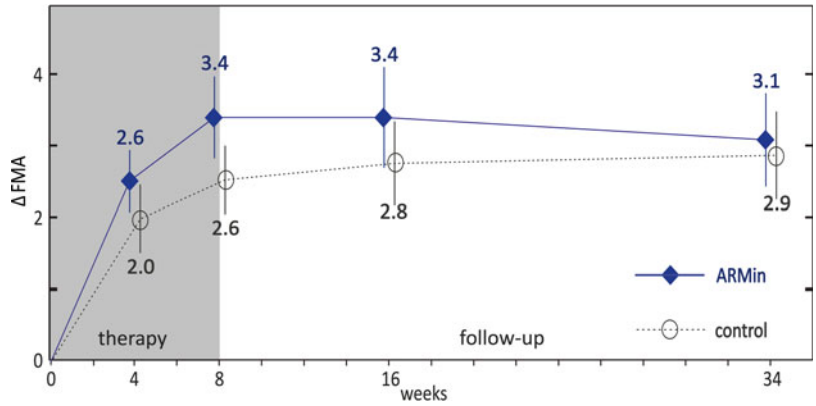

Fig. 17.7 Change in FMA over 8 weeks therapy and during follow-up for ARMin and control groups; error bars are SE

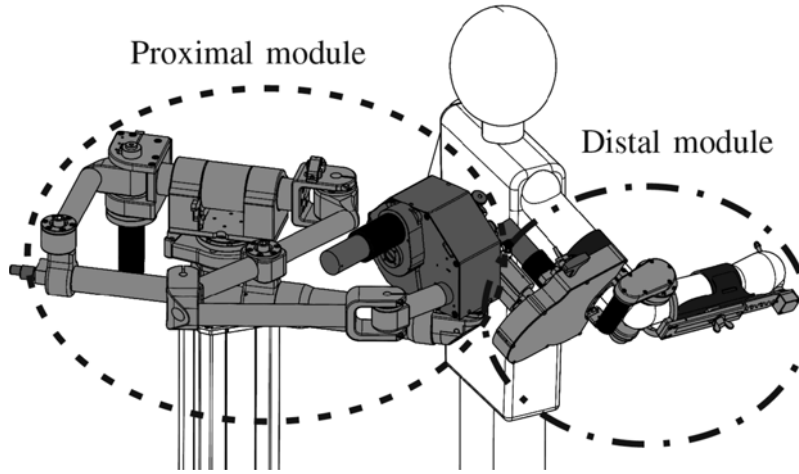

Fig. 17.8 Modular design of the ChARMin exoskeleton. The distal module is exchangeable according to the size of the child being trained. The robot is shown with a 13-year-old avatar. (Copyright IEEE, used with permission)

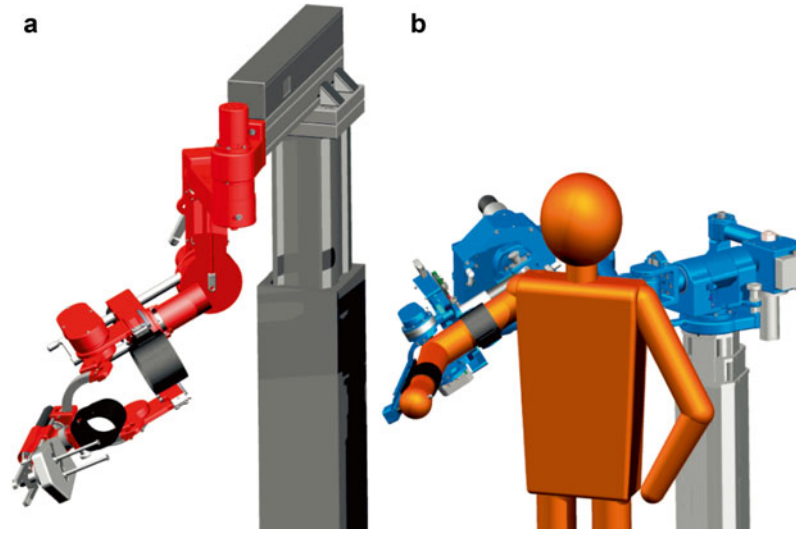

Fig. 17.9 (**a**) ARMin IV robot for rehabilitation of stroke and SCI patients compared with (**b**) the ChARMin robot for pediatric arm rehabilitation (same scale). (Copyright IEEE, used with permission)

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 the 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?

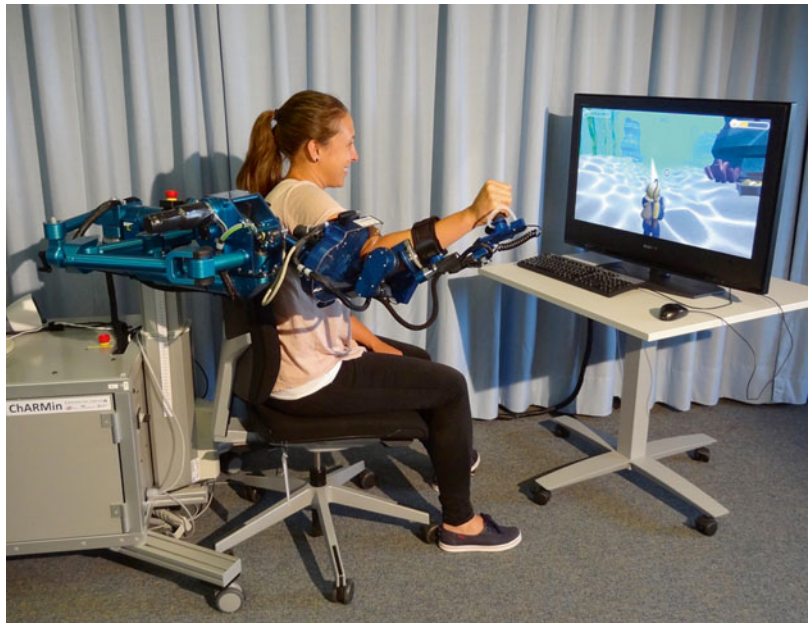

Fig. 17.10 Visualization of a possible setup of ChARMin and the visual interface shown with a healthy subject

The answers to these questions might 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, 70, 71]. 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 and sold by Hocoma AG (Volketswil, Switzerland). The commercial version of the ARMin robot, named Armeo Power, was 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 presented by Hocoma consists of three Armeo products (Fig. 17.12) 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 or her motor function improves and some active movements are possible, the patient continues arm training with the nonmotorized, weight-supported exoskeleton ArmeoSpring (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 still exhibit reduced workspace and poor motor control [72].

Further distribution of the commercialized products would allow selling companies such as Hocoma AG to increase the body of clinical data of specific rehabilitation robots since a large number of rehabilitation facilities would use the same device for clinical practice and for research.

Fig. 17.11 Various games are available for ChARMin that can be played on joint- or end-effector level. (**a**) Airplane multi-joint, (**b**) diver multi-joint, (**c**) whack-a-mole single-joint and multi-joint, (**d**) tennis multi-joint, (**e**) ball single-joint, (**f**) spaceship multi-joint

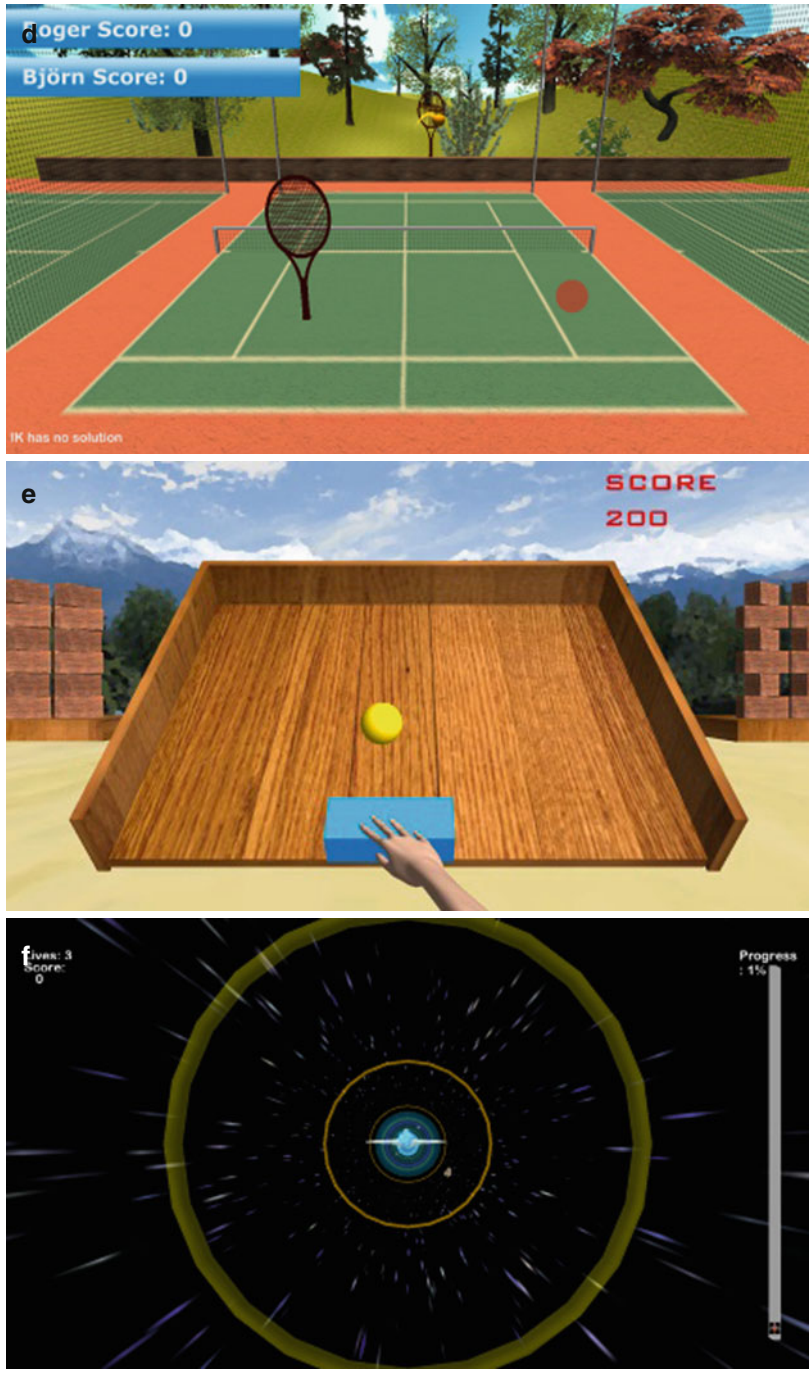

Fig.17.11 (continued)

Fig. 17.12 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; used with permission)

17.4 Perspectives and Conclusions

Upper-limb rehabilitation is one of the fastest growing fields in modern neurorehabilitation. Quality of life can be significantly improved when applying efficient arm therapy. The results of the pilot studies 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 manual and additional robot-supported therapy. The technology for upper-limb rehabilitation with three-dimensional multi-degree-of-freedom arm robots is mature and has been made commercially available. Multicenter randomized clinical trials have shown significant improvements in motor function using arm robot therapy over conventional therapy particularly for patients with severe impairment. Further studies should focus on the first days to weeks after a stroke, when the chance for sustainable recovery is highest. Also, 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 is used widely in clinical organizations.

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References

1. Brainin M, Bornstein N, Boysen G, Demarin V. Acute neurological stroke care in Europe: results of the European Stroke Care Inventory. Eur J Neurol. 2000;7:5–10.
2. Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Stroke. 1995;26(3):361–7.
3. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2007;115:69–171.
4. Maeurer HC, Diener HC. Der Schlaganfall. Stuttgart: Georg Thieme Verlag; 1996.
5. Rossini PM, Calautti C, Pauri F, Baron JC. Post-stroke plastic reorganisation in the adult brain. Lancet Neurol. 2003;2:493–502.
6. Nakayama H, Jrgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1994;75:394–8.
7. Barreca S, Wolf SL, Fasoli S, Bohannon R. Treatment interventions for the paretic upper limb of stroke survivors: a critical review. Neurorehabil Neural Repair. 2003;17(4):220–6.
8. Platz T. Evidence-based arm rehabilitation—a systematic review of the literature. Nervenarzt. 2003;74(10):841–9.
9. Dobkin BH. Strategies for stroke rehabilitation. Lancet Neurol. 2004;3(9):528–36.
10. Ottenbacher KJ, Jannell S. The results of clinical trials in stroke rehabilitation research. Arch Neurol. 1993;50:37–44.
11. Kwakkel G, Wagenaar RC, Koelman TW, Lankhorst GJ, Koetsier JC. Effects of intensity of rehabilitation after stroke. A research synthesis. Stroke. 1997;28(8):1550–6.
12. Nelles G. Cortical reorganization-effects of intensive therapy. Arch Phys Med Rehabil. 2004;22:239–44.
13. Sunderland A, Tinson DJ, Bradley EL, Fletcher D, Langton Hewer R, Wade DT. Enhanced physical therapy improves recovery of arm function after stroke. A randomised controlled trial. J Neurol Neurosurg Psychiatry. 1992;55(7):530–5.
14. Kwakkel G, Kollen BJ, Wagenaar RC. Long term effects of intensity of upper and lower limb training after stroke: a randomised trial. J Neurol Neurosurg Psychiatry. 2002;72:473–9.
15. Butefisch C, Hummelsheim H, Denzler P, Mauritz KH. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the

centrally paretic hand. J Neurol Sci. 1995;130:59–68.
16. Prange GB, Jannink MJA, Groothuis-Oudshoorn CGM, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev. 2006;43:171–84.
17. Riener R, Nef T, Colombo G. Robot-aided neurorehabilitation for the upper extremities. Med Biol Eng Comput. 2005;43:2–10.
18. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabil Neural Repair. 2008;22(2):111–21.
19. Krebs HI, Ferraro M, Buerger SP, et al. Rehabilitation robotics: pilot trial of a spatial extension for MIT-Manus. J Neuroeng Rehabil. 2004;1:5–9.
20. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002;83(7):952–9.
21. Hesse S, Werner C, Pohl M, Mehrholz J, Puzich U, Krebs HI. Mechanical arm trainer for the treatment of the severely affected arm after a stroke: a single-blinded randomized trial in two centers. Am J Phys Med Rehabil. 2008;87(10):779–88.
22. Coote S, Murphy B, Harwin W, Stokes E. The effect of the GENTLE/s robot-mediated therapy system on arm function after stroke. Clin Rehabil. 2008;22(5):395–405.
23. Dewald J, Ellis MD, Holubar BG, Sukal T, Acosta AM. The robot application in the rehabilitation of stroke patients. Neurol Rehabil. 2004;4:S7.
24. Nef T, Guidali M, Riener R. ARMin III—arm therapy exoskeleton with an ergonomic shoulder actuation. Appl Bionics Biomech. 2009;6(2):127–42.
25. Stienen AHA, Hekman EEG, Van der Helm FCT, et al. Dampace: dynamic force-coordination trainer for the upper extremities. Proc IEEE. 2007;10: 13–5.
26. Sanchez RJ, Liu J, Rao S, et al. Automating arm movement training following severe stroke: functional exercise with quantitative feedback in a gravity reduced environment. IEEE Trans Neural Syst Rehabil Eng. 2006;14:378–89.
27. Carignan C, Liszka M. Design of an arm exoskeleton with scapula motion for shoulder rehabilitation. Paper presented at: Proceedings of the 12th international conference on advanced robotics, Seattle; 18–20 Jul 2005.
28. Frisoli A, Borelli L, Montagner A, et al. Arm rehabilitation with a robotic exoskeleleton in virtual reality. In: 2007 IEEE 10th international conference on rehabilitation robotics, vols 1 and 2, Noordwijk; 2007. p. 631–42.
29. Rosen J, Perry JC, Manning N, Burns S, Hannaford B. The human arm kinematics and dynamics during daily activities—toward a 7 DOF upper limb powered exoskeleton. In: 2005 12th international conference on advanced robotics, Seattle; 2005, p. 532–9.
30. Zhang LQ, Park FS, Ren YP. Developing an intelligent robotic arm for stroke rehabilitation. In: 2007 IEEE 10th international conference on rehabilitation robotics, vols 1 and 2, Noordwijk; 2007, p. 984–93.
31. Nef T, Mihelj M, Riener R. ARMin: a robot for patient-cooperative arm therapy. Med Biol Eng Comput. 2007;45:887–900.
32. Bayona NA, Bitensky J, Salter K, Teasell R. The role of task-specific training in rehabilitation therapies. Top Stroke Rehabil. 2005;12:58–65.
33. Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremity to reverse the effect of learned nonuse among chronic stroke and head-injured patients. Exp Neurol. 1989;104:125–32.
34. Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation—a clinical review. J Rehabil Res Dev. 1999;36:237–51.
35. Miltner WHR, Bauder H, Sommer M, Dettmers C, Taub E. Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke. A replication. Stroke. 1999;30:586–92.
36. Dromerick AW, Edwards DF, Hahn M. Does the application of constraint-induced movement therapy during acute rehabilitation reduce arm impairment after ischemic stroke? Stroke. 2000;31:2984–8.
37. Lambercy O, Dovat L, Gassert R, Burdet E, Teo CL, Milner T. A haptic knob for rehabilitation of hand function. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):356–66.
38. Hesse S, Schulte-Tigges G, Konrad M, Bardeleben A, Werner C. Robot-assisted arm trainer for the passive and active practice of bilateral forearm and wrist movements in hemiparetic subjects. Arch Phys Med Rehabil. 2003;84:915–20.
39. Krebs HI, Volpe BT, Williams D, et al. Robot-aided neurorehabilitation: a robot for wrist rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):327–35.
40. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau ML. Computerized arm training improves the motor control of the severely affected arm after stroke: a single-blinded randomized trial in two centers. Stroke. 2005;36(9):1960–6.
41. Muellbacher W, Richards C, Ziemann U, et al. Improving hand function in chronic stroke. Arch Neurol. 2002;59(8):1278–82. 42. Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neurorehabilitation. IEEE Trans Rehabil Eng. 1998;6:75–87.
42. Ellis MD, Sukal-Moulton TM, Dewald JP. Impairment-based 3-D robotic intervention improves upper extremity work area in chronic stroke: targeting abnormal joint torque coupling with progressive shoulder abduction loading. IEEE Trans Robot. 2009;25(3):549–55.
43. Bolliger M, Banz R, Dietz V, Lunenburger L. Standardized voluntary force measurement in a

lower extremity rehabilitation robot. J Neuroeng Rehabil. 2008;5:23.
44. Krebs HI, Mernoff S, Fasoli SE, Hughes R, Stein J, Hogan N. A comparison of functional and impairment-based robotic training in severe to moderate chronic stroke: a pilot study. Neurorehabil. 2008;23(1)81–7. PMID: 18356591
45. Lunenburger L, Colombo G, Riener R. Biofeedback for robotic gait rehabilitation. J Neuroeng Rehabil. 2007;4:1.
46. Housman SJ, Scott KM, Reinkensmeyer DJ. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. Neurorehabil Neural Repair. 2009;23(5):505–14.
47. Nef T, Mihelj M, Colombo G, Riener R. ARMin robot for rehabilitation of the upper extremities. In: IEEE international conference on robotics and automation, Orlando; 2006, p. 3152–7.
48. Mihelj M, Nef T, Riener R. ARMin II—7 DoF rehabilitation robot: mechanics and kinematics. In: Proceedings of the 2007 IEEE international conference on robotics and automation, vols 1–10, Rome; 2007, pp. 4120–5.
49. Nef T, Lum P. Improving backdrivability in geared rehabilitation robots. Med Biol Eng Comput. 2009;47(4):441–7.
50. Staubli P, Nef T, Klamroth-Marganska V, Riener R. Effects of intensive arm training with the rehabilitation robot ARMin II in chronic stroke patients: four single-cases. J Neuroeng Rehabil. 2009;6:46.
51. Nef T, Quinter G, Muller R, Riener R. Effects of arm training with the robotic device ARMin I in chronic stroke: three single cases. Neurodegener Dis. 2009;6(5–6):240–51.
52. Nef T, Mihelj M, Kiefer G, Perndl C, Mueller R, Riener R. ARMin—exoskeleton for arm therapy in stroke patients. In: 2007 IEEE 10th international conference on rehabilitation robotics, vols 1 and 2, Noordwijk; 2007, p. 68–74.
53. Guidali M, Duschau-Wicke A, Broggi S, Klamroth-Marganska V, Nef T, Riener R. A robotic system to train activities of daily living in a virtual environment. Med Biol Eng Comput. 2011;49(10):1213–23. doi:10.1007/s11517-011-0809-0.
54. Mihelj M, Nef T, Riener R. A novel paradigm for patient-cooperative control of upper-limb rehabilitation robots. Adv Robot. 2007;21(8):843–67.
55. Duschau-Wicke A, von Zitzewitz J, Caprez A, Lunenburger L, Riener R. Path control: a method for patient-cooperative robot-aided gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2010;18(1):38–48.
56. Dewald JP, Beer RF. Abnormal joint torque patterns in the paretic upper limb of subjects with hemiparesis. Muscle Nerve. 2001;24:273–83.
57. Schmartz AC, Meyer-Heim AD, Muller R, Bolliger M. Measurement of muscle stiffness using robotic assisted gait orthosis in children with cerebral palsy: a proof of concept. Disabil Rehabil Assist Technol. 2011;6(1):29–37.
58. Klamroth-Marganska V, Blanco J, Campen K, et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2):159–66.
59. Byl NN, Abrams GM, Pitsch E, Fedulow I, Kim H, Simkins M, Nagarajan S, Rosen J. Chronic stroke survivors achieve comparable outcomes following virtual task specific repetitive training guided by a wearable robotic orthosis (UL-EXO7) and actual task specific repetitive training guided by a physical therapist. J Hand Ther. 2013;26:343–52.
60. Reinkensmeyer DJ, Wolbrecht ET, Chan V, Chou C, Cramer SC, Bobrow JE. Comparison of 3D, assist-as-needed robotic arm/hand movement training provided with Pneu-WREX to conventional table top therapy following chronic stroke. Am J Phys Med Rehabil. 2012;91:S232.
61. Milot M-H, Spencer SJ, Chan V, Allington JP, Klein J, Chou C, Bobrow JE, Cramer SC, Reinkensmeyer DJ, et al. A crossover pilot study evaluating the functional outcomes of two different types of robotic movement training in chronic stroke survivors using the arm exoskeleton BONES. J Neuroeng Rehabil. 2013;10:112.
62. Sakzewski L, Gordon A, Eliasson A-C. The state of the evidence for intensive upper limb therapy approaches for children with unilateral cerebral palsy. J Child Neurol. 2014;29(8):1077–90.
63. Damiano D. Activity, activity, activity: rethinking our physical therapy approach to cerebral palsy. Phys Ther. 2006;86(11):1534–40.
64. Fasoli S, Fragala-Pinkham M, Hughes R, Hogan N, Krebs H, Stein J. Upper limb robotic therapy for children with hemiplegia. Am J Phys Med Rehabil. 2008;87(11):929.
65. Fluet G, Qiu Q, Kelly D, Parikh HD, Ramirez D, Saleh S, Adamovich S. Interfacing a haptic robotic system with complex virtual environments to treat impaired upper extremity motor function in children with cerebral palsy. Dev Neurorehabil. 2010;13(5):335–45.
66. Gilliaux M, Renders A, Dispa D, Holvoet D, Sapin J, Dehez B, Detrembleur C, Lejeune TM, Stoquart G. Upper limb robot-assisted therapy in cerebral palsy a single-blind randomized controlled trial. Neurorehabil Neural Repair. 2014;29(2):183–92.
67. http://www.hocoma.com/products/armeo/armeospring-pediatric/.
68. Keller H, Riener R. Design of the pediatric arm rehabilitation robot ChARMin. In Biomedical robotics and biomechatronics (BioRob), 2014 IEEE international conference on. IEEE; 2014. p. 530–5.
69. Keller U, Schölch S, Albisser U, Rudhe C, Curt A, Riener R, Klamroth-Marganska M. Robot-assisted arm assessments in spinal cord injured patients: a consideration of concept study. PLoS One. 2015;10(5):e0126948.

70. Riener R, Lunenburger L, Jezernik S, Anderschitz M, Colombo G, Dietz V. Patient-cooperative strategies for robot-aided treadmill training: first experimental results. IEEE Trans Neural Syst Rehabil Eng. 2005;13(3):380–94.
71. Marchal-Crespo L, Reinkensmeyer DJ. Review of control strategies for robotic movement training after neurologic injury. J Neuroeng Rehabil. 2009;6:20.
72. Prange GB, Jannink MJ, Stienen AH, van der Kooij H, Ijzerman MJ, Hermens HJ. Influence of gravity compensation on muscle activation patterns during different temporal phases of arm movements of stroke patients. Neurorehabil Neural Repair. 2009;23(5):478–85.

18 Implementation of Impairment-Based Neurorehabilitation Devices and Technologies Following Brain Injury

Jules P.A. Dewald, Michael D. Ellis, Ana Maria Acosta, Jacob G. McPherson, and Arno H.A. Stienen

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 allow the clinician to quantitatively control task practice and dosage, but, more importantly, allow for direct targeting of specific impairments, such as the loss of independent joint control (Dewald et al. Top Stroke Rehabil. 8(1):1–12, 2001), that are informed by a body of scientific evidence. Acceptance of these new technologies is dependent on proof of their effectiveness in the reduction of movement impairments and activity limitations, as opposed to compensation, and ultimately on carryover of benefits to 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

J.P.A. Dewald, PT, PhD (✉)
Department of Physical Therapy and Human Movement Sciences, Northwestern University, Feinberg School of Medicine, Chicago, IL 60611, USA
e-mail: j-dewald@northwestern.edu

M.D. Ellis, PT, DPT • A.M. Acosta, PhD
Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL 60611, USA
e-mail: m-ellis@northwestern.edu; a-acosta@northwestern.edu

J.G. McPherson, PhD
Department of Biomedical Engineering, Florida International University, Miami, FL 33174, USA
e-mail: jmcphers@fiu.edu

A.H.A. Stienen, BSc, MSc, PhD
Department of Biomedical Engineering, University of Twente, Enschede 7500 AE, OV, The Netherlands
e-mail: arnostienen@gmail.com

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acceptance in the clinic on a large scale. Finally, it is crucial that we demonstrate that electromechanical technologies augment existing rehabilitative care and serve to reduce treatment time and costs while maintaining, and even improving, functional outcomes. This is a requirement for future technology development especially in a healthcare environment where rehabilitation services have become less accessible.

Keywords
Stroke • Hemiparesis • Arm • Movement • Impairment • Function • Robotics • Rehabilitation robotics

18.1 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 and subsequent function. It is with the advent of rehabilitation robotics and associated robotic technologies that scientists have begun to rigorously study both movement impairments and their amenability to restorative interventions. An important distinction in the employment of robotics in rehabilitation is whether the application attempts to more efficiently replicate aspects of conventional care such as repetitive functional task practice or if it directly targets specific impairments with a goal of movement restoration through the amelioration of impairment. For example, some rehabilitation robotic therapies aim to more efficiently deliver conventional approaches such as practicing functional tasks but with the added benefit of a greater number of repetitions [2–4], whereas others attempt to ameliorate specific impairments such as loss of independent joint control/inter-joint coordination ([5, 6], respectively) or general motor impairment through a multifaceted approach [7–9]. Computational motor learning principles suggest that the optimal rehabilitation robotics strategy may be to employ both approaches by first directly targeting impairments during early recovery to maximize restoration of impairment and then to progress toward functional task practice to maximize restoration of activity limitations [10].

In this chapter, we focus on the first component of Huang and Krakauer's suggestion of an optimal rehabilitation strategy, that is, targeting impairment restoration. Since robotic devices are superior at quantifying movement impairments such as loss of independent joint control/inter-joint coordination [11–14], weakness [15, 16], and spasticity [17–25], clinical decision-making regarding the response to and progression of interventions can be quantitatively driven, optimizing implementation of the rehabilitation strategy. Here we will discuss evidence for the use of robotics in providing high-resolution measures of motor impairment in the upper limb of individuals with stroke, 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 impairment-based therapeutic interventions that can be implemented in current rehabilitation clinics to augment conventional rehabilitation. Considerations for successful transition to clinical practice, both in rehabilitation clinics and at home, 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 (Table 18.1).

Table 18.1 Upper limb synergies in hemiparetic stroke [26]

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

18.2 Quantification of Impairment

18.2.1 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 [26–28]. 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 EMGs from elbow and shoulder muscles in the paretic arm of individuals with stroke during static force exertions in various directions and of various magnitudes [29]. 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 [30, 31]. 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 [1, 31]. Conversely, control subjects, and individuals with stroke in their non-paretic 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 [30]. 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 1 26). 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. Precise quantification of this fundamental impairment was only possible through the implementation of multi-degree-of-freedom force-/torque-sensing technologies as opposed to conventional clinical evaluation with the Fugl-Meyer Motor Assessment [32] that is limited by its ordinal scale of measurement and reliance upon subjective observational movement analysis. Application of these new technologies would then set the stage for the execution of dynamic experiments and subsequent robotic development.

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 [1, 33, 34]. 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. For either limb of control subjects, as well as the non-paretic 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. 18.1). 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 3D (ACT-3D) device shown in Fig. 18.1. This unique combination of technologies allows for the measurement of shoulder abduction loading and induced shoulder and elbow coupling during reaching. It provides a 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 3D workspace, features unavailable in the early isometric and dynamic studies [1, 30, 31, 33]. 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 results from a single moderately to severely affected subject (Fugl-Meyer upper extremity score of 23/66, and Chedoke-McMaster Arm Scale of 3/7) is shown in Fig. 18.2. 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. 18.2 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

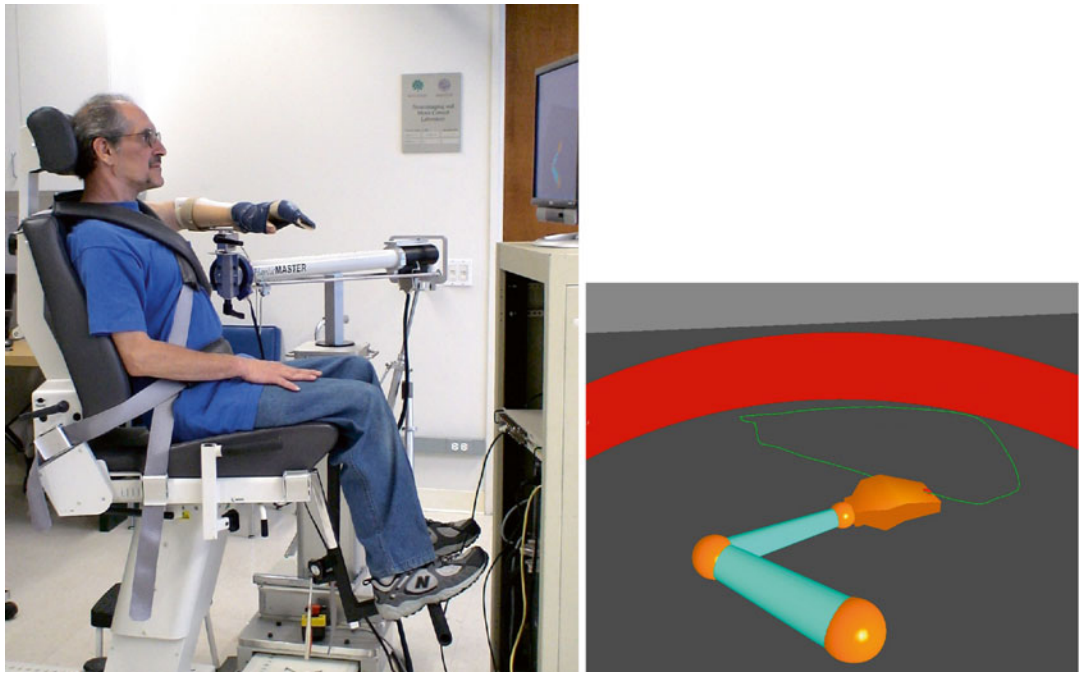

Fig. 18.1 (*left*) Illustrating ACT ^{3D} robot with gimbal and orthosis (*right*). Example of the visual feedback. The haptic table is shown by the *darker gray*, which the arm is resting on. In the envelope protocol (see measurement of work area below), subjects will use the *red arc* as their goal, with the *green tracer* shown to give them a reference to their performance in previous circles (From Sukal et al. [11]; with kind permission from Springer Science + Business Media)

portion of the envelope; this area coincides with the direction requiring primarily elbow extension (the upper 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 non-paretic side, where no change or effect of abduction level related to shoulder and elbow range of motion is observed (see Fig. 18.2). 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 [11]. 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 [26].

The paretic wrist and fingers have also been the focus of extensive research [35–37]; 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 ([38] – Fig. 18.3, 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. 18.3 (bottom), secondary finger/wrist forces increase as shoulder abduction loads increase in individuals with adult-onset stroke [14]. Continued research using the wrist/finger force-sensing device will allow for the further characterization of abnormal coupling at the hand and wrist during 3D movements. This is likely to result in the development of a progressive

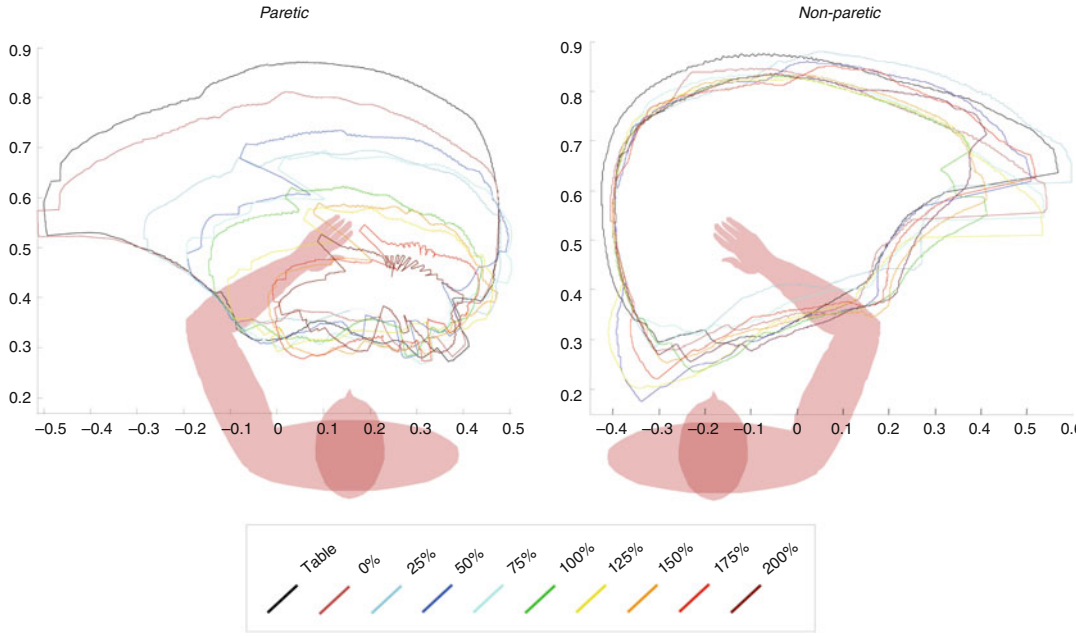

Fig. 18.2 Envelope traces consisting of shoulder/elbow flexion/extension combinations during various levels of limb support in the paretic limb (*left arm*) of a single subject [11]. Conditions listed in the legend are percentages of limb weight. Note the significant reduction in work area for increasing levels of shoulder abduction/external rotation. Axes units are in meters (From Sukal et al. [11]; with kind permission from Springer Science + Business Media)

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.

18.2.2 Quantification of Spasticity Using Electromechanical Devices

Spasticity, defined as an increased velocity sensitive stretch reflex [39], has been studied using electromechanical devices for four decades [18, 20, 22, 23, 40–44]. 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 [17–22, 40–44]. 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 [45, 46].

Relatively little is known of spasticity in active contracting muscle despite its obvious relevance

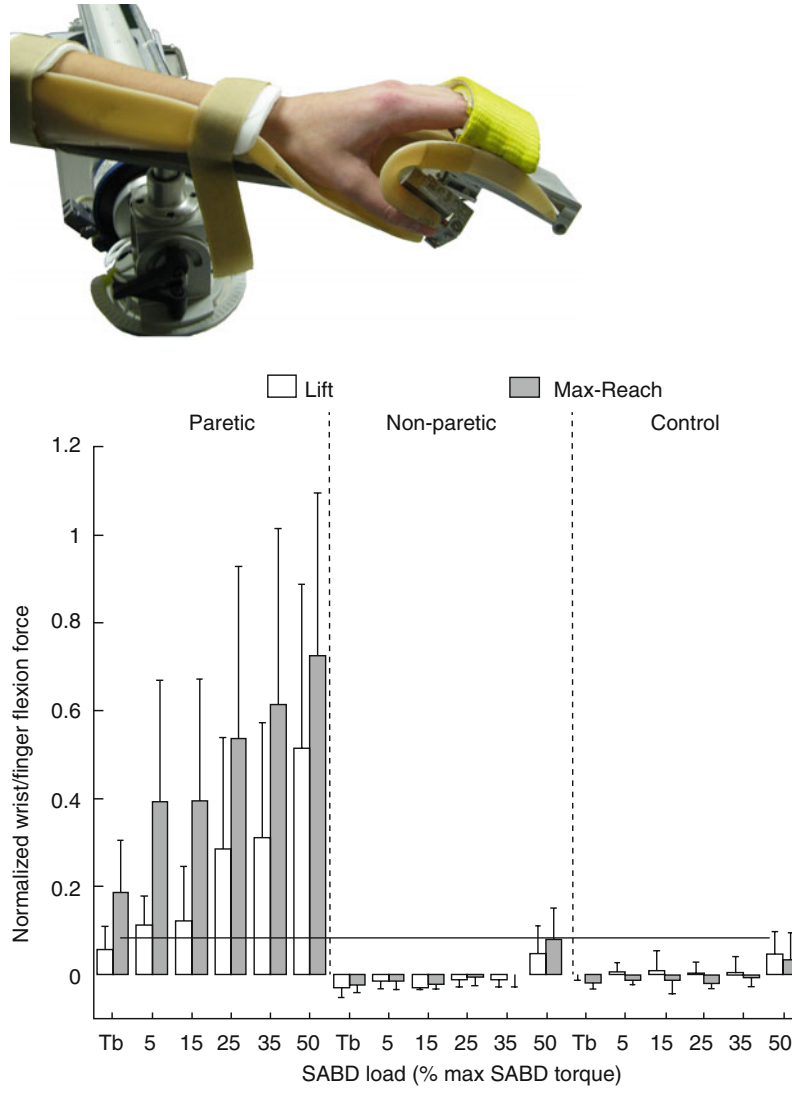

Fig. 18.3 *Top*: instrumented hand finger orthosis (From Miller et al. [38]; used with permission). *Bottom*: relative level of finger force (normalized for each subject by the largest forces measured over the five shoulder abduction-loading conditions) generated for increasing levels of load as percentage of maximum shoulder abduction (SABD) torque (From Miller and Dewald [14]; used with permission). This demonstrates that increasing levels of shoulder abduction generates involuntary increases in finger flexion in the paretic hand. The *error bars* represent intersubject standard errors

to active movement and subsequent treatment. Even a small voluntary background contraction leads to prominent reflex activity and increased passive resistance in normal limbs [44, 47]. Additionally, there is no clear demonstration that reflex EMG and torque magnitude are significantly higher in spastic limbs under analogous background activation conditions [17, 22, 40, 41, 48–50]. 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 multi-joint 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 [17], then multi-joint movements may still be affected. This is especially true during multi-joint 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 [34]. 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 multi-joint movements, it may also be affected by the expression of abnormal muscle synergies (see section above). This is not addressed in spasticity quantification studies at the elbow that support the weight of the paretic limb with the measurement system [17, 18, 20, 22, 49]. However, steps have now been taken to investigate the influence of proximal joint demands (shoulder) on reflex excitability of the elbow flexors during passive single-joint elbow rotations and have suggested an interaction between synergy-related activation and reflex-related activation of elbow flexors. For example, stretch reflex excitability in elbow flexors has been shown to be modulated by abductor activation for a single abduction load level [23] and as a function of abduction loading [51]. Investigating the interplay of spasticity and abnormal flexion synergy during a dynamic multi-joint reaching task has also now begun in our lab. Analysis of preliminary data of elbow flexor activation during an outward reach under various abduction loads indicates a small, if not negligible, contribution of reflex-related flexor activation superimposed upon much larger synergy-related flexor activation. These data support an interaction between reflex- and synergy-related flexor activation and suggest a dominant and deleterious contribution of synergy-related flexor activation to impaired reaching function. State-of-the-art robotic technologies, some of which are currently under development in our laboratory, will be required to fully elucidate the interaction between stretch reflex excitability/spasticity and impairments such as abnormal synergies during movement under a variety of abduction-loading conditions similar to that experienced during functional arm activities.

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 and 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.

18.3 Impairment-Based Robotic Interventions

18.3.1 Introduction to a Scientifically Underpinned Concept

Focused impairment-based interventions for individuals with stroke have had a reduced emphasis in conventional care over the last 15 years, giving way to a greater focus on functional training of the arm [52–54]. A recent review has suggested that function training is more appropriate for mild to moderate stroke, whereas classical approaches of impairment reduction are more appropriate for severe stroke [55]. In order to optimize recovery of individuals with severe stroke, an innovative solution that allows for the amelioration of fundamental impairments such as abnormal synergies and weakness is needed. Specific to abnormal synergies, 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 [11, 13, 14]. This phenomenon is attributed to abnormal coactivation of groups of muscles and results in the loss of independent joint control/inter-joint coordination 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 loss of independent joint control with an impairment-based intervention is the most likely avenue for optimizing functional outcomes 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.

18.3.2 An Isometric Impairment-Based Approach

Our initial and foundational intervention work [56] sought to determine the amenability of abnormal flexion synergy to an impairment-based intervention. The intervention entailed intensive practice of an isometric multi-joint (shoulder and elbow) task comprised of both a multi-joint coordination element and a resistance element that ultimately proved to be successful in reducing the impairment but difficult to interpret the relative importance of therapeutic elements responsible for the observed improvement [56]. The abnormal flexion synergy impairment was directly targeted by having individuals generate multi-joint 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 multi-joint coordination element of the exercise, while the resistive element was the requirement of maximal isometric torque generation. Individuals practiced these multi-joint 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 impairment-based intervention targeting loss of independent joint control. 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 multi-joint 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.

18.3.3 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 multi-joint coordination element without the confounding effects of other potential therapeutic elements such as resistance training as incorporated in our initial isometric intervention work [6, 57]. 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 multi-joint 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 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. 18.4). 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 multi-joint coordination must have occurred [6]. 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.

18.4 Successful Translation to Clinical Practice

18.4.1 Device Design That Facilitates Successful Translation

Recent advances in robotic technology have given rise to multiple systems for upper extremity rehabilitation in stroke [11, 58–65]. 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 [2–4] suggest improvement in motor function of the paretic upper limb but are less conclusive on improvement of functional abilities or activities of daily living. Recent studies have perpetuated the equivocal evidence by investigating multifaceted approaches targeting both impairment and

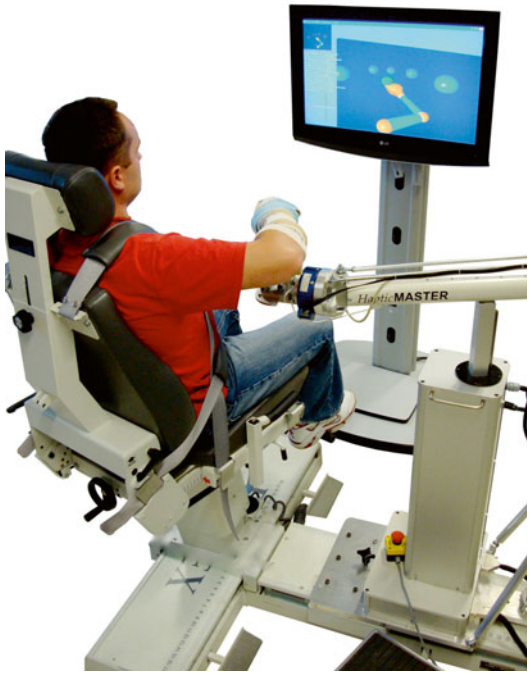

Fig. 18.4 Example of a research participant positioned with the ACT-3D showing the five reaching targets (From Ellis et al. [6]; used with permission)

activities of daily living with robotics. A randomized controlled trial following a multifaceted robotic intervention found functional improvement; however, clinical meaningfulness of the gains was in question [7]. In contrast, a high-quality large-scale randomized controlled trial employing a multifaceted robotic intervention targeting impairment reduction did not show improvements in arm function [8]. Furthermore, a robotic study specifically investigating the difference between motor function [impairment] gains and clinical functional outcome found that improvements only occurred for impairments of motor function [66]. The continued equivocal evidence raises the question of what attributes of robotic training are most relevant to successful impairment restoration, functional recovery, and/or both. What is clear though is that for electromechanical systems to successfully translate to practice, a clear advantage beyond conventional neurorehabilitation therapies must be realized.

Many rehabilitation systems are based on traditional therapeutic approaches of functional task practice similar to conventional hands-on rehabilitation. For example, implementing a task-oriented approach where subjects complete a pick-and-place or grasp and release in a virtual task [3, 67–77] is similar to conventional therapeutic strategies [53, 78–80]. A few groups have implemented systems based on a more constrained approach where the reaching movement or task is guided by a predefined trajectory or set of rules [81–83], again, similar to traditional interventions where the movement is guided by the therapist(s). The sole focus on functional task practice may explain the equivocal evidence for benefits over that of conventional care. On the other hand, some systems provide robotic-assistance to the task or movement being performed either by smartly assisting the arm in a programmed endpoint or joint-space trajectory and/or by supporting the weight of the limb [72, 76, 84–90], thus taking advantage of the unique features of their device to address motor impairments during functional task practice which is difficult to be replicated by a person.

Device design has primarily been driven by a focus on conventional functional task practice with a limited emphasis on targeting and reducing impairments. Even with a multifaceted functional and impairment-based robotic approach, only limited success is possible [8]. Therefore, we believe a sole focus on ameliorating loss of independent joint control will be most effective especially in more moderate to severely impaired individuals where function task practice is not possible. The Dewald laboratory has taken the approach of shifting the sole focus of the robotic training intervention to reducing the most prominent impairment, loss of independent joint control, based on years of research of the mechanisms underlying upper extremity movement impairment in individuals with brain injury. Based on results from previous studies [1, 16, 29–31, 33, 34, 85], we have designed robotic systems to directly target loss of independent joint control believed to most strongly impact upper extremity function.

Attempting to ameliorate the loss of independent joint control may be a more effective strategy in improving arm function during activities of daily living in individuals with moderate to severe hemiparetic stroke that struggle to benefit from functional task practice due to the severe abnormal muscle synergies throughout the arm and hand. The ACT-3D [11, 13], 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 – [6, 57]). Other systems like the T-WREX, Pneu-WREX, ARMin, L-EXOS, Freebal, ArmeoPower, and BONES [11, 60, 64, 70] have adjustable limb weight support abilities and are capable of progressively loading shoulder abduction. The ability to target inter-joint coordination through progressive shoulder abduction loading is a key component for therapeutic interventions attempting to improve arm function during activities of daily living because it is the loss of independent joint control that is the most detrimental impairment in moderate to severe stroke and it is correlated with upper extremity function [13].

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-2D, was designed to further our understanding of spasticity during movement in stroke (see Fig. 18.5). This device was designed to allow investigation of the interaction between the abnormal flexion synergy and spasticity, through its ability to provide various shoulder abduction loads while stretching the elbow flexors without volitional activation of elbow muscles. Concurrently, a new version of the ACT-3D, the NACT-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 during multi-joint dynamic conditions in order to better understand the mechanisms underlying movement dysfunction in this population (see Fig. 18.6). In doing so, 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.

18.4.2 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 is possible [6, 57]. 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 practicing functional tasks which may only be appropriate once impairment restoration has been optimized [10].

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

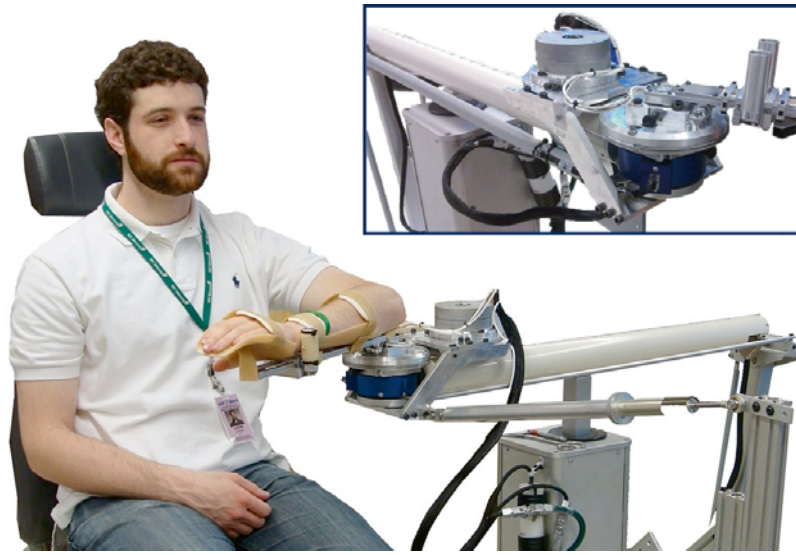

Fig. 18.5 The ACT-2D robotic device allows for single-joint perturbations at the elbow combined with adjustable shoulder abduction loading to study the relationship between synergies and abnormal stretch reflex or spasticity following brain injury

evidence from large-scale clinical trials is 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 has recently made substantial efforts to merge quantitative evaluation of movement with high-resolution neuroimaging to evaluate intervention-related experience-dependent neuroplasticity addressing this requirement [91]. Future work should also seek to evaluate how other aspects of motor learning [92], beyond our current employment of optimal practice scheduling, task specificity, and augmented feedback, can be brought to bear when targeting loss of independent joint control. With convincing quantitative evidence and sound scientific underpinning, the rehabilitation specialist will readily accept the impairment-based approach catalyzing the translation to clinical practice.

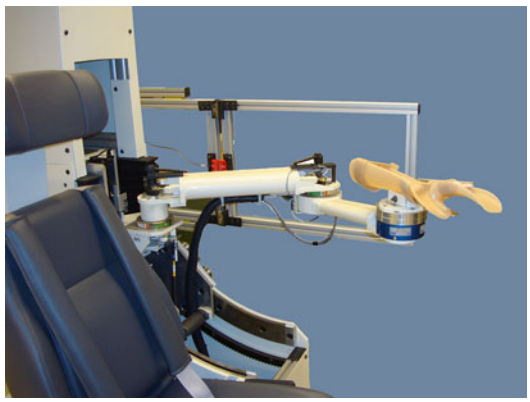

Fig. 18.6 New version of the ACT-3D, the NACT-3D, is designed to allow greater workspace measurements as well as for the application of multi-joint perturbations in the plane of movement

18.4.3 Motivation, Ease of Use, Practical Implications, and Translation into Rehabilitation Clinics

Patient motivation is one principle of motor learning that can be readily brought to bear in targeting impairment restoration in rehabilitation robotics by integrating with video game platforms. Combining impairment-based interventions with a game has the potential to moti-

vate 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 [11, 58–65]. 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 three-dimensional environment simulated in a computer and integrated with haptic feedback. Reviews on the effectiveness of virtual reality programs for stroke rehabilitation [93–95] support its 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 [96]. 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. The combination of increased motivation and improved outcomes will facilitate successful translation to practice.

Another important element that needs to be considered for the successful translation of robotics to clinical practice, and possibly to the home environment, 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 the 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. A shifted focus to impairment restoration was suggested in contrast with the current application of robotics that focuses on greater intensity of existing rehabilitation approaches and multifaceted approaches of impairment-based and functional-based task practice. 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 therapeutic interventions grounded in a body of scientific evidence. And that robotic interventions 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 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 achsieve 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 healthcare environment.

References

1. Dewald JP, Sheshadri V, Dawson ML, Beer RF. Upper-limb discoordination in hemiparetic stroke: implications for neurorehabilitation. Top Stroke Rehabil. 2001;8(1):1–12.
2. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabil Neural Repair. 2008;22(2):111–21.
3. Mehrholz J, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving arm function and activities of daily living after stroke. Stroke. 2009;40:e392–3.
4. Prange GB, Jannink MJ, Groothuis-Oudshoorn CG, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev. 2006;43(2):171–84.
5. Brokaw EB, Nichols D, Holley RJ, Lum PS. Robotic therapy provides a stimulus for upper limb motor recovery after stroke that is complementary to and distinct from conventional therapy. Neurorehabil Neural Repair. 2014;28(4):367–76.
6. Ellis MD, Sukal-Moulton TM, Dewald JP. Impairment-based 3-D robotic intervention improves upper extremity work area in chronic stroke: targeting abnormal joint torque coupling with progressive shoulder abduction loading. IEEE Trans Robot. 2009;25(3):549–55.
7. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2):159–66.
8. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362(19):1772–83.
9. Milot MH, Spencer SJ, Chan V, Allington JP, Klein J, Chou C, et al. A crossover pilot study evaluating the functional outcomes of two different types of robotic movement training in chronic stroke survivors using the arm exoskeleton BONES. J Neuroeng Rehabil. 2013;10:112.
10. Huang VS, Krakauer JW. Robotic neurorehabilitation: a computational motor learning perspective. J Neuroeng Rehabil. 2009;6:5.
11. Sukal TM, Ellis MD, Dewald JP. Shoulder abduction-induced reductions in reaching work area following hemiparetic stroke: neuroscientific implications. Exp Brain Res. 2007;183(2):215–23.
12. Brokaw EB, Murray T, Nef T, Lum PS. Retraining of interjoint arm coordination after stroke using robot-assisted time-independent functional training. J Rehabil Res Dev. 2011;48(4):299–316.
13. Ellis MD, Sukal T, DeMott T, Dewald JP. Augmenting clinical evaluation of hemiparetic arm movement with a laboratory-based quantitative measurement of kinematics as a function of limb loading. Neurorehabil Neural Repair. 2008;22(4):321–9.
14. Miller LC, Dewald JP. Involuntary paretic wrist/finger flexion forces and EMG increase with shoulder abduction load in individuals with chronic stroke. Clin Neurophysiol. 2012;123(6):1216–25.
15. Koo TK, Mak AF, Hung L, Dewald JP. Joint position dependence of weakness during maximum isometric voluntary contractions in subjects with hemiparesis. Arch Phys Med Rehabil. 2003;84(9):1380–6.

16. Beer RF, Ellis MD, Holubar BG, Dewald JP. Impact of gravity loading on post-stroke reaching and its relationship to weakness. Muscle Nerve. 2007;36(2):242–50.
17. Burne JA, Carleton VL, O'Dwyer NJ. The spasticity paradox: movement disorder or disorder of resting limbs? J Neurol Neurosurg Psychiatry. 2005;76(1):47–54.
18. Schmit BD. Mechanical measures of spasticity in stroke. Top Stroke Rehabil. 2001;8(1):13–26.
19. Schmit BD, Dhaher Y, Dewald JP, Rymer WZ. Reflex torque response to movement of the spastic elbow: theoretical analyses and implications for quantification of spasticity. Ann Biomed Eng. 1999;27(6):815–29.
20. Schmit BD, Dewald JP, Rymer WZ. Stretch reflex adaptation in elbow flexors during repeated passive movements in unilateral brain-injured patients. Arch Phys Med Rehabil. 2000;81(3):269–78.
21. Powers RK, Marder-Meyer J, Rymer WZ. Quantitative relations between hypertonia and stretch reflex threshold in spastic hemiparesis. Ann Neurol. 1988;23(2):115–24.
22. Powers RK, Campbell DL, Rymer WZ. Stretch reflex dynamics in spastic elbow flexor muscles. Ann Neurol. 1989;25(1):32–42.
23. Trumbower RD, Ravichandran VJ, Krutky MA, Perreault EJ. Contributions of altered stretch reflex coordination to arm impairments following stroke. J Neurophysiol. 2010;104(6):3612–24.
24. de Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. J Neuroeng Rehabil. 2010;7:35.
25. Meskers CG, Schouten AC, de Groot JH, de Vlugt E, van Hilten BJ, van der Helm FC, et al. Muscle weakness and lack of reflex gain adaptation predominate during post-stroke posture control of the wrist. J Neuroeng Rehabil. 2009;6:29.
26. Brunnstrom S. Movement therapy in hemiplegia: a neurophysiological approach. 1st ed. New York: Medical Department, Harper & Row; 1970, 192 p.
27. Foester O. Motorische Felder und Bahnen. In: Bumke O, Foester O, editors. Handbuch der Neurologie. Berlin: Springer; 1933.
28. Twitchell TE. The restoration of motor function following hemiplegia in man. Brain. 1951;74(4):443–80.
29. Dewald JP, Pope PS, Given JD, Buchanan TS, Rymer WZ. Abnormal muscle coactivation patterns during isometric torque generation at the elbow and shoulder in hemiparetic subjects. Brain. 1995;118(Pt 2):495–510.
30. Beer R, Dewald J. Task-dependent weakness at the elbow in patients with hemiparesis. Arch Phys Med Rehabil. 1999;80(7):766–72.
31. Dewald JP, Beer RF. Abnormal joint torque patterns in the paretic upper limb of subjects with hemiparesis. Muscle Nerve. 2001;24(2):273–83.
32. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13–31.
33. Beer RF, Dewald JP, Dawson ML, Rymer WZ. Target-dependent differences between free and constrained arm movements in chronic hemiparesis. Exp Brain Res. 2004;156(4):458–70.
34. Beer RF, Dewald JP, Rymer WZ. Deficits in the coordination of multijoint arm movements in patients with hemiparesis: evidence for disturbed control of limb dynamics. Exp Brain Res. 2000;131(3):305–19.
35. Colebatch JG, Gandevia SC. The distribution of muscular weakness in upper motor neuron lesions affecting the arm. Brain. 1989;112(Pt 3):749–63.
36. Lang CE, Wagner JM, Edwards DF, Sahrmann SA, Dromerick AW. Recovery of grasp versus reach in people with hemiparesis poststroke. Neurorehabil Neural Repair. 2006;20(4):444–54.
37. Turton A, Wroe S, Trepte N, Fraser C, Lemon RN. Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. Electroencephalogr Clin Neurophysiol. 1996;101(4):316–28.
38. Miller LC, Ruiz-Torres R, Stienen AH, Dewald JP. A wrist and finger force sensor module for use during movements of the upper limb in chronic hemiparetic stroke. IEEE Trans Biomed Eng. 2009;56(9):2312–7.
39. Lance JW. The control of muscle tone, reflexes, and movement: Robert Wartenberg lecture. Neurology. 1980;30(12):1303–13.
40. Ada L, Vattanasilp W, O'Dwyer NJ, Crosbie J. Does spasticity contribute to walking dysfunction after stroke? J Neurol Neurosurg Psychiatry. 1998;64(5):628–35.
41. Ibrahim IK, Berger W, Trippel M, Dietz V. Stretch-induced electromyographic activity and torque in spastic elbow muscles. Differential modulation of reflex activity in passive and active motor tasks. Brain. 1993;116(Pt 4):971–89.
42. Meyer M, Adorjani C. Tonic stretch reflex for quantification of pathological muscle tone. In: Feldman RG YR, Koella WP, CIBA-GEIGY Corporation, editors. Spasticity: disordered motor control, vol. xviii. Chicago: Year Book Medical Publishers; 1980. p. 310–30. Miami, FL.
43. Meyer M, Adorjani C. Quantification of the effects of muscle relaxant drugs in man by tonic stretch reflex. Adv Neurol. 1983;39:997–1011.
44. Neilson PD. Interaction between voluntary contraction and tonic stretch reflex transmission in normal and spastic patients. J Neurol Neurosurg Psychiatry. 1972;35(6):853–60.
45. Brown TI, Rack PM, Ross HF. Electromyographic responses to imposed sinusoidal movement of the human thumb. J Physiol. 1982;332:87–99.
46. Yeo W, Ada L, O'Dwyer NJ, Neilson PD. Tonic stretch reflexes in older able-bodied people. Electromyogr Clin Neurophysiol. 1998;38(5):273–8.

47. Gottlieb GL, Agarwal GC. Dependence of human ankle compliance on joint angle. J Biomech. 1978;11(4):177–81.
48. Dietz V, Trippel M, Berger W. Reflex activity and muscle tone during elbow movements in patients with spastic paresis. Ann Neurol. 1991;30(6):767–79.
49. Lee WA, Boughton A, Rymer WZ. Absence of stretch reflex gain enhancement in voluntarily activated spastic muscle. Exp Neurol. 1987;98(2):317–35.
50. Sinkjaer T, Toft E, Larsen K, Andreassen S, Hansen HJ. Non-reflex and reflex mediated ankle joint stiffness in multiple sclerosis patients with spasticity. Muscle Nerve. 1993;16(1):69–76.
51. McPherson JG, Stienen AH, Drogos JM, Dewald JP. The relationship between the flexion synergy and stretch reflexes in individuals with chronic hemiparetic stroke. IEEE Int Conf Rehabil Robot. 2011;2011:5975516.
52. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006;296(17):2095–104.
53. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil. 2004;18:833–62.
54. Bonifer NM, Anderson KM, Arciniegas DB. Constraint-induced movement therapy after stroke: efficacy for patients with minimal upper-extremity motor ability. Arch Phys Med Rehabil. 2005;86(9):1867–73.
55. Oujamaa L, Relave I, Froger J, Mottet D, Pelissier JY. Rehabilitation of arm function after stroke. Literature review. Ann Phys Rehabil Med. 2009;52(3):269–93.
56. Ellis MD, Holubar BG, Acosta AM, Beer RF, Dewald JP. Modifiability of abnormal isometric elbow and shoulder joint torque coupling after stroke. Muscle Nerve. 2005;32(2):170–8.
57. Ellis MD, Sukal-Moulton T, Dewald JP. Progressive shoulder abduction loading is a crucial element of arm rehabilitation in chronic stroke. Neurorehabil Neural Repair. 2009;23(8):862–9.
58. Burgar CG, Lum PS, Shor PC, Machiel Van der Loos HF. Development of robots for rehabilitation therapy: the Palo Alto VA/Stanford experience. J Rehabil Res Dev. 2000;37(6):663–73.
59. Fazekas G, Horvath M, Toth A. A novel robot training system designed to supplement upper limb physiotherapy of patients with spastic hemiparesis. Int J Rehabil Res. 2006;29(3):251–4.
60. Frisoli A, Borelli L, Montagner A, Marcheschi S, Procopio C, Salsedo F, et al., editors. Arm rehabilitation with a robotic exoskeleton in virtual reality. IEEE 10th International Conference on Rehabilitation Robotics, 2007 ICORR 2007. Noordwijk, Netherlands; 2007.
61. Hesse S, Schulte-Tigges G, Konrad M, Bardeleben A, Werner C. Robot-assisted arm trainer for the passive and active practice of bilateral forearm and wrist movements in hemiparetic subjects. Arch Phys Med Rehabil. 2003;84(6):915–20.
62. Krebs HI, Hogan N, Volpe BT, Aisen ML, Edelstein L, Diels C. Overview of clinical trials with MIT-MANUS: a robot-aided neuro-rehabilitation facility. Technol Health Care. 1999;7(6):419–23.
63. Masiero S, Celia A, Armani M, Rosati G. A novel robot device in rehabilitation of post-stroke hemiplegic upper limbs. Aging Clin Exp Res. 2006;18(6):531–5.
64. Nef T, Mihelj M, Riener R. ARMin: a robot for patient-cooperative arm therapy. Med Biol Eng Comput. 2007;45(9):887–900.
65. Reinkensmeyer DJ, Kahn LE, Averbuch M, McKenna-Cole A, Schmit BD, Rymer WZ. Understanding and treating arm movement impairment after chronic brain injury: progress with the ARM guide. J Rehabil Res Devel. 2000;37(6):653–62.
66. Kitago T, Marshall RS. Strategies for early stroke recovery: what lies ahead? Curr Treat Options Cardiovasc Med. 2015;17(1):356.
67. Broeren J, Claesson L, Goude D, Rydmark M, Sunnerhagen KS. Virtual rehabilitation in an activity centre for community-dwelling persons with stroke. The possibilities of 3-dimensional computer games. Cerebrovasc Dis. 2008;26(3):289–96.
68. Fischer HC, Stubblefield K, Kline T, Luo X, Kenyon RV, Kamper DG. Hand rehabilitation following stroke: a pilot study of assisted finger extension training in a virtual environment. Top Stroke Rehabil. 2007;14(1):1–12.
69. Holden MK, Dyar TA, Dayan-Cimadoro L. Telerehabilitation using a virtual environment improves upper extremity function in patients with stroke. IEEE Trans Neural Syst Rehabil Eng. 2007;15(1):36–42.
70. Housman SJ, Scott KM, Reinkensmeyer DJ. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. Neurorehabil Neural Repair. 2009;23(5):505–14.
71. Kuttuva M, Boian R, Merians A, Burdea G, Bouzit M, Lewis J, et al. The Rutgers Arm, a rehabilitation system in virtual reality: a pilot study. Cyberpsychol Behav. 2006;9(2):148–51.
72. Nef T, Quinter G, Muller R, Riener R. Effects of arm training with the robotic device ARMin I in chronic stroke: three single cases. Neurodegener Dis. 2009;6(5–6):240–51.
73. Reinkensmeyer DJ, Pang CT, Nessler JA, Painter CC. Web-based telerehabilitation for the upper extremity after stroke. IEEE Trans Neural Syst Rehabil Eng. 2002;10(2):102–8.
74. Sivak M, Mavroidis C, Holden MK. Design of a low cost multiple user virtual environment for rehabilitation (MUVER) of patients with stroke. Stud Health Technol Inform. 2009;142:319–24.
75. Stewart JC, Yeh SC, Jung Y, Yoon H, Whitford M, Chen SY, et al. Intervention to enhance skilled arm and hand movements after stroke: a feasibility study

using a new virtual reality system. J Neuroeng Rehabil. 2007;4:21.
76. van der Kooij H, Prange GB, Krabben T, Renzenbrink GJ, de Boer J, Hermens HJ, et al. Preliminary results of training with gravity compensation of the arm in chronic stroke survivors. Conf Proc IEEE Eng Med Biol Soc. 2009;1:2426–9.
77. Broeren J, Rydmark M, Sunnerhagen KS. Virtual reality and haptics as a training device for movement rehabilitation after stroke: a single-case study. Arch Phys Med Rehabil. 2004;85(8):1247–50.
78. van Peppen RP, Hendriks HJ, van Meeteren NL, Helders PJ, Kwakkel G. The development of a clinical practice stroke guideline for physiotherapists in The Netherlands: a systematic review of available evidence. Disabil Rehabil. 2007;29(10):767–83.
79. Dobkin BH. Strategies for stroke rehabilitation. Lancet Neurol. 2004;3(9):528–36.
80. Woldag H, Hummelsheim H. Evidence-based physiotherapeutic concepts for improving arm and hand function in stroke patients: a review. J Neurol. 2002;249(5):518–28.
81. Adamovich SV, Merians AS, Boian R, Tremaine M, Burdea GS, Recce M, et al., editors. A virtual reality based exercise system for hand rehabilitation post-stroke: transfer to function. Engineering in Medicine and Biology Society, 2004 IEMBS '04 26th Annual International Conference of the IEEE; 2004.
82. Merians AS, Poizner H, Boian R, Burdea G, Adamovich S. Sensorimotor training in a virtual reality environment: does it improve functional recovery poststroke? Neurorehabil Neural Repair. 2006;20(2):252–67.
83. Piron L, Turolla A, Agostini M, Zucconi C, Cortese F, Zampolini M, et al. Exercises for paretic upper limb after stroke: a combined virtual-reality and telemedicine approach. J Rehabil Med. 2009;41(12): 1016–102.
84. Frisoli A, Bergamasco M, Carboncini MC, Rossi B. Robotic assisted rehabilitation in virtual reality with the L-EXOS. Stud Health Technol Inform. 2009;145:40–54.
85. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau ML. Computerized arm training improves the motor control of the severely affected arm after stroke: a single-blinded randomized trial in two centers. Stroke. 2005;36(9):1960–6.
86. Kahn LE, Zygman ML, Rymer WZ, Reinkensmeyer DJ. Robot-assisted reaching exercise promotes arm movement recovery in chronic hemiparetic stroke: a randomized controlled pilot study. J Neuroeng Rehabil. 2006;3:12.
87. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002;83(7):952–9.
88. Macclellan LR, Bradham DD, Whitall J, Volpe B, Wilson PD, Ohlhoff J, et al. Robotic upper-limb neurorehabilitation in chronic stroke patients. J Rehabil Res Dev. 2005;42(6):717–22.
89. Staubli P, Nef T, Klamroth-Marganska V, Riener R. Effects of intensive arm training with the rehabilitation robot ARMin II in chronic stroke patients: four single-cases. J Neuroeng Rehabil. 2009;6:46.
90. Housman S, Le V, Rahman T, Sanchez R, Reinkensmeyer D, editors. Arm-training with T-WREX after chronic stroke: preliminary results of a randomized controlled trial. Noordwijk, Netherlands; 2007.
91. Yao J, Chen A, Carmona C, Dewald JP. Cortical overlap of joint representations contributes to the loss of independent joint control following stroke. Neuroimage. 2009;45(2):490–9.
92. Muratori LM, Lamberg EM, Quinn L, Duff SV. Applying principles of motor learning and control to upper extremity rehabilitation. J Hand Ther. 2013;26(2):94–102, quiz 3.
93. Henderson A, Korner-Bitensky N, Levin M. Virtual reality in stroke rehabilitation: a systematic review of its effectiveness for upper limb motor recovery. Top Stroke Rehabil. 2007;14(2):52–61.
94. Lucca LF. Virtual reality and motor rehabilitation of the upper limb after stroke: a generation of progress? J Rehabil Med. 2009;41(12):1003–100.
95. Mumford N, Wilson PH. Virtual reality in acquired brain injury upper limb rehabilitation: evidence-based evaluation of clinical research. Brain Inj. 2009;23(3): 179–91.
96. Acosta AM, Dewald HA, Dewald JP. Pilot study to test effectiveness of video game on reaching performance in stroke. J Rehabil Res Dev. 2011;48(4): 431–44.

Part IV

Robotics for Locomotion Recovery

Technology of the Robotic Gait Orthosis Lokomat

19

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 the most widely used system known as "Lokomat" including features such as hip abduction/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

19.1 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.

R. Riener, Dr.-Ing
Sensory-Motor Systems Lab, Institute of Robotics and Intelligent Systems, Department of Health Sciences and Technology, ETH Zurich, Tannenstrasse 1, Zurich 8092, Switzerland

Spinal Cord Injury Center, Balgrist Campus, Lengghalde 5, 8008 Zurich, Switzerland
e-mail: riener@hest.ethz.ch

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Fig. 19.1 Current version of the Lokomat system with a spinal cord-injured patient (Printed with permission of Hocoma AG, Volketswil)

Manually assisted BWSTT involves therapist assistance, while the patient practices stepping movements on a motorized treadmill 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. Recently, a large randomized clinical trial, known as the LEAPS study, has confirmed that walking training on a treadmill using body weight support and practice overground at clinics was superior to usual care in improving walking, regardless of severity of initial impairment [3].

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 its training time [4]. Furthermore, manual forces provided by human trainers are highly variable between trainers [5]. The success and promise of BWSTT, the limitations and resource constraints in the therapeutic environment, and the variability between human trainers have inspired the design and development of robotic devices to assist the rehabilitation of ambulation in patients following stroke or spinal cord injury (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 (Fig. 19.1). It is the most widely used rehabilitation robot worldwide, with about 700 sold devices till summer 2015. Later on, other exoskeletal systems

were developed including the "AutoAmbulator" by Healthsouth Inc. (USA). As the Lokomat, the AutoAmbulator is a four degrees-of-freedom (DOF) treadmill-based rehabilitation device, which consists of actuated robotic orthoses that guide the patient's knee and hip joints within the sagittal plane. In Europe, the device is sold as "ReoAmbulator" (www.motorica.com). Another treadmill-based robotic exoskeleton is LOPES [6]. It combines an actuated pelvis segment with a leg exoskeleton. The pelvis can move in translational directions, whereas the legs have two active rotary DOF at the hip (flexion/extension and abduction/adduction) and one active DOF at the knee (flexion/extension). The leg joints of the robot are actuated with Bowden cable-driven series elastic actuators. The lateral pelvis translation is equipped also with the same actuation principle, whereas the anterior/posterior motion is driven by a linear actuator. Another gait rehabilitation robot is the active leg exoskeleton (ALEX) [7]. A so-called walker supports the weight of the device, and the orthosis has several passive and actuated DOF with respect to the walker. The trunk of the orthosis (connected to the walker) has three DOF, namely, vertical and lateral translations and rotation about the vertical axis. All the DOF in the trunk are passive and held in position by springs. The hip joint of the orthosis has two DOF with respect to the trunk of the orthosis allowing actuated hip flexion/extension and passive abduction/adduction movements. David Reinkensmeyer from UC Irvine together with colleagues from UCLA developed the exoskeletal device "PAM" (pelvic assist manipulator), which is a device that assists the pelvic motion during human gait training on a treadmill [8] and "POGO" (pneumatically operated gait orthosis), which moves the patient's legs with linear actuators attached to a frame placed around the subject [9].

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. As the Gait Trainer moves each leg only in one degree of freedom (DOF), Hesse and colleagues from the Fraunhofer Institute IPK developed a more complex device, called the "HapticWalker" [10]. The device comprises two end effector-based platforms that move each foot in three DOF. Based on the knowledge gained with Gait Trainer and HapticWalker, Hesse et al. [11] developed G-EO robot (EO is Latin meaning "I walk"), which is commercially available by the company Reha Technology AG in Switzerland (www.rehatechnology.com). As in the HapticWalker, G-EO consists of two footplates, which move each foot with three DOF in the sagittal plane and enables the training of freely programmable tasks such as stair climbing. Another end effector-based robot developed by the group of D. Reinkensmeyer together with colleagues from UCLA and University of Louisville was ARTHUR, which is a backdrivable two DOF planar robot to measure and assist the stepping of the right leg. This robot uses a two-coil linear motor and a pair of lightweight linkages to drive the robot's apex, which is attached to the subject through a revolute joint and running shoe modified to include an embedded footplate [12, 13].

19.2 Orthosis Design

19.2.1 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. 19.1). 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 special version of the Lokomat 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 can 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.

19.2.2 Drives

Ruthenberg and coworkers [14] 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 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.

19.2.3 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 backdrivability and mechanical end stops 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 when 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.

19.3 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 [15]. 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 [16]. 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 [16]. 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 system can perform changes of up to 20 kg in desired unloading within less than 100 ms. With this 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 [17].

19.4 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" [18] is considered to be a crucial requirement and is also supported by recent advances in computational models describing motor learning [19]. More specifically, a recent study by Lewek et al. [20] 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. Another study performed with transected spinal rats also showing that kinematic variability facilitates spinal learning [21].

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 [22, 23]. 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. In a simple version of such kind of impedance controller, the impedance is kept constant in a world coordinate frame, i.e., a PD controller in world coordinates. It only depends on the amount of deviation, which 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 first or second order) function of angular position and its derivatives. This torque is more generally called mechanical impedance [24]. In more complex versions of such an impedance controller, an additional dead band has been added or the amount of impedance force varies with space and time. Figure 19.2 depicts a block diagram of an impedance controller [22].

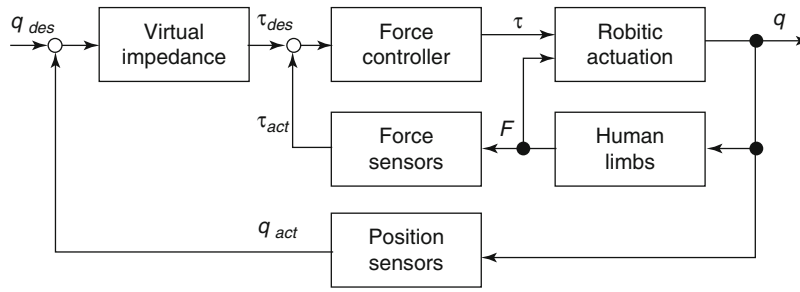

Fig. 19.2 Example of an impedance control architecture for the compliance of rehabilitation robot [22]. Symbols: q is the vector of generalized positions or joint angles; τ is the vector of generalized joint torques; F is the interaction force between robot and human; index "des" refers to the desired reference signal; index "act" refers to the actual, measured signal

The impedance controller was initially tested in several subjects without neurological disorders and several subjects with incomplete paraplegia [22]. 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 [23], 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) [23]. 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. The path controller has been evaluated in several single-case studies [25–27]. Most stroke patients improved their gait performance after several weeks of training with the path controller.

19.5 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. It is assumed that 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 degrees of freedom perform hip adduction/

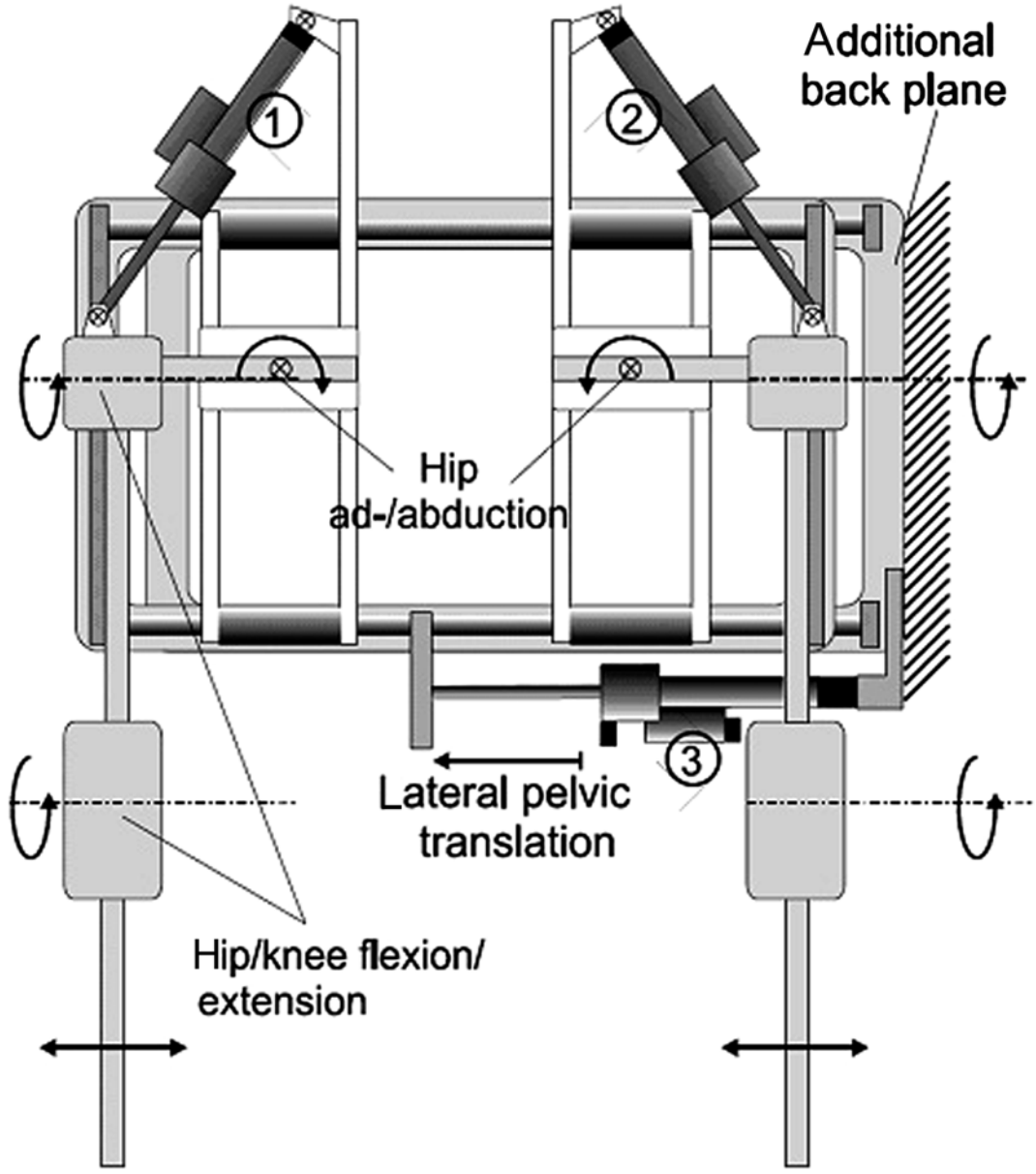

Fig. 19.3 Sketch of the front view of the extended Lokomat hardware

abduction, and 1 degree of freedom enables the Lokomat to accomplish a lateral pelvis displacement movement (Fig. 19.3). Three linear actuators have been added to drive the adduction/abduction (No. 1 and 2 in Fig. 19.3) 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 closed-loop admittance and impedance controllers 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 and is currently being tested with single stroke patients. All subjects agreed that gait training with lateral pelvis displacement and adduction/abduction feels more physiological and comfortable than without. The optimal amplitudes of lateral pelvis displacement and adduction/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.

19.6 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.

19.6.1 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 hyperexcitability of stretch reflexes" [28]. It appears as an increased joint resistance during passive movements. Sanger et al. [29] used 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 [30] or Modified Ashworth Test [31]. 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 [32, 33], 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 [32, 33]. Assessment of spasticity is still in an experimental status and needs further validation in future studies.

19.6.2 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 [32], 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 [34]. 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 [34].

19.6.3 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.

19.7 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 [35, 36].

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 [22, 37, 38].

Fig. 19.4 Walking through a virtual environment. Lokomat in combination with a virtual reality back-projection display system

In order to obtain relevant biofeedback values, the gait cycle is divided into stance phase and swing phase. For each phase, weighted averages 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 [39, 40]. 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. 19.4). 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 forest scenario and other scenarios [41]. Wagner et al. showed how such kind of VR-enhanced Lokomat training activates premotor and parietal areas [42].

19.8 Clinical Outcomes

Robotic technology is still very much in development, and there are a lot of new devices and technical features that might further enhance the potential of therapeutic training. Nevertheless, there have already been more than 200 clinical investigations applying the Lokomat technology to different patient groups. It was applied for the therapy of patients with SCI, hemiplegia after stroke, traumatic brain injuries, multiple sclerosis, Parkinson's disease, cerebral palsy, and other pathologies (see [43]). Most of these studies show positive outcomes with the Lokomat compared to conventional therapies or usual care.

The majority of clinical studies was done with stroke subjects. Often cited are the ones from Hidler et al. [44] and Hornby et al. [45], who applied the Lokomat on subacute and chronic stroke patients, respectively, and compared it with conventional gait therapy. Both studies showed that

participants who received conventional training experienced greater gains in gait parameters such as walking speed, walking distance, or single limb stance than those trained on the Lokomat. Hidler et al. and Hornby et al. concluded that for stroke participants, conventional gait training interventions appear to be more effective than robot-assisted gait training. However, both studies included only ambulatory patients, although the Lokomat is recommended to be used primarily for nonambulatory patients. Furthermore, the Lokomat was used in most simple control modes (position controller or impedance controller with reduced guidance force), without any other features such as augmented feedback or biofeedback functions. Of course, this kind of mode cannot compete with the quality and gentleness of a trained therapist or more advanced robotic features, such as cooperative and self-adaptive control strategies.

A recent Cochrane report [46] analyzing 17 trials with 837 stroke patients revealed that people who receive electromechanical-assisted gait training, such as provided by the Lokomat or the Gait Trainer, in combination with physiotherapy after stroke are more likely to achieve independent walking than people who receive gait training without these devices. Specifically, people in the first 3 months after stroke and those who are not able to walk seem to benefit most from this type of intervention. The role of the type of device is not clear. Further research should consist of a large definitive, pragmatic, phase III trial undertaken to address specific questions such as: "What frequency or duration of electromechanical-assisted gait training might be most effective?" and "how long does the benefit last?" One of the latest studies was the one by Dundar et al. [47] who compared conventional physiotherapy and robotic training combined with conventional therapy, on 107 subacute and chronic stroke patients. They found that robotic training combined with conventional therapy produced better improvement in a large number of different stroke scales.

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 inter-subject comparison that the researcher and the therapist require to evaluate the rehabilitation process of individual patients and entire patient groups. Some 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.

Several clinical trials have been performed showing that the application of rehabilitation devices is at least as effective as the application of conventional therapies. Further clinical studies are required to find predictors for the success of a Lokomat treatment in order to distinguish therapy responders from nonresponders. From such investigations it is expected to figure out which choice of technical Lokomat features (controller complexity, number of actuated joints, kind of feedback, etc.) have to be applied to which kind of patient characteristics (kind of pathology, severity, and time since lesion, anthropometry, etc.) in order to obtain the best therapeutic outcome. New sensitive assessment methods will be required to better distinguish among the different patient characteristics and detect already small changes in the therapeutic outcomes.

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References

1. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37:693–700.
2. Hesse S, Uhlenbrock D. A mechanized gait trainer for restoration of gait. J Rehabil Res Dev. 2000; 37:701–8.
3. Nadeau SE, Wu SS, Dobkin BH, Azen SP, Rose DK, Tilson JK, Cen SY, Duncan PW. Effects of task-specific and impairment-based training compared with usual care on functional walking ability after inpatient stroke rehabilitation: LEAPS trial. Neurorehabil Neural Repair. 2013;27(4):370–80.
4. Morrison SA, Backus D. Locomotor training: is translating evidence into practice financially feasible? J Neurol Phys Ther. 2007;31:50–4.
5. Galvez JA, Budovitch A, Harkema SJ, Reinkensmeyer DJ. Trainer variability during step training after spinal cord injury: implications for robotic gait training device design. J Rehabil Res Dev. 2011;48(2): 147–59.
6. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, van der Kooij H. Design and evaluation of the lopes exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15:379–86.
7. Banala SK, Kim SH, Agrawal SK, Scholz JP. Robot-assisted gait training with active leg exoskeleton (alex). IEEE Trans Neural Syst Rehabil Eng. 2009;17:2–8.
8. Aoyagi D, Ichinose WE, Harkema SJ, Reinkensmeyer DJ, Bobrow JE. A robot and control algorithm that can synchronously assist in naturalistic motion during body weight supported gait training following neurologic injury. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):387–400.
9. Reinkensmeyer DJ, Aoyagi D, Emken JL, Galvez J, Ichinose W, Kerdanyan G, Maneekobkunwong S, Minakata K, Nessler JA, Weber R, Roy RR, de Leon R, Bobrow JE, Harkema JE, Edgerton VR. Tools for understanding and optimizing robotic gait training. J Rehabil Res Dev. 2006;43(5):657–70.
10. Schmidt H, Hesse S, Bernhardt R, Kruger J. HapticWalker—a novel haptic foot device. ACM Trans Appl Percept (TAP). 2005;2(2):166–80.
11. Hesse S, Waldner A, Tomelleri C. Research innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients. J Neuroeng Rehabil. 2010;7:30.
12. Emken JM, Wynne JH, Harkema SJ, Reinkensmeyer DJ. A robotic device for manipulating human stepping. IEEE Trans Robot. 2006;22(1):185–9.
13. Emken JL, Beres-Jones J, Harkema SJ, Ferreira C, Reinkensmeyer DJ. Feasibility of manual teach-and-replay and continuous impedance shaping for robotic locomotor training following spinal cord injury. IEEE Trans Biomed Eng. 2008;55:322–34.
14. Ruthenberg BJ, Wasylewski NA, Beard JE. An experimental device for investigating the force and power requirements of a powered gait orthosis. J Rehabil Res Dev. 1997;34:203–13.
15. Lunenburger L, Lam T, Riener R, Colombo G. Gait retraining after neurological disorders. In: Akay M, editor. Wiley encyclopedia for biomedical engineering. Hoboken: Wiley; 2006.
16. Frey M, Colombo G, Vaglio M, Bucher R, Jorg M, Riener R. A novel mechatronic body weight support system. IEEE Trans Neural Syst Rehabil Eng. 2006;14:311–21.
17. Colombo G, Bucher R. Device for adjusting the prestress of an elastic means around a predetermined tension or position patent. Patent filed in the US, Europe, China, etc. 2007.
18. Bernstein NA. The co-ordination and regulation of movements. 1st ed. Oxford: Pergamon Press Ltd; 1967.
19. Huang VS, Krakauer JW. Robotic neurorehabilitation: a computational motor learning perspective. J Neuroeng Rehabil. 2009;6:5.
20. Lewek MD, Cruz TH, Moore JL, Roth HR, Dhaher YY, Hornby TG. Allowing intralimb kinematic variability during locomotor training poststroke improves kinematic consistency: a subgroup analysis from a randomized clinical trial. Phys Ther. 2009;89:829–39.
21. Ziegler MD, Zhong H, Roy RR, Edgerton VR. Why variability facilitates spinal learning. J Neurosci. 2010;30(32):10720–6.
22. Riener R, Lunenburger L, Jezernik S, Anderschitz M, Colombo G, Dietz V. Patient-cooperative strategies for robot-aided treadmill training: first experimental results. IEEE Trans Neural Syst Rehabil Eng. 2005;13:380–94.
23. Duschau-Wicke A, von Zitzewitz J, Caprez A, Lunenburger L, Riener R. Path control: a method for patient-cooperative robot-aided gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2010;18:38–48.
24. Hogan N. Impedance control: an approach to manipulation. Articles I, II, III J Dyn Syst-T. ASME. 1985;107:1–23.
25. Krishnan C, Kotsapouikis D, Dhaher YY, Rymer WZ. Reducing robotic guidance during robot-assisted gait training improves gait function: a case report on a stroke survivor. Arch Phys Med Rehabil. 2013;94(6): 1202–6.
26. Krishnan C, Ranganathan R, Kantak SS, Dhaher YY, Rymer WZ. Active robotic training improves locomotor function in a stroke survivor. J Neuroeng Rehabil. 2012;9(1):1–13.

27. Schück A, Labruyère R, Vallery H, Riener R, Duschau-Wicke A. Feasibility and effects of patient-cooperative robot-aided gait training applied in a 4-week pilot trial. J Neuroeng Rehabil. 2012;9:31.
28. Lance JW. Pathophysiology of spasticity and clinical experience with Baclofen. In: Lance JW, Feldmann RG, Young RR, Koella WP, editors. Spasticity: disordered motor control. Chicago: Year Book; 1980. p. 184–204.
29. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Classification and definition of disorders causing hypertonia in childhood. Pediatrics. 2003;111:e89–97.
30. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. Practitioner. 1964;192:540–2.
31. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67:206–7.
32. Lunenburger L, Colombo G, Riener R, Dietz V. Clinical assessments performed during robotic rehabilitation by the gait training robot Lokomat. In: Proceedings of the international conference on rehabilitation robotics (ICORR). Proceedings of the IEEE. Chicago; 2005. p. 345–8.
33. Riener R, Lunenburger L, Colombo G. Human-centered robotics applied to gait training and assessment. J Rehabil Res Dev. 2006;43:679–94.
34. Bolliger M, Lunenburger L, Bircher S, Colombo G, Dietz V. Reliability of measuring isometric peak torque in the driven gait orthosis "Lokomat". In: 4th world congress of neurorehabilitation. Hong Kong; 2006.
35. Basmajian JV. Muscles alive: their functions revealed by electromyography. 4th ed. Baltimore: Williams and Wilkins; 1978. p. 495.
36. Schmidt RA, Wrisberg CA. Motor learning and performance. 2nd ed. Champaign: Human Kinetics; 2000.
37. Lunenburger L, Colombo G, Riener R, Dietz V. Biofeedback in gait training with the robotic orthosis Lokomat. Conf Proc IEEE Eng Med Biol Soc. 2004;7:4888–91.
38. Lunenburger L, Colombo G, Riener R. Biofeedback for robotic gait rehabilitation. J Neuroeng Rehabil. 2007;4:1.
39. Banz R, Bolliger M, Colombo G, Dietz V, Lunenburger L. Computerized visual feedback: an adjunct to robotic-assisted gait training. Phys Ther. 2008; 88:1135–45.
40. Banz R, Bolliger M, Muller S, Santelli C, Riener R. A method of estimating the degree of active participation during stepping in a driven gait orthosis based on actuator force profile matching. IEEE Trans Neural Syst Rehabil Eng. 2009;17:15–22.
41. Lunenburger L, Wellner M, Banz R, Colombo G, Riener R. Combining immersive virtual environments with robot-aided gait training. In: Proceedings 10th international conference on rehabilitation robotics (ICORR). Noordwijk; 2007.
42. Wagner J, Solis-Escalante T, Scherer R, Neuper C, Müller-Putz G. It's how you get there: walking down a virtual alley activates premotor and parietal areas. Front Hum Neurosci. 2014;8:93. doi:10.3389/fnhum.2014.00093.
43. Riener R, Lünenburger L, Maier IC, Colombo G, Dietz V. Locomotor training in subjects with sensorimotor deficits: an overview of the robotic gait orthosis Lokomat. J Healthc Eng. 2010;1(2):197–216.
44. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, Hornby TG. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5–13.
45. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke. A randomized controlled study. Stroke. 2008;39: 1786–92.
46. Mehrholz J, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2013;7: CD006185.
47. Dundar U, et al. A comparative study of conventional physiotherapy versus robotic training combined with physiotherapy in patients with stroke. Top Stroke Rehabil. 2014;21(6):453–61.

Beyond Human or Robot Administered Treadmill Training

20

Hermano Igo Krebs, Konstantinos Michmizos, Tyler Susko, Hyunglae Lee, Anindo Roy, and Neville Hogan

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 (AHA) and of the Veterans Administration/Department of Defense (VA/DoD) endorsed the use of the rehabilitation robotics for upper-extremity

H.I. Krebs, PhD (✉)
Department of Mechanical Engineering, MIT-Massachusetts Institute of Technology, Cambridge, MA, USA

Department of Neurology, University of Maryland, School of Medicine, Baltimore, MD, USA

Institute of Neuroscience, University of Newcastle, Newcastle Upon Tyne, UK

Department of Rehabilitation Medicine I, Fujita Health University, School of Medicine, Nagoya, Japan

Department of Mechanical Science and Bioengineering, Osaka University, Osaka, Japan
e-mail: hikrebs@mit.edu

K. Michmizos, MEng, PhD
Department of Computer Science, Rutgers University, Piscataway, NJ, USA

T. Susko, PhD
Department of Mechanical Engineering, University of California Santa Barbara, Santa Barbara, CA, USA

H. Lee, PhD
School for Engineering of Matter, Transport, and Energy, Arizona State University, Tempe, AZ, USA

A. Roy, PhD
Department of Neurology, University of Maryland, School of Medicine, Baltimore, MD, USA

N. Hogan, PhD
Department of Mechanical Engineering, Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA

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post-stroke care, but concluded that lower-extremity robotic therapy is much less effective as compared to usual care practices in the USA and declared "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 rhythmic 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 AHA and VA/DoD for rehabilitation robotics for lower-extremity post-stroke care.

Keywords
Rehabilitation robotics • Robot-assisted therapy • Robotic therapy • Anklebot • MIT-Skywalker • Lower extremity • Stroke • Cerebral palsy

20.1 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 inevitable 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 can not only support the labor-intensive tasks of therapists but also help by increasing the intensity of therapy. In addition, direct interaction with a robotic device enables quantitative measurement of human performance, which is essential for systematic training and tracking recovery. 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, 2].

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" [2]. While the AHA and VA recommendations compared robotic outcomes to usual care as practiced in the USA, results are only marginally better when considering a mixture of usual care practices around the world with the latest Cochrane report stating that while robotics alone was not superior to a mixture of usual care, robotic walking training plus usual care leads to better outcomes than equal time in usual care alone [3].

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 and for subacute stroke patients in North America [4, 5]. Figure 20.1 shows the results of two studies comparing LE rehabilitation robotics with usual care.

The top 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 as practiced in North America improved significantly more than the Lokomat trained group and retained that advantage at 6-month follow-up. This was true for both severely and moderately impaired patients [4]. 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-month follow-up, but patients in the usual care group improved more, and the difference between groups was statistically significant [5].

There are many plausible reasons for these results that indicate the immaturity of lower-extremity robotic therapy. First, the technologists assumed that body-weight-supported treadmill training (BWSTT) 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 [6]. 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 over-ground carry-over training did not lead to superior results when compared to a home program of strength training and balance (LEAPS Study) [7]. 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 simply automate current rehabilitation practices, which for the most part lack a scientific evidential basis, primarily due to the lack of tools to properly assess the practices themselves. In fact,

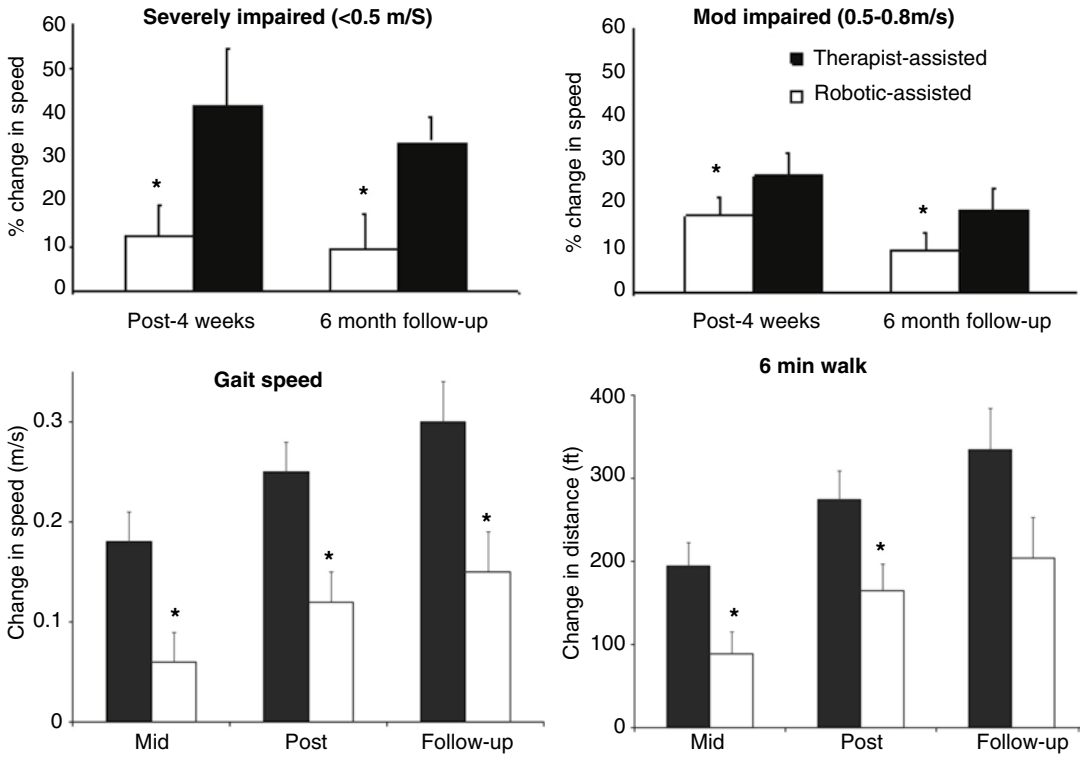

Fig. 20.1 Clinical results of robotic therapy in stroke using Lokomat. *Top row* shows the results with chronic stroke (enrollment >6 months post-stroke), and the *bottom row* shows results of subacute stroke trials (enrollment between 3 and 6 months post-stroke)

the lead authors of the LEAPS study have caustically urged a wake-up call in their paper: "Should Body Weight-Supported Treadmill Training and Robotic-Assistive Steppers for Locomotor Training Trot Back to the Starting Gate?" [8].

To move LE robotics beyond its infancy, we must determine what constitutes best practice and how to assess it. Alternatives must be carefully examined. Here we will review our working model for walking, explore basic psychophysical aspects of lower limb control that have been hitherto been unknown, and describe some clinical results.

20.2 A Competent Model for Walking

We propose a competent model of human walking based on dynamic primitives. By "competent model" we mean that it may only be a first approximation of a fundamental theory, but it is good enough to improve the design of robots and regimens for LE therapy. The theory of dynamic motor primitives is succinctly outlined by Hogan and Sternad [9]. To accommodate real-life walking with all its variations, we propose that walking is a composite of three dynamic primitives, specifically submovements (discrete movements), oscillations (rhythmic movements), and mechanical impedances (balance). The three primitives are related via the concept of a virtual trajectory [9]. To render precision, a discrete movement is defined as one with a clear start and stop posture. Because the term "rhythmic" has numerous confusing variations of meaning, the corresponding dynamic primitive is defined as an almost-periodic oscillation [10]. Mechanical impedance is defined as the operator that determines the force or torque evoked by imposed displacement [11].

These dynamic primitives have different neural substrates. In a functional MRI study, Schaal et al. demonstrated that a discrete wrist movement recruited more regions of the brain than did the same movement performed rhythmically [12]. Perhaps more important, they influence learning in different ways. It has been shown that motor learning of discrete movements has a positive transfer to rhythmic movements but not vice versa [13]. To the extent that recovery after neural injury resembles motor learning, this suggests that discrete training may be more effective than rhythmic training of locomotion [13]. Discrete locomotor therapy would consist of patients working on self-directed, visually guided, discrete steps or pointing movements to targets with the lower limb [14].

Upright walking requires active balance mechanisms that often include modulating mechanical impedance. The posture or configuration of the limbs profoundly affects the response to perturbations, i.e., mechanical impedance. Challenges to balance commonly evoke changes of lower limb posture, for example, a wider stance. Impaired balance is a common symptom in most neurological injuries such as stroke and cerebral palsy [15–18]. Balance training has been shown to reduce postural asymmetry associated with hemiparesis and was a part of the home-based protocol in the LEAPS study which resulted in walking benefits similar to those achieved with body-weight-supported treadmill training (BWSTT) [19].

A similar combination of dynamic primitives has been proposed to underlie upper-extremity actions [20]. This suggests that the differences between upper-extremity and lower-extremity control may be smaller than previously considered in the literature (see Chap. 16).

20.3 Our Lower-Extremity Robotic Tools

In the following we review two of our robotic devices, Anklebot [21] and MIT-Skywalker [22], both specifically designed to depart from existing LE robotic therapy, and some of the initial results obtained from investigating what might constitute best practice. Our approach to lower-extremity therapeutic robots is guided by our model of dynamic primitives in locomotion, by the principle that the machine should allow the patient to express those dynamic primitives as much as he/she can (i.e., it should be able to "get out of the way"), and by the need to accommodate a vast spectrum of pathological gaits and impairment levels as defined in [23]. The Anklebot and the MIT-Skywalker exemplify our approach, affording at least three independent training modes (rhythmic, discrete, and balance training) that can be added or subtracted depending on the patient's needs as showcased later.

20.3.1 Anklebot

We focused our initial LE robotics development efforts on the ankle because it is critical for propulsion, shock absorption, 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 drag). 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, major cause of ankle injuries. Lack of proper control during these phases increases the likelihood of trips and falls. In fact, deficits of swing clearance, propulsion, and balance contribute to more than 70 % of stroke survivors sustaining a fall within 6 months [15], leading to higher risks for hip and wrist fractures in the first year [16–18]. The ankle is also the largest source of mechanical power during terminal stance [25]. The plantarflexors contribute as much as 50 % of positive mechanical work in a single stride to enable forward propulsion [26–29]. In pre-swing plantarflexors also act to advance the leg into swing phase while promoting knee flexion at toe-off [30]. Additionally, the ankle helps maintain body-weight support during gait [31–33] and bal-

ance. Finally, the ankle musculature helps absorb impact forces during foot strike to enable controlled landing. In summary, given its importance in overground foot-floor swing clearance, propulsion, shock absorption, and balance, we elected to focus first on the ankle. The Anklebot has the potential to address both swing clearance and propulsion, as well as balance problems since it is actuated in both the sagittal and frontal planes [21] (Fig. 20.2).

The design, characterization, donning procedure, and safety features of the adult and pediatric version of the Anklebot have been previously described [24, 34]. Here, we will briefly summarize the salient design features and measurement capabilities of the two versions of the robot. 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 plantar flexion, 25° of inversion, 20° of eversion, and 15° of internal or external rotation). It also provides independent assistance or resistance in two of those degrees of freedom (dorsi-plantarflexion and eversion/inversion) via two linear actuators mounted substantially 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. Underactuation, i.e., actuating fewer degrees of freedom than are anatomically present, affords one 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, an inversion-eversion torque results.

The Anklebot is a backdrivable robot with low intrinsic mechanical impedance, weighs less than 3.6 kg (2.5 kg for the pediatric version), and can deliver a continuous net torque of approximately 23 Nm in dorsi-plantarflexion and 15 Nm in eversion-inversion (7.21 Nm and 4.38 Nm for the pediatric version). The robot can estimate ankle angles with an error less than 1° in both planes of movement 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 maximize backdrivability. Of course, the Anklebot torque capability does

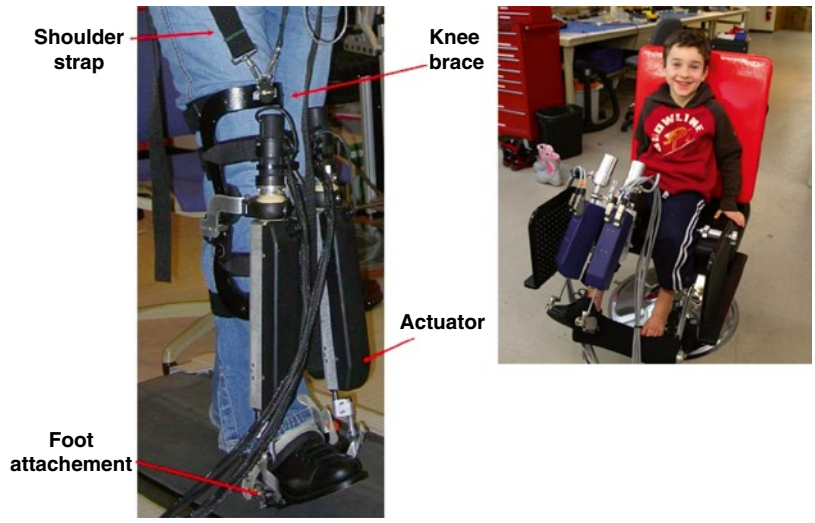

Fig. 20.2 Adult and pediatric Anklebots. *Left* photo shows the adult Anklebot and on the *right* the pediatric version (ages 6–9 years old). The devices have 3° of freedom (DOF) with active dorsi-plantaflexion and inversion-eversion. They can be employed in seated position or while standing or walking overground or on a treadmill

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 activity during push-off. We can also generate torque during the mid-swing 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 (~7 Nm for the pediatric version), which is higher than required to position the foot in dorsiflexion during mid-swing.

We 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 or pediatric Anklebot's additional mass had no detrimental effect on the gait pattern of subjects with chronic hemiparesis or children with cerebral palsy [35, 36].

20.3.2 MIT-Skywalker

The MIT-Skywalker robot is inspired by the concept of passive dynamic walkers [37]. 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 using the concepts of the passive walker 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. 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. 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 [22].

Figure 20.3 provides a conceptual sketch of the device and illustrates several phases of the walking cycle. In addition, the MIT-Skywalker

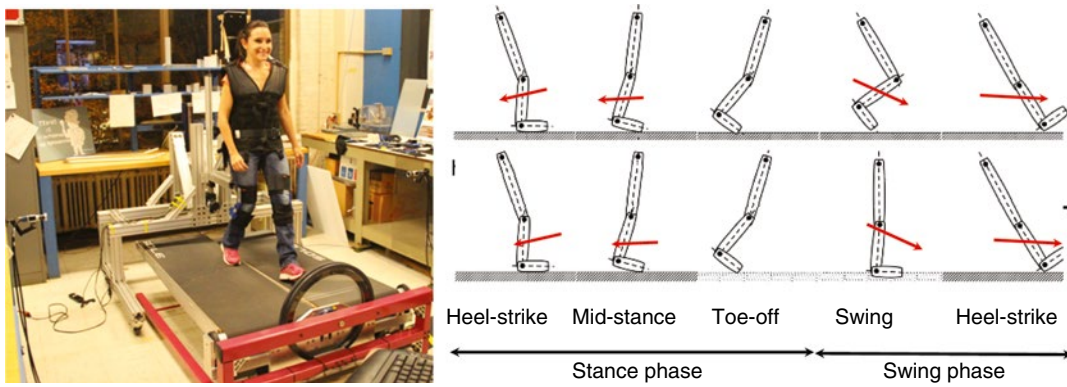

Fig. 20.3 The *top left* panel shows the MIT-Skywalker platform equipped with two cameras on the sides to monitor the position of *red* markers placed on the user's heels. The *right* panels depict the gait phases for walking on a flat surface (*top row*) and a surface that drops between toe-off and heel strike (*bottom row*)

rotates in the frontal plane affording balance training. More details on the hardware architecture and characteristics of MIT-Skywalker can be found elsewhere [22, 38], 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 [39, 40].

20.4 Basis for Our Competent Model

20.4.1 Inter-limb Coordination in Body-Weight-Supported Locomotion: It Goes Beyond Central Pattern Generator

The coordination of the limbs during locomotion can be seen as a rhythmic activity of circuits that control different muscles and are specialized in repeating particular actions over and over again [6, 42, 43]. For locomotion, the term used is central pattern generator (CPG), which usually refers to a functional network of neurons within the spinal cord. This network is responsible for generating the rhythm and shape of the motor pattern [44]. Although the CPG might receive supraspinal and afferent inputs, it is defined as being able to produce self-sustained patterns of behavior, independent of any sensory input. This understanding of the basic principle of such a CPG is mainly based on evidences acquired from animal studies, primarily on experiments with cats [45, 46].

Although there is some evidence that a CPG may exist in humans similar to the one in cats [47–51], its significance for human walking remains unclear. Nonetheless, rhythmic activity has only rarely been observed in spinal cord injured (SCI) patients. For patients with a completely transected spinal cord, it is possible to induce, modulate, and stop rhythmic contractions of the trunk and lower limb extensor muscles; however, these rhythmic contractions never occurred spontaneously and had only a one-step cycle duration [45]. On the other hand, for patients with incomplete lesions, several studies reported subjects with the presence of alternating flexor and extensor activity [52].

We investigated inter-limb coordination by applying unilateral perturbations and analyzing the response of the contralateral limb at a slow speed comparable to the preferred speed of our stroke patients. We perturbed gait by unexpectedly lowering the walking surface under one leg at mid-stance employing the MIT-Skywalker [22]. Although the kind of perturbation is similar to ones used in previous studies [53–57], our experimental paradigm included high body-weight support (80 %) and torso stabilization in order to limit the afferent feedback as well as the loading of the legs. We focused on analyzing the responses of the contralateral muscles in order to study the inter-limb coordination in body-weight-supported walking at slow speeds.

The latency of the effect of the perturbations on the activation of the contralateral ankle flexor and extensor was "large" (TA, 193 ± 80 ms; SOL, 207 ± 74 ms). The overall mean value and its standard deviation for all contralateral muscle responses are shown in Table 20.1. These numbers are comparable to those found in simple reaction time tasks.

Our findings question the hypothesis that a spinal response could fully explain the results and give support to the role of a supraspinal pathway in inter-limb coordination. The large latency in the contralateral leg muscle response makes such an argument plausible. TA activation during unperturbed walking has been shown to involve both spinal (CPG) and cortical origin [58]. Moreover, it was observed that the disturbance in sensory information from the perturbed leg evoked muscular activity in the contralateral leg and the necessity of supraspinal input for walking [59]. For many motor functions, the cortex is

Table 20.1 Muscle activity onset time for the four muscles RF, ST, TA, and SOL calculated with the amplitude thresholding method by Di Fabio (1987). The values shown are mean ± one standard deviation over all six subjects

Muscle activity onset time			
RF	ST	TA	SOL
163 ± 22 ms	129 ± 68 ms	193 ± 80 ms	207 ± 74 ms

known to be able to control automated functions executed at lower CNS levels. A cerebellar contribution via reticulospinal neurons has been suggested in humans [60], while evidence was presented for a cortical control of inter-limb coordination in the past [61]. Our work adds evidence that the control of stability in walking is a combination of both supraspinal and spinal neural control.

20.4.2 Sensorimotor Control of Ankle Discrete Movements

Three of our recent studies on the ankle sensorimotor control were focused on revealing the similarities and the differences between the UE and the LE. Our findings provide additional evidence for a remarkable behavioral similarity of LE and UE movements. Since it is known for years that the sensorimotor control of the UE is driven by cortical and subcortical areas, our main finding that UE and LE behave similarly expands the role of a presumptive supraspinal pathway from coordinating the two lower limbs to controlling discrete LE movements.

Functionally, the LE supports the body weight, provides locomotion, and maintains stability, whereas the UE are better suited for dexterity [62]. This difference between "working" (UE) and "walking" (LE) comes alongside differences in limbs, muscles, joints, tendons, and ligaments [63].

When compared to usual care as practiced in the USA, the lack of superior results in LE robotic therapy could be attributed to therapeutic approaches that lack scientific bases. Since the paradigm shift on activity-dependent plasticity [64, 65], UE movements have been studied extensively. Kinematic analyses of reaching movements (e.g., [66]) have been followed up by analyses of single-peak speed profiles [67] and of more complex movements that were modeled as a combination of elementary movements (submovements) [68]. The understanding of how the CNS controls and learns UE movements was developed from these and subsequent studies, and they provided a basis for the design of UE therapeutic robots as well as the establishment of quantitative metrics for patients' motor recovery [69]. The lack of understanding or, at least, modeling the neurophysiological signature of ankle discrete movements may limit the validity of any effort to design an ideal therapeutic intervention for the ankle or evaluate its performance.

To address this limitation, we studied the sensorimotor control of ankle pointing movements at three modeling levels. In our first, macroscopic study, we demonstrated the adequacy of Fitts' law to describe the mean time of major ankle pointing movements and to support the use of linear models to predict the ankle average performance in dorsal-plantar (DP) and inversion-eversion (IE) directions in healthy subjects [70]; this study verified that the central nervous system commands and controls the speed and accuracy of ankle movement in both DP and IE directions in the same way as in UE. In our second, mesoscopic study, we found a remarkable similarity between the models that described the speed profiles of unimpaired ankle pointing movements and the ones previously found for the upper extremities both during arm reaching and wrist pointing movements [71]. In our third, microscopic study, we found that the reaction time (RT) measured in both DP and IE ankle movements increased with the number of stimuli at an equal pace, as would be predicted by the Hick-Hyman law in UE [72]. Interestingly, there are clear differences when examining movements in DP and IE direction; this could be attributed to differences in the cognitive components known to affect RT, including motor preparation and execution. Below, we describe in more detail the main findings of our studies on whether our knowledge of how the CNS controls the UE can generalize and to what extent to the LE [73, 74].

20.4.3 Ankle Pointing Movements: Fitts' Law

Fitts' law has been widely used for more than half a century to quantify the human motor system [75, 76]. Fitts' law models the speed-accuracy trade-off in untrained movements by

establishing the existence of a linear relationship between (a) the time, MT, required to complete a discrete movement over different distances, D, to targets of different size, W, and (b) the difficulty of the task, measured by the index of difficulty, ID, in bits as a logarithmic ratio of D to W. Traditionally, Fitts' law is formulated as:

$$MT = a + b(ID), \qquad where \;\; ID = \log_2\left(\frac{2D}{W}\right)$$

where a and b are empirical constants that depend on the conditions under which movement is made. The intercept, a, can be thought of as an indicator of the reaction time and the slope, b, as the sensitivity of the motor system to a change in difficulty of the task. Although Fitts' law was originally used to describe human forearm movement, numerous studies have established that it is a reliable predictor of MT in psychomotor studies involving a variety of limb and muscle groups, including the upper limbs, head, and trunk movements in children, adults, and the elderly both in healthy and persons with neurodegenerative and neurodevelopmental disorders (for more details, see [70]).

The apparent robustness of Fitts' law in a wide range of neural disorders and across different limb segments led us to place the speed-accuracy trade-off at the core of our adaptive assist-as-needed robotic therapy delivered to both upper and the lower limbs [69, 77]. Twenty years after the early studies for neurorehabilitation with the MIT-Manus [78], we are focusing our research on what constitutes an ideal therapy intervention and on how to tailor therapy to a particular patient's needs [79], including children with CP [80, 81]. We introduced and tested extensively the concept of adaptive assist-as-needed control for upper extremities [69]. We extended the concept of performance-based progressive robotic therapy to meet the needs and special characteristics of the lower extremities in children with CP [24, 77]. Briefly, visually guided, visually evoked games assist us in identifying the ability of children to move and point with the ankle. In view of Fitts' law, we then alter the speed of the gameplay and the size of the targets accordingly. To our knowledge, no study has examined the ankle's sensorimotor control in terms of obeying (or not) Fitts' law. Establishing a speed-accuracy trade-off in human ankle movement could be coupled with the metrics anticipated to quantify separately the ability to move fast and accurately. Our experimental protocol was designed for the adult Anklebot [34]; we tested the presence of the speed-accuracy trade-off in ankle movements of healthy young adults.

We were interested primarily in the MT-ID relationship in the subtalar and talocrural ankle joints but also whether there were indications that the control processes changed between the two joints. As expected from Fitts' law, average MT was highly correlated with the task difficulty for each 1D movement direction in both IE and DP movements. In addition, although Vpeak remained virtually unchanged in the ID range, Vavg decreased linearly with the increase of accuracy demand. Differences in average MTs and Vavg were not found to be significant between movements of the same joint in the tested ID range; however, significant differences in MTs were found between DP and IE movements. As the visual gain was the same for DP and IE experiments, the findings may serve as an indication of a difference in control capability between subtalar and talocrural ankle joints.

Like in UE reaching movements, the conjecture of submovements following an initial ballistic movement was supported by the analysis of the kinematic data for large ID target acquisitions in both DP and IE directions. A single, smooth submovement covered most of the total displacement and was usually followed by subsequent, smaller, and slower ankle movements that corrected any undershoot or overshoot of the initial movement, i.e., fine motor control (Fig. 20.4, W2). Our findings are supported by Woodworth's venerable model that entails both a central and a (feedback-based) current control component ([82], p. 41) as well as models able to approximate Fitts' law at a high level, such as the stochastic optimized-submovement model [83], and several other empirical and theoretical studies

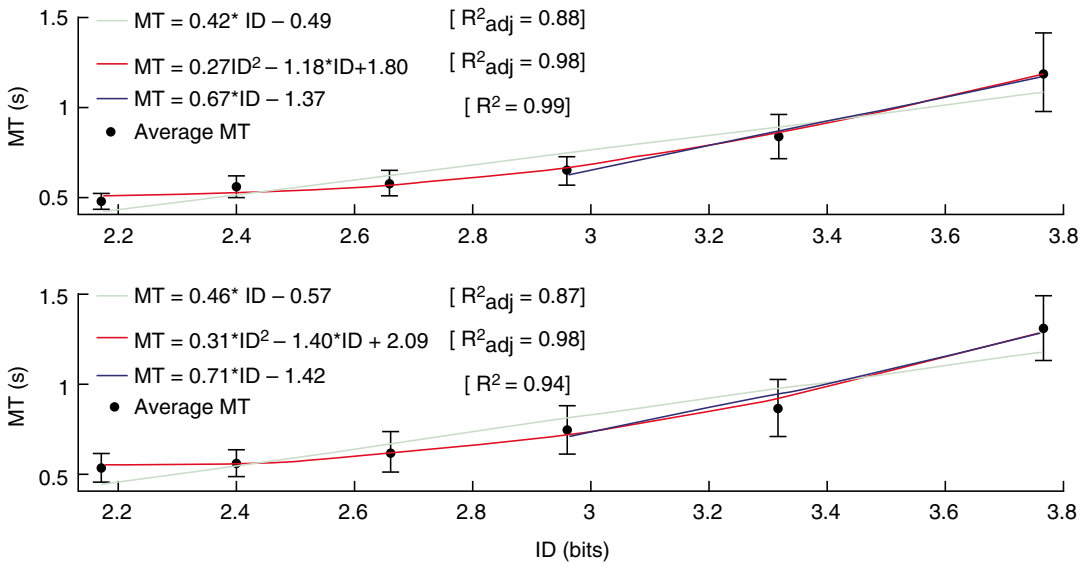

Fig. 20.4 Movement time as dependent of Fitts' index of difficulty, averaged across subjects for dorsiflexion (*up*) and plantar flexion (*bottom*) ankle movements. *Error bars* correspond to 95 % precision uncertainty values

[84–86]. However, Fitts' law has been shown to hold in tasks where no visual feedback of the target and the moving limb was available; this excludes visual corrective mechanisms [87]. Whether Fitts' law emerges at the level of motor planning or at that of movement correction is an ongoing research question.

20.4.4 Stereotypical Ankle Speed Profile

Given the importance of active participation during therapy, we have translated the concept of adaptive assist-as-needed robotic therapy, introduced for the UE [69], to our LE rehabilitation devices. For the pediAnklebot, our algorithm identifies the ability of young kids to point with their ankle [88], and then in line with Fitts' law, we alter the speed of the gameplay and the size of the target. The goal is to initially track and eventually challenge the children [24, 88]. Our adaptive games have embedded the assumption that ankle movements follow a minimum jerk profile [67, 89]. However, to our knowledge, no study had ever modeled ankle pointing movements. To mitigate the lack of descriptive models for ankle pointing movement, we tested whether the CNS has developed distinct control strategies for the ankle. We tested a multitude of existing kinematic models, initially developed to describe simple UE movements, and determined if any were competent to describe ankle pointing movements. The ankle presents a second fundamental constraint for our modeling purposes: Ankle and wrist movements are defined as finite spatial rotations [90–92], which do not form a vector space. We selected the same nineteen models selected by Plamondon et al. [93] and Stein et al. [94] used in reaching movements and wrist modeling [92]. We recorded and analyzed the speed profiles of target-directed discrete ankle pointing movements by young healthy adults. For each movement and model, we used a nonlinear, least-squares optimization procedure to extract a set of parameters that minimized the error between the experimental data and the reconstructed speed profiles. The outlines indicate a noteworthy similarity between the top performing models of ankle pointing movements and the ones previously found for the upper extremities both during arm reaching [93] and wrist pointing movements

[92]. The top performers included the support-bounded lognormal model that has a neurophysiological basis (the lgnb is derived as converging behavior of a system of a sequentially acting cascade of velocity generators [93, 95–97]) and the beta model that has a kinematic-oriented basis and has been successfully used in upper-extremity studies with normal subjects and patients [68]. The same model can be applied to different "human" hardware, perhaps revealing a key invariant in human motor control.

20.4.5 Ankle Pointing Movements: Reaction Time

The connection between reaction time (RT) measurements and the underlying neurophysiological processes has been known since 1868 [98] and formulated as a robust model by Hick and Hyman [99, 100]. According to the Hick-Hyman law, there is a positive linear relationship between the response latency, T, and the stimulus information. Using the measure of information entropy [101], the average T can be approximated by:

$$T = a + b\sum \frac{n}{i} p_i \log_2 \left(\frac{1}{p_i} + 1 \right),$$

where P_i refers to the probability of the i^{th} stimulus-response (S-R) alternative, n is the number of S-R alternatives, and *a, b* are empirically determined constants. For $n = 0$, there is one S-R and subjects execute a simple RT experiment; for $n \geq 1$, there are n S-R alternatives and subjects execute a choice RT experiment. Simple RT in healthy subjects averages 220 ms [102], whereas a typical average choice RT increases by 100 ms per doubling of the S-R alternatives [103]. As the time for motor preparation and response is the same across simple and choice RT experiments [104], differences in RT are attributed to processing time.

RT is a well-studied behavioral indicator of neurological integrity including cognitive motor function. Significant delays in RT measures have been found in basal ganglia disorders, such as Parkinson's disease (PD) [105–107] and Huntington's disease [108], and are commonly related to a deficit in motor planning [109, 110]. RT deficits have also been used to assess the severity of cognitive dysfunction, such as in Alzheimer's disease [111, 112] and mild cognitive impairment (MCI) [113] in adults as well as cerebral palsy (CP) [114, 115], autism [116], attention deficit hyperactivity disorder [117, 118], and dyslexia [119] in children. A recent shift of interest from RT slowing to intraindividual RT variability over the trials of a given task has also linked RT to structural and functional brain characteristics, such as white matter degradation [120, 121], disconnectivity in associated pathways [122], impaired top-down executive and attentional control processes [123], cognitive disorder, neurotransmitter dysfunction, fatigue, and stress [124]. Interestingly, impaired RTs appear responsive to intervention. RT has been used to quantify restoration of motor functions according to the given cognitive contexts in PD patients treated with deep brain stimulation [125]. In addition, exercise and practice improve simple and choice RT in both young and older adults [126–129]. RT has been studied extensively in the past but never before in the ankle.

In the design of the games that we developed for the pediAnklebot, we have embedded ankle discrete movements for simple and choice RT up to 4 S-R (2 bits) [see Figs. 20.2, 20.3, 20.4, and 20.5, 88]. RT shows a great potential to be integrated into our adaptive assist-as-needed robotic therapy delivered to both the upper and lower limbs of CP children [69, 77]. Establishing a speed-accuracy trade-off in human ankle movement can be coupled with the metrics anticipated to quantify separately the ability to move fast and accurately. This will allow for better personalization of the therapy both in terms of adapting the therapeutic parameters and assessing the response to treatment.

We combined an experimental data analysis with diffusion modeling of ankle RT, which revealed interesting similarities and important differences in controlling the ankle joints.

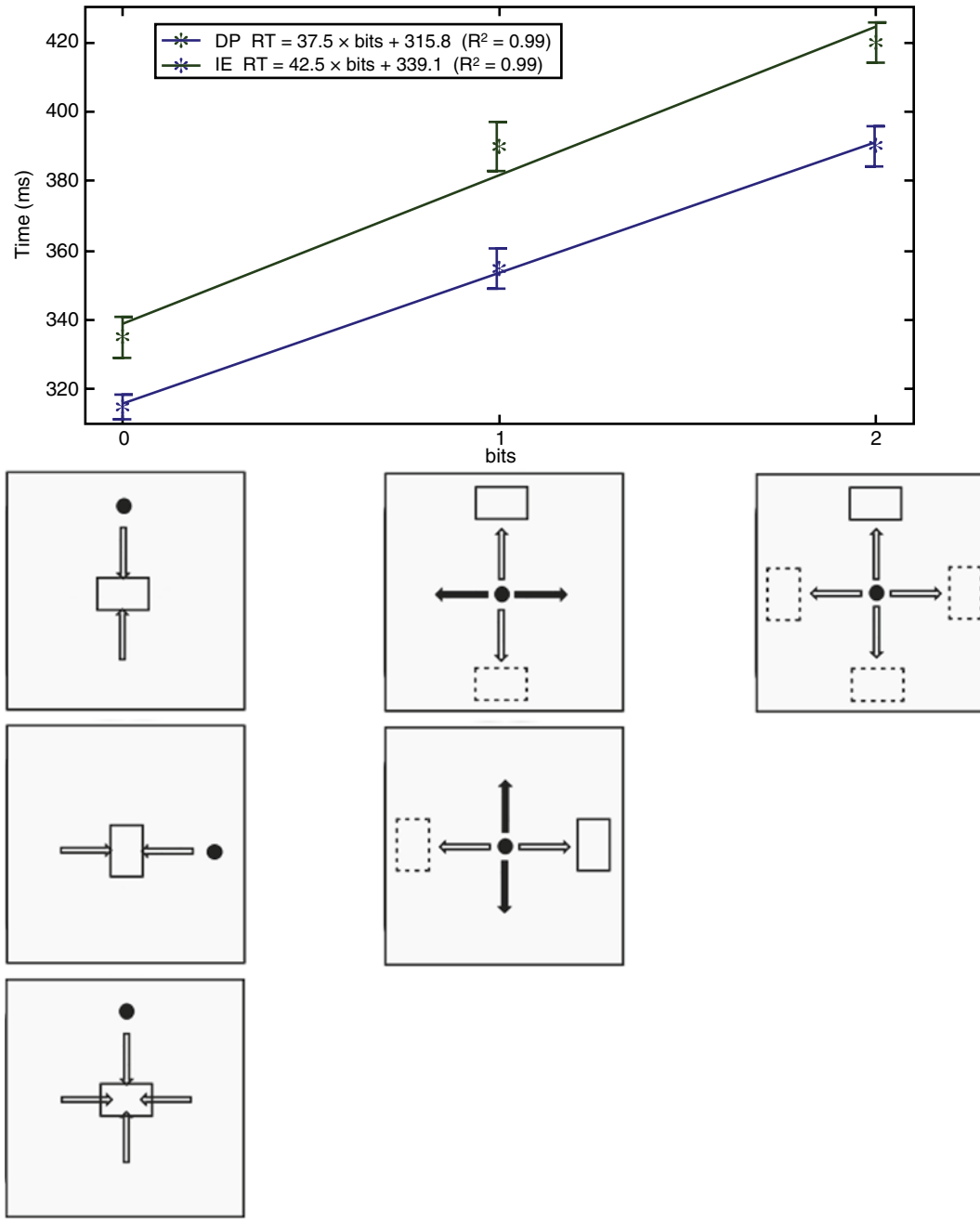

Fig. 20.5 Average RT as a function of bits of information, for DP and IE ankle movements (*upper panel*). *Error bars* correspond to standard errors; the three different configurations that the subjects played by moving their ankle in DP or IE direction correspond to 0 bits (simple), 1 bit (2-choice task), and 2 bits (4-choice task) (*lower panel*)

Specifically, the goals of this study were four. The first was to test whether the Hick-Hyman law applied to ankle movements. The second goal was to determine whether the slope and intercept of the Hick-Hyman law changed systematically between DP and IE. The third goal was to determine whether RT changed with spatial accuracy constraints, i.e., visually evoked and visually

guided ankle movements toward targets with different widths. This question is important as behavioral studies in UE suggest that spatially precise movements restrict control to the contralateral hemisphere in unilateral and bilateral movements [130, 131]. These findings are reinforced by neural studies indicating that there are cortical cells responsible for controlling movement precision and that the involvement of these cells is based on a selective mechanism dependent on task requirements [132]. The fourth goal was to explain any systematic relationship found in RT between DP and IE movements by fitting a structured model to the experimental data and using it as a basis for possible neurophysiological explanations.

RT increased as a linear function of potential target stimuli, as would be predicted by Hick-Hyman law. The intercept in the regression was significantly smaller in dorsal-plantar (DP) than in inversion-eversion (IE) direction. To explain the difference, we used a hierarchical Bayesian estimation of Ratcliff's (1978) diffusion model parameters and divided processing time into cognitive components. The hierarchical Bayesian model gave a good account of RTs, their distribution, and accuracy values and explained the difference between the RT in DP and IE directions. The model also proposed that there was no systematic change in nondecision processing time or drift rate when spatial accuracy constraints were altered. Thus, RT was not found to change with spatial accuracy constraints defined by the width of the target in the direction of ankle movement.

Our study revealed an interesting similarity and an important difference between DP and IE movements of the ankle. The similarity is that the RTs measured in the ankle increased equally with the number of stimuli (Fig. 20.5). The important difference is that the cognitive components that affect RT seem to have a different effect when the ankle movement is controlled by the subtalar rather than the talocrural joint. Our analysis using the hierarchical Bayesian diffusion model gave behavioral and neurophysiological insights on the processing components that seem to affect RT differences measured in DP and IE ankle movements [72]. This result suggests that it may be helpful to look at the effects of LE rehabilitation, for each joint separately, at least in the ankle, or limit the number of potential targets displayed at any particular time.

20.4.6 Ankle Mechanical Impedance

Discrete and rhythmic movements may provide a basis for unconstrained movements, but intermittent contact and physical interaction are an essential element of locomotion. To account for it, a third class of dynamic primitives is required, mechanical impedance. Loosely speaking, mechanical impedance is a generalization of stiffness to encompass nonlinear dynamic behavior [134]. Mechanical impedance is an intrinsic property that emerges solely from the dynamics of the neuro-mechanical system supporting the foot. It is completely independent of contact and exhibits the robustness we require for a dynamic primitive.

Modulating mechanical impedance is a particularly effective way to control interaction, and it is an essential dynamic primitive for locomotion [135–137]. 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 [138, 139], and there is increasing evidence that modulation of ankle stiffness is the primary mechanism for adjusting leg stiffness under a variety of circumstances [139]. Others have shown that the non-disabled human ankle appears to change stiffness characteristics as gait speed changes [140]. Further, there is evidence that adequate ankle joint stiffness is critical during the single-support phase to control forward and downward body momentum [141]. Tracking ankle mechanical impedance in neurologically impaired individuals over the course of a therapy or intervention program may yield better characterization and assessment of a patient's improvement [142].

For the estimation of the multivariable mechanical impedance, a wide-bandwidth pseu-

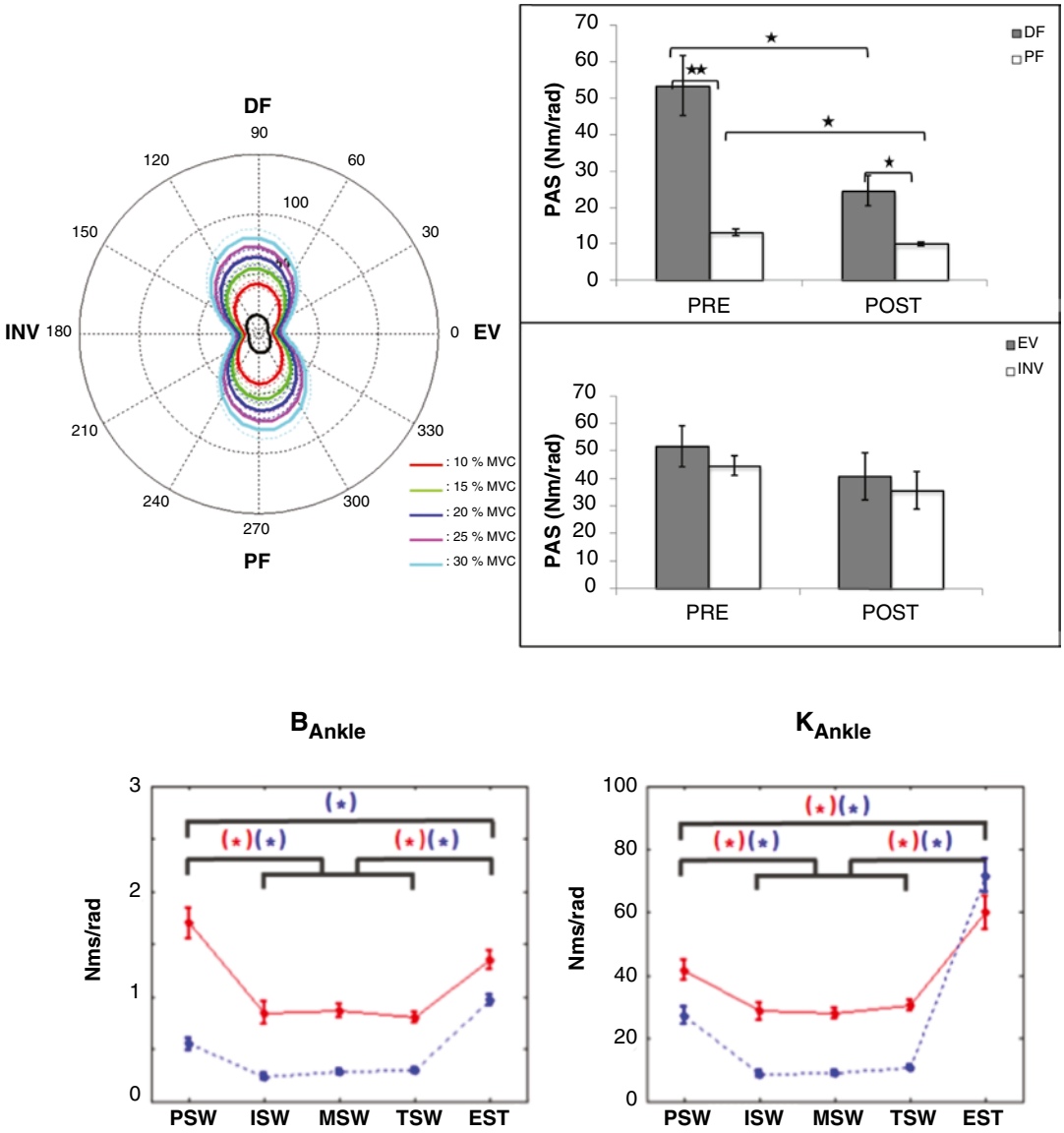

Fig. 20.6 *Top left panel*: Directional variation of ankle stiffness when tibialis anterior is active from 10 to 30% MVC. Results were obtained from measurements of dynamic ankle mechanical impedance. *Dark solid bands*: Mean of 10 young healthy subjects. *Thin dotted bands*: Mean ± SE. *Top right panels* show the ankle stiffness at admission (PRE) and at discharge (POST) after 18 Anklebot pointing therapy sessions. Data from ten persons with chronic gait impairment due to stroke show significant changes of stiffness with training. *Bottom row*: Representative time-varying ankle parameters of a healthy subject (BAnkle, damping; KAnkle, stiffness) across gait phases: *PSW* pre-swing, *ISW* initial swing, *MSW* mid-swing, *TSW* terminal swing, *EST* early stance. *Red solid line*: Dorsi-plantarflexion direction, *blue dash line*: inversion-eversion direction. Mean ± 1SE is presented. Asterisks denote statistical difference (significance $p<0.05$)

dorandom vibratory force can be applied continuously and the resulting motion measured. Due to the precision of our instrumentation, impedance identification can be achieved with unobtrusively small forces [133, 143]. We can identify the time-varying impedance at the ankle during multiple and distinct conditions [144] (Fig. 20.6).

20.4.7 Translating to Practice: Training in Seated Position

Initial clinical results with stroke survivors with chronic hemiparetic gait who underwent a 6-week interactive seated Anklebot training program were quite promising [14]. 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 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. Task difficulty (i.e., target locations on the screen) was initially set proportional to baseline deficit severity (i.e., paretic ankle active range of motion). Training parameters (i.e., target locations, speed) were adjusted every 2 weeks based on individual subject performance. Figure 20.7 shows the training and Table 20.2 shows subject's changes with training. 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 in key aspects of walking function.

Of course, we must take this pilot study result 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 this is a noncontrolled study.

Similar results were observed when training children with cerebral palsy (CP) in seated position. Table 20.3 below shows example of a feasibility study with children age 7–11 with CP that trained during 8 weeks (two times per week) for an hour with the pediatric Anklebot. We observed promising changes in all metrics with the change in the 6-min walk test (6MWT) getting within striking distance of the minimum clinical important difference (MCID) of 54 m [145]. Ultimately, these studies will allow us to better understand how to tailor lower-extremity therapy and how to change the perception that robotics for the lower extremity are still in its "infancy" [1] (Table 20.4).

20.4.8 Translating to Practice: MIT-Skywalker

Here we report on our initial feasibility study in which the MIT-Skywalker was employed to deliver three distinct modes of training in line with our model of walking: rhythmic, discrete, and balance.

20.4.8.1 Rhythmic Training Mode

The timing of the track drops is determined by the vision system estimating the position of the heel on the track. When a minimum x-position is found (indicating the onset of patient-directed swing phase), a signal is sent to drop the track. In the interest of a quick but soft drop, the sagittal plane drive was programmed to drop 2.5° (approx. 3.3 cm below the horizontal plane at the mid-frontal plane) and back to horizontal in 0.7 s. Acceleration of the initial drop was four times the deceleration at the end of the perturbation, resulting in a soft feel on heel strike. Our initial target of 0.4 s for swing was based on healthy gait at 2 m/s. Training speeds for study participants were mostly done below or at 1 m/s resulting in longer swing times of the paretic limb. The soft feel of the final track movement was comfortable

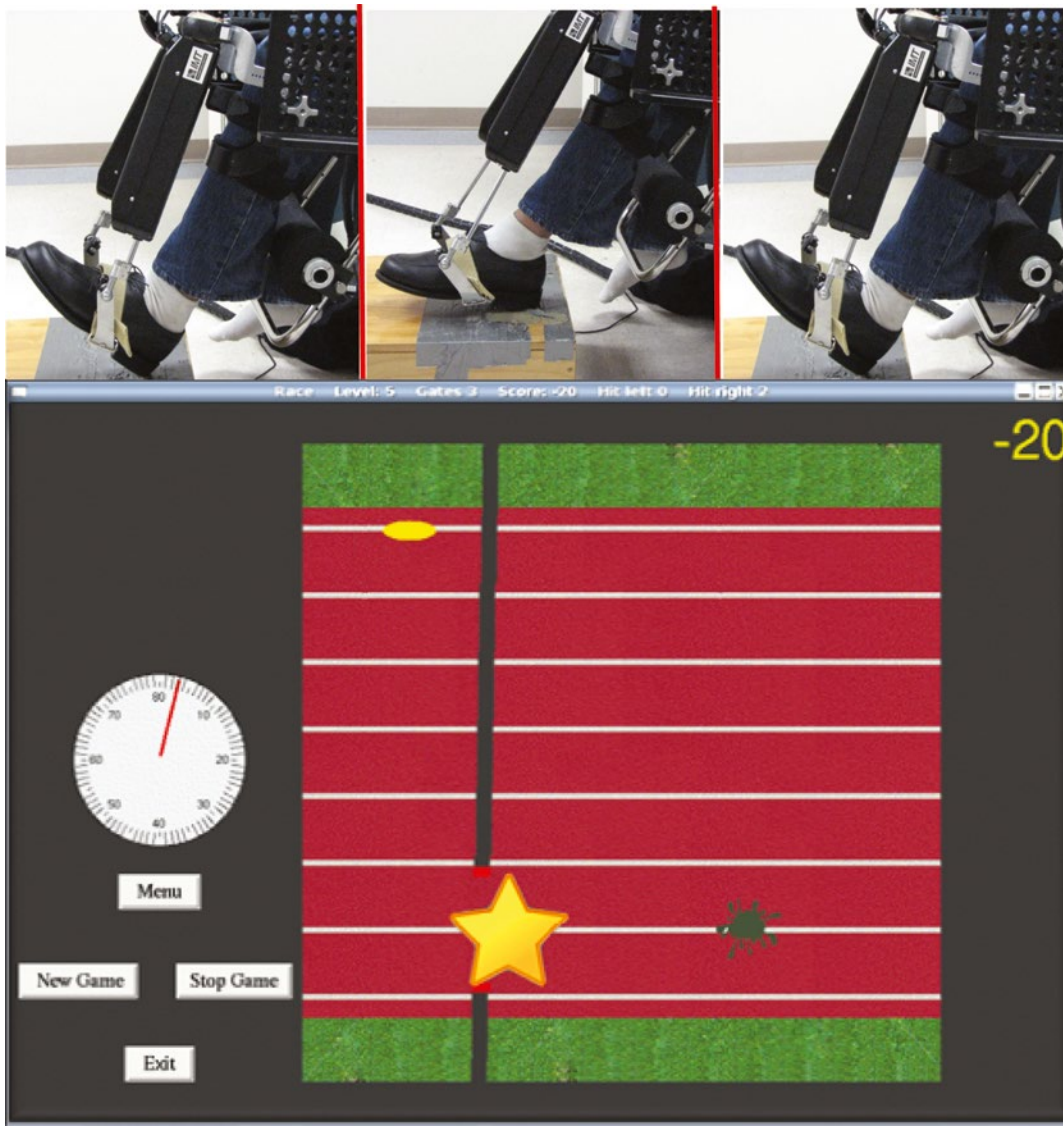

Fig. 20.7 The *upper panels* depict a target moving from *right to left* across the screen as shown by the *arrows* (which are not part of the actual video display). The *oval-shaped* cursor is moved vertically by corresponding changes in dorsi- and plantarflexion movements, as depicted in lower panels. 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 plantar- and dorsiflexion. The level of difficulty can be programmed by altering the speed of target progression across the screen, by 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

for subjects even if the foot hit the track early. When delivering the rhythmic program, three additional goals were implemented for some participants.

20.4.8.2 Speed-Enhancing Programs

On top of the standard rhythmic protocol described above, the speed-enhancing programs focused on raising participant's training speed.

Table 20.2 Selected spatiotemporal gait parameters before and after 6 weeks of seated ankle robot training (mean ± SE)

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
Double support (%)	46.6 ± 4.6	40.3 ± 4.0	−14 %	0.010

P paretic

Table 20.3 Demographics and outcome of the feasibility study. Children improved in the TUG. Children with single-side paresis improved the outcome in the 6MWT. The child with bilateral paresis who trained unilaterally did not. It is assumed that a change of 54 m in the 6MWT corresponds to the minimal clinical important difference [145]

Age y.o.	Gender	CP type	Trained side	6MWT admission (m)	6MWT change (m)	6MWT change (m)	TUG adm (s)	6TUG disch (s)	6TUG change (s)
9	Male	Bilateral paresis	Left	513	491	−22	13.2	11.8	−1.4
11	Female	Left paresis	Left	438	474	36	8.6	7.8	−0.8
7	Female	Right paresis	Right	405	491	86	11.9	10.7	−1.2
7	Female	Left paresis	Left	387	405	18	10.9	9.7	−1.2

Table 20.4 Clinical evaluations before and after 1-month training

	Participant 1		Participant 2		Participant 3	
	Initial	Final	Initial	Final	Initial	Final
6-min walk test (m)	478	546	200	209	213	204
SSV (m/s)	0.89	1.17	0.50	0.50	0.24	0.22
MSV (m/s)	1.50	1.65	0.59	0.63	0.26	0.26
Berg balance test	54	55	10	37	52	55

20.4.8.3 Asymmetric Speed Programs

The asymmetric speed programs focused on altering the step-length asymmetry via speed distortion (asymmetric split-belt speeds).

20.4.8.4 Vision Distortion Programs

A visual display presented in front of patients distorted the perceived length of each step while instructing participants to equalize the distorted steps to induce changes in step-length symmetry as seen in [40].

20.4.8.5 Discrete Training Mode

The MIT-Skywalker is the first rehabilitation robot to introduce discrete training for post-stroke lower-extremity training. In this mode of training, the treadmill tracks operate in position mode. A random target is projected onto the treadmill track from an overhead projector (Fig. 20.8). The patient is instructed to land the heel on the target. Once the vision system recognizes that the patient's heel has landed, the algorithm compares the x-position of the heel with the x-position of the target to determine if the target was hit. The treadmill track gently moves the heel back to a neutral position underneath the body. A half second later, a new target is displayed. The number of successfully hit targets and the success rate is displayed at the front end of the treadmill, and the level of difficulty (target

Fig. 20.8 Discrete training mode stepping. A target is shown (*white bar*). The participant locates the target position with the heel. The success rate can be seen in front of the participant to keep her engaged in the training session

Fig. 20.9 View from the MIT-Skywalker. A large screen is used to display games and real-time webcam video of the subject

size) and location can be adjusted. Patients considered this simple game very engaging.

20.4.8.6 Balance Training

The MIT-Skywalker system is capable of imposing perturbations in both frontal and sagittal planes. This is achieved by lowering or raising the walking surface or rotating the whole system in the frontal plane. In this feasibility study, only frontal plane perturbations were used with a stereotyped sinusoidal profile ranging from 0 degrees to 2.5 degrees and back to 0 degrees in 1.4 s. This is a fairly gentle profile for a healthy subject but challenging for our patients. The initial rotational direction was presented randomly and perturbation timing was randomized between 2 and 4 s. For stroke and cerebral palsy adult participants with a moderate impairment, the frontal plane perturbations were used in concert with the rhythmic program. For our most severe participant, the frontal plane perturbations were used exclusively to develop balance during standing alone. We employed a video game in the form of a surfer (Fig. 20.9) to indicate the frontal plane rotation.

Before and after each session, participants in this feasibility study were asked to walk for approximately 30 s to 1 min while the MIT-Skywalker vision system recorded hip and knee kinematics. During training, kinematics and heart rate were also recorded. Clinical evaluations were performed by a physical therapist before and after the 1-month long study at least 1 day removed from therapy. Subjects underwent clinical evaluations that included a 6-min walk test, self-selected and maximum walking velocity tests (measured as the average velocity of the middle 6 m of a 10 m walk test), the Berg balance scale, the Tardieu scale, and sagittal plane kinematic analysis using a 3D Guidance trakSTAR system (Ascension Technology Co., Milton, VT). Furthermore, we monitored heart rate. We observed an average increase in heart rate between the standing and training periods of 14.7 bpm for rhythmic training sessions. Each training block lasted approximately 5 min, and each rest period was between 1 and 5 min depending on the state of the participant (Fig. 20.10).

This initial study marks the first time the MIT-Skywalker system has been tested with persons with neurological impairments. This initial study demonstrated the feasibility of the three different training routines and showed their promise for the rehabilitation therapy of various disabilities (stroke and cerebral palsy) at three impairment levels. MIT-Skywalker showed its versatility to accommodate each. Further, each participant was able to make substantial gains in one or more of the tested parameters even though the injury onset was more than 5 years in the past (in the case of our CP patients, the injury was over 25 and 56 years prior).

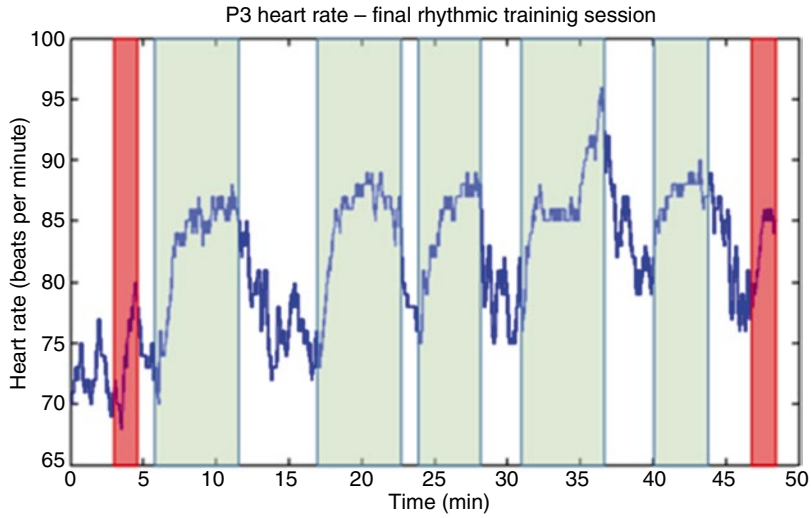

Fig. 20.10 Heart rate during training. *Red* areas represent the two diagnostic phases when the participant is walking at 0.22 m/s. The *green* areas represent the rhythmic training blocks with treadmill speed at 0.45 m/s

That said, these is just a feasibility study, and proper clinical controlled studies must be performed to better understand how to tailor lower-extremity therapy and how to move robotics for the lower extremity beyond its "infancy" [1].

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: the Anklebot and the Skywalker, discussing our initial studies that aim to determine the basic psychophysics of lower-extremity motor control, which suggested 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 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 don't 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, i.e., joint based, non-task specific) or functionally based approaches (as in body-weight-supported treadmill training, i.e., whole body, task specific) and to whom: severe,

moderate, mild strokes? How can we predict potential responders vs. nonresponders based on stratification of impairments and deficit severities? What types of serious games should be designed and which patients' behavioral metrics should be used to drive these games? 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 guidelines from the American Heart Association, from the Veterans Administration, and the Department of Defense will endorse lower-extremity robotics as well.

Acknowledgment This work was supported in part by NIH grant #1 R01-HD045343, the Veterans Administration Baltimore Medical Center "Center of Excellence on Task-Oriented Exercise and Robotics in Neurological Diseases" B3688R, the Cerebral Palsy International Research Foundation (CPIRF) and the Niarchos Foundation, and Toyota Motor Corporation's Partner Robot Division. H. I. Krebs and N. Hogan are coinventors in several MIT-held patents for the robotic technology. They hold equity positions in Interactive Motion Technologies, Watertown, MA, USA, the company that manufactures this type of technology under license to MIT.

References

1. Miller EL, Murray L, Richards L, Zorowitz RD, Bakas T, Clark P, Billinger SA, N. American Heart Association Council on Cardiovascular, C. the Stroke. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association. Stroke. 2010;41:2402–48.
2. G. Management of Stroke Rehabilitation Working. VA/DOD clinical practice guideline for the management of stroke rehabilitation. J Rehabil Res Dev. 2010;47:1–43.
3. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke: updated evidence. Stroke. 2013;44: e127–8.
4. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39: 1786–92.
5. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, Hornby TG. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23:5–13.
6. Dietz V. Spinal cord pattern generators for locomotion. Clin Neurophysiol. 2003;114:1379–89.
7. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Cen S, Hayden SK, Team LI. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011;364:2026–36.
8. Dobkin BH, Duncan PW. Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil Neural Repair. 2012; 26:308–17.
9. Hogan N, Sternad D. Dynamic primitives in the control of locomotion. Front Comput Neurosci. 2013;7:71.
10. Hogan N, Sternad D. On rhythmic and discrete movements: reflections, definitions and implications for motor control. Exp Brain Res. 2007;181:13–30.
11. Mussa-Ivaldi FA, Hogan N, Bizzi E. Neural, mechanical, and geometric factors subserving arm posture in humans. J Neurosci. 1985;5:2732–43.
12. Schaal S, Sternad D, Osu R, Kawato M. Rhythmic arm movement is not discrete. Nat Neurosci. 2004;7:1136–43.
13. Ikegami T, Hirashima M, Taga G, Nozaki D. Asymmetric transfer of visuomotor learning between discrete and rhythmic movements. J Neurosci. 2010;30:4515–21.
14. Forrester LW, Roy A, Krebs HI, Macko RF. Ankle training with a robotic device improves hemiparetic gait after a stroke. Neurorehabil Neural Repair. 2011;25(4):369–77.
15. Forster A, Young J. Incidence and consequences of falls due to stroke: a systematic inquiry. BMJ. 1995;311:83–6.
16. Ramnemark A, Nyberg L, Borssen B, Olsson T, Gustafson Y. Fractures after stroke. Osteoporos Int. 1998;8:92–5.
17. Dennis MS, Lo KM, McDowall M, West T. Fractures after stroke: frequency, types, and associations. Stroke. 2002;33:728–34.

18. Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. Stroke. 2001;32:702–6.
19. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Team LI. Protocol for the Locomotor Experience Applied Post-stroke (LEAPS) trial: a randomized controlled trial. BMC Neurol. 2007;7:39.
20. Hogan N, Sternad D. Dynamic primitives of motor behavior. Biol Cybern. 2012;106:727–39.
21. Roy A, Krebs HI, Williams DJ, Bever CT, Forrester LW, Macko RM, Hogan N. Robot-aided neurorehabilitation: a novel robot for ankle rehabilitation. Robot IEEE Trans. 2009;25:569–82.
22. Susko TG and Massachusetts Institute of Technology. Department of mechanical engineering. MIT Skywalker: a novel robot for gait rehabilitation of stroke and cerebral palsy patients.
23. Cai LL, Fong AJ, Otoshi CK, Liang Y, Burdick JW, Roy RR, Edgerton VR. Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. J Neurosci. 2006;26:10564–8.
24. Michmizos K, Rossi S, Castelli E, Cappa P, Krebs H. Robot-aided neurorehabilitation: a pediatric robot for ankle rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2015;23(6):1056–67.
25. Robertson DG, Winter DA. Mechanical energy generation, absorption and transfer amongst segments during walking. J Biomech. 1980;13:845–54.
26. Sawicki GS, Ferris DP. A pneumatically powered knee-ankle-foot orthosis (KAFO) with myoelectric activation and inhibition. J Neuroeng Rehabil. 2009;6:23.
27. Eng JJ, Winter DA. Kinetic analysis of the lower limbs during walking: what information can be gained from a three-dimensional model? J Biomech. 1995;28:753–8.
28. Teixeira-Salmela LF, Nadeau S, Milot MH, Gravel D, Requiao LF. Effects of cadence on energy generation and absorption at lower extremity joints during gait. Clin Biomech (Bristol, Avon). 2008;23:769–78.
29. Umberger BR, Martin PE. Mechanical power and efficiency of level walking with different stride rates. J Exp Biol. 2007;210:3255–65.
30. Perry J, Davids JR. Gait analysis: normal and pathological function. J Pediatr Orthop. 1992;12(6):815.41
31. Neptune RR, Kautz SA, Zajac FE. Contributions of the individual ankle plantar flexors to support, forward progression and swing initiation during walking. J Biomech. 2001;34:1387–98.
32. Meinders M, Gitter A, Czerniecki JM. The role of ankle plantar flexor muscle work during walking. Scand J Rehabil Med. 1998;30:39–46.
33. Gottschall JS, Kram R. Energy cost and muscular activity required for propulsion during walking. J Appl Physiol (1985). 2003;94:1766–72.
34. Roy A, Krebs HI, Williams DJ, Bever CT, Forrester LW, Macko RM, Hogan N. Robot-aided neurorehabilitation: a novel robot for ankle rehabilitation. IEEE Trans Robot. 2009;25:569–82.
35. Khanna I, Roy A, Rodgers MM, Krebs HI, Macko RM, Forrester LW. Effects of unilateral robotic limb loading on gait characteristics in subjects with chronic stroke. J Neuroeng Rehabil. 2010;7:23.
36. Rossi S, Colazza A, Petrarca M, Castelli E, Cappa P, Krebs HI. Feasibility study of a wearable exoskeleton for children: is the gait altered by adding masses on lower limbs? PLoS One. 2013;8:e73139.
37. Collins S, Ruina A, Tedrake R, Wisse M. Efficient bipedal robots based on passive-dynamic walkers. Science. 2005;307:1082–5.
38. Bosecker CK, MIT-Skywalker HI. Proc IEEE 11th international conference on rehabilitation robotics. 2009:542–9.
39. Artemiadis PK, Krebs HI. On the control of the MIT-skywalker. Conf Proc IEEE Eng Med Biol Soc. 2010;2010:1287–91.
40. Kim SJ, Krebs HI. Effects of implicit visual feedback distortion on human gait. Exp Brain Res. 2012;218:495–502.
41. Seiterle S, Susko T, Artemiadis PK, Riener R, Krebs H.I. Interlimb coordination in body-weight supported locomotion: a pilot study. J Biomech. 2015;48:2837–43.
42. Bernshtein NA. The co-ordination and regulation of movements. 1st ed. Oxford: Pergamon Press; 1967.
43. Bizzi E, Tresch MC, Saltiel P, d'Avella A. New perspectives on spinal motor systems. Nat Rev Neurosci. 2000;1:101–8.
44. Grillner S, Wallen P. Central pattern generators for locomotion, with special reference to vertebrates. Annu Rev Neurosci. 1985;8:233–61.
45. Bussel B, Roby-Brami A, Neris OR, Yakovleff A. Evidence for a spinal stepping generator in man. Paraplegia. 1996;34:91–2.
46. Brown TG. The intrinsic factors in the act of progression in the mammal. Proc R Soc Lond Ser B Containing Pap Biol Charact. 1911;84:308–19.
47. Duysens J, Van de Crommert HW. Neural control of locomotion: the central pattern generator from cats to humans. Gait Posture. 1998;7:131–41.
48. Grasso R, Ivanenko YP, Zago M, Molinari M, Scivoletto G, Castellano V, Macellari V, Lacquaniti F. Distributed plasticity of locomotor pattern generators in spinal cord injured patients. Brain. 2004;127:1019–34.
49. Ivanenko YP, Cappellini G, Dominici N, Poppele RE, Lacquaniti F. Modular control of limb movements during human locomotion. J Neurosci. 2007;27:11149–61.
50. Scivoletto G, Ivanenko Y, Morganti B, Grasso R, Zago M, Lacquaniti F, Ditunno J, Molinari M. Plasticity of spinal centers in spinal cord injury patients: new concepts for gait evaluation and training. Neurorehabil Neural Repair. 2007;21:358–65.
51. Dominici N, Ivanenko YP, Cappellini G, d'Avella A, Mondì V, Cicchese M, Fabiano A, Silei T, Di Paolo A, Giannini C, Poppele RE, Lacquaniti F. Locomotor primitives in newborn babies and their development. Science. 2011;334:997–9.
52. Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G, Green BA. Involuntary stepping after

chronic spinal cord injury. Evidence for a central rhythm generator for locomotion in man. Brain. 1994;117(Pt 5):1143–59.
53. Sinkjaer T, Andersen JB, Ladouceur M, Christensen LO, Nielsen JB. Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man. J Physiol. 2000;523(Pt 3):817–27.
54. Nakazawa K, Kawashima N, Akai M, Yano H. On the reflex coactivation of ankle flexor and extensor muscles induced by a sudden drop of support surface during walking in humans. J Appl Physiol (1985). 2004;96:604–11.
55. van der Linden MH, Marigold DS, Gabreels FJ, Duysens J. Muscle reflexes and synergies triggered by an unexpected support surface height during walking. J Neurophysiol. 2007;97:3639–50.
56. Af Klint R, Nielsen JB, Sinkjaer T, Grey MJ. Sudden drop in ground support produces force-related unload response in human overground walking. J Neurophysiol. 2009;101:1705–12.
57. Marigold DS, Patla AE. Adapting locomotion to different surface compliances: neuromuscular responses and changes in movement dynamics. J Neurophysiol. 2005;94:1733–50.
58. Duysens J, Bastiaanse CM, Smits-Engelsman BC, Dietz V. Gait acts as a gate for reflexes from the foot. Can J Physiol Pharmacol. 2004;82:715–22.
59. Nielsen JB. How we walk: central control of muscle activity during human walking. Neuroscientist. 2003;9:195–204.
60. Bonnet M, Gurfinkel S, Lipchits MJ, Popov KE. Central programming of lower limb muscular activity in the standing man. Agressologie. 1976; 17(SPECNO):35–42.
61. Debaere F, Swinnen SP, Beatse E, Sunaert S, Van Hecke P, Duysens J. Brain areas involved in interlimb coordination: a distributed network. Neuroimage. 2001;14:947–58.
62. Netter FH. Atlas of human anatomy. 6th ed. Philadelphia: Saunders/Elsevier; 2014.
63. Waugh A, Grant A. Ross and Wilson anatomy and physiology in health and illness. 12th ed. Edinburgh: Elsevier; 2014.
64. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science. 1996;272:1791–4.
65. Jenkins WM, Merzenich MM. Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. Prog Brain Res. 1987;71:249–66.
66. Soechting JF, Lacquaniti F. Invariant characteristics of a pointing movement in man. J Neurosci. 1981;1:710–20.
67. Flash T, Hogan N. The coordination of arm movements: an experimentally confirmed mathematical model. J Neurosci. 1985;5:1688–703.
68. Krebs HI, Aisen ML, Volpe BT, Hogan N. Quantization of continuous arm movements in humans with brain injury. Proc Natl Acad Sci U S A. 1999;96:4645–9.
69. Krebs HI, Palazzolo JJ, Dipietro L, Ferraro M, Krol J, Rannekleiv K, Volpe BT, Hogan N. Rehabilitation robotics: performance-based progressive robot-assisted therapy. Auton Robot. 2003;15:7–20.
70. Michmizos KP, Krebs HI. Pointing with the ankle: the speed-accuracy trade-off. Exp Brain Res. 2014;232:647–57.
71. Michmizos KP, Vaisman L, Krebs HI. A comparative analysis of speed profile models for ankle pointing movements: evidence that lower and upper extremity discrete movements are controlled by a single invariant strategy. Front Hum Neurosci. 2014;8:962.
72. Michmizos KP, Krebs HI. Reaction time in ankle movements: a diffusion model analysis. Exp Brain Res. 2014;232:3475–88.
73. Emken JL, Reinkensmeyer DJ. Robot-enhanced motor learning: accelerating internal model formation during locomotion by transient dynamic amplification. IEEE Trans Neural Syst Rehabil Eng. 2005;13:33–9.
74. Lam T, Anderschitz M, Dietz V. Contribution of feedback and feedforward strategies to locomotor adaptations. J Neurophysiol. 2006;95:766–73.
75. Fitts PM. The information capacity of the human motor system in controlling the amplitude of movement. J Exp Psychol. 1954;47:381–91.
76. Fitts PM, Peterson JR. Information capacity of discrete motor responses. J Exp Psychol. 1964;67: 103–12.
77. Krebs HI, Rossi S, Kim SJ, Artemiadis PK, Williams D, Castelli E, Cappa P. Pediatric anklebot. IEEE Int Conf Rehabil Robot. 2011;2011:5975410.
78. Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neurorehabilitation. IEEE Trans Rehabil Eng. 1998;6:75–87.
79. Krebs HI, Hogan N. Robotic therapy: the tipping point. Am J Phys Med Rehabil. 2012;91:S290–7.
80. Fasoli SE, Ladenheim B, Mast J, Krebs HI. New horizons for robot-assisted therapy in pediatrics. Am J Phys Med Rehabil. 2012;91:S280–9.
81. Krebs HI, Fasoli SE, Dipietro L, Fragala-Pinkham M, Hughes R, Stein J, Hogan N. Motor learning characterizes habilitation of children with hemiplegic cerebral palsy. Neurorehabil Neural Repair. 2012;26:855–60.
82. Woodworth RS. Accuracy of voluntary movement. Psychol Rev. 1899;3:13.
83. Meyer DE, Abrams RA, Kornblum S, Wright CE, Smith JE. Optimality in human motor performance: ideal control of rapid aimed movements. Psychol Rev. 1988;95:340–70.
84. Crossman ER, Goodeve PJ. Feedback control of hand-movement and Fitts' law. Q J Exp Psychol A. 1983;35:251–78.
85. Novak KE, Miller LE, Houk JC. The use of overlapping submovements in the control of rapid hand movements. Exp Brain Res. 2002;144:351–64.
86. Elliott D, Helsen WF, Chua R. A century later: Woodworth's (1899) two-component model of goal-directed aiming. Psychol Bull. 2001;127:342–57.

87. Wu J, Yang J, Honda T. Fitts' law holds for pointing movements under conditions of restricted visual feedback. Hum Mov Sci. 2010;29:882–92.
88. Michmizos KP, Krebs HI. Serious games for the pediatric anklebot. In: Biomedical robotics and biomechatronics (BioRob), 2012 4th IEEE RAS & EMBS international conference on. 2012, p. 1710–14.
89. Michmizos KP, Krebs HI. Assist-as-needed in lower extremity robotic therapy for children with cerebral palsy. In: Biomedical robotics and biomechatronics (BioRob), 2012 4th IEEE RAS & EMBS international conference on. 2012, p. 1081–86.
90. Pretterklieber ML. Anatomy and kinematics of the human ankle joint. Radiologe. 1999;39:1–7.
91. Charles SK, Hogan N. Dynamics of wrist rotations. J Biomech. 2011;44:614–21.
92. Vaisman L, Dipietro L, Krebs HI. A comparative analysis of speed profile models for wrist pointing movements. IEEE Trans Neural Syst Rehabil Eng. 2013;21:756–66.
93. Plamondon R, Alimi AM, Yergeau P, Leclerc F. Modelling velocity profiles of rapid movements: a comparative study. Biol Cybern. 1993;69:119–28.
94. Stein RB, Cody FW, Capaday C. The trajectory of human wrist movements. J Neurophysiol. 1988;59:1814–30.
95. Plamondon R. A theory of rapid movements. In: Stelmach GE, Requin J, editors. Tutorials in motor behavior II. Amsterdam: Distributors for the U.S. and Canada, Elsevier Science Pub. Co; 1992. p. 55–69.
96. Mitnitski AB. Kinematic models cannot provide insight into motor control. Behav Brain Sci. 1997;20:318–19.
97. Plamondon R, Feng CH, Woch A. A kinematic theory of rapid human movement. Part IV: a formal mathematical proof and new insights. Biol Cybern. 2003;89:126–38.
98. Donders FC. On the speed of mental processes. Acta Psychol (Amst). 1969;30:412–31.
99. Hick WE. On the rate of gain of information. Q J Exp Psychol. 1952;4:11–26.
100. Hyman R. Stimulus information as a determinant of reaction time. J Exp Psychol. 1953;45:188–96.
101. Shannon CE, Weaver W. The mathematical theory of communication. Urbana: University of Illinois Press; 1949.
102. Laming DRJ. Information theory of choice-reaction times. London: Academic Press; 1968.
103. Boff KR, Kaufman L, Thomas JP. Handbook of perception and human performance. vol. 2. Cognitive processes and performance, DTIC document. 1994.
104. Miller JO, Low K. Motor processes in simple, go/no-go, and choice reaction time tasks: a psychophysiological analysis. J Exp Psychol Hum Percept Perform. 2001;27:266–89.
105. Brown RG, Jahanshahi M, Marsden CD. Response choice in Parkinson's disease. The effects of uncertainty and stimulus-response compatibility. Brain. 1993;116(Pt 4):869–85.
106. Evarts EV, Teravainen H, Calne DB. Reaction time in Parkinson's disease. Brain. 1981;104:167–86.
107. Goodrich S, Henderson L, Kennard C. On the existence of an attention-demanding process peculiar to simple reaction time: converging evidence from Parkinson's disease. Cogn Neuropsychol. 1989;6: 309–31.
108. Jahanshahi M, Brown RG, Marsden CD. A comparative study of simple and choice reaction time in Parkinson's, Huntington's and cerebellar disease. J Neurol Neurosurg Psychiatry. 1993;56:1169–77.
109. Marsden CD. The mysterious motor function of the basal ganglia: the Robert Wartenberg lecture. Neurology. 1982;32:514–39.
110. Rogers MW, Chan CW. Motor planning is impaired in Parkinson's disease. Brain Res. 1988;438:271–6.
111. Gorus E, De Raedt R, Lambert M, Lemper JC, Mets T. Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer's disease. J Geriatr Psychiatry Neurol. 2008;21:204–18.
112. Martelli M, Barban F, Zoccolotti P, Silveri MC. Slowing of information processing in Alzheimer disease: motor as well as cognitive factors. Cogn Behav Neurol. 2012;25:175–85.
113. Fernaeus SE, Ostberg P, Wahlund LO. Late reaction times identify MCI. Scand J Psychol. 2013;54: 283–5.
114. Chang JJ, Wu TI, Wu WL, Su FC. Kinematical measure for spastic reaching in children with cerebral palsy. Clin Biomech (Bristol, Avon). 2005;20:381–8.
115. Horgan JS. Reaction-time and movement-time of children with cerebral palsy: under motivational reinforcement conditions. Am J Phys Med. 1980;59:22–9.
116. Schmitz N, Daly E, Murphy D. Frontal anatomy and reaction time in autism. Neurosci Lett. 2007; 412:12–7.
117. Leth-Steensen C, Elbaz ZK, Douglas VI. Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. Acta Psychol (Amst). 2000;104: 167–90.
118. Zahn TP, Kruesi MJ, Rapoport JL. Reaction time indices of attention deficits in boys with disruptive behavior disorders. J Abnorm Child Psychol. 1991;19:233–52.
119. King B, Wood C, Faulkner D. Sensitivity to visual and auditory stimuli in children with developmental dyslexia. Dyslexia. 2008;14:116–41.
120. Fjell AM, Westlye LT, Amlien IK, Walhovd KB. Reduced white matter integrity is related to cognitive instability. J Neurosci. 2011;31:18060–72.
121. Tamnes CK, Fjell AM, Westlye LT, Østby Y, Walhovd KB. Becoming consistent: developmental reductions in intraindividual variability in reaction time are related to white matter integrity. J Neurosci. 2012;32:972–82.
122. Moy G, Millet P, Haller S, Baudois S, de Bilbao F, Weber K, Lovblad K, Lazeyras F, Giannakopoulos P,

Delaloye C. Magnetic resonance imaging determinants of intraindividual variability in the elderly: combined analysis of grey and white matter. Neuroscience. 2011;186:88–93.
123. Anstey KJ, Mack HA, Christensen H, Li S-C, Reglade-Meslin C, Maller J, Kumar R, Dear K, Easteal S, Sachdev P. Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. Neuropsychologia. 2007;45:1911–20.
124. MacDonald SW, Li SC, Backman L. Neural underpinnings of within-person variability in cognitive functioning. Psychol Aging. 2009;24:792–808.
125. Mirabella G, Iaconelli S, Modugno N, Giannini G, Lena F, Cantore G. Stimulation of subthalamic nuclei restores a near normal planning strategy in Parkinson's patients. PLoS One. 2013;8:e62793.
126. Baird BJ, Tombaugh TN, Francis M. The effects of practice on speed of information processing using the Adjusting-Paced Serial Addition Test (Adjusting-PSAT) and the Computerized Tests of Information Processing (CTIP). Appl Neuropsychol. 2007;14:88–100.
127. Bisson E, Contant B, Sveistrup H, Lajoie Y. Functional balance and dual-task reaction times in older adults are improved by virtual reality and biofeedback training. Cyberpsychol Behav. 2007;10:16–23.
128. Light KE, Reilly MA, Behrman AL, Spirduso WW. Reaction times and movement times: benefits of practice to younger and older adults. J Aging Phys Act. 1996;4:27–41.
129. Rikli RE, Edwards DJ. Effects of a three-year exercise program on motor function and cognitive processing speed in older women. Res Q Exerc Sport. 1991;62:61–7.
130. Garry MI, Franks IM. Reaction time differences in spatially constrained bilateral and unilateral movements. Exp Brain Res. 2000;131:236–43.
131. Garry MI, Franks IM. Spatially precise bilateral arm movements are controlled by the contralateral hemisphere: evidence from a lateralized visual stimulus paradigm. Exp Brain Res. 2002;142:292–6.
132. Schieppati M, Trompetto C, Abbruzzese G. Selective facilitation of responses to cortical stimulation of proximal and distal arm muscles by precision tasks in man. J Physiol. 1996;491:551–62.
133. Lee H, Krebs HI, Hogan N. Multivariable dynamic ankle mechanical impedance with active muscles. IEEE Trans Neural Syst Rehabil Eng. 2014;22:971–81.
134. Hogan N. Impedance control: an approach to manipulation. ASME J Dyn Syst Meas Control. 1985;107:1–24.
135. Franklin DW, Liaw G, Milner TE, Osu R, Burdet E, Kawato M. Endpoint stiffness of the arm is directionally tuned to instability in the environment. J Neurosci. 2007;27:7705–16.
136. Toffin D, McIntyre J, Droulez J, Kemeny A, Berthoz A. Perception and reproduction of force direction in the horizontal plane. J Neurophysiol. 2003;90:3040–53.
137. Hogan N, Buerger SP. Impedance and interaction control. In: Kurfess TR, editor. Robotics and automation handbook. Boca Raton: CRC Press; 2004. 19:1–24.
138. Ferris DP, Farley CT. Interaction of leg stiffness and surfaces stiffness during human hopping. J Appl Physiol (1985). 1997;82:15–22; discussion 13–4.
139. Ferris DP, Louie M, Farley CT. Running in the real world: adjusting leg stiffness for different surfaces. Proc Biol Sci. 1998;265:989–94.
140. Hansen AH, Childress DS, Miff SC, Gard SA, Mesplay KP. The human ankle during walking: implications for design of biomimetic ankle prostheses. J Biomech. 2004;37:1467–74.
141. Lark SD, Buckley JG, Bennett S, Jones D, Sargeant AJ. Joint torques and dynamic joint stiffness in elderly and young men during stepping down. Clin Biomech (Bristol, Avon). 2003;18:848–55.
142. Selles RW, Li X, Lin F, Chung SG, Roth EJ, Zhang LQ. Feedback-controlled and programmed stretching of the ankle plantarflexors and dorsiflexors in stroke: effects of a 4-week intervention program. Arch Phys Med Rehabil. 2005;86:2330–6.
143. Lee H, Krebs HI, Hogan N. Multivariable dynamic ankle mechanical impedance with relaxed muscles. IEEE Trans Neural Syst Rehabil Eng. 2014;22:1104–14.
144. Lee H, Hogan N. Time-varying ankle mechanical impedance during human locomotion. IEEE Trans Neural Syst Rehabil Eng. 2015;23:755–64.
145. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD. 2005;2:125–9.

Toward Flexible Assistance for Locomotor Training: Design and Clinical Testing of a Cable-Driven Robot for Stroke, Spinal Cord Injury, and Cerebral Palsy

21

Ming Wu and Jill M. Landry

Abstract

A cable-driven locomotor training system (3DCaLT) has been developed to improve the locomotor function in adults following hemispheric stroke or spinal cord injury (SCI) and children with cerebral palsy (CP). A key component of this new system is that it is highly backdrivable and allows for variation in the trajectory of the gait pattern. In addition, this new robotic system can provide controlled forces in both the sagittal and frontal planes at targeted phases of gait. The new robotic trainer uses a lightweight cable driven with controlled forces applied to the pelvis and leg (rather than a controlled trajectory). The 3DCaLT is compliant and gives patients the freedom to voluntarily move their pelvis and legs in a natural gait pattern while providing controlled assistance/resistance forces during body-weight-supported treadmill training (BWSTT).

Thirty individuals post stroke, ten patients with SCI, and ten children with CP were recruited to participate in these pilot studies to test the feasibility of using the 3DCaLT for gait training. Results from these clinical studies indicate that locomotor gait training using the 3DCaLT resulted in a significant improvement of walking function in adults post stroke, with SCI, and children with CP. Thus, it seems feasible to use a flexible cable-driven robotic system, i.e., 3DCaLT, to improve the locomotor function in adults post stroke or with SCI, and children with CP. Further studies with a large sample size of subjects and a comparison of the current paradigm with conventional BWSTT are warranted.

Keywords

Locomotion • Treadmill training • Cable driven • Robot • Spinal cord injury • Stroke • Cerebral palsy

M. Wu, PhD (✉) • J.M. Landry, PT
Sensor Motor Performance Program, Rehabilitation Institute of Chicago, Chicago, IL, USA
e-mail: w-ming@northwestern.edu; jlandry78@gmail.com

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21.1 Introduction

Body-weight-supported treadmill training has been used for improving locomotor function in humans with spinal cord injury (SCI) [1–6], stroke [7–13], and children with cerebral palsy [14, 15]. One limitation of this technique is the requirement of greater involvement of physical therapist during locomotor training. In addition, it can be a labor-intensive work for the physical therapist who conducts the training, particularly for those patients who require substantial walking assistance. As a consequence, several robotic gait training systems have been developed. While these robotic gait training systems are effective in reducing the labor intensity of physical therapist, they showed limited functional gains for some patients. As a result, there is a need for the development of new robotic gait training systems and paradigms. In order to fit the need, we developed a 3D cable-driven robotic gait training system. In this chapter, we will focus on the development and clinical tests of this novel cable-driven robotic gait training system.

21.1.1 Relevant Pathophysiology Background

21.1.1.1 Stroke

There are nearly 6.6 million people with stroke living in the United States, and approximately 795,000 people experienced a new or recurrent stroke each year [16]. Stroke is currently the leading cause of serious, long-term disability in the United States [17]. 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 [18].

Impaired mobility is an important factor in determining the degree of physical disability after stroke [19]. While up to 80 % of individuals with stroke may ultimately recover the ability to walk a short distance [20], most of them do not achieve the locomotor capacity necessary for community ambulation [21]. Limited community walking reduces the probability of successful return to work and decreases participation in community activities [22].

Walking ability post stroke is characterized primarily by reduced walking speed [23] and endurance [24], residual spatial and temporal left-right asymmetry [25], and impaired postural stability [26]. Patients suffer a greatly reduced knee flexion at toe off and during swing of the paretic leg, as compared to the non-paretic leg, which is usually associated with compensatory movement such as pelvic hiking and limb circumduction [27]. 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 [28]. These impairments restrict independent mobility and severely impact quality of life of individuals post stroke.

21.1.1.2 Spinal Cord Injury

The estimated prevalence of spinal cord injury (SCI) in the United States is approximately 276,000, with an incidence of approximately 12,500 new cases every year [29]. 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, 20s, or 30s) [30]. Many of them are at their most productive age when injured. After injury, they have to rely increasingly on support from the healthcare 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 [31, 32], as limitations in mobility can adversely affect most activities of daily living [33, 34].

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 [35] require assistive devices, such as rolling walkers, and spend more of the gait cycle in double-limb support [36]. 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 [37], resulting in an abnormal gait pattern.

21.1.1.3 Children with Cerebral Palsy (CP)

CP is the most prevalent physical disability originating in childhood with an incidence of 2–3 per 1,000 live births [38–40]. Of the children who are diagnosed with CP, as much as 90 % of children with CP have difficulty in walking [41, 42]. Reduced walking speed and endurance are two of the main functional problems, particularly in children with more severe disabilities [43].

Attaining functional walking ability is often an important functional goal for children with CP. Ambulation plays a central role in healthy bone development [44] and cardiopulmonary endurance [45], and children who are able to ambulate are more accomplished in activities of daily living and social roles, such as participation in the community, than children who use a wheelchair [46]. The development of independent gait and efficiency of walking are often the focus of therapeutic interventions for children with CP.

21.1.2 Rationale for Application of Current Technology (The Role of Neural Plasticity)

21.1.2.1 Neuroplasticity of Adults with Stroke and SCI and Children with CP

Although the loci of neuraxis lesions obviously differ between stroke, SCI, and CP, 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, SCI, or CP) as much as they rely on the available plasticity in relevant neural networks [47]. 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" [48]. 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 [49, 50]. 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 [51, 52]. Thus, to maximize locomotor recovery, rehabilitation for adults after stroke and SCI and children with CP should emphasize active, repetitive, task-specific practice that maximizes neuromuscular activity.

21.1.3 Therapeutic Action/ Mechanisms and Efficacy

21.1.3.1 Task-Oriented Practice in Individuals Post Stroke

To improve gait performance and functional outcomes following neurological injury, rehabilitation efforts have been focused on reestablishing normal walking patterns [32]. Toward this end, the use of body-weight-supported treadmill training (BWSTT) has demonstrated significant improvements in walking capability in individuals post stroke and SCI [53] and is becoming increasingly popular. Actually, the use of treadmill training for people with neurological disorders has its roots in previous animal studies where spinal cats were able to regain locomotor functions of the hind limbs with weight support through treadmill training [54]. The underlying mechanism of the effectiveness of this technique is thought to be the reorganization capacity of the

central system when task-specific motor practice is provided through treadmill training [55]. In clinics, the 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 [56]. By providing partial body weight support over a treadmill and manual facilitation from therapists, previous research has demonstrated improvements in temporospatial gait patterns, including gait velocity [7–10], endurance [11], balance [8], and symmetry [12, 13]. For instance, previous studies in non-ambulatory hemiparetic subjects revealed that BWSTT was superior to conventional physiotherapy with regard to restoration of gait ability and improvement of overground walking velocity [7]. In addition, a large study involving 100 acute stroke patients compared the effect of treadmill therapy with and without body weight support [8]. 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 [9, 10].

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 [57, 58]. For instance, results from a multicenter 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 Measure (FIM), walking velocity, Fugl-Meyer Stroke Assessment, and balance assessments [57]. However, in a subgroup of severe stroke subjects, the BWSTT group demonstrated a greater improvement of walking speed and endurance compared to the control group [58]. 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 [9, 11]. While significant statistically, these changes are relatively small considering the effort required to perform such training.

21.1.3.2 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 [1–6]. For instance, BWSTT has been shown to provide significant improvements in locomotor ability and motor function in humans with SCI [59]. 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 [59].

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 [5]. 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 [5]. 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 [1, 59]. Despite this, BWSTT often requires the effort of multiple physical therapists (generally up to three) to assist the legs 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.

21.1.3.3 Task-Oriented Practice in Children with CP

BWSTT has also been used to improve the locomotor function in children with CP [14]. While statistically significant improvements in walking capacity with BWSTT have been shown, the function gains are relatively small (increased only 0.07 m/s in walking speed) [15]. In particular, recent randomized controlled studies indicated that BWSTT is not more effective than overground walking for improving walking speed and endurance for children with CP [60, 61], although another randomized controlled study indicated that BWSTT is more effective than overground gait training in improving walking function in children with CP [62]. Thus, there is still insufficient evidence about the effect of BWSTT in improving walking function in children with CP [63–65]. In addition, BWSTT requires greater involvement of the physical therapist [66].

21.2 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 post stroke or SCI and children with CP, including the Lokomat [67], the Gait Trainer (GT) [68], and the AutoAmbulator [69]. The Lokomat is a motorized exoskeleton that drives hip and knee motion in the sagittal plane with a fixed trajectory using four DC motors [67]. The GT rigidly drives the patient's feet through a stepping motion using a crank-and-rocker mechanism attached to foot platforms [67]. The AutoAmbulator is a body-weight-supported treadmill robotic 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 [70], 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 [71].

21.2.1 Robotic Gait Training in Individuals Post Stroke

While robotic gait training relieves the strenuous effort of the therapists, the functional gains are limited for some patients [72, 73]. 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 [72]. 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 [74]. 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 post stroke than physical therapist-assisted locomotor training [75]. In contrast, results from a study with 155 non-ambulatory 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 [76]. Recent literature reviews suggest that robotic gait training in combination with physiotherapy increased the odds of participants becoming independent in walking, although did not significantly increase walking speed (mean difference = 0.04 m/s) and endurance (i.e., mean difference = 3 m walked in 6 min) [77, 78]. In particular, the type of robotic systems (i.e., exoskeleton robotic system, such as the Lokomat vs. end effector, such as the Gait Trainer) might influence the outcome measures of gait rehabilitation of individuals post stroke [77]. For instance, a meta-analysis indicated that the use of end-effector robotic gait training systems significantly increased the walking velocity with the pooled mean difference for walking velocity was 0.15 m/s. In contrast, a meta-analysis indicated that the use of exoskeleton robotic systems for gait rehabilitation even significantly decreased the walking velocity with the pooled mean difference for walking velocity was −0.05 m/s [78], although direct empirical comparisons between two types of robotic gait training systems are still lacking.

21.2.2 Robotic Gait Training in Humans with SCI

Similar results have been observed in humans with SCI [79]. 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 [6]. 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 [71], although the total distance ambulated during robotic BWSTT was significantly greater than that with overground training (i.e., 2,859 ± 111 m vs. 1,282 ± 666 m). Such results suggest that current robotic-assisted BWSTT methods may reduce the requirements and labor effort for the physical therapist, but does not necessarily offer an advantage in terms of regaining gait function in humans with SCI.

21.2.3 Robotic BWSTT in Children with CP

Recently, the Pediatric Lokomat (Hocoma AG, Volketswil, Switzerland) has been developed to provide robotic assistance in children with CP during treadmill training [80]. While the current Pediatric Lokomat is effective in reducing therapist labor intensity during locomotor training and increasing the total duration of training, it shows relatively limited functional gains for some children with CP [80]. For instance, a recent randomized controlled study indicated that robotic treadmill training using the Pediatric Lokomat was not more effective than conventional physical therapy for improving walking function in children with CP [81]. As a consequence, there is a need for the development of novel robotic training paradigms and/or systems.

21.2.3.1 Limitations of Current Robotic Systems

While these first-generation robotic systems are effective in reducing therapist labor in locomotor training, they have obvious limitations [82]. For

example, due to the limited degrees of freedom of the standard Lokomat (i.e., only allows movement in 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 [82, 83]. 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 [84]. A fixed trajectory training eliminates the variability in kinematics of the lower limbs, which may be crucial for successful motor learning as demonstrated in animal studies [85].

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 post stroke, SCI, or children with CP.

In an attempt to improve the efficacy of robotic BWSTT, we have developed a novel cable-driven gait training system (CaLT) [86]. This new robotic trainer uses a lightweight cable driven with controlled forces applied to 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 [67] and the crank-and-rocker mechanism, as used in the Gait Trainer [68] in that it allows for variation in the lower limb kinematics and increases active participation of the patient during training.

Recently, this cable-driven gait training system has been further developed by the integration of the pelvis component [87]. Specifically, two motor and pulley systems have been attached at the side of treadmill to provide controlled assistance force to the pelvis during stance phase of gait (for assisting weight shift) while the subject walks on a treadmill. As suggested in previous studies, these components of gait training are critical to maximize motor learning and functional improvements in adults with stroke and SCI and children with CP.

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 45N (see Fig. 21.1). Four 1-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. Additional two cables, driven by two motors (AKM33H, Kollmorgen), are affixed to custom braces that are strapped to the pelvis and provide controlled assistance forces for facilitating weight shifting in the mediolateral direction during treadmill walking. 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. In addition, the CaLT fits well with subjects of different leg lengths because it used a single end attachment to deliver controlled forces to the pelvis and legs. Thus, it eliminates the requirement of alignment between the lower limb rotation center and the axis of rotation of a robot arm that is needed in other exoskeleton systems. This approach may reduce the time required for set up.

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 to legs starting at pre-swing (~10 % gait cycle prior to toe off)

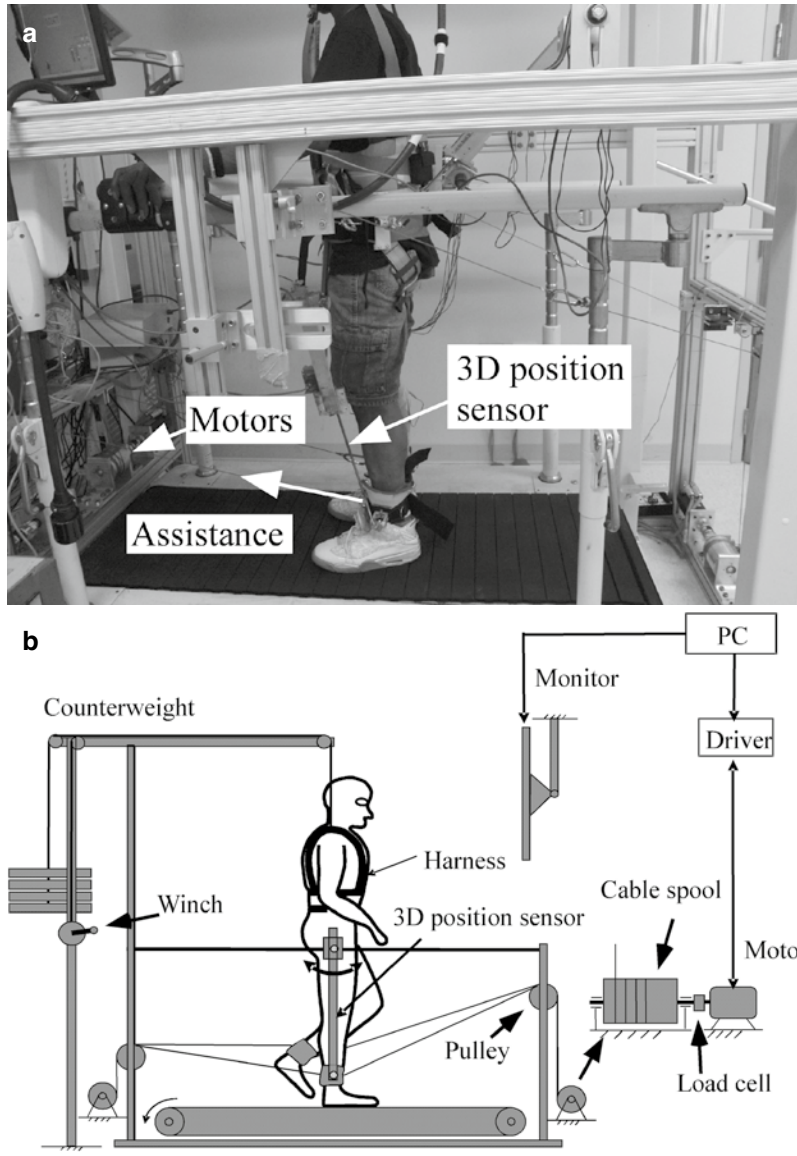

Fig. 21.1 (**a**) This figure illustrates the cable robot, a motor-driven cable apparatus that was used with a treadmill and body weight support system. Six cables driven by six motors, pulleys, and cable spools were used to apply resistance/assistance loads to legs during the swing phase of gait and assistance load to the pelvis during the stance phase of gait. A personal computer was used to control the load produced by the six motors, applying targeted assistance or resistance loads. (**b**) Illustration of the setup for leg resistance or assistance through cable-driven robotic system. (**c**) Illustration of the setup for pelvis assistance through cable-driven robotic system

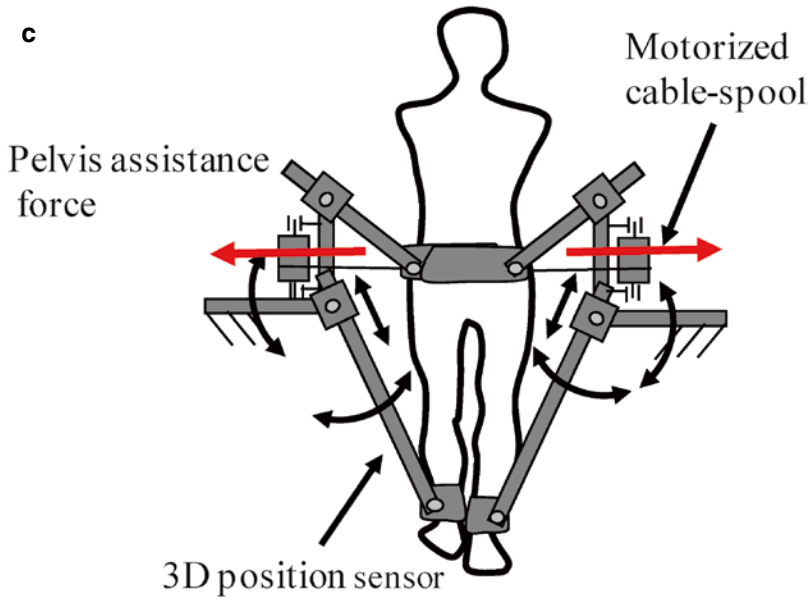

Fig. 21.1 (continued)

through mid-swing of gait [88]. In addition, the pelvis load is applied from heel strike to mid-stance of the ipsilateral leg for facilitating weight shifting. 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:

$$F_a(t) = -k_P\left(x(t) - x_d(t)\right) - K_D\left(\dot{x}(t) - \dot{x}_d(t)\right) \quad (21.1)$$

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), and $x(t)$, $\dot{x}(t)$, $x_d(t)$, *and* $\dot{x}_d(t)$ are the measured and desired 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. For the pelvis assistance paradigm, a control algorithm similar to the leg assistance was used, but the load was applied during the stance phase of gait.

21.3 Current Developments and Ongoing Testing

21.3.1 Locomotor Training in Individuals Post Stroke

21.3.1.1 Introduction

Previous studies demonstrated that active motor training is more effective than passive training in eliciting performance improvement [52]. Further, data from hemiparetic subjects practicing upper limb movements with forces that provide passive guidance vs. error enhancement indicate that greater improvements in performance are achieved when errors are magnified [89]. These results suggest that error-augmentation training may also be used as an effective way to improve locomotor function in individuals post stroke. We postulated that by applying a controlled resistance load to increase kinematic errors of the paretic leg during treadmill walking, motor learn-

ing would be accelerated during treadmill training in individuals post stroke.

On the other hand, providing a controlled assistance load to the paretic leg may facilitate leg swing and induce a longer step length, which mimics the way that clinical therapists provide assistance to the paretic leg during treadmill training. We postulated that providing an assistance load to the paretic leg might also improve locomotor function in individuals post stroke through a use-dependent motor learning mechanism [90]. However, it remains unclear whether leg resistance vs. assistance is more effective in improving locomotor function in individuals post stroke. The purpose of this study was to assess locomotor function (i.e., walking speed, endurance, balance) after resistance versus assistance treadmill training in individuals post stroke. The hypothesis was that subjects from both groups would show improvements in locomotor function, although there would be greater improvements in subjects who underwent resistance training in comparison with those who underwent assistance training [91]. The cable-driven robotic gait training system was used to provide controlled resistance or assistance load to the paretic leg during treadmill training.

21.3.1.2 Subjects and Protocol

Thirty individuals with chronic hemiparetic stroke were recruited to participate in this study. Mean age at the time of study enrollment was 53.6 ± 8.9 and 57.4 ± 9.8 years old for the resistance and assistance training groups, respectively, with no significant difference between two groups ($p = 0.3$, ANOVA). The average interval between stroke and the onset of robotic BWSTT was 7.3 ± 5.6 and 7.1 ± 6.0 years for the resistance and assistance training groups, respectively, again, with no significant difference between two groups ($p = 0.95$).

At the initiation of the 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 the 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.

21.3.1.3 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 (Gait Mat II, E.Q., Inc., Chalfont, PA) and walking distance assessed through the 6-min walk [92]. 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 [93].

21.3.1.4 Results

Thirty individuals with chronic hemiparetic stroke were recruited to participate in this study, with 28 participants finished all the training and test sessions. 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 (14 subjects participated in the resistance group and 14 subjects in the assistance group).

A significant improvement in walking speed was observed for subjects from the resistance group after 6 weeks of robotic BWSTT using the cable-driven robot [91]. Specifically, self-selected and fast walking speeds significantly increased from 0.53 ± 0.25 m/s to 0.61 ± 0.28 m/s ($P = 0.002$, ANOVA) and from 0.72 ± 0.36 m/s to 0.82 ± 0.39 m/s ($P = 0.001$), respectively, after resistance training. Further, improvements in walking speed were partially retained at follow-up ($P = 0.03$ and $P = 0.002$ for self-selected and fast walking speeds, respectively). The 6-min walk

distance increased from 201 ± 84 m to 207 ± 80 m after resistance training, although this was not significant ($P = 0.18$), and was 210 ± 82 m at follow-up test ($P = 0.08$). BBS score also slightly increased from 44.1 ± 8.8 to 45.6 ± 9.3 after resistance training, although this was not significant ($P = 0.11$), and was 44.9 ± 9.09 at follow-up ($P = 0.47$).

On the other hand, a significant improvement in walking function was obtained for subjects from the assistance training group after training. Specifically, self-selected and fast walking speeds significantly increased from 0.47 ± 0.24 m/s to 0.56 ± 0.32 m/s ($P = 0.01$) and from 0.65 ± 0.38 m/s to 0.76 ± 0.45 m/s ($P = 0.002$), respectively, after training. Further, the improvements in walking speeds were partially retained at follow-up ($P = 0.01$ and $P = 0.004$ for self-selected and fast walking speeds, respectively). Also, the 6-min walk distance significantly increased from 177.4 ± 99.9 m to 197.5 ± 109.5 m ($P = 0.002$) and was partially retained at follow-up (191.1 ± 108.5 m, $P = 0.02$). The BBS score significantly increased from 43.6 ± 9.0 to 45.5 ± 8.8 ($P = 0.02$) after assistance training and was 44.1 ± 9.6 at follow-up, although not significant ($P = 0.41$).

There was no significant difference in improvements in walking speed between subjects who underwent resistance vs. assistance training. Specifically, the improvement in self-selected walking speed was 0.07 ± 0.07 m/s and 0.09 ± 0.11 m/s after resistance and assistance training, respectively, with no significant difference between the two groups ($p = 0.75$). In addition, the improvement in fast walking speed was 0.10 ± 0.08 m/s and 0.11 ± 0.12 m/s after resistance and assistance training, respectively, with no significant difference between the two groups ($p = 0.73$). The improvement in the 6-min walk distance tended to be greater for the assistance group than the resistance group (i.e., 20 ± 20 m vs. 6 ± 16 m for assistance and resistance groups, respectively), although this was not significant ($p = 0.06$). In addition, the improvement in the BBS score was comparable, i.e., 1.4 ± 3.1 and 1.9 ± 2.6 for the resistance and assistance training groups, respectively, with no significant difference between the two groups ($P = 0.63$).

21.3.2 Locomotor Training in Human with Incomplete SCI

21.3.2.1 Introduction

Recent reviews of clinical studies on the effectiveness of current robotic training in humans with SCI suggest that robotic-assisted gait training is not superior to other gait training modalities [79, 94]. One possibility is that these robotic training modalities do not provide adequate challenge to drive motor learning in humans with SCI during locomotor training [95]. For instance, muscle activities are significantly lower during passive-guided, robotic locomotor training than with physical therapist-assisted treadmill training in humans with SCI [96]. Recent studies have shown that an error-augmentation training paradigm may enhance arm recovery in individuals post stroke [89]. Thus, we postulated that error-augmentation also would facilitate motor learning during locomotor training in humans with SCI.

By applying a resistance load to the leg during treadmill walking, which may increase leg kinematic errors [97], recent studies have indicated that humans with SCI adapt to the resistance load applied and demonstrate an aftereffect consisting of an increase in step length following load release [98]. The presence of aftereffects suggests the formation of anticipatory locomotor commands in response to the resistance load. In particular, a previous study indicated that this aftereffect could be transferred from treadmill training to overground walking in humans with SCI [99]. However, locomotor adaptation and the aftereffects are generally short lived, i.e., the increase in step length returns back to baseline within tens of steps during the post-adaptation period, after one session of force perturbation training, which may have limited clinical impact on walking function in humans with SCI. A recent study using a split-belt treadmill paradigm indicated that prolonged repeated exposure to split-belt perturbation induces a long-term retention of improved step length symmetry in individuals post stroke [100]. Thus, we postulated that a prolonged repeated exposure to swing resistance perturbations during treadmill training might also induce long-term retention of

improved step length, resulting in improvements in walking function of humans with SCI. The purpose of this study was to determine whether robotic resistance or assistance treadmill training by using cable-driven robotic system would be effective in improving locomotor function in humans with chronic incomplete SCI [101].

21.3.2.2 Subjects and Training Protocol

Ten 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 47 ± 8 years old. The average interval between SCI and the onset of robotic BWSTT was 5.8 ± 3.8 years (range 1–14 years). All subjects were classified by the American Spinal Injury Association (ASIA) as ASIA grade D.

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 stroke patients study 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.

21.3.2.3 Results

In this pilot study, eight out of ten 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 eight 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., the gait speed improved from 0.67 ± 0.20 m/s to 0.76 ± 0.23 m/s (see Fig. 21.2a). Fast walking speed also improved from 0.96 ± 0.31 m/s to 1.06 ± 0.32 m/s, although no significant difference was obtained due to the small sample size ($p = 0.19$, one-way repeated measures ANOVA). In addition, scores on the Berg Balance Scale significantly improved from 42 ± 12 at pretraining to 45 ± 12 post 8-week robotic gait training (see Fig. 21.3). There was no significant changes in walking distance at the pre- and post robotic training evaluation sessions ($p = 0.12$), although averaged 6-min walk distance increased from 223 ± 81 m at pretraining to 247 ± 88 m at post training (see Fig. 21.2b). In addition, we found all subjects in this study had no change in their WISCI II scores at pre- and post robotic treadmill training (17 ± 4). There was no significant change in muscle strength following robotic BWSTT.

21.3.3 Locomotor Training in Children with CP

21.3.3.1 Introduction

Weight shifting in the mediolateral direction is of one of key components during human locomotion [102]. However, the weight-shifting ability is often impaired in children with CP compared to children who are typically developed [103]. For instance, children with CP performed weight shifting less efficiently as demonstrated by a shorter range of motion of center of pressure (COP) and slower velocity of COP displacement during standing compared to children who are typically developed. It was suggested that weight-

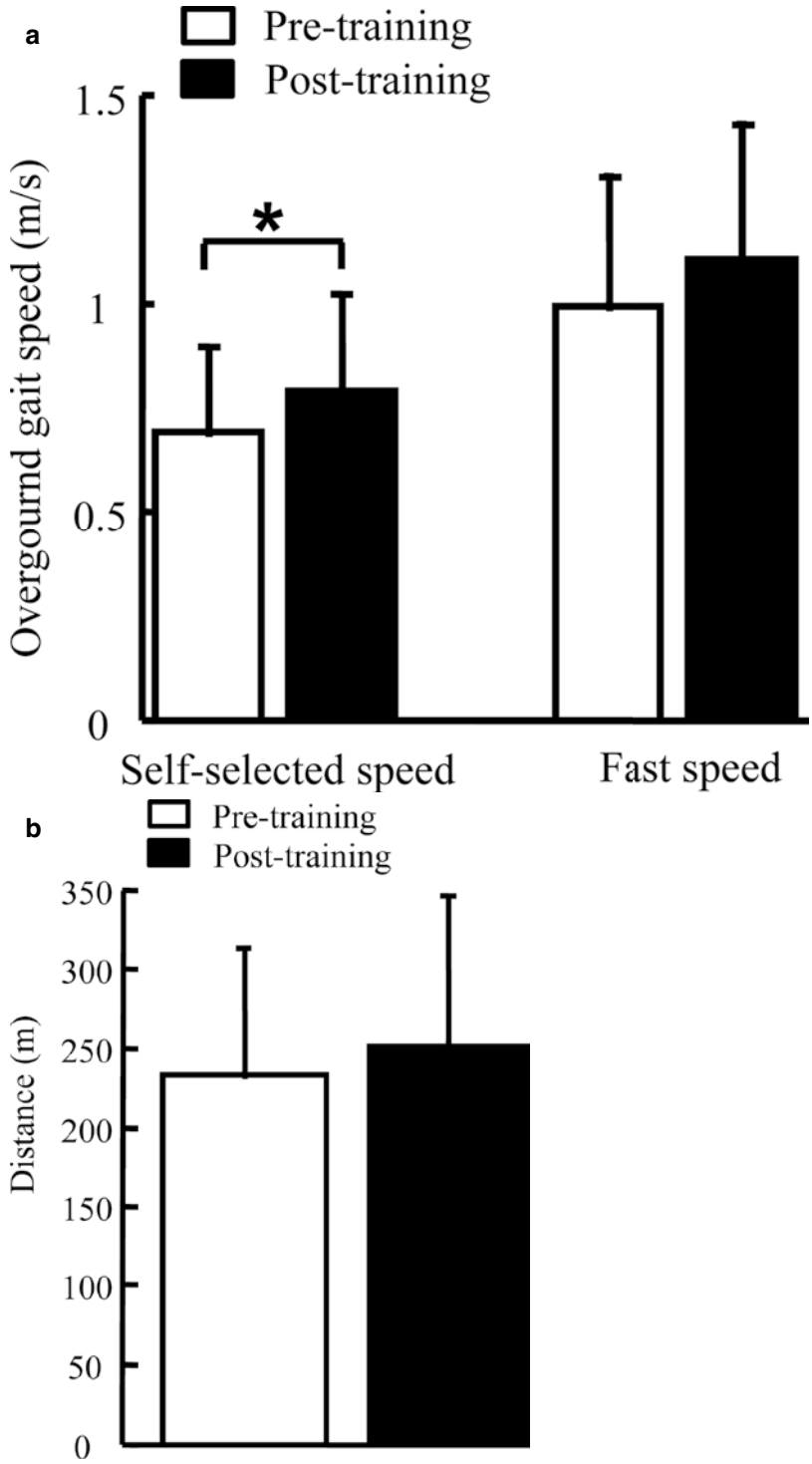

Fig. 21.2 Self-selected overground gait speed (**a**) and 6-min walk distance (**b**) at pre- and post 8-week robotic treadmill training in human SCI. The *bar* and *error bar* indicate the mean and standard deviation of the gait speed and walking distance across eight subjects for pre- and post training. *Asterisk* (*) indicates significant effect of treatment

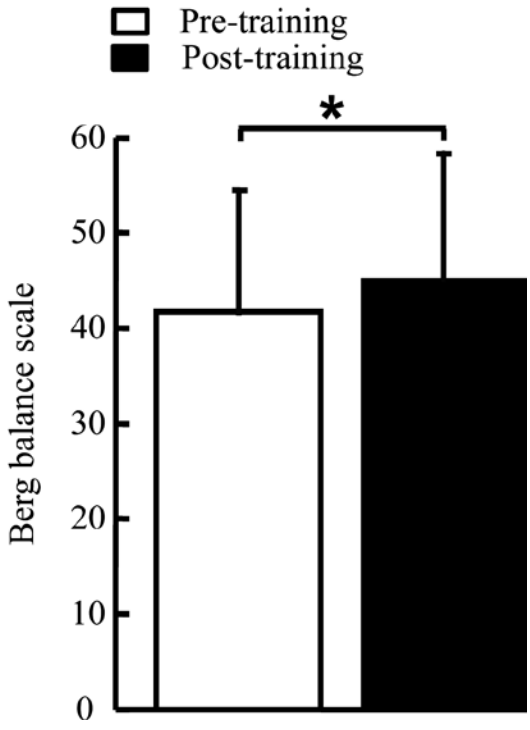

Fig. 21.3 Berg balance scale at pre- and post 8-week robotic treadmill training in humans with SCI. The *bar* and *error bar* indicate the mean and standard deviation across eight subjects for pre- and post training. *Asterisk* (*) indicates significant effect of treatment of robotic gait training

shift training might improve dynamic balance during walking in children with CP [104], although this has not been tested. Thus, we postulated that applying a mediolateral assistance force at the pelvis during stance phase of gait might facilitate weight shifting in children with CP during treadmill walking, and repeat practice of weight shifting during treadmill training may improve dynamic balance and improve walking speed in children with CP.

Evidence from spinalized mice indicates that motor learning is more effective with assistance as needed than with a fixed trajectory paradigm [85]. Thus, a robotic system that allows for variability in the stepping pattern during treadmill training will be effective in improving walking speed in children with CP. In addition, results from motor learning studies indicate that when there are more similarities between learning tasks and the application of those tasks, a greater transfer of motor skills will take place [105]. Thus, a robotic BWSTT technique that provides less constraints and allows for a natural dynamic gait pattern during treadmill walking will be an effective method for transferring motor skills from treadmill training to overground walking in children with CP as measured by increased overground walking speed after robotic BWSTT. The purpose of this study is to assess improvements in locomotor function of children with CP after robotic treadmill training with the application of applying controlled forces to both the pelvis, for facilitating weight shift, and leg at the ankle, for facilitating leg swing, through the 3D cable-driven robotic gait training system [87].

21.3.3.2 Subject and Training Protocol

Ten children (five girls) with spastic CP were recruited to participate in this study. Mean age was 11.8 ± 3.9 years old. According to the Gross Motor Function Classification System (GMFCS) [106], one of them was classified as level I, five of them were classified as level II, three of them were classified as level III, and one of them was classified as level IV. Treadmill training was performed three times per week for 6 weeks with the training time for each visit set at 30–40 min, as tolerated, excluding setup time. The peak value of the pelvis assistance force was set at ~9 % of body weight, and the peak leg assistance force was set at ~3–4 % of body weight, although these peak forces were adjusted based on the tolerance of each subject. The leg assistance load was applied to the ankle starting from late stance to mid-swing, and the pelvis assistance was applied in the mediolateral direction starting heel strike to mid-stance.

Gait assessment was made pre and post 6 weeks of robotic treadmill training and at 8 weeks after the end of training, using gait speed, endurance (6-min walk distance [107]), and clinical measures of motor function (the dimensions D (standing) and E (walking, run-

ning, jumping) of the Gross Motor Function Measure (GMFM-66), [108]).

21.3.3.3 Results

Following 6 weeks of robotic treadmill training through the 3D cable-driven robotic gait training system, self-selected and fast overground gait speeds significantly increased for children with CP; see Fig. 21.4. Specifically, self-selected and fast walking speeds increased from 0.69 ± 0.18 m/s to 0.82 ± 0.21 m/s ($p = 0.05$, ANOVA, $n = 9$) and from 1.09 ± 0.29 m/s to 1.20 ± 0.33 m/s ($p = 0.045 < 0.05$, $n = 9$) after treadmill training; see Fig. 21.4. Further, improvements in walking speed were partially retained at follow-up (i.e., 0.77 ± 0.19 m/s, $p = 0.005 < 0.05$ and 1.15 ± 0.32 m/s, $p = 0.09$, for self-selected and fast walking speeds, respectively, $n = 10$). Six-minute walk distance tended to increase from 297.7 ± 52.6 m to 334.1 ± 100.5 m after robotic-assisted treadmill training, although no significant difference was noted ($p = 0.10$), and was 325.9 ± 91.5 m at follow-up ($p = 0.09$).

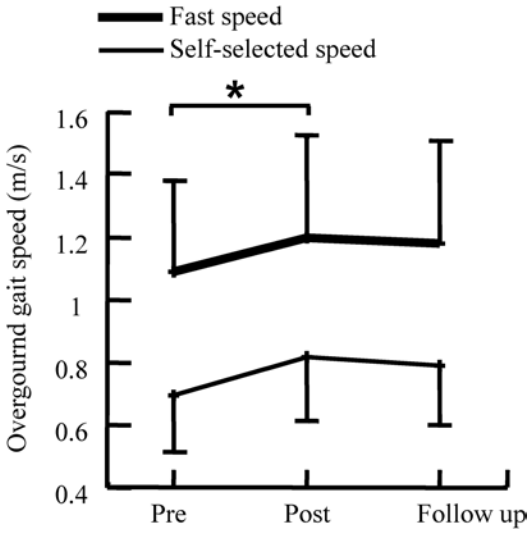

Fig. 21.4 Overground gait speed pre-, post 6-week robotic treadmill training, and 8-week follow-up in children with CP. The *bar* and *error bar* indicate the mean and standard deviation of gait speed across nine subjects for pre- and post training (Data from one subject were not included due to sick right before the posttest), and for ten subjects at follow-up. *Asterisk* (*) indicates significant effect of treatment

In addition, GMFM score also slightly increased from 62.4 ± 6.7 to 63.1 ± 7.8 ($p = 0.39$) after robotic treadmill training and was 63.4 ± 8.7 ($p = 0.39$) at the follow-up, although these were not significant. Spasticity had a modest change after robotic treadmill training. Specifically, the average of Modified Ashworth Scale score which was 0.68 ± 0.44 slightly increased to 0.74 ± 0.59 ($p = 0.75$) after robotic treadmill training and slightly decreased to 0.45 ± 0.38 ($p = 0.12$) at the follow-up, although these were not significant.

21.3.3.4 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 adults with chronic stroke and motor incomplete SCI and children with CP. We found that it was feasible to use the cable-driven robotic system to improve locomotor function in adults with stroke and SCI and children with CP. In particular, significant changes were observed in self-selected overground gait speed after robotic treadmill training. Further, the improvements in walking function were partially retained at 8 weeks after the end of training in individuals post stroke and children with CP, indicating a clinical significance of such intervention.

21.3.3.5 Improved Walking Function in Individuals Post Stroke

Applying a controlled resistance or assistance load to the paretic leg during treadmill training using the cable-driven robotic system significantly improved walking speed in individuals post stroke. The improvements in walking speed obtained through robotic resistance vs. assistance treadmill training were comparable with no significant difference between them. In addition, the 6-min walk distance and the BBS and ABC Scale scores significantly improved after assistance treadmill training but not after resistance treadmill training. These results suggest that resistance training was not superior to assistance training in improving endurance, balance, and balance confidence in individuals post stroke [91].

The increase in kinematic errors produced by the resistance load may elicit an error correction process that accelerates motor learning during locomotor training in individuals post stroke. For instance, for the subjects who were assigned to the resistance training group, the resistance applied to the paretic leg produced a deviation in leg kinematics, that is, increased kinematic errors. Enhanced error has been shown to be more effective than passive guidance in improving arm performance in individuals post stroke [89]. For the lower limb, previous studies indicated that individuals post stroke adapted to the resistance load applied to the paretic leg and showed an aftereffect consisting of increased step length of the paretic leg after load release [109, 110].

Further, repeated exposure to resistance load during treadmill training may induce a prolonged retention of aftereffect of the paretic leg in individuals post stroke. In this study, repeated exposure to a resistance load was applied to the paretic leg during 6 weeks of treadmill training. As a result, the step length of the paretic leg during overground walking increased after resistance training, suggesting that the aftereffect of an increased step length may be accumulated and transferred from one context (i.e., treadmill walking) to another context (i.e., overground walking) in individuals post stroke. In particular, we observed a partial retention of the increased step length of the paretic leg at follow-up.

On the other hand, for subjects who were assigned to the assistance training group, an assistance force provided to the paretic leg may facilitate the leg swing to induce a longer step length on the paretic side during treadmill training. The increased step length of the paretic leg may be accumulated and transferred to overground walking through 6 weeks of locomotor training, resulting in an improvement in walking function after assistance treadmill training in individuals post stroke. However, because the assistance force was applied at the paretic leg facilitating the leg to swing forward, instead of resisting the leg to induce kinematic deviation, we postulated that the motor learning mechanisms involved in robotic assistance training would be different from those involved in resistance training. A use-dependent motor learning mechanism may be involved during robotic-assisted treadmill training [90]. The synaptic efficacy of sensorimotor pathways involved in the leg swing of the paretic leg may be enhanced by repetitive stepping assisted by the cable-driven robot [111].

Results from this study suggest that resistance training was not superior to assistance training in improving speed, endurance, balance, and balance confidence in individuals post stroke. A possible reason is that while the larger size of errors induced by a resistance load may accelerate motor learning, the motor memory resulted from this learning may be less retained [112, 113] and less transferred to overground walking [114]. In addition, cognitive strategies or compensation from the non-paretic arm (because most subjects prefer to hold on the side bar during locomotor training) or leg may be used to quickly reduce errors in response to a leg resistance load, but this rapid performance improvement also vanishes quickly after that resistance load is removed, leading to less retention of motor memory after resistance training.

Maintaining variation in kinematics during BWSTT is considered to be critical in improving the locomotor function in individuals post stroke. For instance, results from animal experiments show that motor learning is more effective with a robotic algorithm that allows variability in the stepping pattern than with a fixed trajectory paradigm [85]. 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 fixed trajectory, which reduces kinematic variability [115].

In the current study, the cable-driven robotic system, which is highly backdrivable, has limited constraint of the leg kinematics during treadmill training [86]. The cable-driven system can be moved by the patient with the smallest possible resistance opposed by the robot. Thus, the cable system allows the patients greater flexibility in controlling their gait pattern. The cable-driven robotic system did not significantly affect the

variability in ankle trajectory while controlled load was applied to legs during treadmill walking; see Fig. 21.5a. For instance, a previous study indicated that there were no significant changes in the variability of ankle trajectory of humans with SCI for different loading conditions (i.e., at baseline, with cable attached, and with assistance load applied (ANOVA, $p=0.6$)); see Fig. 21.5b [86]. This type of training seems more effective than fixed trajectory training in improving locomotor function in individuals post stroke.

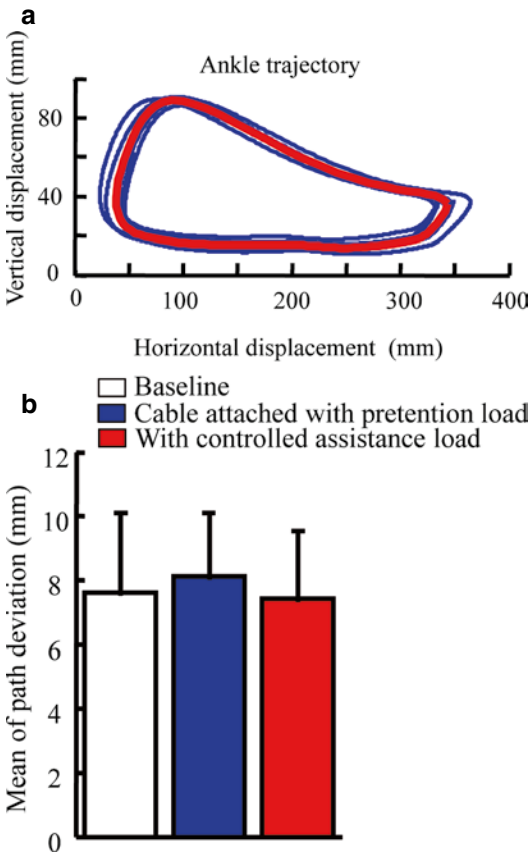

Fig. 21.5 (**a**) Ankle trajectories in the sagittal plane are shown from one patient with incomplete SCI during treadmill walking without the attachment of cable robot. The *solid thick line* shown is the ensemble average trajectory across seven step cycles. (**b**) Variability of ankle trajectory for three different loading conditions, i.e., baseline without attachment of the cable-driven robot, cable robot attached with 4N pretension load, and cable robot attached with controlled assistance load. Path deviation of ankle trajectory in the sagittal plane for each condition was used to quantify the variability of ankle movement of each subject during treadmill walking. The *bar* and *error bar* indicate the mean and SD of the RMS error of ankle trajectory across subjects (Modified from Wu et al. [86])

Results from basic neuroscience studies indicated that motor learning is more effective when human subjects actively practice movement rather than being passively moved [33, 34]. 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 post stroke. 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 the limb for them [84]. 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 post stroke.

The subjects who participated in the current study were all ambulatory chronic patients with self-selected walking speeds ranging from 0.12 to 0.89 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 effective in improving the locomotor function of individuals who are more severely affected. In addition, we do not know whether robotic treadmill training through the cable-driven system is more effective than conventional treadmill training in improving locomotor function in individuals post stroke.

21.3.3.6 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) [6, 116]. 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 [4]. 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 3.3 ± 2.3. 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 mediolateral 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 [117, 118]. 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 [119].

The effect of BWSTT in enhancing motor recovery and improving ambulation in human SCI has been studied intensely for the past two decades [120]. 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 therapy is the labor-intensive efforts 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 [121]. As the therapist fatigues, maintaining appropriate spatial and temporal gait pattern of 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 0.09 ± 0.10 m/s (13 %) and 3.3 ± 2.3 (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 [6]. 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). The initial self-selected over-ground 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 eight subjects who completed all training and evaluation sessions had an injury at the cervical level. In addition, three out of eight 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 [122] 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 manual-assisted BWSTT in humans with SCI.

21.3.3.7 Improved Walking Function in Children with CP

The 3D cable-driven robotic gait training system was used to improve overground walking speed and endurance in children with CP through 6 weeks of robotic treadmill training. Further, the improvement in walking speed was still partially retained at the follow-up, suggesting clinical significance of these robotic training paradigms. Results from this study suggest that treadmill training in conjunction with the application of applying controlled forces to both the pelvis and legs, while allowing for a natural stepping pattern, seems feasible in improving walking function in children with CP.

Applying assistance load to the pelvis during treadmill training may improve weight-shifting ability in children with CP. In this study, the 3D cable-driven robotic system provided no constraints on pelvis 3D movement but only assistance force for facilitating weight shift at targeted phase of gait while children with CP walking on a treadmill. Repeat practice of weight shifting during treadmill training may improve the weight-shifting ability of children with CP through a use-dependent motor learning mechanism [90].

In addition, applying a mediolateral assistance force at the pelvis may enhance muscle activation of hip abductors/adductors, key muscles for balance control in the frontal plane during walking [123]. Further, repeat activation of these sensorimotor pathways induced by repeat pelvis assistance load during treadmill training may reinforce circuits and synapses used for lateral balance control during walking through use-dependent neuronal plasticity mechanisms [48], leading to long-term improvements in lateral balance control. The improvement in balance control may lead to improved lateral stability on the stance leg, allowing for the contralateral leg to move forward, resulting improvements in walking speed and endurance in children with CP after training.

In this study, the cable-driven robotic system is highly backdrivable, which may allow a natural gait pattern of children with CP during locomotor training. A natural gait pattern during treadmill training may facilitate transfer of motor skills obtained during treadmill training to overground walking in children with CP. This is supported by results from motor learning studies, which suggest that the more similarities between tasks of learning and application, the more transfer will take place [105]. As a consequence, we observed functional improvements in walking speed and endurance of children with CP after robotic treadmill training through the 3D cable-driven robotic gait training system. In particular, we observed a partial retention of the functional gains at 8 weeks after the end of treadmill training, suggesting a clinical significant of such training paradigm.

This pilot study has several limitations. For instance, the sample size is small, and we do not know whether robotic treadmill training is more effective than conventional treadmill training in improving walking function in children with CP. A randomized controlled study is ongoing.

21.3.3.8 Other Advantages of the Cable-Driven Robotic System

The cable-driven robotic system can apply compliant assistance as needed or even resistance as tolerated to the paretic leg (s) during treadmill training. The cable-driven robotic system is easy to set up compared to an exoskeleton robotic system, such as the Lokomat, which requires the rotation center of robotic arms to be aligned with the patient's hip and knee joints [67]. The setup time of the cable-driven system is shorter than that of the exoskeleton systems, which is critical for the long-term treadmill training. In addition, the cost of the cable-driven robotic 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.

21.3.3.9 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 [124], LOPES [125], and Haptic Walker [126], 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 [124]. The LOPES is an 8-degree-of-freedom lightweight impedance controlled exoskeleton robot developed for gait training [125]. 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 [126]. 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 individuals post stroke [127].

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 more kinematic variability during robotic-assisted treadmill training through the Lokomat [128, 129]. 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 the locomotor function in individuals post stroke or SCI. In addition, there are several other passive devices that deliver assistance to the leg during treadmill walking [130, 131], but no clinical results are reported.

Robotic-assisted treadmill systems provide for training of a repetitive walking pattern that is critical for locomotor recovery in individuals post stroke 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 [132]. 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 [133]. As a consequence, several overground robotic systems, such as ReWalk (Argo Medical Technologies Ltd., Haifa, Israel), Ekso (Ekso Bionics, Richmond, CA, USA), Rex (Rex Bionics, Auckland, New Zealand), HAL (Cyberdyne, Inc., Japan), and Tibion Bionic Leg (Tibion Corporation, Sunnyvale, California), have been developed. While the safety and feasibility of these overground exoskeleton robotic systems have been tested, the clinical results are still limited [134–136].

Conclusion

The cable-driven locomotor training system proposed in this study provides a promising adjunct for treatment of patients post stroke, patients with incomplete SCI, and children with CP through robotic-assisted treadmill training. This system is highly backdrivable, complaint, and allows patients to voluntarily move their legs during BWSTT. The 3DCaLT can apply controlled assistance/perturbation forces to the pelvis (in the frontal plane) and

legs (in the sagittal plane) at targeted phase of gait while subject walking on a treadmill. 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 pilot studies indicate that it is feasible to improve the locomotor function in individuals post stroke, with incomplete SCI, and children with CP using the cable-driven robotic gait training system.

We acknowledge that there are limitations for these studies. For instance, the sample size is small. In addition, the group assignment was not blinded to the physical therapists who conducted the clinical assessments. We do not know whether robotic treadmill training through the cable-driven robotic system is more effective than conventional BWSTT in improving locomotor function. A randomized controlled study is warranted. Further developments of this cable-driven robotic gait training system, including new control algorithms and paradigms, are needed for the further clinical application of this cable-driven robotic gait training system.

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References

1. Behrman AL, Harkema SJ. Locomotor training after human spinal cord injury: a series of case studies. Phys Ther. 2000;80:688–700.
2. Dietz V, Colombo G, Jensen L, et al. Locomotor capacity of spinal cord in paraplegic patients. Ann Neurol. 1995;37:574–82.
3. Wernig A, Müller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia. 1992; 30:229–38.
4. Wirz M, Zemon DH, Rupp R, et al. Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil. 2005;86:672–80.
5. Dobkin B, Apple D, Barbeau H, et al. Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. Neurology. 2006;66:484–93.
6. Field-Fote EC, Lindley SD, Sherman AL. Locomotor training approaches for individuals with spinal cord injury: a preliminary report of walking-related outcomes. J Neurol Phys Ther. 2005;29:127–37.
7. Hesse S, Bertelt C, Jahnke MT, et al. Treadmill training with partial body weight support compared with physiotherapy in nonambulatory hemiparetic patients. Stroke. 1995;26:976–81.
8. Visintin M, Barbeau H, Korner-Bitensky N, et al. A new approach to retrain gait in stroke patients through body weight support and treadmill stimulation. Stroke. 1998;29:1122–8.
9. Sullivan KJ, Knowlton BJ, Dobkin BH. Step training with body weight support: effect of treadmill speed and practice paradigms on poststroke locomotor recovery. Arch Phys Med Rehabil. 2002; 83:683–91.
10. Pohl M, Mehrholz J, Ritschel C, et al. Speed-dependent treadmill training in ambulatory hemiparetic stroke patients: a randomized controlled trial. Stroke. 2002;33:553–8.
11. Macko RF, Ivey FM, Forrester LW, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. Stroke. 2005;36:2206–11.
12. Silver B, Demaerschalk B, Merino JG, et al. Improved outcomes in stroke thrombolysis with prespecified imaging criteria. Can J Neurol Sci. 2001;28:113–9.
13. Trueblood PR. Partial body weight treadmill training in persons with chronic stroke. NeuroRehabilitation. 2001;16:141–53.
14. Willoughby KL, Dodd KJ, Shields N. A systematic review of the effectiveness of treadmill training for children with cerebral palsy. Disabil Rehabil. 2009;31:1971–9.
15. Dodd KJ, Foley S. Partial body-weight-supported treadmill training can improve walking in children with cerebral palsy: a clinical controlled trial. Dev Med Child Neurol. 2007;49:101–5.
16. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–209.

17. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler 3rd ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29–322.
18. Harwin WS, Patton JL, Edgerton VR. Challenges and opportunities for robot-mediated neurorehabilitation. Proc IEEE. 2006;94(9):1717–26.
19. Perry J, Garrett M, Gronley JK, et al. Classification of walking handicap in the stroke population. Stroke. 1995;26:982–9.
20. Jørgensen HS, Nakayama H, Raaschou HO, et al. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76:27–32.
21. Goldie PA, Matyas TA, Evans OM. Deficit and change in gait velocity during rehabilitation after stroke. Arch Phys Med Rehabil. 1996;77: 1074–82.
22. Treger I, Shames J, Giaquinto S, et al. Return to work in stroke patients. Disabil Rehabil. 2007;29: 1397–403.
23. von Schroeder HP, Coutts RD, Lyden PD, et al. Gait parameters following stroke: a practical assessment. J Rehabil Res Dev. 1995;32:25–31.
24. Dean CM, Richards CL, Malouin F. Walking speed over 10 metres overestimates locomotor capacity after stroke. Clin Rehabil. 2001;15:415–21.
25. Hsu AL, Tang PF, Jan MH. Analysis of impairments influencing gait velocity and asymmetry of hemiplegic patients after mild to moderate stroke. Arch Phys Med Rehabil. 2003;84:1185–93.
26. de Haart M, Geurts AC, Huidekoper SC, et al. Recovery of standing balance in postacute stroke patients: a rehabilitation cohort study. Arch Phys Med Rehabil. 2004;85:886–95.
27. Chen G, Patten C, Kothari DH, et al. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait Posture. 2005;22:51–6.
28. Dobkin BH. The clinical science of neurologic rehabilitation. 2nd ed. New York: Oxford University Press; 2003.
29. NSCISC. Spinal cord injury: facts and figures at a glance. Birmingham: National Spinal Cord Injury Statistical Center; 2014.
30. Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? Spinal Cord. 2006;44:523–9.
31. Anderson CS, Carter KN, Brownlee WJ, et al. Very long-term outcome after stroke in Auckland, New Zealand. Stroke. 2004;35:1920–4.
32. Field-Fote EC. Spinal cord control of movement: implications for locomotor rehabilitation following spinal cord injury. Phys Ther. 2000;80:477–84.
33. Post M, Noreau L. Quality of life after spinal cord injury. J Neurol Phys Ther. 2005;29:139–46.
34. Noreau L, Fougeyrollas P, Post M, et al. Participation after spinal cord injury: the evolution of conceptualization and measurement. J Neurol Phys Ther. 2005;29:147–56.
35. Barbeau H, McCrea DA, O'Donovan MJ, et al. Tapping into spinal circuits to restore motor function. Brain Res Brain Rev. 1999;30:27–51.
36. Pepin A, Ladouceur M, Barbeau H. Treadmill walking in incomplete spinal-cord-injured subjects: 2. Factors limiting the maximal speed. Spinal Cord. 2003;41:271–9.
37. Leroux A, Fung J, Barbeau H. Postural adaptation to walking on inclined surfaces: II. Strategies following spinal cord injury. Clin Neurophysiol. 2006;117: 1273–82.
38. Rosen MG, Dickinson JC. The incidence of cerebral palsy. Am J Obstet Gynecol. 1992;167:417–23.
39. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. Disabil Rehabil. 2006;28:183–91.
40. Van Naarden Braun K, Christensen D, Doernberg N, Schieve L, Rice C, Wiggins L, Schendel D, Yeargin-Allsopp M. Trends in the prevalence of autism spectrum disorder, cerebral palsy, hearing loss, intellectual disability, and vision impairment, metropolitan Atlanta, 1991–2010. PLoS One. 2015;10: e0124120.
41. Pharoah PO, Cooke T, Johnson MA, King R, Mutch L. Epidemiology of cerebral palsy in England and Scotland, 1984–9. Arch Dis Child Fetal Neonatal Ed. 1998;79:F21–5.
42. Hutton JL, Pharoah PO. Effects of cognitive, motor, and sensory disabilities on survival in cerebral palsy. Arch Dis Child. 2002;86:84–9.
43. Duffy CM, Hill AE, Cosgrove AP, Corry IS, Graham HK. Energy consumption in children with spina bifida and cerebral palsy: a comparative study. Dev Med Child Neurol. 1996;38:238–43.
44. Wilmshurst S, Ward K, Adams JE, Langton CM, Mughal MZ. Mobility status and bone density in cerebral palsy. Arch Dis Child. 1996;75:164–5.
45. Chien F, DeMuth S, Knutson L, Fowler E. The use of the 600 yard walk run test to assess walking endurance and speed in children with cerebral palsy. Pediatr Phys Ther. 2006;18:86–7.
46. Lepage C, Noreau L, Bernard PM. Association between characteristics of locomotion and accomplishment of life habits in children with cerebral palsy. Phys Ther. 1998;78:458–69.
47. Dobkin BH. Motor rehabilitation after stroke, traumatic brain, and spinal cord injury: common

denominators within recent clinical trials. Curr Opin Neurol. 2009;22:563–9.
48. Hebb DO. The organization of behavior: a neuropsychological theory. New York: Wiley; 1949.
49. Edgerton VR, de Leon RD, Tillakaratne N, et al. Use-dependent plasticity in spinal stepping and standing. Adv Neurol. 1997;72:233–47.
50. Henry FM. Specificity vs. generality in learning motor skill. In: Brown RC, Kenyon GS, editors. Classical studies on physical activity. Englewood Cliffs: Prentice-Hall; 1968. p. 331–40.
51. Kaelin-Lang A, Sawaki L, Cohen LG. Role of voluntary drive in encoding an elementary motor memory. J Neurophysiol. 2005;93:1099–103.
52. Lotze M, Braun C, Birbaumer N, Anders S, et al. Motor learning elicited by voluntary drive. Brain. 2003;126:866–72.
53. Barbeau H, Fung J. The role of rehabilitation in the recovery of walking in the neurological population. Curr Opin Neurol. 2001;14:735–40.
54. Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in the adult cat. Brain Res. 1987;412:84–95.
55. Rossignol S, Martinez M, Escalona M, Kundu A, Delivet-Mongrain H, Alluin O, Gossard JP. The "beneficial" effects of locomotor training after various types of spinal lesions in cats and rats. Prog Brain Res. 2015;218:173–98.
56. Hesse S, Werner C. Partial body weight supported treadmill training for gait recovery following stroke. Adv Neurol. 2003;92:423–8.
57. Nilsson L, Carlsson J, Danielsson A, et al. Walking training of patients with hemiparesis at an early stage after stroke: a comparison of walking training on a treadmill with body weight support and walking training on the ground. Clin Rehabil. 2001; 15:515–27.
58. Kosak MC, Reding MJ. Comparison of partial body weight-supported treadmill gait training versus aggressive bracing assisted walking post stroke. Neurorehabil Neural Repair. 2000;14:13–9.
59. Wernig A, Muller S, Nanassy A, et al. Laufband therapy based on 'rules of spinal locomotion' is effective in spinal cord injured persons. Eur J Neurosci. 1995;7:823–9.
60. Willoughby KL, Dodd KJ, Shields N, Foley S. Efficacy of partial body weight-supported treadmill training compared with overground walking practice for children with cerebral palsy: a randomized controlled trial. Arch Phys Med Rehabil. 2010;91:333–9.
61. Swe NN, Sendhilnnathan S, van Den Berg M, Barr C. Over ground walking and body weight supported walking improve mobility equally in cerebral palsy: a randomised controlled trial. Clin Rehabil. 2015;29:1108–16.
62. Grecco LA, Zanon N, Sampaio LM, Oliveira CS. A comparison of treadmill training and overground walking in ambulant children with cerebral palsy: randomized controlled clinical trial. Clin Rehabil. 2013;27:686–96.
63. Valentin-Gudiol M, Bagur-Calafat C, Girabent-Farrés M, Hadders-Algra M, Mattern-Baxter K, Angulo-Barroso R. Treadmill interventions with partial body weight support in children under six years of age at risk of neuromotor delay: a report of a Cochrane systematic review and meta-analysis. Eur J Phys Rehabil Med. 2013;49:67–91.
64. Damiano DL, DeJong SL. A systematic review of the effectiveness of treadmill training and body weight support in pediatric rehabilitation. J Neurol Phys Ther. 2009;33:27–44.
65. Mutlu A, Krosschell K, Spira DG. Treadmill training with partial body-weight support in children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2009;51:268–75.
66. Schindl MR, Forstner C, Kern H, Hesse S. Treadmill training with partial body weight support in nonambulatory patients with cerebral palsy. Arch Phys Med Rehabil. 2000;81:301–6.
67. Colombo G, Joerg M, Schreier R, et al. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37:693–700.
68. Hesse S, Uhlenbrock D. A mechanized gait trainer for restoration of gait. J Rehabil Res Dev. 2000;37:701–8.
69. HealthSouth® http://www.healthsouth.com. Accessed 18 Oct 2010.
70. Colombo G, Wirz M, Dietz V. Driven gait orthosis for improvement of locomotor training in paraplegic patients. Spinal Cord. 2001;39:252–5.
71. Hornby TG, Campbell DD, Zemon DH, et al. Clinical and quantitative evaluation of robotic-assisted treadmill walking to retrain ambulation after spinal cord injury. Top Spinal Cord Inj Rehabil. 2005;11:1–17.
72. Husemann B, Müller F, Krewer C, et al. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke. 2007;38:349–54.
73. Mehrholz J, Werner C, Kugler J, et al. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2007; 17:CD006185.
74. Hidler J, Nichols D, Pelliccio M, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23:5–13.
75. Hornby TG, Campbell DD, Kahn JH, et al. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39:1786–92.
76. Pohl M, Werner C, Holzgraefe M, et al. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche

GAngtrainerStudie, DEGAS). Clin Rehabil. 2007;21:17–27.
77. Mehrholz J, Pohl M. Electromechanical-assisted gait training after stroke: a systematic review comparing end-effector and exoskeleton devices. J Rehabil Med. 2012;44:193–9.
78. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2013;7:CD006185.
79. Swinnen E, Duerinck S, Baeyens JP, et al. Effectiveness of robot-assisted gait training in persons with spinal cord injury: a systematic review. J Rehabil Med. 2010;42:520–6.
80. Meyer-Heim A, Ammann-Reiffer C, Schmartz A, Schäfer J, Sennhauser FH, Heinen F, Knecht B, Dabrowski E, Borggraefe I. Improvement of walking abilities after robotic-assisted locomotion training in children with cerebral palsy. Arch Dis Child. 2009;94:615–20.
81. Drużbicki M, Rusek W, Snela S, Dudek J, Szczepanik M, Zak E, Durmala J, Czernuszenko A, Bonikowski M, Sobota G. Functional effects of robotic-assisted locomotor treadmill therapy in children with cerebral palsy. J Rehabil Med. 2013;45:358–63.
82. Edgerton VR, Roy RR. Robotic training and spinal cord plasticity. Brain Res Bull. 2009;78:4–12.
83. Hidler JM, Wall AE. Alterations in muscle activation patterns during robotic-assisted walking. Clin Biomech. 2005;20:184–93.
84. Wolbrecht ET, Chan V, Reinkensmeyer DJ, et al. Optimizing compliant, model-based robotic assistance to promote neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2008;16:286–97.
85. Cai LL, Fong AJ, Otoshi CK, et al. Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. J Neurosci. 2006;26:10564–8.
86. Wu M, Hornby TG, Landry JM, Roth H, et al. A cable-driven locomotor training system for restoration of gait in human SCI. Gait Posture. 2011;33:256–60.
87. Wu M, Kim J, Arora P, Gaebler-Spira DJ, Zhang Y. Locomotor training through a 3D cable-driven robotic system for walking function in children with cerebral palsy: a pilot study. Conf Proc IEEE Eng Med Biol Soc. 2014;177:3529–32.
88. Perry J. Gait analysis: normal and pathological function. Thorofare: SLACK; 1992.
89. Patton JL, Stoykov ME, Kovic M, Mussa-Ivaldi FA. Evaluation of robotic training forces that either enhance or reduce error in chronic hemiparetic stroke survivors. Exp Brain Res. 2006;168:368–83.
90. Sawaki L, Wu CW, Kaelin-Lang A, Cohen LG. Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke. Stroke. 2006;37:246–7.
91. Wu M, Landry JM, Kim J, Schmit BD, Yen SC, Macdonald J. Robotic resistance/assistance training improves locomotor function in individuals post-stroke: a randomized controlled study. Arch Phys Med Rehabil. 2014;95:799–806.
92. Harada ND, Chiu V, Stewart AL. Mobility-related function in older adults: assessment with a 6-minute walk test. Arch Phys Med Rehabil. 1999; 80:837–41.
93. Berg K, Wood-Dauphinee S, Williams JI. The balance scale: reliability assessment with elderly residents and patients with an acute stroke. Scand J Rehabil Med. 1995;27:27–36.
94. Mehrholz J, Kugler J, Pohl M. Locomotor training for walking after spinal cord injury. Cochrane Database Syst Rev. 2012;11:CD006676.
95. Lam T, Pauhl K, Ferguson A, Malik RN, Kin B, Krassioukov A, Eng JJ. Training with robot-applied resistance in people with motor-incomplete spinal cord injury: pilot study. J Rehabil Res Dev. 2015;52:113–30.
96. Israel JF, Campbell DD, Kahn JH, Hornby TG. Metabolic costs and muscle activity patterns during robotic- and therapist-assisted treadmill walking in individuals with incomplete spinal cord injury. Phys Ther. 2006;86:1466–78.
97. Yen SC, Landry JM, Wu M. Size of kinematic error affects retention of locomotor adaptation in human spinal cord injury. J Rehabil Res Dev. 2013;50(9): 1187–200.
98. Houldin A, Luttin K, Lam T. Locomotor adaptations and aftereffects to resistance during walking in individuals with spinal cord injury. J Neurophysiol. 2011;106:247–58.
99. Yen SC, Schmit BD, Landry JM, Roth H, Wu M. Locomotor adaptation to resistance during treadmill training transfers to overground walking in human SCI. Exp Brain Res. 2012;216:473–82.
100. Reisman DS, McLean H, Keller J, Danks KA, Bastian AJ. Repeated split-belt treadmill training improves poststroke step length asymmetry. Neurorehabil Neural Repair. 2013;27:460–8.
101. Wu M, Landry JM, Schmit BD, Hornby TG, Yen SC. Robotic resistance treadmill training improves locomotor function in human spinal cord injury: a pilot study. Arch Phys Med Rehabil. 2012;93:782–9.
102. Inman V, Ralston HJ, Todd F. Human walking. Baltimore: Williams and Wilkins; 1981.
103. Ballaz L, Robert M, Parent A, Prince F, Lemay M. Impaired visually guided weight-shifting ability in children with cerebral palsy. Res Dev Disabil. 2014;35:1970–7.
104. Liao HF, Jeng SF, Lai JS, Cheng CK, Hu MH. The relation between standing balance and walking function in children with spastic diplegic cerebral palsy. Dev Med Child Neurol. 1997;39:106–12.
105. Mulder T, Hochstenbach J. Adaptability and flexibility of the human motor system: implications for neurological rehabilitation. Neural Plast. 2001;8:131–40.
106. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children

with cerebral palsy. Dev Med Child Neurol. 1997;39:214–23.
107. Andersson C, Asztalos L, Mattsson E. Six-minute walk test in adults with cerebral palsy. A study of reliability. Clin Rehabil. 2006;20:488–95.
108. Russell DJ, Rosenbaum PL, Cadman DT, Gowland C, Hardy S, Jarvis S. The gross motor function measure: a means to evaluate the effects of physical therapy. Dev Med Child Neurol. 1989;31:341–52.
109. Yen SC, Schmit BD, Wu M. Using swing resistance and assistance to improve gait symmetry in individuals post-stroke. Hum Mov Sci. 2015;42:212–24.
110. Savin DN, Tseng SC, Whitall J, Morton SM. Poststroke hemiparesis impairs the rate but not magnitude of adaptation of spatial and temporal locomotor features. Neurorehabil Neural Repair. 2013;27:24–34.
111. Edgerton VR, Courtine G, Gerasimenko YP, Lavrov I, Ichiyama RM, Fong AJ, Cai LL, Otoshi CK, Tillakaratne NJ, Burdick JW, Roy RR. Training locomotor networks. Brain Res Rev. 2008;57:241–54.
112. Huang VS, Shadmehr R. Persistence of motor memories reflects statistics of the learning event. J Neurophysiol. 2009;102:931–40.
113. Klassen J, Tong C, Flanagan JR. Learning and recall of incremental kinematic and dynamic sensorimotor transformations. Exp Brain Res. 2005;164:250–9.
114. Kluzik J, Diedrichsen J, Shadmehr R, Bastian AJ. Reach adaptation: what determines whether we learn an internal model of the tool or adapt the model of our arm? J Neurophysiol. 2008;100:1455–64.
115. Lewek MD, Cruz TH, Moore JL, et al. Allowing intralimb kinematic variability during locomotor training poststroke improves kinematic consistency: a subgroup analysis from a randomized clinical trial. Phys Ther. 2009;89:829–39.
116. Mehrholz J, Kugler J, Pohl M. Locomotor training for walking after spinal cord injury. Cochrane Database Syst Rev. 2008;16:CD006676.
117. Scivoletto G, Cosentino E, Mammone A, et al. Inflammatory myelopathies and traumatic spinal cord lesions: comparison of functional and neurological outcomes. Phys Ther. 2008;88:471–84.
118. Lemay JF, Nadeau S. Standing balance assessment in ASIA D paraplegic and tetraplegic participants: concurrent validity of the Berg Balance Scale. Spinal Cord. 2010;48:245–50.
119. Hornby TG, Reinkensmeyer DJ, Chen D. Manually-assisted versus robotic-assisted body weight-supported treadmill training in spinal cord injury: what is the role of each? PM R. 2010;2:214–21.
120. Barbeau H, Fung J, Leroux A, et al. A review of the adaptability and recovery of locomotion after spinal cord injury. Prog Brain Res. 2002;137:9–25.
121. van Hedel HJ, Dietz V. Rehabilitation of locomotion after spinal cord injury. Restor Neurol Neurosci. 2010;28:123–34.
122. Norman KE, Pépin A, Barbeau H. Effects of drugs on walking after spinal cord injury. Spinal Cord. 1998;36:699–715.
123. Winter DA, MacKinnon CD, Ruder GK, Wieman C. An integrated EMG/biomechanical model of upper body balance and posture during human gait. Prog Brain Res. 1993;97:359–67.
124. Aoyagi D, Ichinose WE, Harkema SJ, et al. A robot and control algorithm that can synchronously assist in naturalistic motion during body-weight-supported gait training following neurologic injury. IEEE Trans Neural Syst Rehabil Eng. 2007;15:387–400.
125. Veneman JF, Kruidhof R, Hekman EE, et al. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15:379–86.
126. Schmidt H, Werner C, Bernhardt R, et al. Gait rehabilitation machines based on programmable footplates. J Neuroeng Rehabil. 2007;9(4):2.
127. Hesse S, Tomelleri C, Bardeleben A, Werner C, Waldner A. Robot-assisted practice of gait and stair climbing in nonambulatory stroke patients. J Rehabil Res Dev. 2012;49:613–22.
128. Riener R, Lünenburger L, Jezernik S, et al. Patient-cooperative strategies for robot-aided treadmill training: first experimental results. IEEE Trans Neural Syst Rehabil Eng. 2005;13:380–94.
129. Duschau-Wicke A, von Zitzewitz J, Caprez A, et al. Path control: a method for patient-cooperative robot-aided gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2010;18:38–48.
130. Agrawal SK, Banala SK, Fattah A, et al. Assessment of motion of a swing leg and gait rehabilitation with a gravity balancing exoskeleton. IEEE Trans Neural Syst Rehabil Eng. 2007;15:410–20.
131. Gottschall JS, Kram R. Energy cost and muscular activity required for leg swing during walking. J Appl Physiol. 2005;99:23–30.
132. Torres-Oviedo G, Bastian AJ. Seeing is believing: effects of visual contextual cues on learning and transfer of locomotor adaptation. J Neurosci. 2010;30:17015–22.
133. Reisman DS, Wityk R, Silver K, Bastian AJ. Split-belt treadmill adaptation transfers to overground walking in persons poststroke. Neurorehabil Neural Repair. 2009;23:735–44.
134. Benson I, Hart K, Tussler D, van Middendorp JJ. Lower-limb exoskeletons for individuals with chronic spinal cord injury: findings from a feasibility study. Clin Rehabil. 2016;30(1):73–84.
135. Watanabe H, Tanaka N, Inuta T, Saitou H, Yanagi H. Locomotion improvement using a hybrid assistive limb in recovery phase stroke patients: a randomized controlled pilot study. Arch Phys Med Rehabil. 2014;95:2006–12.
136. Zeilig G, Weingarden H, Zwecker M, Dudkiewicz I, Bloch A, Esquenazi A. Safety and tolerance of the ReWalk™ exoskeleton suit for ambulation by people with complete spinal cord injury: a pilot study. J Spinal Cord Med. 2012;35:96–101.

Robot-Aided Gait Training with LOPES

22

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 modest positive effects on walking ability. It is widely acknowledged that the control and design of the robotic devices need 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 and 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, chronic stroke survivors, and incomplete spinal cord injury subjects. Future clinical testing has to demonstrate whether the outcome of robot-aided gait training can indeed be improved by increasing its task specificity and the active contribution of the patient and by allowing different movement strategies.

Keywords

Impedance control • Assist as needed • Recovery and compensation • Task specific • Stroke • Spinal cord injury • Gait training

E.H.F. van Asseldonk, PhD (✉)
H. van der Kooij, ir, PhD
Department of Biomechanical Engineering,
University of Twente, Enschede, The Netherlands
e-mail: e.h.f.vanasseldonk@utwente.nl;
h.vanderkooij@utwente.nl

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22.1 State of the Art in Robot-Aided Gait Training

Robotic gait training devices have been on the market since the start of the millennium. Currently, among others are the Gait Trainer GT I (Reha-Stim, Germany) [1], the G-EO System (Reha Technology, Switzerland), the ReoAmbulator (Motorika, USA), and the market-leading Lokomat (Hocoma AG, Switzerland) [2]. In addition, different research institutes and companies are developing robotic gait trainers among which are ALEX (Active Leg EXoskeleton) [3], a combination of PAM (Pelvic Assist Manipulator) and POGO (Pneumatically Operated Gait Orthosis) [4] and LOPES (Lower-Extremity Powered ExoSkeleton) [5]. All these devices support the patients during treadmill walking. There are also developments in the design of wearable exoskeletons that were originally developed for assistive use but are now also being used as a therapeutic device in clinics [6, 7] like Ekso GT (Ekso Bionics, USA), HAL (Cyberdyne, Japan) [8], ReWalk (Argo Medical Technologies Ltd., Israel).

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 22.1 provides an overview of the DOFs of the aforementioned devices. Notably most 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, only Lokomat is now available with a module that allows pelvis mediolateral translation and transverse rotation. Regarding the control of the devices, the most distinctive feature is whether the device controls/enforces positions of the limbs or controls the interaction forces between the robot and the limbs. Whereas the earlier versions of the commercially available devices were all position controlled, more and more of these devices become available with force control. The majority of research devices are force controlled.

The effectiveness of robot-aided gait training has been extensively studied over the years in many (randomized) clinical trials primarily using 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 [9, 10]. Some studies even showed an increase in the number of subjects that could ambulate independently after receiving robot-aided gait training [11]. However, later two large randomized clinical trials, one in chronic stroke survivors [12] and one in subacute stroke survivors [13], 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 [13]. A recent Cochrane review [14] included 23 trials involving 999 participants and concluded that stroke survivors receiving robot-aided gait training in combination with physical therapy are more likely to achieve independent gait than stroke survivors who only receive physical therapy. Especially the people in the first few months after stroke who cannot walk independently seem to profit most. For spinal cord injury subjects, the effects of robot-aided gait training have also been frequently assessed. However, here a systematic review concluded that robotic gait training did not improve functional recovery more than other forms of gait training [15].

There is still much room for improvement to further optimize robot-aided gait training such that patients show larger and/or faster functional improvement and that a larger proportion of patients can benefit from it. Clinicians, (neuro) scientist, 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 [16]. 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.

Table 22.1 Overview of the major features of the mechanical design and control for different robotic gait devices

		Gait trainer GT I	G-EO system	Lokomat	ReoAmbulator	ALEX III	PAM/POGO	LOPES I	LOPES II	Ekso	HAL	ReWalk
Mechanical design												
Type[a]		EE	EE	EX	EX	EX	EX	EX	EE[c]	EX	EX	EX
Supports walking on		P	P	TR	TR	TR	TR	TR	TR	OG	OG	OG
Degrees of freedom												
Pelvis	Vertical translation	–	–	F	F	F	A	F	F	F	F	F
	Horizontal translation	–	–	C[b]	C	A	A	A	A	F	F	F
	Rotations	C/–	C/–	C[b]	C	A	A	C	F	F	F	F
Hip	Flexion/extension	–	–	A	A	A	A	A	A	A	A	A
	Abduction/adduction	–	–	C	C	A	F	A	A	C	C	C
	Exo-/endoration	C	C	C	C	C	F	C	F	C	C	C
Knee	Flexion/extension	–	–	A	A	A	A	A	A	A	A	A
Ankle	Plantar-/dorsiflexion	–	–	F	F	A	F	F	F	C	C	C
Foot	Vertical translation	A	A	–	–	–	–	–	–	–	–	–
	Forward/backward translation	A	A	–	–	–	–	–	–	–	–	–
Control		pos	for	pos/for	for	for	for	for	for	pos/for	for	pos

Every year several new devices are developed and introduced. This table does not give a complete overview of all existing devices

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 or walking on footplates (*P*). 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. The control of devices is either position (*pos*) control or a form in which interaction forces (*for*) are used

[a]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

[b]Lokomat now also provides an additional module that lets the pelvis mediolateral translation and transverse rotation free

[c]LOPES II is not a typical end-effector as the subject is not only attached to the robot at the feet but also at the shank and pelvis

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 active and/or passive DOFs aim at improving on one or more of these aspects. We have been developing the LOPES robotic gait training device 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 first prototype of the LOPES device into more detail and introduce its mechanical design and control. We will discuss the results that were obtained with the LOPES I device. Finally we will shortly introduce the newly developed LOPES II, and we will elaborate on the future perspectives.

22.2 Background and Rational for Advancement in Robot-Aided Training

22.2.1 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 [17, 18]. 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 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 [19] 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 for (impaired) human gait are constrained. Most 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 or very limited as the devices impose stability [20] by constraining pelvic movements and hip ab-/adduction. Kollen and colleagues [21] 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 allows 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.

22.2.2 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 [22]. 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 one recovery mechanism over the other. Furthermore it seems that with the passage of time, the importance of compensation in attaining functional improvement increases. 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 [23], a limited amount of generated propulsion (coordinated output) by the paretic leg does not necessarily restrict the gait speed [24], and improvements in walking ability during recovery are not accompanied by a restoration of the paretic muscle coordination patterns [25]. An argument heard often against the use of compensation is that, in the long run, it might impede gains in other functional tasks. In the abovementioned 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 interventions result 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 [26]. 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 not only be directed at recovery but also on 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.

22.2.3 Active Training Required to Induce Cortical Plasticity

In 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 [27]. 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 human,

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 [28, 29] that allowed investigation of supraspinal control of walking. For instance, Miyai and colleagues [30] 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 [31–33]. Also in spinal cord injury subjects, 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 [34].

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 [35] 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 [36], 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 plantar- and dorsiflexion, passive training in which subjects were assisted in the pursuit tracking task, or non-skill training consisting of just voluntary performing plantar- 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; they should also be allowed to experience errors in the task execution as in the end task execution errors drive motor learning [30].

22.3 Mechanical Design of LOPES

Robotic gait training devices differ widely in their (actuated) DOFs and how they are controlled (see Table 22.1). 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 for 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 22.1 and Fig. 22.1) are chosen in such a way that they allow unhindered walking in the device (transparent mode), allow the use of compensatory strategies, and 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

Fig. 22.1 Subject attached in the first prototype of the LOPES device. The eight actuated DOFs are schematically indicated

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.

When determining the essential aspects that need to be supported, we took into account 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 [37, 38]. 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 affect foot placement and increases trunk motion [39, 40]. 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 [41], 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 orthosis has been developed to specifically support the ankle during gait [42]. Future clinical testing with these devices has to show the additional value of incorporating ankle plantar flexion [43].

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 built 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 [44]. 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 [45].

22.4 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 patients' legs through a prescribed gait pattern, irrespective of the patients' 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 these approaches to determine the amount of force to apply [46], but recently also some reference-free approaches have been explored in the therapeutic use of wearable exoskeletons [47]. 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 patients' 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 and 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 [48, 49] 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 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 patients.

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. Dushau-Wicke and colleagues [50] 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. A nice approach to achieve the latter is to use 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 which 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 [51]. 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 [52, 53] have provided evidence that healthy humans but also stroke survivors [54, 55] and spinal cord injury subjects [56] 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. 22.2). First, the therapist selects the subtasks, which are impaired in the subject, to be controlled by LOPES [51]. Second, the amount of support in each of the controlled subtasks is adapted to the patient's needs by using an adaptive algorithm [49, 51, 57]. Basically, this algorithms increase the impedance, and as such the amount of support, on a subtask if the patient performs badly and "errors" are large and decreases it if the patient's performance improves [49]. 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, so they don't become reliant on the support [57]. 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. 22.2), and the control is actually reset for every gait cycle. Some of these subtasks are controlled in series; however, at some phases of gait, more than one subtask needs to be controlled. 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.

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 subtask can be presented to the subject (see Fig. 22.2). 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.

22.5 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 [58]. In this study

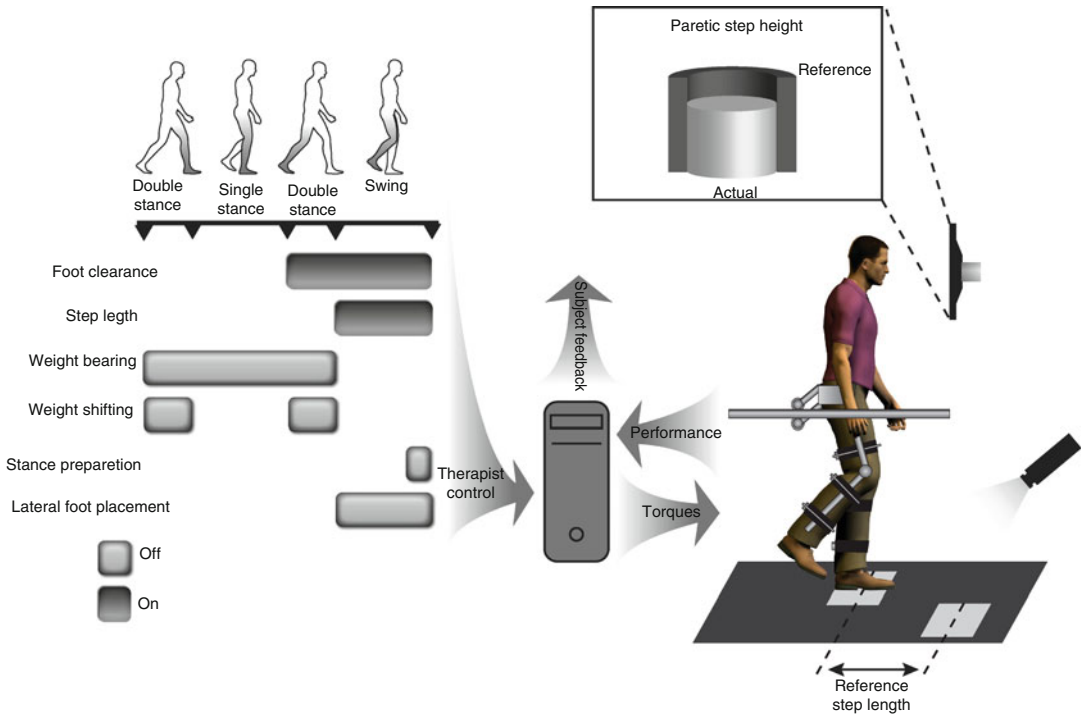

Fig. 22.2 Schematic overview of the used approach to selectively support different subtasks of gait with LOPES. This control allows for an intuitive control for the patient and therapist. The therapist decides on which aspects of gait the patient needs support. Based on this selection, the implemented 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, also its actual performance on each subtask can be displayed

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. The 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. 22.3). 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

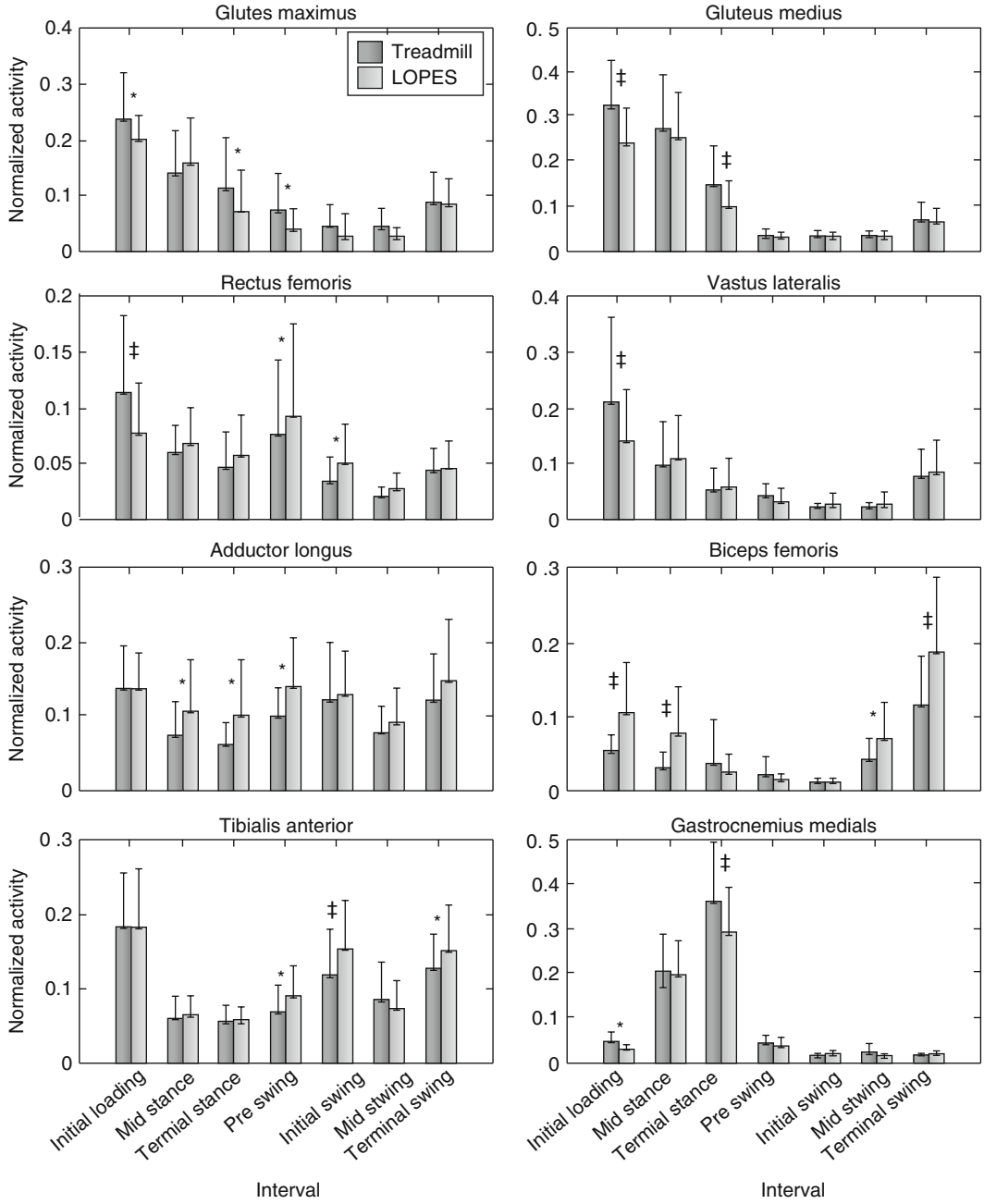

Fig. 22.3 Muscle activity of healthy subjects walking in LOPES when it is controlled to provide no assistance. Mean normalized integrated activity for eight leg muscles over seven gait intervals for LOPES walking and treadmill walking. The *vertical bars* indicate the standard deviation over the different subjects. Significant difference between LOPES walking and treadmill walking are indicated with a * for $p<0.05$ and with a ‡ for $p<0.001$ (Reprinted from Van Asseldonk et al. [58]; with permission. © 2008 IEEE)

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. 22.4). Most subjects compensated for this by using a hip circumduction strategy

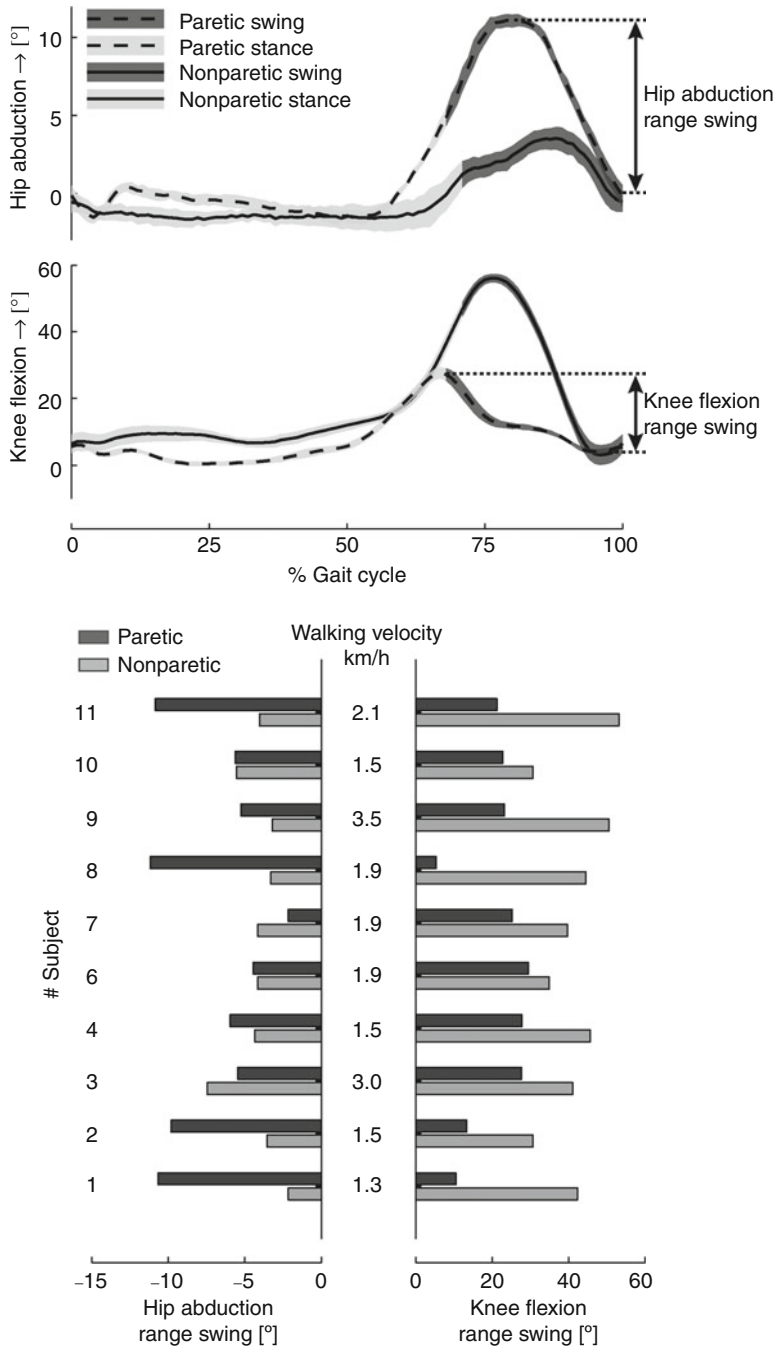

Fig. 22.4 Compensatory strategies of chronic stroke survivors walking with LOPES. The upper graphs show averaged trajectories of hp ab-/adduction and knee flexion/extension of a typical chronic stroke survivor (subject 11) walking with LOPES, which is controlled to provide no assistance. The shaded areas 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

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 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 [51] and weight bearing [59]. In this experiment 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. The reference values were set at a 15 % increase with respect to their normal values (when walking without support), and two different support levels, compliant and stiff, were used. The support of step height resulted in an increase of the step height (see Fig. 22.5) in the healthy subjects as well as the stroke survivors. This increase was caused by an increase of the knee flexion during swing. The use of the stiff support resulted in a larger increase of the step height for the healthy subjects as well as the stroke survivors. The support was selective in that it did not affect the relative duration of the different gait phases or other basic gait parameters like step length or cycle time.

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 [60, 61] 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 [62] allow the modulation of the amount of support 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 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 [59]. This 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 [49] in the selective control of step height [51, 57]. 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 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

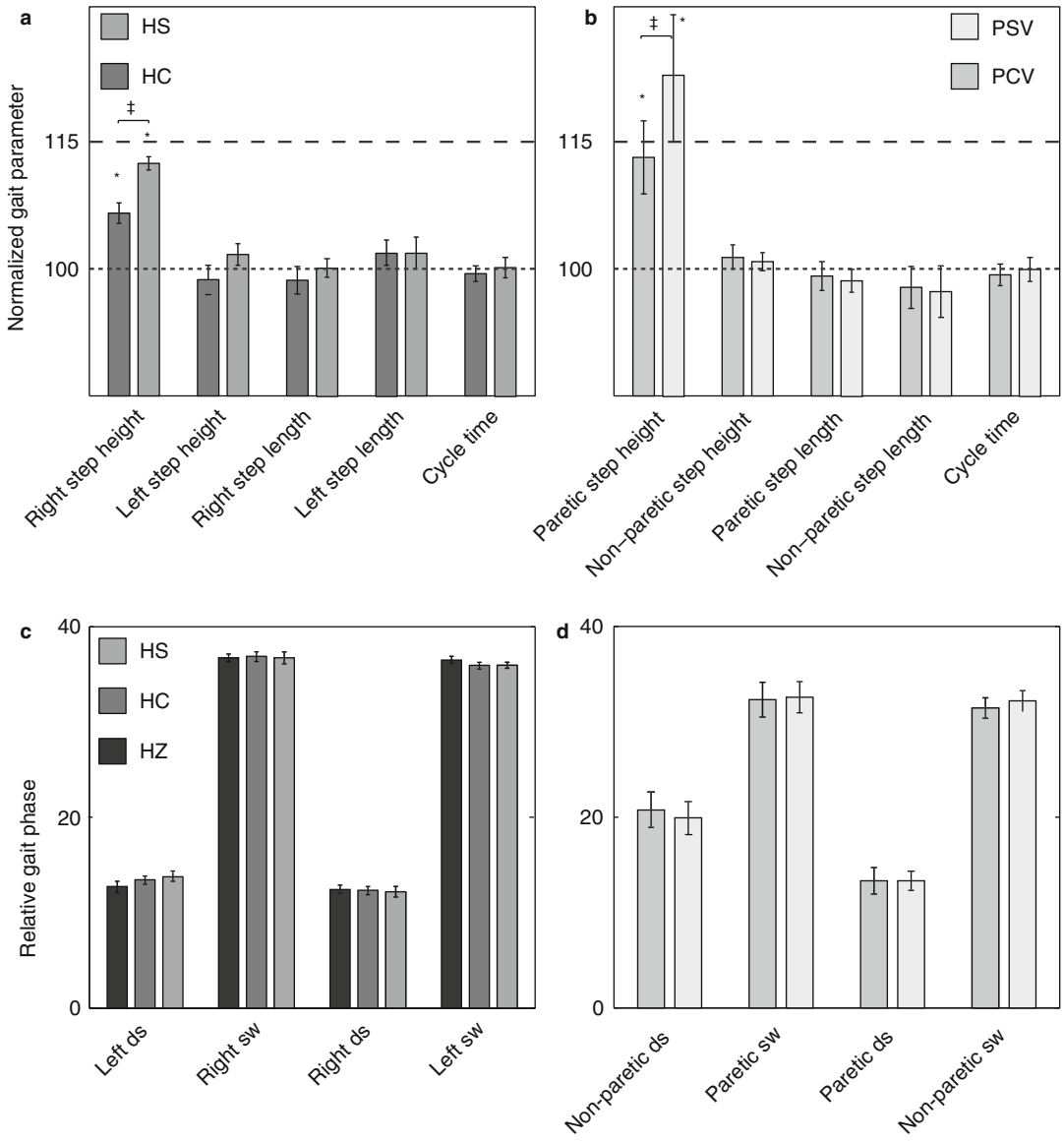

Fig. 22.5 Effects of exposure to selective subtask control of step height on different gait variables (**a**, **b**) and relative phase duration (**c**, **d**) in healthy subjects (**a**, **c**) and chronic stroke survivors (**b**, **d**). The *bars* indicate average values when subjects were receiving support. The healthy subjects walked with compliant (HC) and stiff (HS) support of step height. As a reference, also the relative gait phases during walking when receiving no assistance are shown (HZ). Stroke survivors also walked with the compliant (PCV) and stiff support (PSV) but also received visual feedback in the form of a bar graph on their step height in the completed step. *DS* indicates double stance and *Sw* indicates the swing phase. The *error bars* indicate the standard error of the mean. $*p<0.05$. ++ indicates a significant difference between the compliant and stiff control. The *dashed horizontal lines* indicate the set reference values (Reprinted from Koopman et al. [51]; with permission)

subject's capabilities (see Fig. 22.6). 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

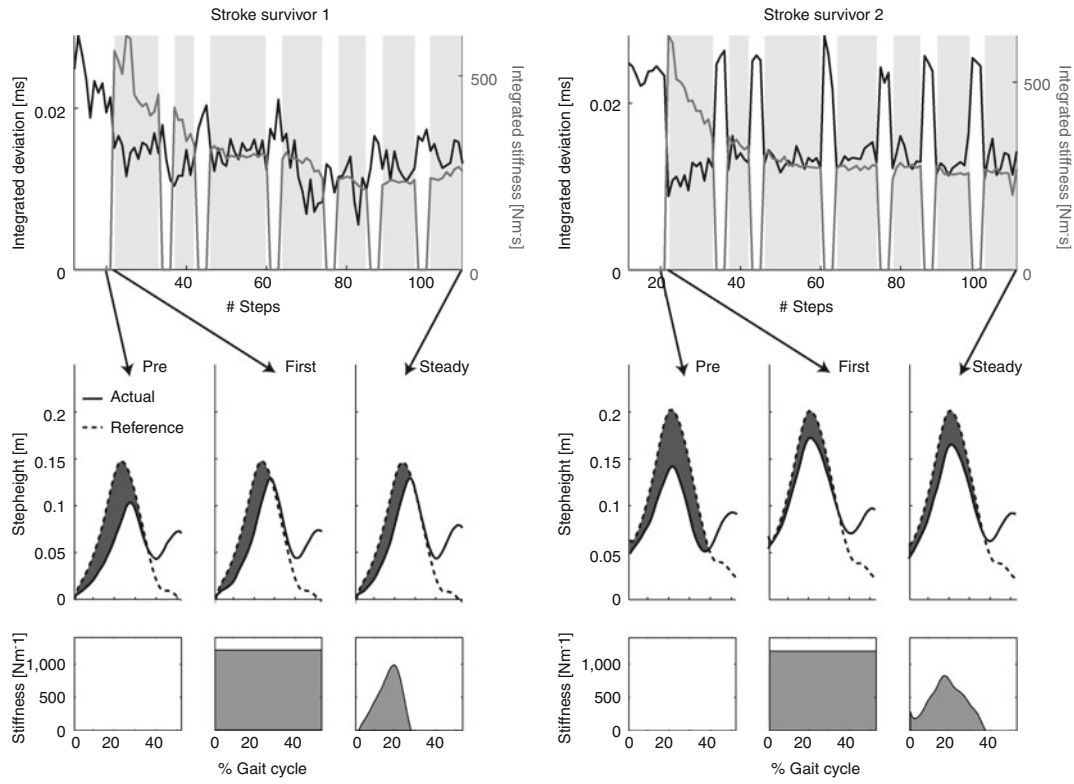

Fig. 22.6 Shaping of the virtual stiffness of the step height controller in two ambulatory chronic stroke survivors. The left and right set of graphs shows the responses for two different chronic stroke survivors. The *upper row* shows the course of the deviation from the reference (*light gray line 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), the first step of exposure (stiffness is constant, no shaping), and for a step when subjects walked for 70 steps with the support

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. 22.6) 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 pre-support values. Still, the subjects did not rely on the support, since the deviation did not increase above the pre-support values. Other subjects utilized the robotic support (see subject on the left in Fig. 22.6) to improve their own performance. In these subjects the integrated error during the catch trials decreased in comparison to the pre-support 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.

22.5.1 Explorative Clinical Trials Using LOPES

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 gait was 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. 22.7). A larger gain in speed during training compared to overground walking has also been reported for body weight support training. 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.

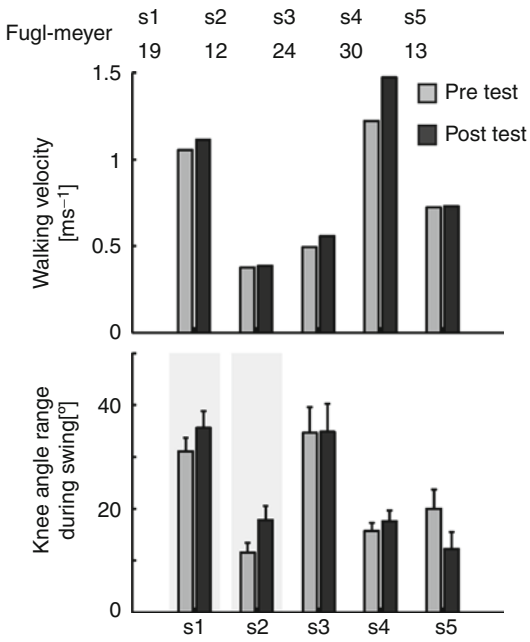

Fig. 22.7 Effect of training with selective support of step height on overground walking velocity and knee angular movement in chronic ambulatory stroke survivors. *Vertical bars* indicate the standard deviation. Subject 5 experienced a serious fall in a home situation during the training period, but was able to complete the training

Recently we performed an explorative clinical trial in a group of ten chronic incomplete spinal cord injured individuals to assess the effect of training in LOPES on walking ability and quality [63]. After training three times a week for 8 weeks, the participants improved significantly on walking speed (10-m walk test, pre, 0.61 m/s; post, 0.64 m/s), walking endurance (6-min walk test, pre, 184.4 m; post, 212.9 m), and muscle strength (lower extremity motor score [64], pre, 34.4; post, 37.8). These improvements were retained during the 8-week follow-up. The improvements in walking ability were accompanied by significant improvements in walking quality (spatiotemporal variables and joint kinematics) as assessed by using clinical gait analysis. Here, the increase in step length and hip range of motion on the more affected side exceeded the changes observed on the stronger leg. As we did not include a control group, we do not know yet whether training in

LOPES was more effective than conventional gait training. The magnitude of the observed improvements was similar to those observed in other studies assessing the effects of robot-aided gait training in chronic SCI subjects [65].

In this study we focused on having a large active contribution from the patients by minimizing the impedance levels and thus the amount of support given by the robot. As a result, some participants, especially the slow walkers, could not walk in the device for the intended 45 min. The mean effective walking duration in each session was 19 min which is considerably lower than the training duration of 45 min that is often achieved in studies using position-controlled robotic gait trainers [65–67]. Since the observed improvements were similar as in other studies [65], we concluded that similar gains in walking ability can be accomplished with less training time. Actually, the biggest gains in walking ability were observed in slow walkers with the lowest training duration, suggesting that active participation is at least as important as training duration.

22.6 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, that the amount of support can automatically be adapted to the specific needs of the patients, and that the effectiveness of gait therapy in chronic SCI subjects is significant and comparable to results obtained with other robotic gait trainers.

22.6.1 Development of LOPES II

From the knowledge and expertise gained with the first LOPES, two companies (MOOG and Demcon) and the University of Twente developed the LOPES II (Fig. 22.8). The differences with the first prototype are that Lopes II:

Fig. 22.8 Impression of the LOPES II. LOPES II has two shadow legs that are connected to the human legs by push-pull rods. The shadow leg is actuated in shank flexion/extension and thigh flexion/extension and abduction/adduction. The shadow leg is suspended on a stage connected to the patient's pelvis with rods, actuated in pelvis forward/aft- and mediolateral direction. The other degrees of freedom are not powered but also not constrained by the use of passive joints. (Permission from Gijs van Ouwerkerk)

Uses admittance control instead of impedance control which decreases the minimal impedance as needed for zero support and increases the maximal impedance used during full support

Has a lower reflected inertia, which is important since a too high reflected inertia affects the kinematics, and metabolic cost of human gait [68] and dynamic balance control

Has more passive degrees of freedom, including all pelvis rotations, and does not constrain any physiological joint so that the device interferes even less with the natural dynamics of human gait

Has a non-exoskeleton structure, which minimizes donning and doffing time to about 10 min for the first session to about 6 min for recurring sessions, and allows free arm swing during walking

Has an improved intuitive interactive graphical user interface, intended for usage by therapists

Preliminary evaluations of the LOPES II showed that when the powered degrees of freedom are set to its minimal impedance, walking in the device resembles free walking, which is an important requisite to allow task-specific training. Clinical pilots, including subjects with functional ambulation category scores from 0 to 5, demonstrate that LOPES II can provide sufficient support to let severely affected SCI subjects and stroke survivors walk and that we can provide selective support to impaired aspects of gait of mildly affected patients.

A randomized clinical trial in (sub)acute patients with LOPES II has started to test the hypothesis that selective support subtasks according to the minimal robotic intervention principle increase the active participation of patients and result in functional improvements that are larger than obtained with conventional therapy. Clinical gait analysis will be performed for each patient before starting the training to determine which aspect of gait is most affected and will be primarily targeted.

22.7 Perspectives

The application of robots in gait training is a relatively new development. The functional outcome after training with the first-generation devices already showed modest improvements with respect to conventional training; however, there seems substantial room for larger improvements. 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 the task-specificity of training, to increase the active participation and to facilitate different recovery processes, whereas other researchers and companies might want to improve the training on other aspects. Clinical trials need to prove that the new 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 cannot only be used to apply the training but also to predict whether the training will be effective and what the content of the training should be.

References

1. Hesse S, Uhlenbrock D. A mechanized gait trainer for restoration of gait. J Rehabil Res Dev. 2000; 37(6):701–8.
2. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37(6):693–700.
3. Banala S, Kim S, Agrawal S, Scholz J. Robot assisted gait training with active leg exoskeleton (ALEX). IEEE Trans Neural Syst Rehabil Eng. 2009;17(1):2–8.
4. Aoyagi D, Ichinose W, Harkema S, Reinkensmeyer D, Bobrow J. A robot and control algorithm that can synchronously assist in naturalistic motion during body-weight-supported gait training following neurologic injury. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):387–400.

5. Veneman J, Kruidhof R, Hekman E, Ekkelenkamp R, Van Asseldonk E, Van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379–86.
6. Nilsson A, Vreede KS, Häglund V, Kawamoto H, Sankai Y, Borg J. Gait training early after stroke with a new exoskeleton—the hybrid assistive limb: a study of safety and feasibility. J Neuroeng Rehabil. 2014;11(1):92.
7. Benson I, Hart K, Tussler D, van Middendorp JJ. Lower-limb exoskeletons for individuals with chronic spinal cord injury: findings from a feasibility study. Clin Rehabil. 2015;30:73–84.
8. Kawamoto H, Sankai Y. Power assist system hal-3 for gait disorder person. Int Conf Comp Handicapped Persons. 2002;2398:196–203.
9. Husemann B, Müller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke. 2007;38(2):349–54.
10. Mayr A, Kofler M, Quirbach E, Matzak H, Frohlich K, Saltuari L. Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair. 2007;21(4):307–14.
11. Pohl M, Werner C, Holzgraefe M, Kroczek G, Mehrholz J, Wingendorf I, et al. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). Clin Rehabil. 2007;21(1):17–27.
12. Hornby T, Campbell D, Kahn J, Demott T, Moore J, Roth H. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39(6):1786–92.
13. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5–13.
14. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2013;7:CD006185.
15. Swinnen E, Duerinck S, Baeyens J-P, Meeusen R, Kerckhofs E. Effectiveness of robot-assisted gait training in persons with spinal cord injury: a systematic review. J Rehabil Med. 2010;42(6):520–6.
16. Dobkin BH, Duncan PW. Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil Neural Repair. 2012;26(4):308–17.
17. van Peppen R, Kwakkel G, Wood-Dauphinee S, Hendriks H, van der Wees P, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil. 2004;18(8):833–62.
18. Bayona N, Bitensky J, Salter K, Teasell R. The role of task-specific training in rehabilitation therapies. Top Stroke Rehabil. 2005;12(3):58–65.
19. Neckel ND, Blonien N, Nichols D, Hidler J. Abnormal joint torque patterns exhibited by chronic stroke subjects while walking with a prescribed physiological gait pattern. J Neuroeng Rehabil. 2008;5:19.
20. Domingo A, Ferris DP. Effects of physical guidance on short-term learning of walking on a narrow beam. Gait Posture. 2009;30(4):464–8.
21. Kollen B, van de Port I, Lindeman E, Twisk J, Kwakkel G. Predicting improvement in gait after stroke: a longitudinal prospective study. Stroke. 2005;36(12):2676–80.
22. Levin M, Kleim J, Wolf S. What do motor "recovery" and "compensation" mean in patients following stroke? Neurorehabil Neural Repair. 2009;23(4):313–9.
23. Kim C, Eng J. Magnitude and pattern of 3D kinematic and kinetic gait profiles in persons with stroke: relationship to walking speed. Gait Posture. 2004;20(2):140–6.
24. Bowden MG, Balasubramanian CK, Neptune RR, Kautz SA. Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking. Stroke. 2006;37(3):872–6.
25. Buurke JH, Nene AV, Kwakkel G, Erren-Wolters V, IJzerman MJ, Hermens HJ. Recovery of gait after stroke: what changes? Neurorehabil Neural Repair. 2008;22(6):676–83.
26. Jonsdottir J, Cattaneo D, Recalcati M, Regola A, Rabuffetti M, Ferrarin M, et al. Task-oriented biofeedback to improve gait in individuals with chronic stroke: motor learning approach. Neurorehabil Neural Repair SAGE Publ. 2010;24(5):478–85.
27. van de Crommert H, Mulder T, Duysens J. Neural control of locomotion: sensory control of the central pattern generator and its relation to treadmill training. Gait Posture. 1998;7(3):251–63.
28. Gwin JT, Gramann K, Makeig S, Ferris DP. Electrocortical activity is coupled to gait cycle phase during treadmill walking. Neuroimage. 2011;54(2):1289–96.
29. Petersen TH, Willerslev-Olsen M, Conway BA, Nielsen JB. The motor cortex drives the muscles during walking in human subjects. J Physiol. 2012;590(Pt 10):2443–52.
30. Miyai I, Tanabe H, Sase I, Eda H, Oda I, Konishi I, et al. Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. Neuroimage. 2001;14(5):1186–92.
31. Miyai I, Yagura H, Hatakenaka M, Oda I, Konishi I, Kubota K. Longitudinal optical imaging study for locomotor recovery after stroke. Stroke. 2003;34(12):2866–70.
32. Enzinger C, Dawes H, Johansen-Berg H, Wade D, Bogdanovic M, Collett J, et al. Brain activity changes associated with treadmill training after stroke. Stroke. 2009;40(7):2460–7.

33. Luft A, Macko R, Forrester L, Villagra F, Ivey F, Sorkin J, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. Stroke. 2008;39(12): 3341–50.
34. Thomas SL, Gorassini MA. Increases in corticospinal tract function by treadmill training after incomplete spinal cord injury. J Neurophysiol. 2005;94(4):2844–55.
35. Lotze M, Braun C, Birbaumer N, Anders S, Cohen L. Motor learning elicited by voluntary drive. Brain. 2003;126(Pt 4):866–72.
36. Perez M, Lungholt B, Nyborg K, Nielsen J. Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. Exp Brain Res. 2004;159(2):197–205.
37. Hof A. The "extrapolated center of mass" concept suggests a simple control of balance in walking. Hum Mov Sci. 2008;27(1):112–25.
38. Kooij HVD, Jacobs R, Koopman B, Helm FVD. An alternative approach to synthesizing bipedal walking. Biol Cybern. 2003;88(1):46–59.
39. Veneman J, Menger J, Van Asseldonk E, van der Helm F, Van der Kooij H. Fixating the pelvis in the horizontal plane affects gait characteristics. Gait Posture. 2008;28(1):157–63.
40. Bauby C, Kuo A. Active control of lateral balance in human walking. J Biomech. 2000;33(11):1433–40.
41. Zajac F, Neptune R, Kautz S. Biomechanics and muscle coordination of human walking: part II: lessons from dynamical simulations and clinical implications. Gait Posture. 2003;17(1):1–17.
42. Ferris D, Czerniecki J, Hannaford B. An ankle-foot orthosis powered by artificial pneumatic muscles. J Appl Biomech. 2005;21(2):189–97.
43. Duerinck S, Swinnen E, Beyl P, Hagman F, Jonkers I, Vaes P, et al. The added value of an actuated ankle-foot orthosis to restore normal gait function in patients with spinal cord injury: a systematic review. J Rehabil Med. 2012;44(4):299–309.
44. Veneman J, Ekkelenkamp R, Kruidhof R, van der Helm F, Van der Kooij H. A series elastic- and bowden-cable-based actuation system for use as torque actuator in exoskeleton-type robots. Int J Robot Res. 2006;25(3):261–81.
45. Vallery H, Ekkelenkamp R, Van der Kooij H, Buss M. Passive and accurate torque control of series elastic actuators. IEEE/RSJ International Conference on Intelligent Robots and Systems, IEEE. San Diego, United States. 2007. p. 3534–8.
46. Marchal-Crespo L, Reinkensmeyer DJ. Review of control strategies for robotic movement training after neurologic injury. J Neuroeng Rehabil. 2009;6:20.
47. Murray SA, Ha KH, Hartigan C, Goldfarb M. An assistive control approach for a lower-limb exoskeleton to facilitate recovery of walking following stroke. IEEE Trans Neural Syst Rehabil Eng. 2014;23:441–9.
48. Emken J, Benitez R, Reinkensmeyer D. Human-robot cooperative movement training: learning a novel sensory motor transformation during walking with robotic assistance-as-needed. J Neuroengineering Rehabil. 2007;4:8.
49. Emken JL, Harkema SJ, Beres-Jones JA, Ferreira CK, Reinkensmeyer DJ. Feasibility of manual teach-and-replay and continuous impedance shaping for robotic locomotor training following spinal cord injury. IEEE Trans Biomed Eng. 2008;55(1):322–34.
50. Duschau-Wicke A, Zitzewitz Von J, Caprez A, Lunenburger L, Riener R. Path control: a method for patient-cooperative robot-aided gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng IEEE. 2010;18(1):38–48.
51. Koopman B, van Asseldonk EHF, van der Kooij H. Selective control of gait subtasks in robotic gait training: foot clearance support in stroke survivors with a powered exoskeleton. J Neuroeng Rehabil. 2013;10:3.
52. McGowan CP, Neptune RR, Clark DJ, Kautz SA. Modular control of human walking: adaptations to altered mechanical demands. J Biomech. 2010;43(3):412–9.
53. Neptune RR, Clark DJ, Kautz SA. Modular control of human walking: a simulation study. J Biomech. 2009;42(9):1282–7.
54. Allen JL, Kautz SA, Neptune RR. The influence of merged muscle excitation modules on post-stroke hemiparetic walking performance. Clin Biomech (Bristol, Avon). 2013;28(6):697–704.
55. Coscia M, Monaco V, Martelloni C, Rossi B, Chisari C, Micera S. Muscle synergies and spinal maps are sensitive to the asymmetry induced by a unilateral stroke. J Neuroeng Rehabil. 2015;12(1):39.
56. Hayes HB, Chvatal SA, French MA, Ting LH, Trumbower RD. Neuromuscular constraints on muscle coordination during overground walking in persons with chronic incomplete spinal cord injury. Clin Neurophysiol. 2014;125(10):2024–35.
57. van Asseldonk EHF, Koopman B, Buurke JH, Simons CD, Van der Kooij H. Selective and adaptive robotic support of foot clearance for training stroke survivors with stiff knee gait. IEEE International Conference on Rehabilitation Robotics, Kyoto, Japan. 2009. p. 602–7.
58. Van Asseldonk E, Veneman J, Ekkelenkamp R, Buurke J, van der Helm F, Van der Kooij H. The effects on kinematics and muscle activity of walking in a robotic gait trainer during zero-force control. IEEE Trans Neural Syst Rehabil Eng. 2008;16:360–70.
59. Van der Kooij H, Koopman B, van Asseldonk E. Body weight support by virtual model control of a impedance controlled exoskeleton (LOPES) for gait training. 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Vancouver, Canada. 2008. p. 1969–72.
60. van Hedel H, Tomatis L, Muller R. Modulation of leg muscle activity and gait kinematics by walking speed and bodyweight unloading. Gait Posture. 2006; 24(1):35–45.
61. Threlkeld A, Cooper L, Monger B, Craven A, Haupt H. Temporospatial and kinematic gait alterations during treadmill walking with body weight suspension. Gait Posture. 2003;17(3):235–45.
62. Frey M, Colombo G, Vaglio M, Bucher R, Jorg M, Riener R. A novel mechatronic body weight support

system. IEEE Trans Neural Syst Rehabil Eng. 2006;14(3):311–21.
63. Fleerkotte BM, Koopman B, Buurke JH, van Asseldonk EHF, van der Kooij H, Rietman JS. The effect of impedance-controlled robotic gait training on walking ability and quality in individuals with chronic incomplete spinal cord injury: an explorative study. J Neuroengineering Rehabil. 2014;11(1):26.
64. Maynard Jr FM, Bracken MB, Creasey G, Ditunno Jr JF, Donovan WH, Ducker TB, et al. International standards for neurological and functional classification of spinal cord injury. Spinal Cord. 1997;35(5):266–74.
65. van Nunen MPM. Recovery of walking ability using a robotic device. PhD Thesis. Amsterdam: Free University, Amsterdam; 2013.
66. Wirz M, Zemon DH, Rupp R, Scheel A, Colombo G, Dietz V, et al. Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil. 2005;86(4):672–80.
67. Field-Fote EC, Roach KE. Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Phys Ther. 2011;91(1):48–60.
68. Meuleman JH, van Asseldonk EHF, Van der Kooij H. The effect of directional inertias added to pelvis and ankle on gait. J Neuroeng Rehabil. 2013;10(1):40.

Robotic Devices for Overground Gait and Balance Training

23

Joseph M. Hidler, Arno H.A. Stienen, and Heike Vallery

Abstract

In recent years, we have seen the emergence of numerous robotic technologies that focus on assisting individuals during overground gait and balance therapy following neurological injury and diseases. In general, these systems provide patients active body-weight support used for fall protection, to enhance postural stability, and to compensate for bilateral weakness during overground gait and balance training. As a result, such systems 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, climbing stairs, 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 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 a range of robotic and non-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 reha-

Disclaimer Author Joseph Hidler is the owner of Aretech, LLC, the manufacturer of the ZeroG gait and balance training system. Author Heike Vallery is one of the inventors of the FLOAT body-weight support system, and she receives revenues from sales of that technology.

J.M. Hidler, PhD (✉)
Aratech, LLC, Ashburn, VA, USA
e-mail: hidler@aretechllc.com

A.H.A. Stienen, BSc, MSc, PhD
Department of Biomechanical Engineering, University of Twente, Enschede, Netherlands

H. Vallery
Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands

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bilitation 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 • Body-weight support • Gait • Walking • Stroke • Spinal cord injury

23.1 Overground Gait Training Systems

Body-weight-supported gait training has been the subject of intensive study over the last two decades. Here, a harness is placed around the torso of the individual being trained, which is then connected to an 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 start walking early after neurological and musculoskeletal injuries. The first generation of body-weight support systems were mounted over a treadmill with therapists sitting were the treadmill providing assistance to the patient. This therapy concept was based on a rich literature of animal studies that demonstrated treadmill-based gait training with body-weight support could restore stable, reliable stepping patterns in felines and rodents [1–3]. The obvious thinking was that if such an intervention worked in animals, perhaps it could also have clinical benefits to humans.

A number of large randomized clinical studies have been designed to evaluate the efficacy of training individuals with neurological injuries using body-weight-supported treadmill training with therapist assistance. For example, a multicenter randomized clinical trial compared the effects of body-weight-supported treadmill training with comparable overground gait training in individuals with incomplete spinal cord injury [4]. One hundred and 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) or overground walking speed.

Similar results have been reported in stroke populations. Duncan and colleagues enrolled 408 subacute stroke patients into a three-arm study that compared body-weight-supported treadmill training beginning at 2 months post stroke to the same intervention beginning at 6 months post stroke [5]. Both of these groups were compared to a cohort of participants who home-based exercises. All subjects completed 36 sessions over a 12-week period. The investigators reported no differences between the groups at 12 months in terms of improvements in walking speed or 6-min walk tests, yet the group in the home-based exercise group fell significantly less than the other groups trained on the treadmill.

One potential limitation with manual-assisted treadmill training with body-weight support is that training sessions are often inconsistent and limited in duration due to therapist fatigue. Hidler et al. [6] investigated whether robotic-assisted gait training on a treadmill with body-weight support was more effective than conventional overground gait training in subacute stroke patients. Sixty-three subjects completed the study where half of the subjects were trained for 24 1-h sessions on the treadmill with robotic assistance, while the control group received an equal dose of therapy focusing on walking, postural control, and balance activities. It was found that the group of subjects trained with overground, conventional gait and balance therapy improved their walking speed

by twice as much as those trained by the robot and were able to walk significantly further in a 6-min walk test than the robot group.

While training individuals with spinal cord injury, stroke, and other neurological injuries on a treadmill with therapist or robotic assistance can certainly benefit patients of a particular functional ability, there are many changes in the biomechanics of gait when walking on a treadmill [7]. In addition, the long-term goal of all patients is to safely walk at home and in the community in order to regain functional independence. Yet providing patients overground gait and balance training is challenging because of the risk of patients falling and getting injured. It is postulated that providing patients partial body-weight support during functional activities, such as sit-to-stand, getting off the floor, or stepping over objects, may allow patients to practice therapy activities not otherwise possible in a safe manner [8]. Until recent years, training patients with partial body-weight support during overground gait and balance training was not possible; however, the development of new types of gait training systems now supports this type of gait and balance therapy.

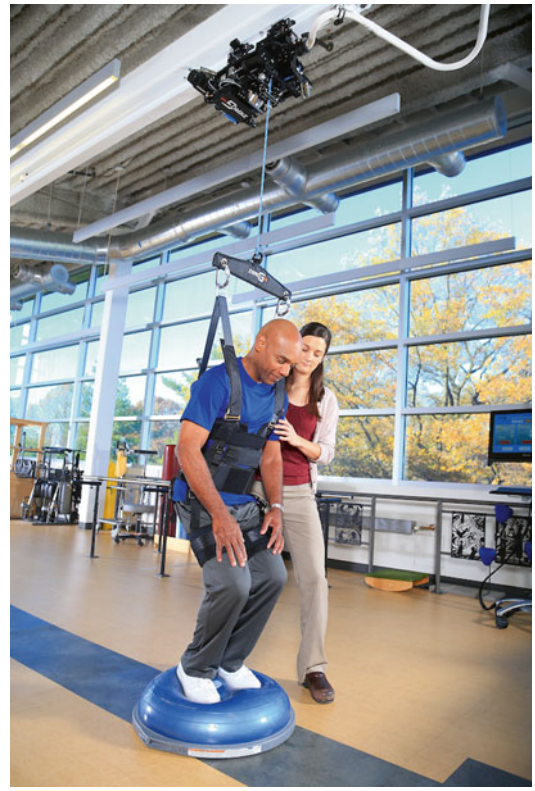

Fig. 23.1 ZeroG gait and balance training system (Aretech, LLC, Ashburn, Virginia, USA)

23.1.1 ZeroG® Gait and Balance Training System

The ZeroG gait and balance training system has been under development since 2005 and is now commercially available through Aretech, LLC (Ashburn, Virginia, USA). The system (shown in Fig. 23.1), which can provide up to 400 lbs of static body-weight support and 200 lbs 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.

One of the key advantages of ZeroG is that, 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 every day in their normal lives. Additionally, because more than one ZeroG trolley can be placed on the same track, multiple patients can be trained simultaneously.

The performance of ZeroG has been evaluated using both benchtop testing and human trials [9]. Example plots of ZeroG's ability to maintain constant levels of force are shown in Fig. 23.2. 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 lbs. The error in force was approximately ±2.5 lbs, mainly due to inertial effects internal to 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 lbs 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.

The clinical benefits of using ZeroG to improve gait and balance have been evaluated in a variety of patient populations, notably in toddlers with cerebral palsy [10] and individuals post stroke [11]. For example, Prosser et al. [10] showed that toddlers trained for 6 weeks using ZeroG experienced gains in gross motor function that exceeded the expected rate in four of the five participants. Rates of motor development during treatment were 10.8, 3.8, 7.0, 15.1, and 0.3 times greater than during baseline for the five participants, respectively [10]. A pilot study by Ness [11] looked at the influence of ZeroG training in three patients with lateropulsion after stroke. Lateropulsion, sometimes referred to "pusher syndrome," is a gait pattern commonly exhibited by individuals following stroke whereby the patient tends to list toward the hemiparetic side. Each patient was trained for 30 min with ZeroG two times per week. All three patients made improvements in 3-min walking distance (mean Δ = 83.6 ft), total distance walked (mean Δ = 123.3 ft), change in total FIM (mean Δ = 37.6), and BLS (mean Δ = 10 points) scores. There was also improvement in the 3-min walk and total distance walk data when the overground (BWS) training was initiated. Additional clinical studies are currently underway evaluating the clinical benefits of using ZeroG to help improve walking ability, balance, and postural control in numerous patient populations.

23.1.2 FLOAT: Free Levitation for Overground Active Training

The FLOAT is a 3D body-weight support system that capitalizes on wire robot technology developed at ETH Zürich [12, 13]. As shown in Fig. 23.3, FLOAT transmits forces to a human subject via wires that are actuated by motorized winches positioned at the ceiling, in the four corners of the desired workspace. To allow this workspace to stretch over a long distance without excessive wire forces, the FLOAT also uses a new mechanical configuration of moving wire deflection units (pulleys) [14], which are guided along two parallel rails confining the workspace. These deflection units are not actuated; instead, they are moved by means of the forces in the wires they deflect. The design reduces moving masses to an absolute minimum, and it enables accurate control of a three-dimensional force vector acting on a human subject during gait within a large workspace of about 8 m length by 1.5 m width by 2.8 m height [15]. The FLOAT is now commercially available through Lutz Medical Engineering (Rüdlingen, CH) (Fig. 23.4).

Like the ZeroG, the FLOAT can also relieve patients of a percentage of their body weight during diverse activities, and it can gently catch subjects when they start falling. In addition, it can also provide forces in both horizontal directions, for example, to guide subjects along a path, to provide resistance or assistance in walking direction, or to apply perturbations [16].

Unless such horizontal forces are desired, the subject can freely perform tasks in the three-dimensional work space, while the unloading force vector remains vertical also when the subjects moves sideways. A major advantage is that restoring horizontal forces do not occur this way, which could potentially disturb balance or support it more than needed [17].

So far, no clinical results are published for the device. Preliminary experiments with unimpaired subjects showed that the system exhibits good control performance and applies only minimal undesired forces to users (less than 10 N root-mean-square error) during free overground gait [15].

23.1.3 Limitations with Robotic Overground Body-Weight Support Systems

The potential limitations with the gait training technologies described above are device–specific. For example, with ZeroG, patients are restricted to walk under the track and cannot deviate more

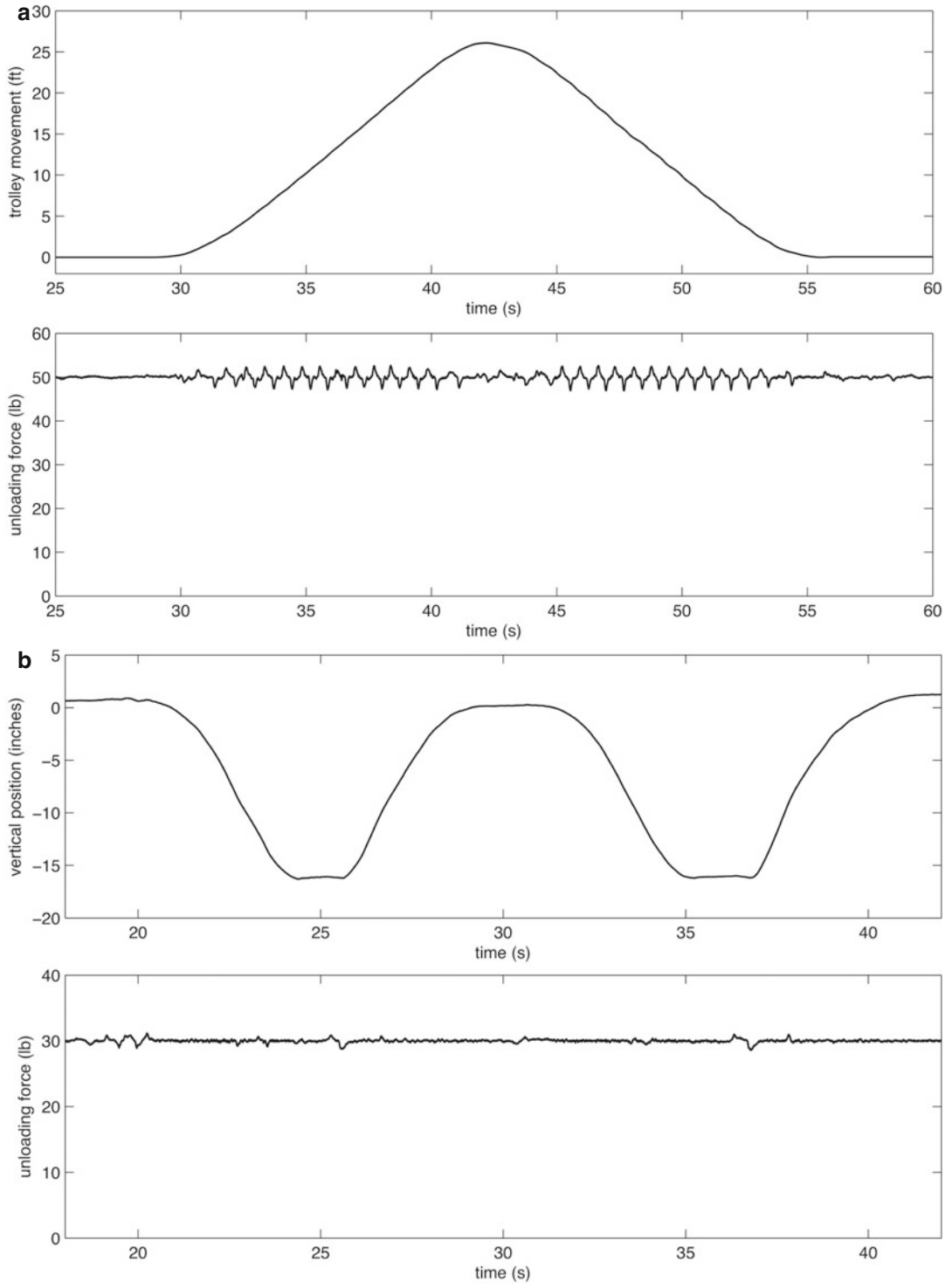

Fig. 23.2 ZeroG performance during an overground walking trial (**a**) and a balance task (**b**)

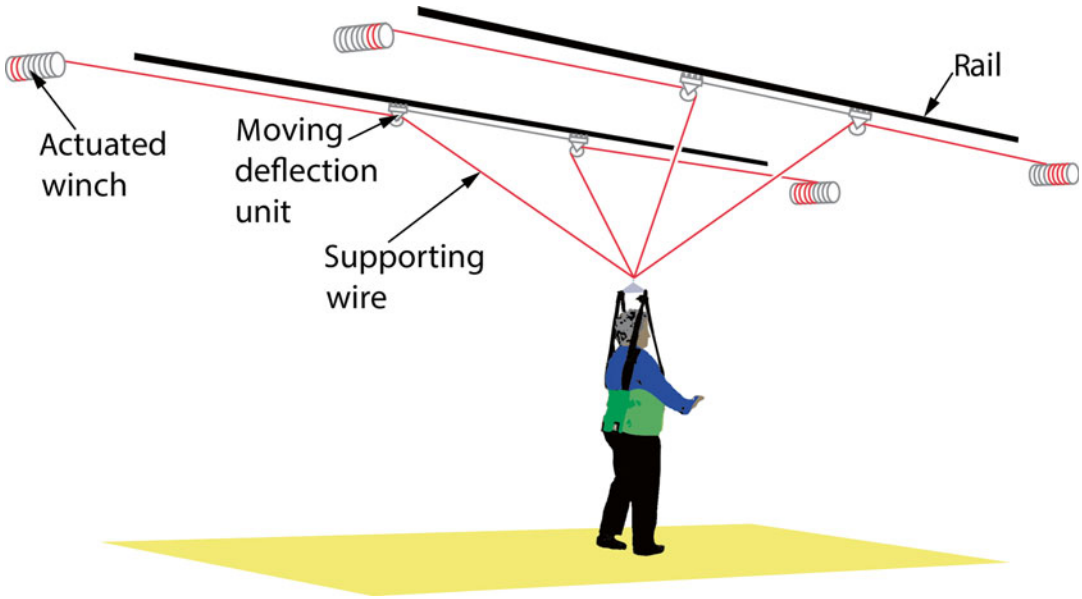

Fig. 23.3 Free levitation for overground active training (FLOAT)

than a couple of feet without feeling a large horizontal restoring force. In some cases, these horizontal forces have been shown to be helpful in training subjects with particular gait abnormalities, such as lateropulsion after stroke [11]. However, in other patients, this may restrict movement freedom or disturb the natural balance mechanisms [17].

With the FLOAT, achievable workspace dimensions depend on room size. The workspace is limited to the space inside the four winches. Therefore, the system cannot cover non-square workspaces, such as curved corridors. Due to the wire geometry, the ceiling height also influences the workspace: the lower the ceiling, the closer the parallel rails need to be placed to each other, such that the size of the workspace is reduced. Furthermore, the system does not allow training of multiple users simultaneously.

Another major disadvantage of these devices is cost. Because these systems contain numerous actuators, precision sensors, and other custom components, the pricing for these systems only allows the largest rehabilitation centers to adopt the technology. The ZeroG gait and balance training system retails for $214,900 (US), while the FLOAT retails for 250,000 CHF (pricing as of 2015). Perhaps with increases in production volume, the costs will come down so that smaller, outpatient clinics can also adopt these devices.

23.2 Non-robotic Overground Gait Training Systems

A number of less expensive, non-robotic systems are available on the market that provide patients static body-weight support while practicing overground gait and balance training. Static body-weight support is similar to being supported by a strap of fixed length. If the patient moves vertically from the neutral position, the strap will go slack. However, if the patient descends from the neutral position, the strap will become taut and prevent a fall. The principle advantage of such systems is that because they are not actuated and do not have sensors, the cost is only a fraction of the systems described above.

23.2.1 Caster-Based Overground Systems

Two commonly used non-robotic overground gait training system are the LiteGait by Mobility

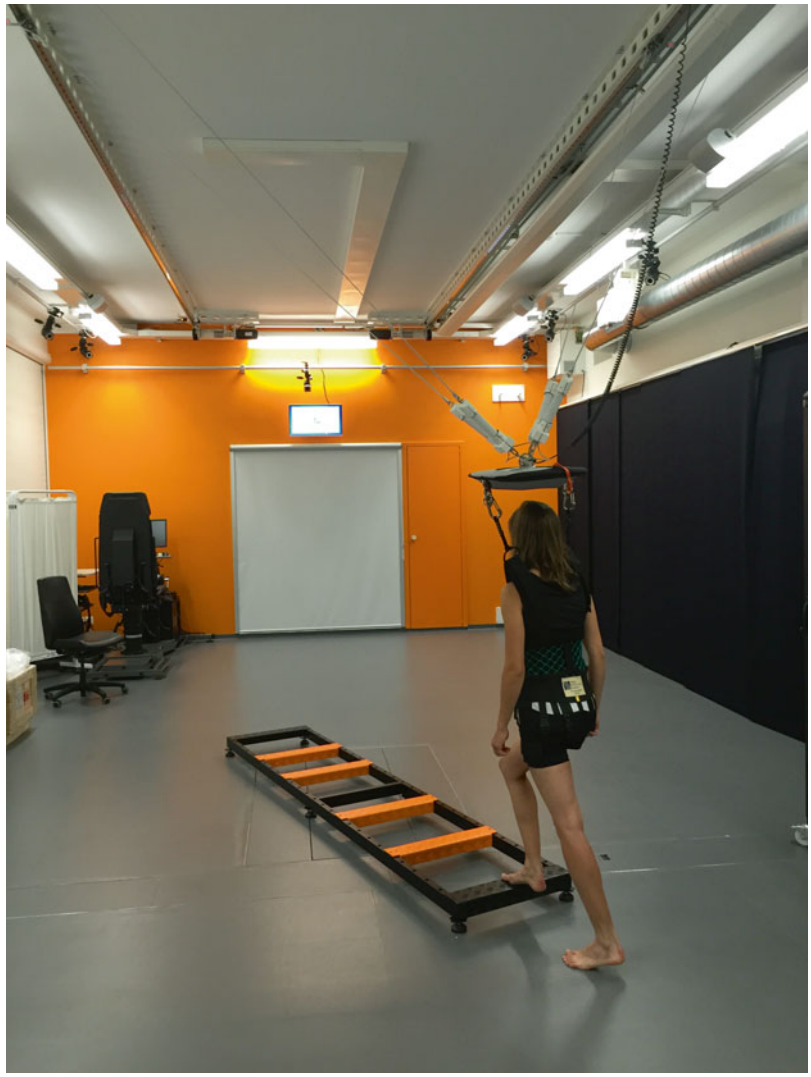

Fig. 23.4 Unimpaired subject walking in FLOAT, along a diagonal of the workspace

Research (Tempe, AZ) and the Unweighing system by Biodex (Shirley, New York, USA). The systems consist of a mobile cart with an overhead bracket through which the patient's harness is attached (Fig. 23.5). The casters on the bottom of the frame can be locked so that the subject can walk on a treadmill or released for overground gait training. The height of the LiteGait system can be adjusted to accommodate different subject heights, while the Unweighing system is preset to allow patients up to 6′ 11″ (210 cm) to be trained. When patients are attached to these devices, the possibility of falling is eliminated, thereby removing the risk of injury. And because the systems roll on casters, patients can move throughout the gym and hospital.

23.2.2 Track-Based Overground Systems

While the LiteGait and Unweighing systems are popular with clinics because of the cost, the two key limitations with these devices are (a) the

Fig. 23.5 Unweighing system (Biodex Inc, Shirley, New York, USA) (Photo courtesy of Biodex Medical Systems, Inc)

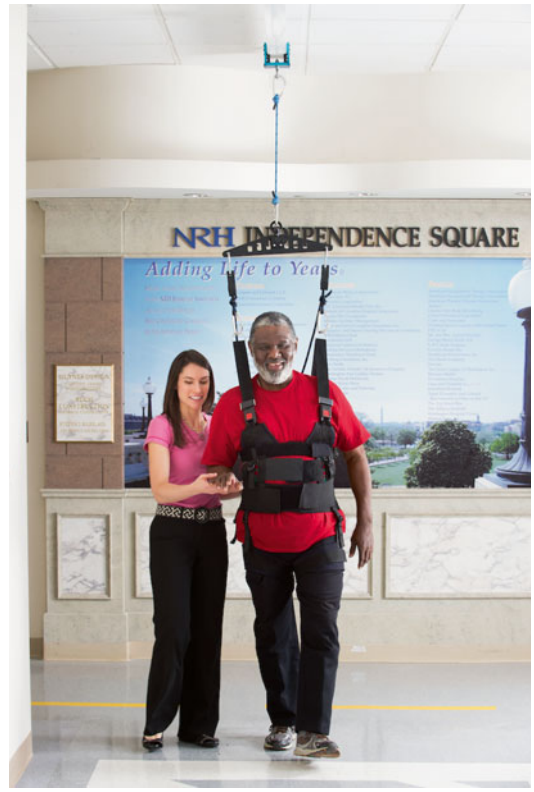

Fig. 23.6 ZeroG-Passive gait training system (Aretech, LLC, Ashburn, Virginia, USA)

configuration places obstructions between the patient and therapist, which makes assisting the patients' movements challenging, and (b) the weight of the frame requires the patient to physically pull it when walking overground. There are a number of track-based systems that eliminate these restrictions.

The ZeroG-Passive system (Aretech, LLC, Ashburn, VA, USA) and FreeStep (Biodex, Inc, Shirley, New York, USA) utilize small, lightweight trollies on a track (Figs. 23.6 and 23.7). Similar to the LiteGait and Unweighing systems, the patient is connected to the ZeroG-Passive and FreeStep trollies with a harness, and then as the patient ambulates, they simply pull the trolley along the track. Because the weight of the trollies is low (i.e., less than 5 lbs or 2.3 kg), there are minimal inertial effects. Both systems only provide static body-weight support where the length of the harness shoulder straps is adjusted with the subject in a standing position and then become tight if they try to descend below this point.

23.3 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. Non-actuated devices such as those described in Sect. 23.2 offer the advantages of cost and simplicity yet are limited in the types of activities patients can practice because of the static body-weight support. Conversely, the robotic devices described in Sect. 23.1 offer a number of clinical advantages, yet a number of

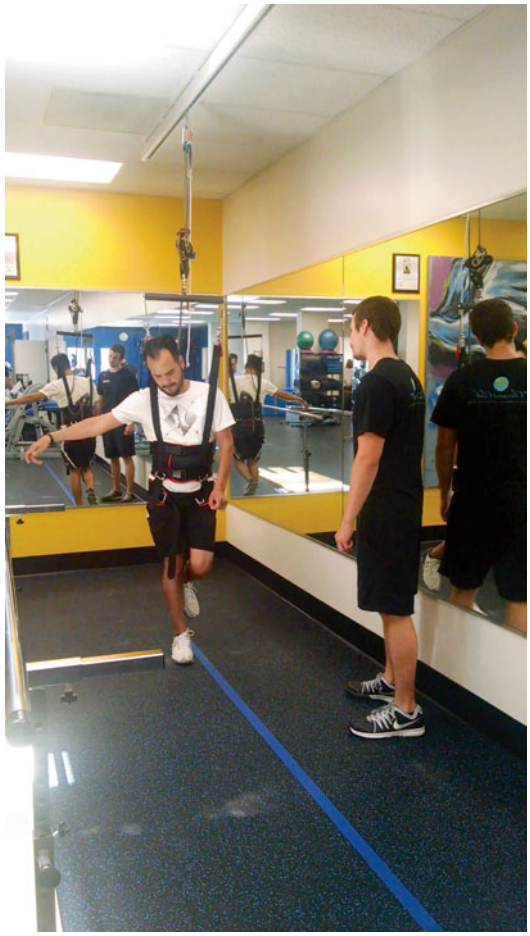

Fig. 23.7 FreeStep (Biodex Inc, Shirley, New York, USA) (Photo courtesy of Biodex Medical Systems, Inc)

factors need to be addressed before gaining widespread clinical acceptance:

- Cost: The current price of devices such as ZeroG and FLOAT restricts them to only the larger rehabilitation centers and some skilled nursing facilities. Developing derivative devices with fewer features may result in reduced costs.
- Proven Efficacy: While overground body-weight support systems can provide high-level safety to patients, administrators at hospitals are also interested in efficacy. Randomized clinical trials will need to demonstrate superior efficacy before widespread adoption will occur.
- Therapist Acceptance: While today's physical therapists are becoming more accepting of using technologies to help treat their patients, these devices will need to be easy to use, offer short setup times, and be user-friendly for the therapists to accept them as part of routine therapy.

References

1. Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in the adult cat. Brain Res. 1987;412:84–95.
2. De Leon RD, Hodgson JA, Roy RR, Edgerton VR. Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats. J Neurophysiol. 1998;79:1329–40.
3. Rossignol S, Chau C, Brustein E, Belanger M, Barbeau H, Trevor D. Locomotor capacities after complete and partial lesions of the spinal cord. Acta Neurobiol Exp. 1996;56:449–63.
4. Dobkin B, Apple D, Barbeau H, Basso M, Behrman A, Deforge D, Ditunno J, Dudley G, Elashoff R, Fugate L, Harkema S, Saulino M, Scott M, Spinal Cord Injury Locomotor Trial (SCILT) Group. Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. Neurology. 2006;66:484–93.
5. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Cen S, Hayden SK, LEAPS Investigative Team. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011;364(21):2026–36.
6. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell D, Kahn J, Hornby TG. Multi-center randomized clinical trial evaluating the effectiveness of the Lokomat in sub-acute stroke. Neurorehabil Neural Repair. 2009;23(1):5–13.
7. Lee SJ, Hidler J. Biomechanics of treadmill versus over-ground walking in healthy individuals. J Appl Physiol. 2008;104(3):747–55.
8. Hidler J, Sainburg B. Role of robotics in neurorehabilitation. Top Spinal Cord Rehabil. 2011;17(1):42–29.
9. Hidler J, Brennan D, Black I, Nichols D, Brady K, ZeroG NT. Overground gait and balance training system. J Rehabil Res Dev. 2011;48(4):287–98.
10. Prosser L, Ohlrich L, Curatalo L, Alter K, Damiano D. Feasibility and preliminary effectiveness of a novel mobility training intervention in infants and toddlers with cerebral palsy. Dev Neurorehabil. 2012;15(4):259–66.
11. Ness D. Over-ground body weight support training in patients with pusher syndrome after stroke: case series. Las Vegas: American Physical Therapy Combined Sections Meeting; 2013.

12. Von Zitzewitz. A reconfigurable rope robot as a versatile haptic interface for a cave automatic virtual environment. 2011. PhD Thesis, ETH Zurich.
13. von Zitzewitz J, Morger A, Rauter G, Marchal-Crespo L, Crivelli G, Wyss D, Bruckmann T, Riener R. A reconfigurable, tendon-based haptic interface for research into human-environment interactions. Robotica. 2012;31(03):441–53.
14. von Zitzewitz, Fehlberg L, Bruckmann T, Vallery H. Use of passively guided deflection units and energy-storing elements to increase the application range of wire robots. Cable-Driven Parallel Robots. Stuttgart; Springer. 2012.
15. Vallery H, Lutz P, von Zitzewitz J, Rauter G, Fritschi M, Everarts C, Ronsse C, Curt A, Bolliger M. Multidirectional transparent support for overground gait training. 2013. Proceedings of the IEEE International Conference on Rehabilitation Robotics (ICORR). The conference took place in Seattle, Washington, USA.
16. Fritschi M, Jelinek HF, McGloughlin T, Khalaf K, Khandoker AH, Vallery H. Human balance responses to perturbations in the horizontal plane. 2014. 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). Chicago. p. 4058–61.
17. Pennycott A, Wyss D, Vallery H, Riener R. Effects of added inertia and body weight support on lateral balance control during walking. 2011. International Conference on Rehabilitation Robotics (ICORR). Zürich, Switzerland.

Using Robotic Exoskeletons for Over-Ground Locomotor Training

24

Arun Jayaraman, Sheila Burt, and William Zev Rymer

Abstract

Once designed to augment the capability of soldiers in combat, robotic exoskeletons are now emerging as promising assistive technologies in neurorehabilitation. Exoskeletons have the potential to help individuals maintain or regain neuromuscular health and to provide personal mobility or over-ground locomotor training for individuals recovering from stroke, spinal cord injury (SCI), or other neurological injuries. Preliminary data suggest that these individuals may benefit from the use of exoskeletons, either alone or as a compliment to traditional rehabilitation strategies. Further research in this emerging field, including clinical trials to assess the therapeutic benefits and limitations of exoskeletons, is required to achieve a greater understanding of how to use these devices inside and outside of the clinic. Use of exoskeletons as clinical tools requires clinicians to understand how to operate and monitor the device, which patient population(s) are appropriate and would most benefit from the device, and the limitations and safety measures required for each device.

Keywords

Exoskeleton • Spinal cord injury • Neurological injury • Stroke • Assistive robots • Robotics • Rehabilitation

A. Jayaraman, PT, PhD (✉)
Max Näder Lab for Rehabilitation Technologies and Outcomes Research, Departments of Physical Medicine and Rehabilitation, Medical Social Sciences, Physical Therapy and Human Movement Sciences, The Rehabilitation Institute of Chicago, Northwestern University, Chicago, IL, USA
e-mail: a-jayaraman@northwestern.edu

S. Burt, BS
Center for Bionic Medicine, Rehabilitation Institute of Chicago, Chicago, IL, USA

W.Z. Rymer, MD, PhD
Sensory Motor Performance Program, Department of Research, Rehabilitation Institute of Chicago, Chicago, IL, USA

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24.1 Introduction and Brief History of Exoskeletons

Exoskeletons are wearable technologies designed to augment human capabilities and, in more recent applications, to provide therapeutic benefits to people with neuromuscular impairments following stroke, spinal cord injury (SCI), or other neurological injuries. Some of the earliest concepts of exoskeleton-like devices date back to the late nineteenth century, described in a series of U.S. patents issued to Nicholas Yagn of Russia in 1890. It is not known whether this device was ever successfully built [1, 2]. In the 1940s, numerous concepts for other exoskeleton-like devices were developed in the form of hip-knee-ankle-foot orthoses (HKAFOs). These are simple spring-based orthoses that do not require any external power sources and can stabilize a user's knee and hip joints to prevent involuntary flexion. However, the practicality of these devices was severely limited outside of the clinic (weight, comfort, usability), and many patients abandoned these braces in favor of the wheelchair [3].

In the 1960s, as advancements in electronics and motor design ushered in a new era of technology, more quests to design a powered exoskeleton arose. In 1965, General Electric—in partnership with the U.S. military—established the Hardiman I Project with the aim of developing an exoskeleton suit that would dramatically improve soldiers' capabilities. With 28 joints and two grasping arms powered by hydraulics, the Hardiman was designed to mimic the user's natural movements and enable soldiers to lift in excess of 1,500 lbs [4]. However, engineers still faced several major design limitations, and the Hardiman never transitioned past this prototype stage due to its size, weight, and power-supply issues [4]. While power-supply issues remained difficult to solve, several reciprocating gait orthoses (RGOs) were developed. RGOs incorporate an ankle-foot orthosis with a custom-made brace at the hip to lock the joints in place for patients with impaired or reduced lower-limb muscular strength. These passive orthoses allowed for static standing and some limited mobility (users could move their legs reciprocally as opposed to "hopping" with HKAFOs). However, these devices required a significant amount of upper-body strength, and demanded large subject energy expenditures for their operation. Patients also had difficultly donning and doffing these devices and walking on uneven surfaces [3]. Many of these limitations motivated engineers to design better assistive technologies, and further improvements in electronics and controllers allowed for more feasible powered rehabilitation technologies to appear.

24.2 Robotic Treadmill Trainers and the Birth of Modern Exoskeletons

Beginning in the early 2000s, funding from the Department of Defense drove the development of several exoskeletons designed to augment soldiers' capabilities in combat, and around the same time, a global interest in developing machines to assist the aging population and those with neuromuscular weakness flourished. Specifically, this was the period when the use of body-weight supported treadmill training (BWSTT) became a recognized form of treatment to improve locomotion in individuals with spinal cord injury and stroke. However, BWSTT proved physically very intense for the physical therapy trainers, as they had to move the patient's limbs manually over the treadmill, resulting in clinician fatigue very quickly. Furthermore, the number of clinicians [3, 4] needed for the BWSTT was becoming impractical in an everyday clinical environment. Thus, several treadmill-based robotic gait trainers also surfaced, most notably the Lokomat® (Hocoma Norwell, MA USA and Volketswil, Switzerland) and the AutoAmbulator® (Birmingham, AL USA). These machines provide training in a controlled environment—patients move their legs on a treadmill, based on a preprogrammed gait training settings while strapped to a harness providing body-weight support. In addition to having large actuators that allow for precise torque control of the joints, these treadmill-based "exoskeletons" reduce the need for therapist assistance while still providing the effects of BWSTT. On the other hand, their large size and high cost often precluded them for use outside of the clinic, and their

clinical efficacy still remains uncertain, even after numerous clinical trials and research studies [5].

More recently, lower-extremity exoskeletons have been developed and commercialized specifically to fill current clinical gaps in therapy and for personal mobility purposes. The populations they currently target are individuals with SCI, as well as persons recovering from stroke or those who have other neurological disorders. The therapeutic use of exoskeletons may eventually fill the gap in effective treatments for restoring lower-limb function in these individuals. Compared to robotic treadmill trainers, which are massive and require the user to be strapped into a harness at all times, over-ground exoskeletons are designed to be portable, anthropomorphic devices that can ideally cooperate seamlessly with users. Though still in their infancy and very limited in use outside of the laboratory setting, current iterations of exoskeletons allow users to practice over-ground walking along with balance and postural control in standing. For persons with SCI who are confined to wheelchairs and experience secondary medical complications due to immobility and continuous sitting, exoskeletons may help these individuals build endurance and strengthen muscle groups related to walking. They may prevent adverse effects associated with SCI by initiating upright standing and walking, leading to increased loading of bones and muscles, as well as better cardiovascular, neural, endocrinal, and other physiological functions related to regular upright activities. Finally they may help users regain mobility if they choose to use the device for ambulation in the home or community. For persons with considerable gait deficits due to stroke or other medical conditions, exoskeletons may also offer therapeutic benefits such as continuous over-ground stepping practice, loading of the limbs, and balance and posture control, while reducing the need for therapist assistance.

24.3 Currently Available Devices

Although current exoskeletons differ in structure, weight, hardware, and control systems, most include a rigid outer framework; sensors that detect the user's desired movements; a computerized controller that processes information from the sensors to operate the device; motors or actuators that power the joints; and lightweight batteries. For each device, training protocols for locomotor activities as well as the suitability of the device for specific patient populations differ. Below, we will discuss some currently available exoskeletons, their clinical evaluation and use, and appropriate patient population(s).

ReWalk™ (ReWalk Robotics, Inc., Marlboro, MA, USA and Yokneam Illit, Israel) ReWalk Robotics, Inc., formerly Argo Medical Technologies, was founded in 2001 by Amit Goffer, PhD, an electrical and computer engineer whose own experience with SCI inspired him to develop the ReWalk [6]. The ReWalk provides powered hip and knee motion to assist individuals with SCI in standing upright and walking, as well as ascending and descending stairs. Due to regulation by the Food and Drug Administration (FDA) and insufficient studies on safety, the stair function can only be used in research settings in the United States.

ReWalk Inc. produces two exoskeleton products that differ slightly—the ReWalk Rehabilitation, for therapeutic purposes, and the ReWalk Personal, designed to provide personal mobility in the home and community. The ReWalk Personal is one of two exoskeletons to have received FDA clearance for personal use in the United States; this device is also available in parts of Europe. In both the United States and Europe, the ReWalk Personal Unit must be used with the supervision of a caregiver at all times. For the purposes of this chapter, we will focus on the ReWalk Rehabilitation unit (ReWalk) (Fig. 24.1).

Features Designed for both personal mobility and therapeutic purposes, the ReWalk comprises a motorized exoskeleton with bilateral hip and knee joint actuator motors powered by rechargeable batteries, as well as sensors that measure upper-body tilt angle, leg joint angles, and ground contact [7, 8]. Once the device is adjusted to fit the user, a series of Velcro straps around the trunk, waist, thighs, knees, and calves

Fig. 24.1 The ReWalk (Photo courtesy of ReWalk Robotics, Inc.)

secure the user into the device. Users' feet are placed over the footplate with the shoe worn over the footplate. The ReWalk is used primarily with forearm crutches; these ensure stability, safety, and help the user sense the ground [7]. The exoskeleton cannot be used without an assistive device due to lack of innate balance reactions. In older models, users wear a backpack that contains the control system, the main battery, and a backup battery. However in the latest version of the ReWalk the backpack has been integrated into the pelvic band. Additional padding can be used to provide further comfort and to reduce the risk of skin abrasion.

Control System A wireless remote controller is worn by the user on his or her wrist (like a watch) and can be used to select different sitting/standing/walking modes [8, 9]. To initiate the first step, users must put the ReWalk into walk mode via the controller. The user must gradually learn to balance with one crutch to change settings. Users operate the ReWalk through minor trunk movements; they must shift their trunk forward until a tilt sensor located on the lateral trunk support detects an 8° change in sagittal plane position, which will initiate leg swing. The user must then return the trunk to a more upright position after step initiation to complete the swing and ensure that the leg clears the ground. As users move with the ReWalk, a tilt sensor detects trunk motions and changes in the user's center of gravity; software then produces a preset stepping pattern, resulting in a forward step [7, 8].

Target Population The FDA has approved if for use by people with injuries at level T7–L5 for home use when accompanied by a trained caregiver, and levels T4–L5 when used in a rehabilitation setting [10]. Individuals who use the ReWalk must have adequate bilateral upper limb strength, adequate trunk control, adequate thigh muscle and lower leg length, and sufficient lower-extremity range of motion that allows for ambulation. They must also have adequate bone density (no history of fractures), adequate blood pressure tolerance for upright positioning, and be able to tolerate standing and participating in a walking program. Additionally, individuals should receive a prescription or medical clearance from their physician before they begin using the device.

Mobility Training with the ReWalk™ The safety and efficacy of the ReWalk to help restore locomotor abilities in people with SCI has been evaluated [7, 9, 11]. Although no data have been published on the safety and efficacy of using the ReWalk in the home setting yet, studies have looked at the therapeutic benefit and safety of using the device inside the clinic. Studies are also currently underway at the Rehabilitation Institute of Chicago to assess training strategies for the

ReWalk (for ambulation over level surfaces, non-level surfaces, stairs, ramps, and curbs) in persons with SCI.

It is not yet known how many training sessions are necessary for individuals to become proficient with the device. During therapy sessions, the goal is for the individual to use the device with as little assistance from the therapist as possible. Early training sessions should focus on specific balance exercises, how to move with the crutches, how to weight shift, and finding a center standing position [8, 9]. The user must be proficient in these tasks before he or she begins to walk with the device. Users must then master triggering the first step, followed by learning proper weight shifts and timing with the crutches. Device settings are changed as users' walking ability improves. Specific training guidelines are outlined in a training manual provided by ReWalk Robotics Inc. Additionally, Esquenazi et al. outlined a gait training schedule involving 18 sessions. In sessions 1–4, therapists should perform all necessary measurements and begin helping the subject with sit-to-stand and stand-to-sit transitions within parallel bars; progressively, subjects should begin walking with the crutches (manual trigger mode followed by using the tilt sensor) and start performing sit-to-stand and stand-to-sit transitions using the crutches [7].

Primary outcome measures used are the 6 minute walk test and 10 meter walk test. Other outcome measures included spasticity testing, the number of individuals who successfully completed the study, the number of training sessions required until stair climbing could be considered safe and acceptable, as well as the reasons for any disruptions in the training schedule. Additionally, psychological factors were assessed by questionnaires [7, 8, 11].

In a 2-year clinical trial, Esquenazi et al. examined the safety and performance of the ReWalk in enabling 12 individuals with paraplegia due to SCI to carry out routine ambulatory functions, such as sit-to-stand transitions or walking [7]. The authors concluded that subjects could walk without physical assistance using the ReWalk for at least 50–100 m, continuously, for a period of at least 5–10 min, and perform transfers without therapist assistance. Walking velocities ranged from 0.03 to 0.45 m/s (mean, 0.25 m/s). Additionally, some subjects reported enhanced physical benefits, such as reduced spasticity and pain, as well as improved bowel and bladder function.

Some adverse effects have been reported with using the ReWalk, including minor falls, skin breakdown issues, and hairline fractures; however, no serious adverse events have been reported [9]. Benson et al. evaluated the neurological and functional effects of using the ReWalk in individuals with chronic SCI [9]. They observed that walking speeds and distances improved in ReWalk users compared to patients who did not use the device; however, perceived benefits of using the exoskeleton did not always meet subjects' expectations, and the authors also noted a relatively high number of device-related skin breakdowns and cuts and bruises [9].

Ekso™ (Ekso Bionics, Berkeley CA, USA) Researchers from the University of California Berkeley Robotics & Human Engineering Laboratory formed Ekso Bionics—formerly known as Berkeley Bionics—in 2005 with grant support from the Department of Defense. The company also has partnerships with UC Berkeley and licensing technology agreements with Lockheed Martin Corporation [12]. Initially named eLEGS, the Ekso (Fig. 24.2) is a lower-extremity exoskeleton intended for use as a gait training tool. It was designed for individuals with lower-extremity weakness following spinal cord injury, stroke, acquired brain injury, multiple sclerosis, Guillain- Barre syndrome, or other similar conditions. The FDA has approved it for clinical use by patients with stroke and SCI. Compared to other exoskeletons, the Ekso is currently the only device to feature a variable assist program that, based on the user's needs and current ability, allows therapists to adjust how much assistance the device provides at the hip and knee motors. Before the device is used in a therapy session, patients must learn to balance and shift

Fig. 24.2 The Ekso™ (Photo courtesy of Ekso Bionics™)

their weight when wearing the Ekso, so that they can safely and effectively ambulate with the device.

Features Weighing about 50 lb, the Ekso comprises two upper and lower leg segments that are connected to a rigid torso structure, which contains a computer and batteries. Four motors actuate the hip and knee joints in the sagittal plane. Upper and lower leg lengths of the exoskeleton can be adjusted to fit the user and to align the user's joints with the Ekso joints [13]. Additional features include a backpack and chest straps; a torso pad; foot binding; and shin and thigh support for comfort and fit. The Ekso also includes additional pads, spacers, and extenders to enhance fit and comfort.

Control System The Ekso has an LCD Controller Navigation panel. A therapist can manipulate settings such as gait parameters and the amount of robotic assistance provided to the user. Early in training sessions, therapists set predetermined targets to match the user's weight shifts with the software settings of the device. These targets can be adjusted progressively based on users' needs. The Ekso has three functions—sit-to-stand, walk, and stand-to-sit. Walking modes include FirstStep, in which a trained physical therapist controls each stepin order to set appropriate gait parameters; ProStep, in which the patient weight shifts to meet predetermined targets; and ProStep Plus, in which the patient weight shifts to meet the lateral target and initates swing with the trailing leg.

Patient Selection and Training The Ekso is most appropriate for individuals who have lower-extremity weakness or paralysis as a result of SCI (motor complete paralysis C7 or below; incomplete SCI with functional bilateral upper extremity strength or functional strength of one upper extremity and one lower extremity) or stroke (hemiparesis or hemiplegia). During patient evaluation and selection, precautions should be taken in persons with cognitive impairments that interfere with their ability to communicate, open wounds, uncontrolled orthostatic hypotension, or active heterotopic ossification. Detailed inclusion and exclusion criteria are provided by Ekso Bionics in their training manual.

Patients must receive a prescription or medical clearance from a physician and be evaluated by a physical therapist prior to training with the device. Training will differ for each population and their specific needs and goals; however, for all populations, the first step should focus on teaching the patient how to balance and weight shift properly in order to operate the exoskeleton using the appropriate assistive device. The ekso may be used with a walker, forearm crutches, large or small based quad cane, or straight cane. Although the Ekso provides external stability in order to keep the patient upright, the patient must practice static and dynamic standing balance activities to ensure they can maintain their balance without strenuous physical effort. Once the

patient can adequately find balance, the user can begin walking in the Ekso using an appropriate assistive device, with the goal of achieving a natural heel-strike pattern. Currently, the Ekso has collaborated with a commercial functional electrical stimulation (FES) company to provide a 12 channel FES system which synchs with the Ekso available for clinical use in Europe and research use in the United States.

Locomotor Training Clinical trials of the device began in 2012 and have focused on the safety and feasibility of using the device on individuals with spinal cord injury, and evaluating its potential as an effective therapeutic training device. Training sessions have ranged from 6 to 24 sessions, from one to three times a week [13–18]. Outcome measures have included energy expenditure, walking speeds and distances, temporospatial gait parameters, overall balance, exercise conditioning effects, changes in spasticity, as well as blood pressure and pain levels [13–18]. Decreasing the amount of robotic assistance during training sessions allows patients to increase their volitional muscle activation so they can progressively achieve systematic stepping during ambulation—this cannot be replicated with traditional physical therapy (cannot progressively increase loading and stepping frequency in consistent manner). Thus, for individuals affected by moderate to severe stroke, the Ekso has the potential to increase step length, stride length, gait speed, walking endurance, overall balance, and confidence with ambulation [19].

Individuals with SCI may also benefit from using the Ekso. With practice, some subjects with SCI demonstrated minimal clinically important improvements in walking speed and balance, though larger clinical trials are needed before widespread use is proposed [15, 20]. In a prospective pilot study, Kolakowsky-Hayner et al. evaluated the feasibility and safety of using the Ekso to aid individuals with SCI (complete TI SCI or below) with ambulation and found the device safe for use in a controlled environment with a trained professional [14].

Indego (Parker Hannifin Corporation, Macedonia, OH) The Indego (Fig. 24.3)—formerly known as the Vanderbilt exoskeleton or Parker Hannifin exoskeleton—is a lower-extremity exoskeleton device designed at Vanderbilt University currently under evaluation in Europe and the United States. The FDA has approved the Indego for personal use in individuals with spinal cord injuries at T7-L5 and for rehabilitation use for patients with T4-L5 injuries. The device, which weighs approximately 26 lb, assists users in sit-to-stand transitions, stand-to-sit transitions, and when walking [21]. It is intended to be used with platform walkers, rolling walkers, forearm crutches, or other devices that assist with stability.

Features The Indego features five modular components—right and left upper leg segments, a hip segment, as well as right and left lower leg segments—that come in three different sizes and can be mixed and matched to fit different body types. Due to this modular design, the Indego can theoretically be donned in a user's wheelchair if there is adequate space. The device's rechargeable lithium-ion battery, power buttons, and other electronics are contained in the hip segment of the device. The hip attaches to the upper leg segments, which contain the actuation units and some of the electronics. The lower leg segments with an ankle-foot orthosis (AFO) attach to the upper leg segments at the knee. Hip, thigh, calf, and ankle straps secure the user in the device, and torso and hip pads provide additional comfort and protection.

Control System The Indego features an ipod application that allows therapists to set gait parameters of the exoskeleton and capture and export data (such as stride length and step frequency). The Indego has three operation modes—sit, stand, walk—and within these modes there are two states (*Standby*, which allows users to pause between modes; or *Go*!, which allows users to freely transition between modes). All movements (standing, sitting, or walking) are based on the user's shift in body

Fig. 24.3 The Indego (Photo courtesy of Parker Hannifin Corporation)

weight and change in body position. In order to perform sit-to-stand transitions, the user's body must be positioned at the edge of the seat with their feet flat on the floor. They must lean forward until they reach the hip flexion threshold, which is cued by a hip vibration. The vibration feedback can be set to low, medium, or high. The Indego uses a Individual's center of pressure (CoP) projection onto the horizontal ground plane to estimate movement needs. By tilting the body forward or back the CoP moves in the anterior or posterior direction, which commands the controller to transition to stand or walk mode. In the future, Functional Electrical Stimulation (FES) may be incorporated into the system [22, 23].

Patient Selection The device is intended for users with complete or incomplete SCI level C5 or lower, although the FDA has set stricter regulations. In addition to meeting specific height and weight ranges, users must have adequate passive range of motion at their shoulders, hips, knees and ankles, and must demonstrate sufficient upper-body strength. Contraindications include insufficient upper extremity strength, uncontrolled spasticity, spinal instability, and conditions that prevent proper fit of the device (e.g., excessive soft tissue).

Locomotor Training Training includes a series of approximately 5–28 sessions, lasting about an hour and a half each, that involve evaluating users' walking distance, endurance, and community ambulation skills (going through automatic doors, getting on/off elevators). The first sessions will focus on achieving the correct fit and balance when upright, and practicing sit-to-stand transitions. Further sessions focus on standing, taking steps, and assessing changes to parameters. Outcome measures have included walking speed, endurance, as well as measures of a person's independence, muscle strength, stability, ability to walk on various surfaces, and ease of donning and doffing the device [24, 25]. In a pilot clinical trial at Shepherd Center in Atlanta, Georgia

involving 16 subjects with SCI, Hartigan et al. reported that individuals with tetraplegia and paraplegia learned to use the Indego on a variety of indoor and outdoor surfaces at the end of five sessions that lasted 1.5 h each. Some individuals in this study also achieved walking speeds and distances that indicated they could potentially become limited community ambulators—average walking speed was 0.22 m/s for individuals with C5–6 motor complete tetraplegia and distances covered in 6 min averaged 64 m for the same group [25]. Additionally, Evans et al., in a pilot study involving five subjects with chronic SCI (AIS A), found that using an exoskeleton during assisted over-ground walking resulted in participants experiencing cardiorespiratory and metabolic demands that were "consistent with physical activities performed at a moderate intensity" supporting the potential exercise benefits of using these devices [24]. Currently, Parker is finalizing a multi-channel FES system for the Indego aimed at activating the lower-limb musculature to drive the exoskeleton, thereby enhancing the rehabilitative effect of the device and reducing the load of the motors, leading to increased battery life.

HAL® (Cyberdyne Inc., Tsukuba, Ibaraki Prefecture, Japan) The Hybrid Assistive Limb, or HAL, is a wearable exoskeleton developed by Dr. Yoshiyuki Sankai of Tsukuba University, Ibaraki, Japan and his engineering team. It is being commercialized by Cyberdyne Inc., a robotics and technology company established by Dr. Sankai. Different series of the HAL device have been developed and improved over the years for both augmentative and therapeutic purposes, including medical and emergency aid relief applications (most notably following the 2011 nuclear disaster in Fukushima, Japan) [26, 27]. The HAL for Medical Use-Lower Limb Model, which this chapter will focus on, is a full-body exoskeleton developed to assist the elderly and to help individuals with disabilities walk, climb stairs, and lift objects. The HAL has not yet been certified as a medical device in Japan, although Cyberdyne Inc. received Medical Device Directive (MDD) certification from the European Union in 2013, and began applying for approval from the U.S. Food and Drug Administration for medical use of the HAL in 2014 [28]. In Europe, the HAL has received certification for use in patients with spinal cord injuries, traumatic brain injuries, cerebrovascular diseases, and other conditions affecting the neuromuscular system. The device is currently being used extensively in workman's compensation clinics in Germany [26].

Features The HAL contains power units and angle sensors for the upper and lower limbs, a floor reaction force sensor, and a control unit housed in the back of the device. The suit attaches to the user's hips and legs via belts and cuffs and weighs approximately 23 kg (50.7 lb) [29, 30]. Sensors embedded along the suit detect electromyographic (EMG) signals from the skin surface to anticipate the user's intended movement [31]. The HAL is the only exoskeleton that can be used for training on both a treadmill and over-ground.

Control System The control system of the HAL has two modes: "cybernics voluntary control," which assists users in locomotion based on the EMG signals generated by volitional activation, and a "cybernics robotic autonomous control," for more severely paralyzed users who are not able to generate strong enough EMG signals [32, 33]. The autonomous control system is based on a user's weight shifts, as well as information from force pressure sensors embedded in the device's shoes [30, 34]. An algorithm infers the user's intention based on their preliminary motion, and the HAL then independently supports this desired movement [33]. Therapists use a detachable controller to activate the different modes of operation, such as start/stop assistance and motion statuses.

Locomotor Training Clinical trials evaluating the therapeutic benefits of using the HAL in training sessions began at five hospitals in Japan in 2012, where the device is being evaluated in patients

with chronic hemiparesis or spinal cord injury. Outcome measures have included stride length, walking speed, and physiological measures; the number of training sessions, generally performed 5 days per week, has ranged from 6 to 31 [32, 35].

The HAL has been shown to increase walking speed in some patients with hemiplegic stroke [32]. Maeshima et al. observed that the HAL increased stride length and walking speed in 4 of 16 patients with severe hemiplegia, though the authors also noted that walking with the HAL required users to adapt to a new gait pattern, which may be difficult for patients with severe hemiplegia [32]. The HAL has also been studied in patients with SCI in more limited studies involving treadmill training with the device [34, 36]. In a single case experimental study with eight SCI subjects (chronic incomplete or complete paraplegia), Aach et al. found that mean walking speed and average walking time increased with treadmill training using the HAL. Improvements in the 10 m Walk Test and 6 min Walk Test were also observed, suggesting that the HAL can be used a therapeutic gait training tool for SCI patients [34, 36].

Honda Stride Management Assist (Honda Research and Development Company, Ltd., Wako, Japan) The Honda Stride Management Assist (SMA) is an assistive exoskeleton (Fig. 24.4) designed to regulate walking pace in individuals who can walk but have mild gait disturbances due to aging or medical conditions such as osteoarthritis or stroke [37]. Honda initiated research into developing an assistive walking device in 1999, and began conducting collaborative testing of the device in 2008 with Shinseikai Medical Group at Kasumigaseki-Minami Hospital in Kawagoe, Japan [38]. In 2013, the company began leasing the device to hospitals in Japan in order to monitor its use and study its applicability; clinical research in the United States evaluating the device for therapeutic purposes in individuals who have experienced stroke also began in 2013 at the Rehabilitation Institute of Chicago.

Features The device, which fits around the user's hips and thighs and is worn like a belt, is much smaller and lighter than full-body exoskeleton suits. It weighs approximately 2.8 kg (6.1 lb), and comes in three different sizes. The system is comprised of a waist frame, two thigh supports, two thigh frames, two brushless DC motors, two electrical actuators, and a rechargeable lithium-ion battery [39]. Assist torque generated by the SMA actuators is transmitted to the thighs via the thigh frames, and the device assists in hip flexion and extension for each side independently. Individual assist levels can be set for each leg, and the device's actuators are equipped with sensors that monitor torque and the range of motion of the user's hip joints.

Control System The control computer and battery are housed in the lower back portion of the device. A physical therapist operates the device through software run on a tablet; and settings can be remotely adjusted while the user is wearing the SMA. The control system can analyze users'

Fig. 24.4 Honda stride management assist (Photo courtesy of Honda Research and Development Company, Ltd.)

stride, and adjust their stride and walking rhythm within a preprogrammed range in order to improve their walking pattern [39]. In order to synchronize itself with user input, the device's control system employs neural oscillators in conjunction with a user's Central Pattern Generators (CPGs). CPGs are neural networks that generate rhythmic patterns of output independent of sensory feedback [40]. Angle sensors embedded in the actuators detect the wearer's hip joint angles throughout the gait cycle. These angles are input into the device's controller, which calculates hip joint angle symmetry. The SMA then produces assist torques at specific instances during the gait cycle to regulate walking patterns. Additionally, the walking data recorded during training sessions can be reviewed by the user or a therapist after a session.

Patient Selection and Training The SMA has been tested in healthy young adults and elderly people in Japan, and is currently undergoing clinical evaluation in the U.S. in persons recovering from stroke. All potential subjects must be assessed for strength, flexibility, balance, sensation, endurance, transfers, and gait. Contraindications to use of the SMA include symptomatic cardiovascular disease, hypertension, heart failure, or severe pain. In studies involving young adults, subjects were excluded if they had a presence and history of any disease (lower-limb orthopedic diseases, neurological disorders) that may affect walking capacity, energy expenditure, and endurance [39].

Initial gait training with the SMA emphasizes safety and balance, to minimize the risk of falls. In studies involving elderly adults, subjects walked on a treadmill or outside anywhere from 30 to 90 min [39, 40]. Stride lengths and cadences with and without the assistive device were evaluated [41]. These studies found that the device improved subjects' walk ratio, waking speed, and step length, indicating that using the SMA alongside a walking intervention program may improve the walking ability of the elderly [41, 42]. In stroke survivors (≥30-days post stroke, 18–85 years old) the training protocol involved 18 sessions of outpatient physical therapy training (lasting 45–60 min) and post-training sessions evaluating speed and distance outcome measures (6 min Walk Test, 10 m Walk Test, Berg Balance Scale, Functional Gait Assessment test). A recently published study indicated the SMA was therapeutically as effective/slightly better than high-intensity physical therapy on spatiotemporal parameters measured using the GAITRite® system [43].

NASA-IHMC Mina (Institute of Human and Machine Cognition, Pensacola and Ocala, FL) Developed by researchers at the Florida Institute for Human and Machine Cognition (IHMC), the Mina (Fig. 24.5) is a lower-extremity exoskeleton designed in collaboration with NASA to assist individuals with paraplegia and paresis. It is currently being developed for a range of applications, including mobility assistance, rehabilitation, and exercise [44]. In its current iteration, the Mina has four 'compliant control actuators' that are aligned with the wearer's hip and knee joints to provide hip and knee flexion/extension. Sensory feedback is provided through F-Scan (Tekscan Inc., Boston, MA) insoles that help the user detect ground reaction [44]. Other features include a rigid ankle joint and compliant footplate made of carbon fiber; a rigid back plate that connects users to the device and has a curvature designed to match the human spine; and nested aluminum tubing. Current prototypes require a tether to power the device and prevent falls; however, a later version of the

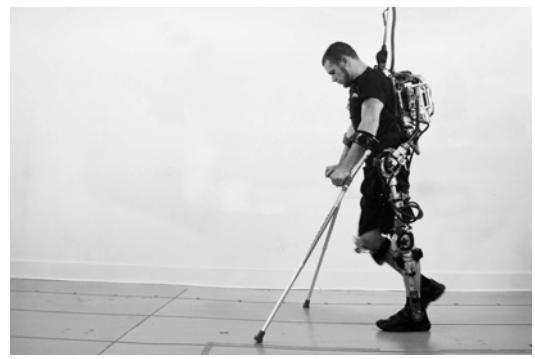

Fig. 24.5 NASA-IHMC X1 Mina exoskeleton (Photo courtesy of the Institute of Human and Machine Cognition)

device will be untethered and will combine battery power and wireless communications technologies [41]. The control system of the Mina consists of an embedded PC-104 computer mounted on the back plate of the device [45]. This system stores the control software and relevant trajectories used for walking modes. This information is transmitted to a host computer for monitoring and display in real-time [45]. A future feedback system will incorporate sensory information to assist users in balancing during the stance and dynamic phases of walking; a video game interface to assist with static posturing with and without sensory feedback is also being investigated [45].

REX (Rex Bionics Ltd., Auckland, New Zealand) New Zealand-based Rex Bionics Ltd. produces two exoskeleton products: the REX, designed to be used in therapy by people with mobility impairments due to stroke, SCI, or other neurological conditions; and the REX Personal (REX P), designed as a personal mobility device [46]. These devices are operated by a joystick control, and are self balancing; thus they do not require crutches or a walking frame [46]. According to the company's website, the REX features five actuated degrees of freedom (DOF) and has electric motors that enable the user to sit, stand, and make turns. The REX Personal has 29 on-board processors while the REX Rehab has 27. Currently, the REX is labeled for use by individuals with complete spinal cord injury from C4/5 level. Researchers at the University of Houston are currently evaluating the potential in using the REX with noninvasive brain-machine interface (BMI) technology, specifically EEG, to interpret user intent [47]. The company is also working with therapists to develop "Robot-Assisted Physiotherapy" sessions in which the REX lifts patients from a sitting position into a robot-supported standing position to begin supported walking and stretching exercises [46]. In April 2015, Rex Bionics announced a distribution agreement with Deltason Medical Ltd. to commercialize the REX in Hong Kong for use in clinics and for personal mobility purposes [46].

The list of aforementioned exoskeletons is only partial—there are several other exoskeletons currently being designed and tested across the world, and we expect more clinical trials to begin from these developments. Currently an estimated 16–20 fully lower-extremity exoskeletons are under development or clinical testing. We estimate an additional 15–20 modular robotic devices which power single joints for therapeutic and mobility benefits are currently being clinical tested for future commercialization (Table 24.1).

24.4 Summary

Currently, the utility and purported benefits of all these exoskeletons are still exploratory. ReWalk and Indego, are the only FDA approved devices for home use. So far the ReWalk has been used by nearly 20 individuals in a home environment without any major adverse events (as reported to the FDA). The Ekso is currently being used in numerous clinical populations for therapeutic purposes. Most of the reported benefits have been in either severely impaired populations or in research and clinical facilities (Europe mainly) where long-term use of the device is permitted. Anecdotally, prolonged use of the device has been shown to have therapeutic benefits even in the complete-SCI population, with some indicated return of sensory and motor function. Ekso Bionics is working on their third generation controller while ReWalk has most recently put out a new version of their device which feature removal of the backpack and integration of the battery and computer into the pelvic band. Anecdotally, the Indego is more user-friendly as a personal mobility device due to its light weight and modular design which allows the user to independently transport the device. Rex Bionics is also working on obtaining clinical evidence to receive CE and FDA approval. Currently, all these devices can walk over-ground safely with a help of a trained caretaker or physical therapist. Further evidence through publications is expected later this year and next year.

Table 24.1 Overview of discussed exoskeletons

Exoskeleton	Basic features	Controls	Patient population
ReWalk (ReWalk Robotics Inc.)	Bilateral hip and knee joint actuator motors powered by rechargeable batteries Sensors that measure upper-body tilt angle, joint angles, and ground contact	5–8° anterior displacement External watch controls first step	Persons with lower-extremity paralysis or paresis due to SCI (level T7–L5 for home use when accompanied by a trained caregiver, and levels T4–T6 when used in a rehabilitation setting)
Ekso (Ekso Bionics)	Straps for the shoulders, chest, and feet Backpack with control system Motors at the hip and knees Thigh and hip shanks to support a user's body weight	Forward and lateral weight shifts to initiate steps predetermined by the trainer LCD controller with variable assist motors	SCI patients (motor complete paralysis C7 or below, and any level of incomplete SCI) Stroke patients (hemiparesis or hemiplegia) Potentially suitable for persons with acquired brain injury, multiple sclerosis, Guillain-Barre, or other neurological impairments
Indego (Parker Hannifin)	Modular design Motors at the hip and knee joints power movements Built in ankle-foot-orthoses at ankle joints	Wireless software interface Movements are based on postural cues, based on a user's center of pressure (CoP) projection Includes Indego iOS app to adjust gait training parameters (stride length, step frequency)	Complete or incomplete SCI level C5 or lower Persons with lower-limb weakness or paralysis due to other neurological impairments
HAL (Cyberdyne Inc.)	Rigid frame that attaches to a user's hips and legs; power units at the hip, knee, and ankle joints; sensors that measure a person's EMG signals	Voluntary or autonomous control modes	Persons with weakened leg muscles due to neurological impairments such as stroke, SCI, traumatic brain injuries, or other neuromuscular impairments
Honda stride management assist (Honda Research and Development Company, Ltd.)	Waist frame with two thigh supports, two thigh frames, two brushless DC motors, two electrical actuators, and a rechargeable lithium-ion battery Assist torque generated by the SMA actuators is transmitted to the thighs via the thigh frames Device assists in hip flexion and extension for each side independently	Tablet System can analyze a user's stride, and their walking rhythm can be adjusted within a preprogrammed range	Individuals with lower-extremity weakness due to stroke, aging, or other medical conditions

(continued)

Table 24.1 (continued)

Exoskeleton	Basic features	Controls	Patient population
NASA-IHMC X1 Mina (Institute of Human and Machine Cognition)	Actuators at the hip flexion/extension and knee flexion/extension Passive joints for hip ab/adduction, as well as hip internal/external rotation Adjustable links to fit a person's body size	Embedded PC-104 computer system An external control operator is required to activate or deactivate the system when in paraplegic assistance mode	Currently in development for a range of applications, including mobility assistance (able-bodied persons and those with disabilities), rehabilitation, and exercise purposes
REX (Rex Bionics Ltd.)	5 actuated degrees of freedom (DOFs); electric motors that enable the user to sit, stand, and make turns	Joystick control	Complete SCI from C4/5 level

24.5 The Therapist/Trainer and the Exoskeleton

24.5.1 General Assessment

Before an exoskeleton is prescribed or used in a therapy session, a trained professional (physiatrist or physical therapist) must assess each potential candidate, and potential subjects should also receive medical clearance from their physician. This section describes recommended procedures based on our extensive experience with the ReWalk, Ekso, and the Indego. Recommendations for the Honda Stride Management Assist are different and not detailed here.

As most exoskeleton devices require use of crutches/a walker/bilateral canes to assist the individual with walking and to provide additional stability, an individual's ability to use their hands and shoulders, as well as their overall cardiovascular health and bone density, must be assessed prior to using the device. In general, for most exoskeleton machines, it is recommended that subjects must:

- Be between the ages of 18–70
- Be able to fit into the device and have joint motion to allow ambulation in the device
- Be able to tolerate upright standing for 30 min
- Have sufficient upper extremity strength and balance to allow ambulation with the device
- Have a walking speed of <0.4 m/s, including those considered "non-ambulators"

Persons with joint contractures that limit the range of motion of the lower extremities, and those with any medical issues that prevent them from fully bearing their weight, are also not ideal candidates. Individuals should also be evaluated for any incidence of skin breakdown, and lead to further complications in areas that come in contact with the device.

One of the most important clinical assessments involves optimizing the fit of the exoskeleton, which requires obtaining detailed measurements of the person in order to match the joints of the device with the joints of the person. If the leg or hip length is mismatched, it can change how the user's body moves within the device and can also lead to safety issues. For individuals with spinal cord injuries, poor fit may lead to skin pressure sores, which are not easily detectable by an individual who has lost sensory feedback. In the SCI population, it is important to get a close fit without being too tight as a tight fit ensure proper control of the device and reduces the amount of movements the patient will be require to Additionally, poor fit may decrease the user ability to control the device as a precise fit is necessary for the users movements to be directly transferred to the device.

24.5.2 Documentation

Suggestion for this section: During an evaluation for exoskeleton use, the individuals strength, ROM, spasticity, and overall skin condition should be measured and documented. Additionally, any

measurements for device set up should be performed such as leg length, hip width, and weight. Each therapy session should include documentation of vital signs, device hardware set up, and gait paremeter settings. During sessions, therapists should keep track of any skin irritations, bruises, or other adverse effects. Finally, the number of minutes spent walking, steps per session, any therapeutic interventions and mobility skills (walking on ramps or steps, going in and out of an elevator) performed and how much therapist assistance was needed may also be documented. In the case of device malfunction or overheating the exoskeleton's services team should be contacted and use of the system ceased till cleared for safe use.

24.5.3 General Locomotor Training Strategies

Training strategies differ for each device and for each individual depending on their type or level of injury or the severity of impairment. Training for personal mobility using the exoskeleton will focus on becoming proficient with specific tasks, such as getting in and out of the device safely, over-ground walking, going up and down ramps or curbs, and being able to stop. The training strategies for improved gait outside of the device will emphasize strategies related to balance, strength, and endurance. It is still not known exactly how many training sessions are needed in order for individuals to become proficient in using any device. Psychological factors such as motivation, time since injury, and anxiety may also affect the number of sessions necessary in order to accmilate to the device.

Few long-term clinical studies have evaluated exoskeletons as gait training devices and clinical tools to be used in the rehabilitation setting. However, some studies have compared current exoskeleton technologies for rehabilitation purposes in clinical settings [9, 47, 48].

24.5.4 Current Limitations

There are several limitations that must be addressed before exoskeletons receive more widespread use in the home and clinical setting. For use in the home and community, individuals must be able to achieve speed levels necessary for daily living, such as being able to safely cross a busy intersection in an urban setting. Other limitations include the financial costs of using exoskeletons, as the devices require time-consuming and intense therapy sessions [9]. Finally, exoskeletons are expensive investments, costing anywhere from $50,000–$250,000 (Rewak, $70,000; Ekso, $125,000; Indego, $75,000: Rex, $150,000). This high cost makes the devices out of reach for most individuals, for physical therapy clinics, and for researchers whose grant funds do not allow them to purchase such expensive equipment. Currently, lack of extensive clinical evidence on the efficacy of these devices has limited insurance reimbursement.

24.5.5 Adverse Effects

- *Falls*: There is potential for a number of adverse effects associated with exoskeleton use. These include: With any exoskeleton, there is a risk that a user may fall and be seriously injured. Although the risk of falling is minimized with trained therapists and personnel, as well as some device safety features, currently these devices are not capable of preventing falls and independent fall recovery strategies do not exist. If the user falls, they will need someone to help them recover, which makes the presence of a trained caregiver necessary at all times for use in the home. Falls can be caused by loss of control of the device by the participant or therapist, or more rarely, malfunction of the device. The risk of falling may be particularly high outside of the clinic where variable environmental factors may make using the device more dangerous.
- *Skin breakdown*: Pressure or friction from the device can cause bruising, pain, or swelling. These risks can be reduced by thorough skin checks performed before and after therapy sessions by a trained therapist and by adding supplementary padding as necessary.
- *Muscle soreness*: Exercises performed during therapy sessions may result in soreness. For

this reason, therapists should allow the user to slowly acclimate to using the device.
- *Device malfunction*: (although rare) may cause loss of control of the device by the user or therapist which may result in falls or other injuries.
- *Generic Controller*: Currently, the controllers of these devices do not adapt to impairments such as spasticity, rigidity, tonicity, joint range of motion limitations, contractures, cognitive and balance limitations. Consequently, the motors may "push through these limitations" to complete the kinematic cycle, leading to numerous adverse events.

24.6 Regulatory Status and Future Expectations

In the United States, all exoskeletons must receive approval from the U.S. Food and Drug Administration (FDA) before they can be commercialized and used in clinics and rehabilitation settings. In February 2015, the FDA announced that exoskeletons will be classified as Class II devices (special controls) [49]. The report cited falls, bruising, skin abrasions, changes in blood pressure, adverse tissue reaction, premature battery failure, burns, and device malfunction as potential risks [49]. Currently, the ReWalk and the Indego is the only exoskeleton approved by the FDA (through the FDA's de novo classification for novel devices of low to moderate risk) for home mobility use [50].

Conclusion

Exoskeletons are rapidly evolving technologies that have the potential to restore some lower-limb function and improve overall functional recovery in persons who have experienced stroke, spinal cord injury, or other neuromuscular injuries/diseases. They may also provide personal mobility for persons who are currently confined to a wheelchair. Although promising, exoskeletons are still in early stages of development and require experienced and trained physical therapists and caregivers to monitor and assist users at all times. Most exoskeletons currently have very generic controllers and hardware, which do not specifically fit the needs of any specific neurological disease or condition. Additionally, a large number of individuals with disabilities do not qualify to use these devices as they have physical impairments that prevent the exoskeletons from functioning safely. Only recently have the controllers of these devices been modeled based of prevailing patient populations (Most are currently based on healthy subject models). Currently, there are no fall prevention or fall recovery systems with these devices, making them potentially dangerous for everyday home and community use. The FDA thus mandates that a therapist or trained caregiver be with the exoskeleton user at all times. This is not very practical for long-term use and actually inhibits a patient's ability to be truly independent. The financial constraints of most of these exoskeleton companies or investigators have prevented them from making major changes to the device's hardware or software. Also, it remains unclear whether or not exoskeletons are effective as personal mobility devices, therapeutic devices, or both. Most current research is limited to early stage safety and efficacy data for FDA approval and CE marking in Europe. Long-term health economics data is sorely missing. Further research regarding potential benefits, limitations, and risks is necessary before these devices can enter widespread clinical use.

However, the future of these devices is bright. Over time, controllers and hardware will become more inclusive of larger patient populations. Fall warning and prevention systems under evaluation will become the default in these devices. Clinicians will have a better understanding on how to use these devices for patient populations who do not qualify for traditional therapy or how to gain therapeutic benefits that supersede current gold standard therapy.

Currently, numerous low weight materials are being tested for exoskeletons; specifically, a whole new group of exoskeletons called soft exoskeletons are being developed. These soft exoskeletons can significantly reduce the weight of these devices without sacrificing on power and control mostly, thus paving the way for more safer and efficient use of these devices. In the long-term, artificial muscle and joints will be combined with the motors and mechanical sensors will be controlled by deep learning techniques obtained from neural, muscle, and mechanical intent.

References

1. Yagn N. Apparatus for facilitating walking. USA patent US420179 A. 1890.
2. Dollar AM, Herr H. Lower extremity exoskeletons and active orthoses: challenges and state of-the-art. IEEE Trans Robot. 2008;24:144–58. doi:10.1109/TRO.2008.915453.
3. Sykes L, Edwards J, Powell E, Ross RS. The reciprocating gait orthosis: long-term usage patterns. Arch Phys Med Rehabil. 1995;76:779–83. doi:10.1016/S0003-9993(95)80534-6.
4. Kellner T. The story behind the real 'Iron Man' suit GE reports. [Internet]. 23 Nov 2010 [cited 7 Dec 2015]; Available from: http://www.gereports.com/post/78574114995/the-story-behind-the-real-iron-man-suit.
5. Swinnen E, Duerinck S, Baeyens JP, Meeusen R, Kerckhofs E. Effectiveness of robot-assisted gait training in persons with spinal cord injury: a systematic review. J Rehabil Med. 2010;42:520–6.
6. ReWalk: Company. 2015. www.rewalk.com/company/. Accessed 29 Apr 2015.
7. Esquenazi A, Talaty M, Packel A, Saulino M. The ReWalk powered exoskeleton to restore ambulatory function to individuals with thoracic-level motor-complete spinal cord injury. Am J Phys Med Rehabil. 2012;91:911–21. doi:10.1097/PHM.0b013e318269d9a3.
8. Talaty M, Esquenazi A, Briceno JE. Differentiating ability in users of the ReWalk(TM) powered exoskeleton: an analysis of walking kinematics. In: 2013 IEEE International Conference on Rehabilitation Robotics (ICORR). Proceedings of the 2013 IEEE International Conference on Rehabilitation Robotics, 24–26 Jun 2013. Seattle; 2013. p. 1–5.
9. Benson I, Hart K, Tussler D, van Middendorp JJ. Lower-limb exoskeletons for individuals with chronic spinal cord injury: findings from a feasibility study. Clin Rehabil. 2016;30(1):73–84. doi:10.1177/0269215515575166.
10. FDA allows marketing of first wearable, motorized device that helps people with certain spinal cord injuries to walk. 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm402970.htm. Accessed 6 May 2015.
11. Zeilig G, Weingarden H, Zwecker M, Dudkiewicz I, Bloch A, Esquenazi A. Safety and tolerance of the ReWalk exoskeleton suit for ambulation by people with complete spinal cord injury: a pilot study. J Spinal Cord Med. 2012;35:96–101. http://dx.doi.org/10.1179/2045772312Y.0000000003.
12. Ekso Bionics—Who We Are. 2015. http://www.ekso-bionics.com/ourstory. Accessed 6 May 2015.
13. Kressler J, Thomas CK, Field-Fote EC, Sanchez J, Widerstrom-Noga E, Cilien DC, et al. Understanding therapeutic benefits of overground bionic ambulation: exploratory case series in persons with chronic, complete spinal cord injury. Arch Phys Med Rehabil. 2014;95:1878–87. doi:10.1016/j.apmr.2014.04.026. e4.
14. Kolakowsky-Hayner SA, Crew J, Moran S, Shah A. Safety and feasibility of using the Ekso bionic exoskeleton to aid ambulation after spinal cord injury. J Spine. 2013. doi:10.4172/2165-7939.S4-003.
15. Jayaraman A, et al. Evaluation of the clinical criteria for safe and efficient use of exoskeletons in individuals with SCI. Proceedings of the 2013 American Spinal Injury Association (ASIA) Conference, 5–7 May 2013. Chicago; 2013.
16. Jayaraman A, et al. Effectiveness of robotic exoskeletons in everyday rehabilitation. Proceedings of the 8th ISPRM World Congress, 01–05 Jun 2014. Cancun; 2014.
17. Jayaraman A, Rymer W. Exoskeletons for neurologically impaired individuals. Proceedings of the 2014 Academy of Spinal Cord Injury Professionals, 31–3 Aug–Sept 2014. St. Louis; 2014.
18. Kozlowski A, et al. Assisted walking for persons with neurological conditions: The state of science. Proceedings from the 91st Annual American Congress of Rehabilitation Medicine, 7–11 Oct 2014. Toronto; 2014.
19. Nolan KJ. Gait training of stroke patients using a robotic exoskeleton during inpatient rehabilitation: feasibility study. Proceedings from the International Workshop of Wearable Robotics, 14–19 Sept 2014. Baiona; 2014.
20. Forrest G, et al. The potential of the Ekso exoskeleton for affecting long-term health and well-being in the SCI population. Proceedings from the Academy of Spinal Cord Injury Professionals. 31 Aug–3 Sept 2012. Las Vegas; 2012.
21. Indego: Company. 2015. http://www.indego.com/indego/en/media-downloads. Accessed 5 Aug 2015.
22. Ha K, Murray S, Goldfarb M. An approach for the cooperative control of FES with a powered exoskeleton during level walking for persons with paraplegia.

IEEE Trans Neural Syst Rehabil Eng. 2015. doi:10.1109/TNSRE.2015.2421052.
23. Indego Brochure & Spec Sheet. 2015. http://www.indego.com/indego/en/media-downloads. Accessed 7 Dec 2015.
24. Evans N, Hartigan C, Kandilakis C, Pharo E, Clesson I. Acute cardiorespiratory and metabolic responses during exoskeleton-assisted walking overground among persons with chronic spinal cord injury. Top Spinal Cord Inj Rehabil. 2015;21:122–32. http://dx.doi.org/10.1310/sci2102-122.
25. Hartigan C, Kandilakis C, Dalley S, Clausen M, Wilson E, Morrison S, Etheridge S, Farris R. Mobility outcomes following five training sessions with a powered exoskeleton. Top Spinal Cord Inj Rehabil. 2015;21:93–9. http://dx.doi.org/10.1310/sci2102-93.
26. Cyberdyne—HAL for Medical Use (Lower Limb Type). http://www.cyberdyne.jp/english/products/LowerLimb_medical.html. 2015. Accessed 6 Aug 2015.
27. Ryall J. Robot suit to help in fukushima clean-up. In: The Telegraph: Telegraph Media Group. 2011. http://www.telegraph.co.uk/news/science/science-news/8876233/Robot-suit-to-help-in-Fukushima-clean-up.html.
28. CYBERDYNE Inc. has begun seeking approval from the U.S. Food and Drug Administration (FDA). 2015. http://www.cyberdyne.jp/english/company/PressReleases_detail.html?id=1075. Accessed on 14 May 2015.
29. Kawamoto H, Kamibayashi K, Nakata Y, Yamawaki K, Ariyasu R, Sankai Y, et al. Pilot study of locomotion improvement using hybrid assistive limb in chronic stroke patients. BMC Neurol. 2013;13:141. doi:10.1186/1471-2377-13-141.
30. Kawamoto H, et al. Voluntary motion support control of robot suit HAL triggered by bioelectrical signal for hemiplegia. In: Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference. Proceedings of the 32nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2010 1–4 Sept. Buenos Aires; 2010. p. 462–6.
31. Bogue R. Exoskeletons and robotic prosthetics: a review of recent developments. Ind Robot Int J. 2009;36(5):421–7. http://dx.doi.org/10.1108/01439910910980141.
32. Maeshima S, Osawa A, Nishio D, Hirano Y, Takeda K, Kigawa H, et al. Efficacy of a hybrid assistive limb in post-stroke hemiplegic patients: a preliminary report. BMC Neurol. 2011;11:116. doi:10.1186/1471-2377-11-116.
33. Tsukahara A, Hasegawa Y, Eguchi K, Sankai Y. Restoration of gait for spinal cord injury patients using HAL with intention estimator for preferable swing speed. IEEE Trans Neural Syst Rehabil Eng. 2015;23:308–18. doi:10.1109/TNSRE.2014.2364618.
34. Wall A, Borg J, Palmcrtantz S. Clinical application of the Hybrid Assistive Limb (HAL) for gait training—a systemtic review. Front Neurosci. 2015;9:48. doi:10.3389/fnsys.2015.00048.
35. Nilsson A, Vreede KS, Haglund V, Kawamoto H, Sankai Y, Borg J. Gait training early after stroke with a new exoskeleton—the hybrid assistive limb: a study of safety and feasibility. J Neuroeng Rehabil. 2014;11:92. doi:10.1186/1743-0003-11-92.
36. Aach M, Cruciger O, Sczesny-Kaiser M, Höffken O, Meindl RC, Tegenthoff M, Schwenkreis P, Sankai Y, Schildhauer TA. Voluntary driven exoskeleton as a new tool for rehabilitation in chronic spinal cord injury: a pilot study. Spine J. 2014;14:2847–53. doi:10.1016/j.spinee.2014.03.042.
37. Shimada H, Kimura Y, Suzuki T, Hirata T, Sugiura M, Endo Y, et al. The use of positron emission tomography and [18F]fluorodeoxyglucose for functional imaging of muscular activity during exercise with a stride assistance system. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):442–8. doi:10.1109/TNSRE.2007.903978.
38. Walking assist device with stride management system. 2015. http://corporate.honda.com/innovation/walk-assist/. Accessed 9 Jun 2015.
39. Kitatani R, Ohata K, Takahashi H, Shibuta S, Hashiguchi Y, Yamakami N. Reduction in energy expenditure during walking using an automated stride assistance device in healthy young adults. Arch Phys Med Rehabil. 2014;95:2128–33. doi:10.1016/j.apmr.2014.07.008.
40. Taga G, Yamaguchi Y, Shimizu H. Self-organized control of bipedal locomotion by neural oscillators in unpredictable environment. Biol Cybern. 1991;65:147–59.
41. Shimada H, Suzuki T, Kimura Y, Hirata T, Sugiura M, Endo Y, et al. Effects of an automated stride assistance system on walking parameters and muscular glucose metabolism in elderly adults. Br J Sports Med. 2008;42:922–9.
42. Shimada H, Hirata T, Kimura Y, Naka T, Kikuchi K, Oda K, et al. Effects of a robotic walking exercise on walking performance in community-dwelling elderly adults. Geriatr Gerontol Int. 2009;9:372–81.
43. Buesing C, Fisch G, O'Donnell M, Shahidi I, Thomas L, Mummidisetty CK, et al. Effects of a wearable exoskeleton stride management assist system (SMA®) on spatiotemporal gait characteristics in individuals after stroke: a randomized controlled trial. J Neuroeng Rehabil. 2015;12:1. doi:10.1186/s12984-015-0062-0.
44. Mina. A robotic exoskeleton to help people walk again. 2015. http://www.ihmc.us/research/mina/Mina.php. Accessed 11 Jun 2015.
45. Anil K. Raj, Peter D. Neuhaus, Adrien M. Moucheboeuf, Jerryll H. Noorden, and David V. Lecoutre, "Mina: A Sensorimotor Robotic Orthosis for Mobility Assistance," Journal of Robotics, vol. 2011, Article ID 284352, 8 pages, 2011. doi:10.1155/2011/284352

46. REX bionics—our products. 2015. http://www.rexbionics.com/products/. Accessed 28 May 2015.
47. Lindsey S. UH, Methodist Hospital Research Institute receive $695K to further robotics research. [Internet]. 2013 Jun 11 [cited 1 May 2015]; Available from: http://www.uh.edu/news-events/stories/2013/june/06112013UHMethodistRoboticsGrant.php.
48. del Ama AJ, Koutsou AD, Moreno JC, de los Reyes A, Gil Agudo A, Pons JL. Review of hybrid exoskeletons to restore gait following spinal cord injury. J Rehabil Res Dev. 2012;49:497–514.
49. Medical devices; physical medicine devices; classification ovf the powered exoskeleton, 2015. Docket No. FDA-2014-N-1903. https://federalregister.gov/a/2015–03692. Accessed 27 May 2015.
50. Evaluation of automatic class iii designation—de nova request. Department of Health & Human Services. 2014. http://www.accessdata.fda.gov/cdrh_docs/pdf13/DEN130034.pdf. Accessed 27 May 2015.

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

25

Milos R. Popovic, Kei Masani, and Silvestro Micera

Abstract

Electrical stimulation is a tool that applies low-energy electrical pulses to artificially generate muscle contractions. If electrical stimulation is used to enable functional movements, such as walking and grasping, then this intervention is called functional electrical stimulation (FES). When FES is used as a therapy instead of being used as an orthosis, it is called FES therapy or FET. In this chapter, we introduce recent findings and advances in the field of FET. 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. 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 spinal cord injury (SCI) populations. Although phase I randomized control trials have been completed with chronic SCI population using this new FET technology and preliminary findings are encouraging, further R&D is required before the multichannel FET for walking will be ready for prime time clinical implementation.

Keywords

Functional electrical stimulation (FES) • Therapy • FES therapy • Spinal cord injury • Stroke • Rehabilitation • Neuroprosthesis • Neurorehabilitation • Restoration of voluntary function

M.R. Popovic, PhD, Dipl El Eng (✉)
Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

Lyndhurst Centre, Toronto Rehabilitation Institute – University Health Network, Toronto, Ontario, Canada
e-mail: milos.popovic@utoronto.ca

K. Masani, PhD
Lyndhurst Centre, Toronto Rehabilitation Institute – University Health Network, Toronto, Ontario, Canada

S. Micera, PhD
Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland

Scuola Superiore Sant'Anna, Pisa, Italy

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25.1 Introduction

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) and stroke. 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 she/he 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 embodiment, 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. In other words, FET is used as a short-term intervention to help the central nervous system of the consumer to relearn how to execute impaired functions, instead of making the consumer dependent on neuroprostheses for the rest of her/his life. In this chapter, we introduce recent findings and advances in the field of FET.

25.2 Functional Electrical Stimulation (FES)

25.2.1 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/orthotic device. In literature, this use of FES technology is referred to as neuroprosthesis or neuroprosthetics.

25.2.2 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. 25.1).

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

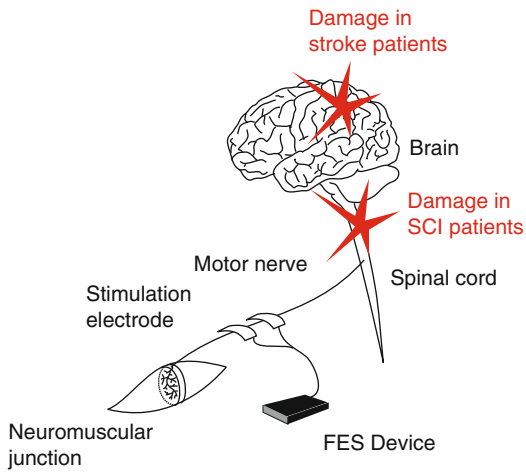

Fig. 25.1 A schematic representation of the surface functional electrical stimulation (FES) system. The FES system causes a muscle contraction by electrically stimulating the motor axons that are connected to the muscles. The electrical stimulation generates action potentials in the motor neurons, which propagate along the motor neurons toward the muscle. When the action potentials reach the muscle, they cause the muscle to contract

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. Nevertheless, it should be noted that an electric stimulator that has been purposefully designed to generate contractions in denervated muscles is currently commercially available. Its name is Stimulette den2x, and it is manufactured by Dr. Schuhfried, Medical technology, Austria (www.schuhfriedmed.at/en/). In the remainder of this document, we will only discuss FES systems that have been developed to stimulate innervated muscles.

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. According to Rushton [3], repeated antidromic stimulation through Hebb-type processes may over time enable week/sparse supraspinal commands to activate anterior motor neuron and enable it to produce desired muscle contraction(s). 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.

25.2.3 Technology

Nerves can be stimulated using either surface (transcutaneous) or subcutaneous (percutaneous or implanted) electrodes. The surface electrodes

are placed on the skin surface above the nerve or muscle that needs to be "activated." They are noninvasive, easy to apply, and generally inexpensive. Until recently the common belief in the FES field has been that 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. This statement is correct for all commercially available stimulators except MyndMove® stimulator (Fig. 25.2), which is manufactured by a Canadian company MyndTec (www.myndtec.com). MyndMove® has implemented a new stimulation pulse that allows the stimulator to generate muscle contractions using electrical pulses, which amplitudes are 10–15 times lower in intensity then those required by other transcutaneous electrical stimulation systems. The key aspects of this new technology are stimulation pulses that have very fast slew rate (US Patent 20130090712) and are able to rapidly engage Aα efferent nerve fibers (i.e., descending nerves from the central nervous system to muscles) using very low stimulation amplitudes and at the same time minimize engagement of afferent Aδ and C nerve fibers responsible for transmission of pain sensation. This new technology not only reduces the intensity of stimulation, but it also reduces discomfort during stimulation, which is a common problem with commercially available transcutaneous electrical stimulation systems.

A major limitation of the transcutaneous electrical stimulation is that some nerves, for example, those innervating the hip flexors, are too deep 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 typically remain in place for a short period of time and are only considered for short-term FES interventions. However, it is worth mentioning that some groups, such as Cleveland FES Center, have been able to safely use percutaneous electrodes with individual patients for months and years at a time. One of the drawbacks of using the percutaneous electrodes is that 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,

Fig. 25.2 Use of MyndMove® to retrain upper arm voluntary movements (Photo courtesy MyndTec, Toronto, ON, Canada)

implanted and percutaneous electrodes potentially have higher stimulation selectivity, which is a 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 [7]. 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.

25.3 FES Therapy (FET)

25.3.1 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 [8]. When the FES technology is used to deliver FET, the purpose of that intervention is to restore voluntary function. In other words, FES 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 her/his 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. Since FET systems are generally noninvasive and are used to produce diverse upper or lower limb movements/therapies, FET-dedicated systems can have many more stimulation protocols (e.g., ten or more for upper limb FET) that at times target different muscle groups and can be used with a single consumer. However, the neuroprostheses that are used as permanent orthotic systems often target one set of muscles or muscle groups and have one or at best two/three consumer-specific stimulation protocols.

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 she/he needs to use the neuroprosthetic system, without which she/he would not be able to perform this task at all. Good examples of such technologies that are commercially available are RT300 FES bike from Restorative Therapies (www.restorative-therapies.com) and RehaBike by Hasomed (www.hasomed.de).

The implanted FES systems are primarily used as permanent neuroprostheses. However, some attempts have been made to use the BION implantable FES system for FET [9]. 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 patients 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 last decade.

25.3.2 Neuroplasticity Effect

Since the 1970s, some researchers and practitioners in the field of FES have observed that many patients who use FES on a regular basis experience significant carry-over in function that

persists even when the device is not in use. This "enigma" of "carry-over effect" has interested researchers [10], 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 [11]. They investigated the carry-over effect of FES on hand opening and elbow extension functions for stroke patients. Three of five patients showed the carry-over effects after a 2-month 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 carry-over effect supported the potential role of neuroprostheses as therapeutic interventions in clinical practice. Despite the fact that FES-related carry-over results were observed as early as the 1970s, a rigorous investigation of FES carry-over effect started only recently.

25.4 Current Evidences of FET

It took almost two decades before the carry-over effect started being examined seriously. As describe next, it was first 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.

Initially, FET did not exist as a field on its own, and the first FET studies were essentially examining carry-over effect of the neuroprostheses. Once, it become clear that FET is actually helping reprogram the central nervous system and that the carry-over effect is not due to the muscle strengthening (which was initially suspected [12]) but was due to neuroplasticity, the FET field has been established and FET-dedicated systems started being developed. The systems used to test FET concept were originally neuroprostheses that were normally used as orthoses. Today we are experiencing the development of FET-dedicated systems, which design requirements are very different from the "garden variety" neuroprosthetic systems developed for orthotic applications.

25.4.1 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. 25.3). There are a 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 (ODFS® Pace) by Odstock Medical (www.odstockmedical.com) [13], the WalkAide® by Innovative Neurotronics (www.walkaide.com) [14], and the NESS L300 for Foot Drop by Bioness (www.bioness.com) [15]. The ActiGait® by Ottobock (www.ottobock.com) [16] and the STIMuSTEP® by Finetech Medical (www.finetech-medical.co.uk) [17] 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 after cochlear implants. Overall, consumer perception of the drop-foot stimulators is they are superior to the ankle-foot orthosis [18].

There has been a great deal of evidence showing the benefits of the drop-foot FES for the lower

Fig. 25.3 NESS L300 for foot drop (Photo courtesy Bioness Inc., Valencia, CA, USA)

limbs of stroke patients. In most of the studies, the effect of the drop-foot stimulator as an orthosis has been studied. Only few studies have investigated the FET effect in stroke patients with drop-foot problem (e.g. [19]). In the early phase, some studies showed a negative result with respect to the FET effect [20, 21], while other studies showed positive effect on the FET effect [13]. For example, Granat et al. [21] investigated the effect of a drop-foot stimulator on hemiplegic patients ($n=19$) in a two-period crossover study design (4-week control period followed by 4-week 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 was not using the FES system, i.e., FET effect). In a randomized controlled trial, Burridge et al. [20] investigated the effect of a drop-foot stimulator on individuals with stroke. The intervention 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 intervention 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 intervention 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 intervention group when the drop-foot stimulator was removed. In other words, they were not able to demonstrate the drop-foot stimulator's FET effect. Taylor et al. [13] 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., FET effect. The MS patients showed similar benefits when they used the drop-foot stimulator as an orthosis, with no noticeable FET effects.

Recently, in a relatively larger population study, Stein et al. [14] 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 FET (17.8 % and 9.1 % for stroke and MS patients, respectively) effects on walking speed, during over ground figure-8 walking. After

11 months of following the baseline, the FET 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 FET 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 stroke.

25.4.2 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 [22]. 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. 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) [23]. Following that, Kralj et al. described a technique for paraplegic gait using surface electrical stimulation, which remains the most popular method in use today [24]. 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 [25, 26], HAS [27], and RGO [28] and the Case Western Reserve University (CWRU)/VA neuroprosthesis [29–32]. The Parastep system is one of most popular products and uses Kralj's technique [25, 26] (Fig. 25.4). 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 [29–32]. 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 stepping 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

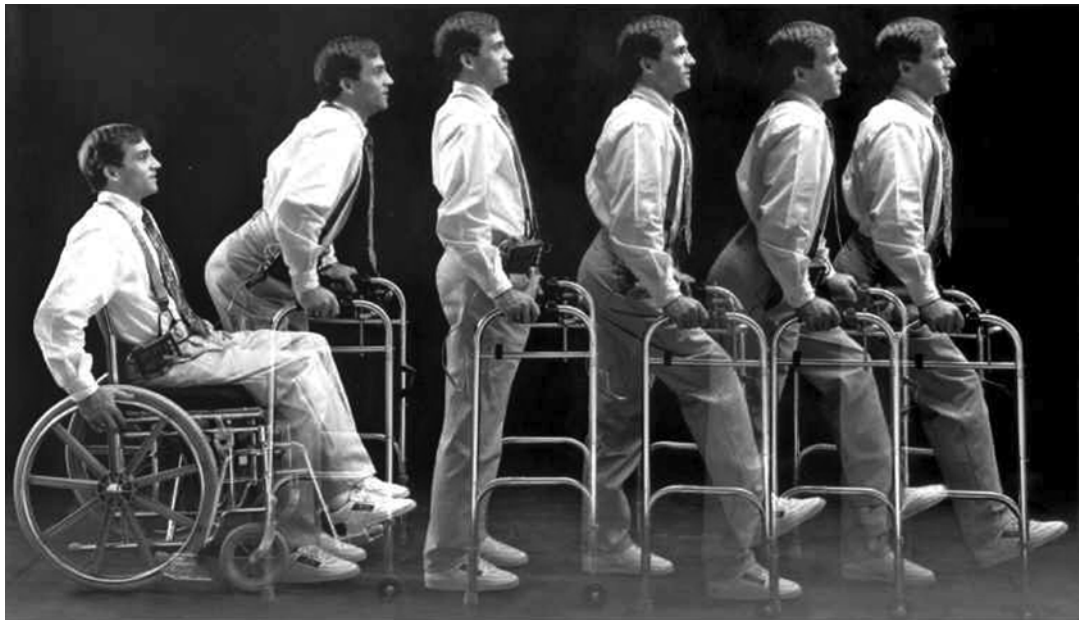

Fig. 25.4 Parastep electrical stimulation system (Photo courtesy Sigmedics, Inc., Fairborn, OH, USA)

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 [29–32], Praxis [33], and Compex Motion neuroprosthesis for walking [34, 35]. The Praxis and CWRU/VA neuroprosthesis are implantable FES device systems 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 to orthotic applications. However, recently the Cleveland team tested the therapeutic effects of their implantable system in a single-subject study [29].

Compex Motion neuroprosthesis for walking is an 8–16 channel surface FES system used to restore walking in stroke and SCI individuals [34]. The system uses a push button control strategy, similar to the one used in the Parastep system, and a gate phase detection sensor [36] 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. [37]. The review concluded that there are various benefits including therapeutic effect of FES for individuals with SCI and of strength training, drop-foot stimulator, and plantar flexor stimulation during gait phase.

In addition to those studies, Wieler et al. [38] 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. Similar findings have been published by Field-Fote and her team [39, 40].

Thrasher et al. [35] 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 significant 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.

Inspired by Thrasher et al. [35] results, Toronto team carried out phase I randomized control trial in which they compared the gait-patterned multichannel FET against equal dose of convectional exercise [41–43]. Patient population was incomplete chronic SCI individuals. The results of the study suggested that 40 h of exercise and 40 h of multichannel FET both generated clinically meaningful improvements in this patient population. At the same time, the differences between the two groups were minimal, meaning that FET in this patient population did not generate superior outcomes compared to the control group. However, it should be noted that the Spinal Cord Independence Measure (SCIM) Mobility Subscore improved in FET group significantly more than in the control group [43].

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 gait-patterned multichannel 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.

25.4.3 FET for Restoration of Upper Limb Function Following Stroke

Impaired reaching and grasping functions are common symptoms among stroke patients. Numerous neuroprostheses have been designed to compensate for lost grasping [44–55] and grasping and reaching [8, 34, 52, 56, 57] functions in stroke patients.

Some notable grasping and/or reaching neuroprostheses are the Freehand system [7], the NESS H200 for Hand Paralysis by Bioness (www.bioness.com) [48] (Fig. 25.5), the Bionic Glove [49, 52, 58], the ETHZ-ParaCare neuroprosthesis for grasping [34, 59, 92], the systems developed by Rebersek and Vodovnik [53], the Belgrade Grasping-Reaching System [60], Compex Motion neuroprosthesis for reaching and grasping [34], the percutaneous systems by Chae et al. [45, 46], and recently MyndMove® by MyndTec (www.myndtec.com). The above 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 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. In addition to these two grasping styles, Compex Motion neuroprosthesis and MyndMove® system offer variety of additional grasping styles, such as pinch grasp, lumbrical grasp, tripod grasp, and proper hand opening that involves activation of the intrinsic muscles of the hand. The Belgrade Grasping-Reaching System, Freehand system, Compex Motion system, and MyndMove® also offer reaching capabilities. Of these systems MyndMove® offers the largest diversity of grasping and/or reaching tasks that can be performed with a single FES system. 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.

The 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

Fig. 25.5 NESS H200 for hand paralysis (Photo courtesy Bioness Inc., Valencia, CA, USA)

of muscle strength after stroke [61]. Recent studies that have specifically examined FET have suggested positive outcomes in acute [8, 49, 50, 56] and chronic [48, 54, 55, 58] stroke patients. These were then followed by randomized control trials that confirmed the positive outcomes of FET in acute [44, 57, 62] and chronic [45, 57] stroke patients. 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. [45, 46]. 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 [6] and a new version of the Bionic Glove [49, 58, 63].

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 or Upper Extremity Fugl-Meyer Assessment Score greater then 30, 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 [56, 57] 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 or Upper Extremity Fugl-Meyer Assessment Score $\leq$15. 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 [57]. The median improvement achieved in this study in the FET group was 24.5 points on the Upper Extremity Fugl-Meyer Assessment, while the median improvement in the control group was 0 [57].

It is worth mentioning that a small study with chronic pediatric stroke patients has been carried out where FET was used to improve reaching and grasping function in this patient population [64]. Although only four individuals participated in this pilot study, the outcomes achieved were very encouraging, and they indicated that FET for upper limb could be effectively delivered in pediatric patients.

In summary, there is mounting evidence that in individuals with moderate and severe upper limb deficit, which results from stroke, FET can enable substantial improvement in their voluntary upper limb function. Also, these studies suggested that the improvements achieved are long lasting.

25.4.4 FET for Restoration of Upper Limb Function Following SCI

A SCI at a 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 help improve those functions in individuals with SCI. Among these interventions, FES devices have shown the most promise [65]. 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, Compex Motion system, and MyndMove®, have been used with SCI subjects almost exclusively 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 as intensely 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. [66] provided some evidence that a few of the SCI patients who used the device experienced a weak FET effect. A clinical trial using Bionic Grove 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 [64].

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 [67]. In this study, the individuals received 40 1-h FET treatments (intervention group) or 40 1-h conventional occupational therapy treatments (control group). The therapy was tested on individuals with complete and incomplete subacute (<6 months) SCI. Although this particular study was underpowered, it provided clear evidence that both individuals with complete and incomplete subacute SCI greatly benefited from the FET for grasping. This study was then followed by another phase II randomized controlled trial; FET for grasping was evaluated in individuals with incomplete, traumatic subacute C3–C7 SCI [68]. What is relevant to mention is that this was a very conservative study with respect to FET. In this study, both control and intervention groups received 1 h of conventional occupational therapy daily, as described in [67]. 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 the intervention 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 12 subjects in the intervention group and nine in the control group. The results obtained were statistically significant and have revealed that FET dramatically improved 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 intervention groups maintained or further improved their hand function as compared to the assessments performed at discharge from the study [69]. In other words, this study suggests that the changes in the hand function produced by FET are dramatic, and they persist over time. Recently, a phase I randomized control trial study was performed using FET for grasping in chronic (>24 months) incomplete SCI individuals [70]. Forty 1-h sessions of FET (intervention group) were compared against 40 1-h sessions of conventional occupational therapy (control group). The results of the study showed that the individuals who received FET improved considerably

better then the individuals who had the same dose of conventional occupational therapy.

In summary, there is mounting evidence that individuals with incomplete C3–C7 SCI, both chronic and subacute, can benefit from the FET for grasping. The existing studies also suggest that early engagement in the FET would result in better outcomes compared to later engagement. Also, a recently published study suggested that simple increase in intensity of conventional therapy is not able to match outcomes that were achieved with FET [71], further confirming that FET for grasping should be considered the new best practice with respect to incomplete SCI population. As for the complete SCI individuals, there is weak evidence that FET is beneficial for that population as well, if it is used early during subacute phase of rehabilitation.

25.4.5 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 [72]. 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) [27, 73, 74]. Such mechanical supports have been used mainly for safety and prevention of adverse events during standing and gait [72].

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 reaching and walking 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 flaccid and spastic muscles in task execution and generate much more significant proprioceptive and sensory feedback, which is critical for retraining the neuromuscular system. Specifically, Takeoka et al. [75] recently demonstrated that muscle spindle feedback is critical and probably essential for the functional recovery following SCI. On the other hand, robotic systems are very good in executing accurate limb movements, but, in general, these systems themselves do not generate muscle activations. However, in order for the muscles to produce proper afferent feedback, in particular proper muscle spindle feedback, they need to be contracted at a proper level of muscle tension, and the their tension needs to be regulated according to the join angle. The FES systems are able to achieve that, although not as good as the intact central nervous system does. The robotic systems, because of the nature of this technology, have neither capability to produce desired muscle tension nor are able to regulate muscle tension as a function of joint angle. In robotic systems, the more substantial afferent feedback can be produced if the consumer has tone. However, it is not clear if the afferent feedback produced under such circumstances matches the one that the intact central nervous system would naturally produce. Therefore, it has been suggested that the combination of FES with robotic devices will enhance the therapeutic effects of both interventions. A recent study by Freeman et al. [76] 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 five stroke patients in treatment sessions comprised of up to 25 1-h visits. For walking, Stauffer et al. [77] 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.

Very recently, a new hybrid robotics-FET system has been proposed for the restoration of grasping and reaching after stroke [78]. The system combines ALEX (an upper limb exoskeleton), which provides the reaching support [79], together with a FES system that uses electrode arrays to provide grasp control. Real reaching and grasping tasks can be achieved by using a satellite robot, which presents the objects to be grasped. Specific rehabilitation tasks can be implemented by taking advantage of the possibility to quantify the support needed by patients and to modulate both the mechanical and FES support over the reachable workspace.

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.

25.5 Potential Mechanisms of FET

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

Three possible "peripheral" mechanisms might be considered. At first, FET may improve the muscle functions in the remaining motor units through 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 limb/joints, and as a consequence, the voluntary function may be improved. However, stretching during physiotherapy should be able to generate similar results. Third, FET reduces 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 FET does improve the spasticity [80, 81], the FET effect has been observed even in the affected limbs that did not have spasticity. Thus, although all three above-listed mechanisms may be possible, they alone could not account for the observed FET effect.

It has been reported that cortical reorganization can occur following stroke recovery [82]. As FES activates both motor and sensory nerve fibers, high-frequency sensory stimulation may be capable of modifying cortical connectivity [83]. Thus, through forced repetitive movements, FET may promote the neuroplasticity in the central nervous system through sensory nerve stimulation [84].

In addition to the cortical reorganization mechanism, Rushton [3] suggested a hypothesis that accounts for the neuroplasticity 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 [85, 86]. However, it should be noted that a facilitation of motor evoked potential using simultaneous TMS and FES (i.e., spinal paired associative stimulation) is not always guaranteed [87] and that the above Rushton's hypothesis yet needs to be confirmed.

Another hypothesis that could also explain the mechanisms behind FET is the one proposed by Popovic et al. [34–57, 67–69]. If a subject, who

attempts to execute a motor task, is assisted with the FET to carry out that task, she/he 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 repetitively for prolonged periods of time, this type of treatment facilitates functional reorganization and retraining of intact parts of the central nervous system and allows them to take over the function of the damaged part of the central nervous system. 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 her/his attention to the tasks performed) may play a critical role in retraining voluntary motor function. This hypothesis and use of FET are fully in tune with recent findings in the field of neuroplasticity and suggest that FET is potentially another effective method that can be used to retrain the neuromuscular system.

Recently a study by Takeoka et al. [75] demonstrated very elegantly that muscle spindle feedback is critical and probably essential for the functional recovery following SCI. They have shown that if muscle spindles are "removed out of the rehabilitation process" that the animal trained is unable to recover its function. Since FET fully engages muscle spindle feedback system during therapy, it is very likely that the high intensity muscle spindle feedback produced by the FET is contributing to the process of recovery of voluntary function. Please note that in the past, it has been frequently suggested that the FES/FET does not activate muscle fibers in physiologically correct manner, i.e., that the fast-twitch muscle fibers are recruited first followed by the slow-twitch muscle fibers [88]. This reverse order of muscle fiber activation could impact the order in which muscle spindle feedback is presented to the central nervous system following FET. However, recent experiments have shown that this notion of reverse muscle fiber recruitment during FES/FET is incorrect [88], suggesting that the order in which muscle spindle feedback is delivered to the central nervous system should be reasonably close to the natural one. More comprehensive discussion about the sensory feedback systems that may be engaged during FET and how they may contribute to the improvement in the voluntary function following FET can be found in Prochazka's recent article [89].

The final hypothesis that Popovic and his team in Toronto proposed previously suggests that it is possible that the phylogenetically older brain structures, which are equally able of control limbs, may be engaged during FET training. Specifically, he hypothesized that FET for reaching and grasping, when it is applied to stroke patients, engages phylogenetically older brain structures and retrains them to perform reaching and grasping tasks, instead of retraining the cortical structures. Recently, Kawai et al. [90] actually demonstrated in rodents that the motor cortex is required for learning new tasks, but that it is not required for execution of already mastered forelimb motor tasks. This finding suggests that Popovic's hypothesis may be correct, but this hypothesis still needs to be properly verified.

In any event, the carry-over 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.

25.6 Comparison of FET and Robotic Therapies

To the best of our knowledge, a proper comparison of the FET and robotic therapy was not conducted to date. The only comparison that we are aware of is the one conducted by Hess at al. [91], where Bi-Many-Track system (Reha-Stim, Germany) (www.reha-stim.de) was compared to electrical stimulation of the wrist extensor

muscles. The study was performed in subacute stroke individuals (between 4 and 8 weeks following stroke) patients, which Upper Extremity Fugl-Meyer scores were less than 18. Bi-Many-Track was used to deliver therapy to the wrist (flexion/extension and pronation/supination), elbow (flexion/extension), and indirectly to shoulder (flexion/extension). The electrical stimulation was delivered to wrist extensors only and was activated manually or using biofeedback approach. Although both therapies were delivered over 30 sessions that were 20 min long (10 h of therapy in total), Bi-Many-Track delivered between 12,000 and 24,000 movement repetitions (spread over different joints) and electrical stimulation delivered between 1,800 and 2,400 wrist flexion/extension repetitions. Please note that the electrical stimulation intervention used in this study does not belong to the FET variety of therapies but rather to a muscle strengthening type of interventions. The study results suggest that at discharge, participants who received Bi-Many-Track had improvement in Upper Extremity Fugl-Meyer scores of 16.7 points, while the participants who received electrical stimulation had improvement in Upper Extremity Fugl-Meyer scores of 3.1 points.

We are hopeful that this study will inspire the research community to start comparing equal dose FET and robotic therapy, which are training the same joints and muscle groups, and are delivering equal dose/intensity of intervention.

25.7 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 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 chronic complete and incomplete SCI and stroke subjects. However, to date, statistically significant results have only been obtained with chronic 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 at least partial 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 next 10–15 years, FET will become one of the dominant interventions for upper and lower limb rehabilitation. Many FET systems are already commercialized, and many more are in the process of being developed and/or commercialized. Thus, we feel very confident that FET filed 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.

References

1. Reichel M, Breyer T, Mayr W, Rattay F. Simulation of the three-dimensional electrical field in the course of functional electrical stimulation. Artif Organs. 2002;26:252–5.
2. Kern H, Hofer C, Mödlin M, Forstner C, Raschka-Högler D, Mayr W, Stöhr H. Denervated muscles in humans: limitations and problems of currently used functional electrical stimulation training protocols. Artif Organs. 2002;26:216–8.
3. Rushton D. Functional electrical stimulation and rehabilitation—an hypothesis. Med Eng Phys. 2003;25:75–8.
4. Kuhn A, Keller T, Micera S, Morari M. Array electrode design for transcutaneous electrical stimulation: a simulation study. Med Eng Phys. 2009;31:945–51.
5. Micera S, Keller T, Lawrence M, Morari M, Popović DB. Wearable neural prostheses. Restoration of sensory-motor function by transcutaneous electrical stimulation. IEEE Eng Med Biol Mag. 2010;29:64–9.
6. Popović DB, Popović MB. Automatic determination of the optimal shape of a surface electrode: selective stimulation. J Neurosci Methods. 2009;178:174–81.
7. Smith B, Tang Z, Johnson MW, Pourmehdi S, Gazdik MM, Buckett JR, Peckham PH. An externally powered, multichannel, implantable stimulator-telemeter for control of paralyzed muscle. IEEE Trans Biomed Eng. 1998;45:463–75.
8. Popovic MB, Popovic DB, Sinkjaer T, Stefanovic A, Schwirtlich L. Restitution of reaching and grasping promoted by functional electrical therapy. Artif Organs. 2002;26:271–5.
9. Davis R, Sparrow O, Cosendai G, Burridge JH, Turk R, Wulff C, Schulman J. Post-stroke arm rehabilitation using 5–7 implanted microstimulators: implantation procedures, safety and efficacy. 12th Ann Conf Int FES Soc, Nov 2007, Philadelphia.
10. Waters RL. The enigma of "carry-over". Int Rehabil Med. 1984;6:9–12.
11. Merletti R, Acimovic R, Grobelnik S, Cvilak G. Electrophysiological orthosis for the upper extremity in hemiplegia: feasibility study. Arch Phys Med Rehabil. 1975;56:507–13.
12. Popovic MR, Popovic DB, Keller T. Neuroprostheses for grasping. Neurol Res. 2002;24:443–52.
13. Taylor PN, Burridge JH, Dunkerley AL, Wood DE, Norton JA, Singleton C, Swain ID. Clinical use of the Odstock dropped foot stimulator: its effect on the speed and effort of walking. Arch Phys Med Rehabil. 1999;80:1577–83.
14. Stein RB, Everaert DG, Thompson AK, Chong SL, Whittaker M, Robertson J, Kuether G. Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders. Neurorehabil Neural Repair. 2010;24:152–67.
15. Hausdorff JM, Ring H. Effects of a new radio frequency-controlled neuroprosthesis on gait symmetry and rhythmicity in patients with chronic hemiparesis. Am J Phys Med Rehabil. 2008;87:4–13.
16. Burridge JH, Haugland M, Larsen B, Svaneborg N, Iversen HK, Christensen PB, Pickering RM, Sinkjaer T. Patients' perceptions of the benefits and problems of using the ActiGait implanted drop-foot stimulator. J Rehabil Med. 2008;40:873–5.
17. Kenney L, Bultstra G, Buschman R, Taylor P, Mann G, Hermens H, Holsheimer J, Nene A, Tenniglo M, van der Aa H, Hobby J. An implantable two channel drop foot stimulator: initial clinical results. Artif Organs. 2002;26:267–70.
18. van Swigchem R, Vloothuis J, den Boer J, Weerdesteyn V, Geurts ACH. Is transcutaneous peroneal stimulation beneficial to patients with chronic stroke using an ankle-foot orthosis? A within-subjects study of patients' satisfaction, walking speed and physical activity level. J Rehabil Med. 2010;42:117–21.
19. Daly JJ, Roenigk K, Holcomb J, Rogers JM, Butler K, Gansen J, McCabe J, Fredrickson E, Marsolais EB, Ruff RL. A randomized controlled trial of functional neuromuscular stimulation in chronic stroke subjects. Stroke. 2006;37:172–8.
20. Burridge JH, Taylor PN, Hagan SA, Wood DE, Swain ID. The effects of common peroneal stimulation on the effort and speed of walking: a randomized controlled trial with chronic hemiplegic patients. Clin Rehabil. 1997;11:201–10.
21. Granat MH, Maxwell DJ, Ferguson AC, Lees KR, Barbenel JC. Peroneal stimulator; evaluation for the correction of spastic drop foot in hemiplegia. Arch Phys Med Rehabil. 1996;77:19–24.
22. Kantrowitz A. Electronic physiological aids: A report of the Maimonides Hospital. Maimonides Hospital, Brooklyn. 1960.
23. Strojnik P, Kralj A, Ursic I. Programmed six-channel electrical stimulator for complex stimulation of leg muscles during walking. IEEE Trans Biomed Eng. 1979;26:112–6.
24. Kralj A, Bajd T, Turk R. Enhancement of gait restoration in spinal injured patients by functional electrical stimulation. Clin Orthop Relat Res. 1988;233:34–43.
25. Graupe D, Davis R, Kordylewski H, Kohn K. Ambulation by traumatic T4–12 paraplegics using functional neuromuscular stimulation. Crit Rev Neurosurg. 1998;8:221–31.
26. Graupe D, Kohn KH. Functional neuromuscular stimulator for short-distance ambulation by certain thoracic-level spinal-cord-injured paraplegics. Surg Neurol. 1998;50:202–7.
27. Popovic D, Tomović R, Schwirtlich L. Hybrid assistive system—the motor neuroprosthesis. IEEE Trans Biomed Eng. 1989;36:729–37.

28. Solomonow M, Baratta R, Hirokawa S, Rightor N, Walker W, Beaudette P, Shoji H, D'Ambrosia R. The RGO generation II: muscle stimulation powered orthosis as a practical walking system for thoracic paraplegics. Orthopedics. 1989;12:1309–15.
29. Bailey SN, Hardin EC, Kobetic R, Boggs LM, Pinault G, Triolo RJ. Neurotherapeutic and neuroprosthetic effects of implanted functional electrical stimulation for ambulation after incomplete spinal cord injury. J Rehabil Res Dev. 2010;47:7–16.
30. Davis JA, Triolo RJ, Uhlir J, Bieri C, Rohde L, Lissy D, Kukke S. Preliminary performance of a surgically implanted neuroprosthesis for standing and transfers—where do we stand? J Rehabil Res Dev. 2001;38:609–17.
31. Davis JA, Triolo RJ, Uhlir JP, Bhadra N, Lissy DA, Nandurkar S, Marsolais EB. Surgical technique for installing an eight-channel neuroprosthesis for standing. Clin Orthop Relat Res. 2001;385:237–52.
32. Hardin E, Kobetic R, Murray L, Corado-Ahmed M, Pinault G, Sakai J, Bailey SN, Ho C, Triolo RJ. Walking after incomplete spinal cord injury using an implanted FES system: a case report. J Rehabil Res Dev. 2007;44:333–46.
33. Johnston TE, Betz RR, Smith BT, Benda BJ, Mulcahey MJ, Davis R, Houdayer TP, Pontari MA, Barriskill A, Creasey GH. Implantable FES system for upright mobility and bladder and bowel function for individuals with spinal cord injury. Spinal Cord. 2005;43:713–23.
34. Popovic MR, Keller T. Modular transcutaneous functional electrical stimulation system. Med Eng Phys. 2005;27:81–92.
35. Thrasher TA, Flett HM, Popovic MR. Gait training regimen for incomplete spinal cord injury using functional electrical stimulation. Spinal Cord. 2006;44:357–61.
36. Pappas IP, Popovic MR, Keller T, Dietz V, Morari M. A reliable gait phase detection system. IEEE Trans Neural Sys Rehabil Eng. 2001;9:113–25.
37. Bajd T, Kralj A, Stefancic M, Lavrac N. Use of functional electrical stimulation in the lower extremities of incomplete spinal cord injured patients. Artif Organs. 1999;23:403–9.
38. Wieler M, Stein R, Ladouceur M, Whittaker M, Smith A, Naaman S, Barbeau H, Bugaresti J, Aimone E. Multicenter evaluation of electrical stimulation systems for walking. Arch Phys Med Rehabil. 1999;80:495–500.
39. Field-Fote EC, Roach KE. Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Phys Ther. 2011;91(1):48–60.
40. Field-Fote EC, Lindley SD, Sherman AL. Locomotor training approaches for individuals with spinal cord injury: a preliminary report of walking-related outcomes. J Neurol Phys Ther. 2005;29(3):127–37.
41. Giangregorio L, Craven BC, Richards K, Kapadia N, Hitzig SL, Masani K, Popovic MR. A randomized trial of functional electrical stimulation for walking in incomplete spinal cord injury: effects on body composition. J Spinal Cord Med. 2012;35(5):351–60.
42. Hitzig SL, Craven BC, Panjwani A, Kapadia N, Giangregorio LM, Richards K, Masani K, Popovic MR. A randomized trial of functional electrical stimulation therapy for walking in incomplete spinal cord injury: effects on quality of life and community participation. Top Spinal Cord Inj Rehabil. 2013;19(4):245–58.
43. Kapadia N, Masani K, Craven BC, Giangregorio LM, Hitzig SL, Richards K, Popovic MR. A randomized trial of functional electrical stimulation for walking in incomplete spinal cord injury: effects on walking competency. J Spinal Cord Med. 2014;37(5):511–24.
44. Chae J, Bethoux F, Bohine T, Dobos L, Davis T, Friedl A. Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. Stroke. 1998;29:975–9.
45. Chae J, Harley M, Hisel T, Corrigan C, Demchak J, Wong Y-T, Fang Z-P. Intramuscular electrical stimulation for upper limb recovery in chronic hemiparesis: an exploratory randomized clinical trial. Neurorehabil Neural Repair. 2009;23:569–78.
46. Chae J, Hart R. Intramuscular hand neuroprosthesis for chronic stroke survivors. Neurorehabil Neural Repair. 2003;17:109–17.
47. Francisco G, Chae J, Chawla H, Kirshblum S, Zorowitz R, Lewis G, Pang S. Electromyogram-triggered neuromuscular stimulation for improving the arm function of acute stroke survivors: a randomized pilot study. Arch Phys Med Rehabil. 1998;79:570–5.
48. Hendricks HT, IJzerman MJ, de Kroon JR, in't Groen FA, Zilvold G. Functional electrical stimulation by means of the 'Ness Handmaster Orthosis' in chronic stroke patients: an exploratory study. Clin Rehabil. 2001;15:217–20.
49. Kowalczewski J, Gritsenko V, Ashworth N, Ellaway P, Prochazka A. Upper-extremity functional electric stimulation-assisted exercises on a workstation in the subacute phase of stroke recovery. Arch Phys Med Rehabil. 2007;88:833–9.
50. Popovic D, Popovic M, Sinkjaer T, Stefanovic A, Schwirtlich L. Therapy of paretic arm in hemiplegic subjects augmented with a neural prosthesis: a cross-over study. Can J Physiol Pharmacol. 2004;82:749–56.
51. Popović D, Stojanović A, Pjanović A, Radosavljević S, Popović M, Jović S, Vulović D. Clinical evaluation of the bionic glove. Arch Phys Med Rehabil. 1999;80:299–304.
52. Prochazka A, Gauthier M, Wieler M, Kenwell Z. The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. Arch Phys Med Rehabil. 1997;78:608–14.
53. Rebersek S, Vodovnik L. Proportionally controlled functional electrical stimulation of hand. Arch Phys Med Rehabil. 1973;54:378–82.

54. Sullivan JE, Hedman LD. A home program of sensory and neuromuscular electrical stimulation with upper-limb task practice in a patient 5 years after a stroke. Phys Ther. 2004;84:1045–54.
55. Sullivan JE, Hedman LD. Effects of home-based sensory and motor amplitude electrical stimulation on arm dysfunction in chronic stroke. Clin Rehabil. 2007;21:142–50.
56. Popovic MR, Thrasher TA, Zivanovic P, Takaki M, Hajek P. Neuroprosthesis for retraining reaching and grasping functions in severe hemiplegic patients. Neuromodulation. 2005;8:58–72.
57. Thrasher TA, Zivanovic V, McIlroy W, Popovic MR. Rehabilitation of reaching and grasping function in severe hemiplegic patients using functional electrical stimulation therapy. Neurorehabil Neural Repair. 2008;22:706–14.
58. Gritsenko V, Prochazka A. A functional electric stimulation-assisted exercise therapy system for hemiplegic hand function. Arch Phys Med Rehabil. 2004;85:881–5.
59. Popovic MR, Keller T, Pappas IP, Dietz V, Morari M. Surface-stimulation technology for grasping and walking neuroprosthesis. IEEE Eng Med Biol Mag. 2001;20:82–93.
60. Popović MB. Control of neural prostheses for grasping and reaching. Med Eng Phys. 2003;25:41–50.
61. Glanz M, Klawansky S, Stason W, Berkey C, Chalmers TC. Functional electrostimulation in post-stroke rehabilitation: a meta-analysis of the randomized controlled trials. Arch Phys Med Rehabil. 1996;77:549–53.
62. Cauraugh JH, Kim S. Two coupled motor recovery protocols are better than one: electromyogram-triggered neuromuscular stimulation and bilateral movements. Stroke. 2002;33:1589–94.
63. Ring H, Rosenthal N. Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. J Rehabil Med. 2005;37:32–6.
64. Kapadia NM, Nagai MK, Zivanovic V, Bernstein J, Woodhouse J, Rumney P, Popovic MR. Functional electrical stimulation therapy for recovery of reaching and grasping in severe chronic paediatric stroke patients. J Child Neurol. 2014;29(4):493–9.
65. Popovic MR, Thrasher TA. Neuroprostheses, Encyclopedia of biomaterials and biomedical engineering. New York: Marcel Dekker Inc.; 2004. p. 1056–65.
66. Mangold S, Keller T, Curt A, Dietz V. Transcutaneous functional electrical stimulation for grasping in subjects with cervical spinal cord injury. Spinal Cord. 2005;43:1–13.
67. Popovic MR, Thrasher TA, Adams ME, Takes V, Zivanovic V, Tonack MI. Functional electrical therapy: retraining grasping in spinal cord injury. Spinal Cord. 2006;44:143–51.
68. Popovic MR, Kapadia N, Zivanovic V, Furlan J, Craven C, McGillivray C. Functional electrical stimulation therapy for restoring voluntary grasping function in patietns with sub-acute incomplete tetraplegia: a randomized single-blind clinical trial. Neurorehabil Neural Repair. 2011;25(5):433–42.
69. Kapadia NM, Zivanovic V, Furlan J, Craven BC, McGillivray C, Popovic MR. Toronto Rehabilitation Institute's functional electrical stimulation therapy for grasping in traumatic incomplete spinal cord injury: randomized control trial. Artif Organs. 2011;35(3):212–6.
70. Kapadia N, Zivanovic V, Popovic MR. Restoring voluntary grasping function in individuals with incomplete chronic spinal cord injury: pilot study. Top Spinal Cord Inj Rehabil. 2013;19(4):279–87.
71. Desai N, Bagher S, Popovic MR. Influence of different rehabilitation therapy models on patient outcomes: hand functiontherapy in individuals with incomplete SCI. J Spinal Cord Med. 2014;37(6):734–43.
72. Tomović R, Popović D. Nonanalytical methods for motor control. World Scientific Publishing Company; Singapore; 1995.
73. Andrews BJ, Baxendale RH, Barnett R, Phillips GF, Yamazaki T, Paul JP, Freeman PA. Hybrid FES orthosis incorporating closed loop control and sensory feedback. J Biomed Eng. 1988;10:189–95.
74. Solomonow M. Biomechanics and physiology of a practical powered walking orthosis for paraplegics. In: Stein RB, Peckham P, Popovic D, editors. Neural prostheses: replacing motor function after disease or disability. Oxford University Press; London; 1992. p. 202–32.
75. Takeoka A, Vollenweider I, Courtine G, Arber S. Muscle spindle feedback directs locomotor recovery and circuit reorganization after spinal cord injury. Cell. 2014;159(7):1626–39.
76. Freeman C, Hughes A, Burridge J, Chappell P, Lewin P, Rogers E. Iterative learning control of FES applied to the upper extremity for rehabilitation. Control Eng Pract. 2009;17:368–81.
77. Stauffer Y, Allemand Y, Bouri M, Fournier J, Clavel R, Metrailler P, Brodard R, Reynard F. The WalkTrainer—a new generation of walking reeducation device combining orthoses and muscle stimulation. IEEE Trans Neural Sys Rehabil Eng. 2009;17:38–45.
78. Crema A, Mancuso M, Frisoli A, Salsedo F, Raschellà F, Micera S. A hybrid NMES-exoskeleton for real objects interaction. IEEE Neural Eng Conference. 2015.
79. Bergamasco M. An exoskeleton structure for physical interaction with a human being. PCT Application N. W02013186701 (A1). 2013.
80. Granat MH, Ferguson AC, Andrews BJ, Delargy M. The role of functional electrical stimulation in the rehabilitation of patients with incomplete spinal cord injury—observed benefits during gait studies. Paraplegia. 1993;31:207–15.
81. Kawashima N, Popovic MR, Zivanovic V. Effect of intensive functional electrical stimulation therapy on the upper limb motor recovery after stroke: single case study of a chronic stroke patient. Physiother Can. 2013;65(1):20–8.
82. Weiller C, Ramsay SC, Wise RJ, Friston KJ, Frackowiak RS. Individual patterns of functional

reorganization in the human cerebral cortex after capsular infarction. Ann Neurol. 1993;33:181–9.
83. Ridding MC, Brouwer B, Miles TS, Pitcher JB, Thompson PD. Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. Exp Brain Res. 2000;131:135–43.
84. Chae J, Yu D. Neuromuscular stimulation for motor relearning in hemiplegia. Crit Rev Phys Rehabil Med. 1999;11:208–29.
85. Thompson A, Doran B, Stein R. Short-term effects of functional electrical stimulation on spinal excitatory and inhibitory reflexes in ankle extensor and flexor muscles. Exp Brain Res. 2006;170:216–26.
86. Thompson AK, Stein R. Short-term effects of functional electrical stimulation on motor-evoked potentials in ankle flexor and extensor muscles. Exp Brain Res. 2004;159:491–500.
87. McGie SC, Masani K, Popovic MR. Failure of spinal paired associative stimulation to induce neuroplasticity in the human corticospinal tract. J Spinal Cord Med. 2014;37(5):565–74.
88. Gregory CM, Bickel CS. Recruitment patterns in human skeletal muscle during electrical stimulation. Phys Ther. 2005;85(4):358–64.
89. Prochazka A. Sensory control of normal movement and of movement aided by neural prostheses. J Anat. 2015;227(2):167–77.
90. Kawai R, Markman T, Poddar R, Ko R, Fantana AL, Dhawale AK, Kampff AR, Ölveczky BP. Motor cortex is required for learning but not for executing a motor skill. Neuron. 2015;86(3):800–12.
91. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau ML. Computerized arm training improves the motor control of the severely affected arm after stroke: a single-blinded randomized trial in two centers. Stroke. 2005;36:1960–6.
92. Popovic MR, Curt A, Keller T, Dietz V. Functional electrical stimulation for grasping and walking: indications and limitations. Spinal Cord. 2001;39:403–12.

Passive Devices for Upper Limb Training

26

Arthur Prochazka

Abstract

About five million people in North America alone have weak or paralyzed upper limbs (UL) 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 exercise therapy on passive devices, in some cases remotely supervised over the Internet and augmented with functional electrical stimulation, is now an affordable and important modality of occupational and physical therapy. Quantitative UL function tests performed with these devices can provide crucial guidance on the selection of patients most likely to benefit from training and exercise, maximizing the meaningful use of scarce healthcare resources.

Keywords

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

A. Prochazka, BEng, MSc, PhD (✉)
Centre for Neuroscience, University of Alberta, Edmonton, AB, Canada
Department of Physiology, University of Alberta, Edmonton, AB, Canada
e-mail: arthur.prochazka@ualberta.ca

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26.1 Introduction

There are about 6.6 million stroke survivors in the USA (2.6 % of the population) [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 upper limb (UL) function [2]. In addition, extrapolating from recent Canadian figures, up to 400,000 people in North America have bilateral UL paresis or paralysis due to spinal cord injury (SCI) of either traumatic or nontraumatic origin [3]. Thus, about five million people in North America alone are in need of effective treatment for UL paresis or paralysis.

In recent years stroke survivors have been treated for only 3–4 weeks in acute care or rehabilitation hospitals. In the USA, 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 UL 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 can relieve hypertonus.

This unsatisfactory state of play has given rise to new methods of delivering UL rehabilitation. These include constraint-induced movement therapy (CIMT) [5], modified CIMT (mCIMT) [6], the Graded Repetitive Arm Supplementary Program (GRASP: [7]), the Accelerated Skill Acquisition Program (ASAP) [8], exercise therapy (ET) with robotic devices [9], therapeutic and functional electrical stimulation (TES and FES) [10, 11], and in-home teletherapy (IHT) supervised over the Internet [12–16].

26.2 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 [17–21] . For example, stroke survivors with some proximal shoulder and elbow control of the upper paretic limb on admission in a rehabilitation center have a fair chance of regaining some UL capacity in the long term after stroke, whereas patients without such proximal arm control have a much poorer prognosis [22]. If there has been no emergence of arm synergies at 4 weeks poststroke, this is associated with a poor outcome at 6 months [17]. 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 [23–25]. Full recovery of UL function has been estimated to occur in only about 12 % of stroke survivors [17].

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 [26].

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 [27–30].

26.3 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 UL that would normally be done with both limbs. Indeed it is suggested that in severely disabled stroke survivors, therapy should be restricted to minimizing contractures and pain [31] and teaching compensatory methods [32]. 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 [33, 34]. It has also been argued that in the initial period after injury, the inability to use the paralyzed UL leads to "learned non-use," a form of motor neglect, which is sustained once compensatory methods have become habitual [35]. The use of compensatory strategies that are effective in coping with ADLs, 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.

26.4 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 SCI can improve functional recovery and possibly reduce spastic hypertonus. Surprisingly, there are few published studies that examine this basic assumption. One systematic review [36] concluded that there was insufficient evidence to draw definitive conclusions about the effectiveness of exercise therapy (ET) on UL function in stroke patients, though differences between the studies included suggested that more ET may be beneficial than less ET. Another review 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" [37]. A more recent review concluded there was a positive relationship between the time scheduled for ET and the outcome, large doses of ET leading to clinically meaningful improvements [38]. The authors pointed out that time scheduled did not necessarily equate to the amount of ET actually performed. They recommended that instead of reporting scheduled time, future studies should report active time in therapy or repetitions of an exercise. The notion that more is better was challenged in a small RCT of subacute stroke participants, which concluded that "higher doses of motor training cannot be assumed to be more beneficial, particularly early after stroke" [39].

The Evidence-Based Review of Stroke Rehabilitation (EBRSR: www.ebrsr.com, [40]) concludes that in patients with less severe initial impairment, defined by a Chedoke McMaster score of stage 4 or greater, an aggressive restorative program geared toward regaining function in the affected UL was recommended. 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 [41].

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 ADLs [42].

CIMT, a particular form of intensive ET introduced over 20 years ago, was originally called forced-use training [43]. It was based on experiments in monkeys in which sensory input in one arm was abolished by deafferentation. Binding of the other, normal arm, led to forced use of the deafferented arm, which was associated with improvements in its motor function [44, 45]. This was accompanied by and attributed to cortical plasticity [46, 47]. 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 therapist-supervised training/day for 2 weeks and currently costs over $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 [48] 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" [40]. However, in a recent survey of 92 therapists working in clinical neurorehabilitation settings in the USA, 75 % reported that it would be difficult or very difficult to administer CIMT in their clinics [49]. Eighty three percent felt that most clinics would not have the resources to implement CIMT. It was felt that managed care payers were either somewhat unlikely or very unlikely to reimburse for CIMT and that patients would experience great difficulty with the duration of clinical sessions. Another issue is whether the functional improvements resulting from CIMT are maintained. A recent RCT indicated that although CIMT resulted in more favorable outcomes than usual care in the short term, the difference was not maintained 6 months later [50].

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) [6, 51, 52], 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 [6]. Studies have indicated that both low-intensity and high-intensity CIMT in stroke survivors result in larger functional gains than conventional UL rehabilitation [53]. Interestingly, the clinical portion of mCIMT was reimbursed prior to this trial, under "Current Procedural Terminology" codes [51].

The recently developed Accelerated Skill Acquisition Program (ASAP) incorporates elements of CIMT and principles of motor learning and exercise physiology. Exercises are customized for individual participants, depending on their level of impairment and their own goals [8]. The benefits of ASAP therapy were recently compared to those of two levels of conventional UL rehabilitation, in a multicenter RCT involving 361 stroke survivors [54]. Results reported at the 2015 International Stroke Conference are summarized online (http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_471848.pdf). A full report is in preparation.

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 [55–58]. In a recent RCT in chronic stroke patients, bilateral training was more effective than unilateral training in improv-

ing the functional ability of the affected arm [59]. It was proposed that simultaneously moving both limbs during stroke rehabilitation training may activate balanced interhemispheric interactions [60]. 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 [61].

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" [62].

26.5 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 [9, 12]. 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 makes them costly. The simplest robotic rehabilitation devices are motors that impose cyclical motion on extremities. They are commonly used in orthopedics [63] and occasionally in stroke and SCI [64]. 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 to assist or resist tracking [65, 66]. A commercial version of this device, with actuators that provided weight support and enabled movements at the shoulder, wrist, and hand, was tested in an RCT involving 127 moderate-to-severe chronic stroke participants of whom 49 received intensive robot-assisted therapy, 50 received intensive comparison therapy, and 28 received usual care [67]. It was concluded that robot-assisted therapy did not significantly improve motor function at 12 weeks, as compared with usual care or intensive therapy. However, over the 36-week study period, robot-assisted therapy resulted in significant but modest improvements in motor capability and motor-task performance, as compared with usual care but not with intensive comparison therapy. An editorial concluded: "In the bigger picture, the potential for robotic therapy after stroke remains enormous" [68]. The KINARM, developed by Dr. Steven Scott at Queens University (bkintechnologies.com), is another example of a robotic device that supports the arm. It is primarily used to quantify functional deficits [69, 70]. The Motorika 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 [71, 72].

The most advanced UL rehabilitation robot is the exoskeleton robot ARMin [73]. This device is a multidegree-of-freedom robot, commercialized by Hocoma, the makers of the Lokomat® gait-training robot [74]. It enables the training of movements in 3-D space, as well as grasp and

release of an instrumented gripper. It detects voluntary effort and assists when needed. It incorporates computer games to motivate the users. In a recent RCT involving chronic stroke participants with moderate-to-severe UL paresis, motor function in the more affected arm in 38 participants assigned to ARMin robotic therapy showed greater improvements over the course of the study than the 35 assigned to conventional therapy. However, the absolute difference was small and of weak statistical significance, which left the clinical relevance in question [75].

It is important to note that the above robots do not have manipulanda that promote the training and exercise of 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 [76], a manipulandum that applies forces about the wrist and elbow [77], a cantilevered device with attachments [78], and an arm support with jointed splints that allow grasp-release movements [79]. Two recent systematic reviews list numerous other robotic devices developed and studied over the years [80, 81]. Some of the UL robots 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. In a recent study, the ARMin robot was used in conjunction with a spring-loaded finger extension device that enabled the manipulation of commonly found objects such as a pop can [82]. The latest version of this device, the ArmeoPower, has a hand component: www.hocoma.com/en/products/armeo/armeopower.

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" [40]. The above devices cost between $60,000 and $150,000 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 [83, 84]. 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.

26.6 Virtual Reality and Passive Exercise Devices

A study entitled "Robot-assisted movement training for the stroke-impaired arm: "Does it matter what the robot does?" [85] 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. It was recently found that individuals whose movements are assisted by robots progressively reduce their own effort [86]. The investigators called this "slacking."

These factors have 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 [87–91]. 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 ADLs 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 [92]. 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 and more recent RCTs (e.g., [93]) indicate that virtual reality ET with the Wii system improves function by about the same amount as conventional UL rehabilitation [94].

A commercially available and affordable passive exercise device, the Tailwind (www.tailwindtherapy.com), provides bilateral arm training with rhythmic auditory cueing [55]. A recent RCT compared the efficacy of bilateral arm training with that of dose-matched therapeutic exercises in 111 stroke survivors [58]. 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 [21] but also in matching individuals to the most suitable type of rehabilitation [95]. 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 Hocoma ArmeoSpring is a spring-loaded, counterbalanced, multi-segmented arm support, developed from the Therapy Wilmington Robotic Exoskeleton (T-WREX) [96]. It is mainly used for range-of-motion exercises. An instrumented gripper attachment that detects grasp and release allows these movements to be incorporated into virtual reality games. An RCT involving chronic stroke survivors compared semiautonomous ET on the T-WREX, with semiautonomous conventional ET in which a tabletop was used to provide gravity support [97]. 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. In a more recent study, 23 chronic hemiparetic patients showed improvements of 2–10 % in the Fugl-Meyer Arm test and the Wolf Motor Function test after 36 1-h sessions on the ArmeoSpring [98]. In another study, 12 tetraplegic people performed unilateral ET on the ArmeoSpring for 15 h in addition to conventional therapy [99, 100]. There were few functional differences in improvement between the trained and untrained limbs across participants, but in a subgroup with partial hand function at baseline, the trained limbs showed some additional functional improvement. The ArmeoSpring costs over $60K and is therefore only suitable for clinics.

A much simpler gravity support system, Hocoma's Armeo®Boom, is also available commercially (Fig. 26.1). A study with a precursor of this device, the "Freebal," in ten patients with

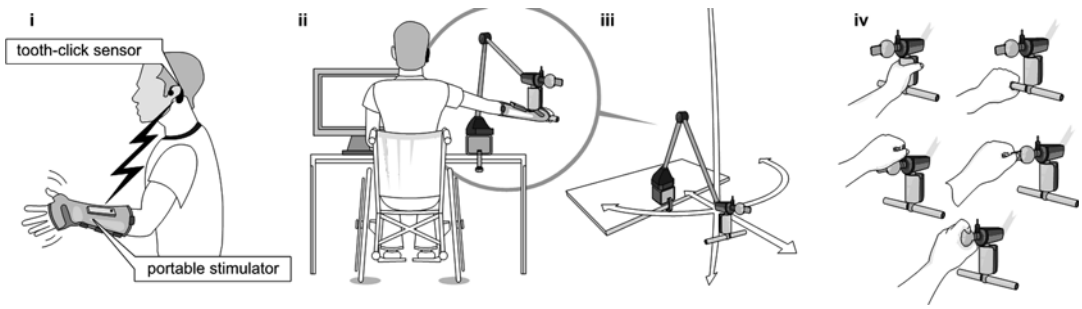

Fig. 26.1 The Armeo®Boom

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 [101]. In another study involving the Freebal device, seven chronic stroke participants performed 18 half-hour sessions over 6 weeks of reach training with computer games [102]. There was a median increase of three points in the FMA after training and a significantly increased work area of the hemiparetic arm, as indicated by the normalized area of circles drawn by the participants. Finally, in a recent multicenter RCT, 70 subacute stroke participants received 6 weeks of training with either the Armeo®Boom or dose-matched conventional training [103]. Arm function evaluated on the FMA and the Stroke Upper Limb Capacity Scale had improved significantly in both groups post-training. The improvements and experienced pain did not differ between groups. The Armeo®Boom group reported higher interest/enjoyment during training than the conventional group.

Several other passive exercise devices have been designed and tested, for example, the AutoCITE workstation [104, 105]; the APBT, a tabletop mechanism that couples the forces generated during contralateral wrist flexion and extension to the affected hand [106]; and the SMART Arm, a linear low-friction slider that exercises movements about the shoulder and elbow [107]. In a single-blind, RCT involving stroke survivors with severe and chronic paresis, 10 received training using the SMART Arm with EMG-triggered electrical stimulation, 13 received training using the SMART Arm alone, and 10 received no intervention (control). Both SMART Arm 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. An interesting new device developed by Reinkensmeyer and colleagues is the MusicGlove. It allows participants to play engaging music-based virtual reality games with individuated movements of the fingers and thumb [108]. In an RCT involving 12 moderately affected stroke participants, those performing 18 h of MusicGlove training showed larger improvements in manipulative tasks than those receiving conventional training, but interestingly, there was no significant difference in broader assessments of UL function. Because overall UL performance depends on the control of movement at the wrist, elbow, and shoulder as well as the hand, it may be beneficial to combine the MusicGlove with proximal limb training, for example, with another interesting device developed by Reinkensmeyer's group, the Resonating Arm Exerciser (RAE). This comprises a lever arm that attaches onto the push-rim of a wheelchair and an elastic band attached between the lever and the wheelchair frame. Rhythmic extension-flexion movements about the shoulder and elbow at the mechanical resonant frequency cause the wheelchair to move back and forth, which acts as a motivator to the user. In a recent RCT, 16 chronic stroke survivors with severe UL impairment were randomized to 3 weeks of exercise with the RAE or conventional exercises [109]. Both groups showed significant improvements in Fugl-Meyer scores posttreatment and although significance was not maintained at the 1-month follow-up, the RAE group had better scores than the controls at this time. The RAE study was inspired by a prior RCT in which stroke participants were positioned on a rocking chair so that when they made voluntary movements of their more affected UL, the chair rocked [110]. Severely affected participants showed improved UL function, but moderately affected individuals did not, which was attributed to a lack of variation and functional meaningfulness in the task. This is interesting, because in the ReJoyce study described below, which involved manipulative tasks mimicking activities of daily life, moderately affected participants fared better than severely affected ones.

The author and his collaborators have developed a passive ET workstation called the Rehabilitation Joystick for Computerized Exercise (ReJoyce) (Fig. 26.2). It comprises a spring-loaded, segmented arm that presents the user with a variety of spring-loaded attachments

Fig. 26.2 (**a**) Tele-coaching of an in-home exercise therapy session using the ReJoyce system; (**b**) participant using ReJoyce workstation to play computer games; (**c**) movements performed, (**d**) selected games

representing ADLs, such as a doorknob, key, gripper, jarlid, and peg. Sensors in the arm and the attachments provide signals that are used by the system's software to control video games that exercise specific types of hand movement.

The system incorporates an automated, quantitative UL function test which takes about 5 min to complete. It provides an overall numerical score that correlates well with the ARAT and Fugl-Meyer arm and hand function tests [111]. It also provides scores for specific tasks such as grasp strength, whole-arm range of motion, pronation-supination, pinch-grip, and manual dexterity. It can be performed in the clinic or remotely via the Internet (see below). Once a user has done the test, the system automatically suggests games and difficulty levels that match his or her abilities. This is achieved by an algorithm that takes into account the user's score on each of the components of the test. If, for example, the user has good range of motion but poor pinch-grip, games that incorporate pinch-grip are excluded from the suggestion list, and games involving range of motion and grasp-release are included, with difficulty levels corresponding to the relevant test scores.

The ReJoyce system also incorporates remote tele-coaching of exercises performed in users'

homes. An RCT was completed involving 13 tetraplegic participants who had sustained a spinal cord injury more than a year previously [16]. Participants were block-randomized into two groups, both performing ET at home with tele-coaching for 1 h/day, 5 days/week for 6 weeks. The control group performed conventional ET, computer games played with a trackball, and 20 min/day TES. The treatment group played computer games on a ReJoyce workstation. Voluntary, hand grasp and release were augmented with FES triggered with a wireless earpiece that detected small voluntary tooth-clicks. The study demonstrated the feasibility of delivering tele-coached FES-assisted ET over the Internet. The treatment group showed clinically important improvements in UL function that significantly exceeded those of the control group. Participants commencing with intermediate functional scores improved the most [112]. In the most recent study, ReJoyce workstations were deployed in the homes of 11 chronic stroke survivors who performed 6 weeks of 1 h/day and 5 days/week tele-coached FES-ET [15, 113]. The primary outcome measure was the Action Research Arm Test (ARAT). Secondary outcome measures included the ReJoyce quantitative UL function test, grasp force measurements, and transcranial magnetic stimulation (TMS). Improvements were seen in the functional tests, but surprisingly, not in the TMS responses [15, 113]. Again, participants commencing with intermediate functional scores improved the most.

Given the increasing weight of evidence that people with very severe motor deficits are unlikely to regain useful UL function, regardless of the rehabilitative efforts made [22, 114], screening of patients with standardized, quantitative tests such as those provided by the ReJoyce system will become increasingly important. This will help identify patients unlikely to benefit in a meaningful way from intensive rehabilitation, reducing healthcare costs and directing resources to those patients who are more likely to benefit.

The ReJoyce system was designed to be affordable for clinics and, through short-term rental, by individual users who could receive tele-supervised treatment in their homes. It is distributed in several countries by Saebo Inc. (USA).

26.7 Therapeutic and Functional Electrical Stimulation (TES and FES)

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 [115, 116]. 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 [117].

Surface FES stimulators for foot-drop have been commercially available in Europe since the late 1970s [118] but only recently in the United States and Canada [119, 120]. 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 [121]. Therapeutic effects have been reported in controlled studies using EMG-triggered FES [122–126]. 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 [127–131]. However, the author's studies in SCI and stroke participants indicate that even after an extended FES-ET program, most people still have better hand function while using their FES devices [15, 132].

The only FES device for hand function currently available is the Bioness H200 (Fig. 26.3a) [133, 134]. It comprises a hinged splint containing pad electrodes and a stimulator triggered by push button. It currently costs around $6,500. In the 1990s the author developed the Bionic Glove, an FES garment triggered by wrist movements

Fig. 26.3 (**a**) Bioness H200 functional electrical stimulator for hand grasp and release; (**b**) Rehabtronics Hand Stimulator activated by voluntary head nods detected by a wireless earpiece; (**c**) the Saeboflex spring-loaded hand-opening splint

[135] and the Impact Cuff, triggered by tapping or bumping the hand [135]. The Bionic Glove was shown to have both functional and therapeutic benefits in people with tetraplegia [136]. An improved version has recently been developed for hemiparetic and tetraplegic users, comprising a neoprene wristlet containing a small stimulator that is controlled by a wireless tooth-click sensor similar to a Bluetooth earpiece [137, 138]. The earpiece in the latest version of this device, currently undergoing regulatory testing for commercial release by Rehabtronics Inc. in late 2015 at an anticipated cost of $2,000, detects small voluntary head nods instead of tooth-clicks (Fig. 26.3b).

26.8 Mechanical Orthoses That Assist Grasp and Release

The Saeboflex (Fig. 26.3c) is a spring-loaded garment that holds the wrist and fingers in extension. The user grasps an object by voluntarily flexing the fingers. The springs assist in reopening the hand to release the object. Another spring-loaded splint, the MossRehab "RELEAS" recently came onto the market at a cost of ~$200. Powered orthoses for hand grasp and release have also entered clinical trials [139].

26.9 Tele-coaching

From all of the above, it is clear that the emerging technologies to deliver ET and FES have the potential greatly to improve UL function in daily life, but providing sufficient support after participants leave rehabilitation clinics is problematic. Although the users may benefit from the devices in the clinic and initially use them on a daily basis at home, in the absence of continuing supervision, usage tends to drop off. This transition is a well-known hurdle in rehabilitation [140]. We reasoned that if participants could only perform regular supervised exercise after discharge, they would benefit much more. However, clinics are not ideal locations for outpatients to perform regular training sessions. Travel is often problematic and stressful, limiting the frequency of attendance. This led us to add the capability of Internet-based, at-home tele-coaching to the ReJoyce system (Fig. 26.2a). In the study mentioned above, Internet-connected ReJoyce workstations were deployed in the homes of 13 tetraplegic participants, located over a wide geographic region in Western Canada. Participants were tele-coached daily by a small team of therapists and students. The logistic challenges that were overcome are detailed in a recent book chapter [141]. A similar study followed on chronic stroke patients in Canada and the UK [15]. Other studies have also shown that tele-coaching can be convenient and effective for both therapists and patients [15, 16, 52, 142].

Unfortunately there are several impediments to the adoption of tele-rehabilitation by healthcare providers and reimbursement agencies [143]. Occupational and physical therapists have traditionally been trained to have hands-on interactions with their patients. Therapists usually have very busy schedules, with little time to deal with new, computer-based technology. It is therefore absolutely vital to provide equipment that is simple to use, with highly intuitive computer interfaces that do not require procedural memorization from one session to the next. Currently there are few published clinical studies demonstrating the clinical efficacy, convenience, and cost-effectiveness of teletherapy. Reimbursement of equipment costs and therapist time can be problematic. Laws regulating tele-rehabilitation, professional licensure portability, and privacy concerns are additional barriers. Private physiotherapy clinics in Canada have recently started using the in-home tele-coaching capabilities of the ReJoyce device, and their early reports have been positive. It is only when therapists and clinics embrace the technology and make it widely available to their patients that it can be considered a success. The case for reimbursing the participants for the cost of renting devices, and the therapists or personal trainers who provide the remote supervision,

must be supported through further RCTs and market analysis.

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

To be adopted clinically, any new rehabilitative approach or device must provide a clear advantage over existing treatments. This must be scientifically demonstrated in clinical trials. Ideally the new treatment should reduce healthcare costs and improve the societal productivity of the individual. Most studies do not measure these effects, yet they are arguably the key determinants of adoption by healthcare providers. Quality of life, though fundamental to patients and clinicians, continues to play a minor role.

The Physiotherapy Evidence Database (PEDro: pedro.fhs.usyd.edu.au/scale_item.html) rates the quality of clinical trials according to ten attributes, including random, concealed, and double-blinded allocation, matched baseline functionality, adequate follow-up, intention to treat analysis, and measures of treatment effect and variability. Regarding controls and blinding, there are two fundamental difficulties; (1) the placebo or expectation effect, the novel treatment can improve morale so that participants become more active, exercise more, attempt more tasks, seek additional therapies, and pay more attention to improvements; and (2) inadequate blinding, because ethics committees require participants to be informed of the details of the interventions, those in the control group often realize that they are not receiving the test treatment, and so they do not develop a placebo effect. The alternative to an RCT is to use participants as their own controls. It is then hard to separate placebo and treatment effects. With the growing influence of the Cochrane Collaboration (www.cochrane.org), study design has become a crucial factor [144].

The difficulties are exemplified in a critique of the pivotal EXCITE trial of CIMT [48, 95]. It was pointed out that the increased attention, encouragement, family support, and motivation rendered the CIMT group quite different from the control group. It was proposed that in future such trials, the new treatment should be compared to an alternative treatment. In their response, the EXCITE authors pointed out that because of dwindling resources, "standard treatment" has in fact become "no treatment" [145]. They argued that policy makers and third-party payers are therefore in fact more interested in whether a new treatment provides a meaningful improvement over no treatment, rather than over an alternative that may or may not be available.

26.11 Perspectives and Conclusions

There is general agreement in the field that the time is ripe for physical and occupational UL therapy to take advantage of new technology. It is time to move from the boring equipment currently used in clinics worldwide to computerized devices that provide task-specific, entertaining games that can also be 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 telecoaching and FES (summarized in Table 26.1). Exercise therapy for UL function on passive devices, with the option of FES assistance, is now an affordable and effective modality of occupational and physical therapy. Standardized, quantitative UL function tests can provide guidance additional to clinical judgment on the selection of patients most likely to benefit, maximizing the use of scarce healthcare resources.

Table 26.1 Summary of passive exercise therapy devices discussed in this chapter

Device	Company	Movements	Computer gaming?	Validated upper limb function test?	Integral tele-coaching and game control?	Recent studies
Armeo®Boom	Hocoma AG	Shoulder, arm, forearm	Yes	No	No	[102, 103]
ArmeoSpring	Hocoma AG	Shoulder, arm, forearm, wrist, hand grasp-release (optional attachment)	Yes	Yes	No	[98–100].
Diego	Tyromotion GMBH	Shoulder, arm, forearm, optional grasp-release of external objects (not sensed)	Yes	No	No	None
MusicGlove	Flint Rehabilitation Devices LLC	Individual finger and thumb movement	Yes	No	No	[108]
Nintendo Wii	Nintendo Corp.	Shoulder, arm, forearm, wrist, thumb (push button)	Yes	No	No	[87, 89, 90]
Pablo	Tyromotion GMBH	Wrist flexion-extension, pronation-supination, grasp-release	Yes	No	No	[146]
ReJoyce	Rehabtronics Inc.	Shoulder, arm, forearm, wrist, hand grasp-release, finger-thumb pinch	Yes	Yes	Yes	[15, 16, 111, 113]
Tailwind	Encore Path, Inc.	Bilateral shoulder, arm, forearm (not monitored with sensors)	No	No	No	[58]

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29–322.
2. van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Deville WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. Stroke. 1999;30(11):2369–75.
3. Noonan VK, Fingas M, Farry A, Baxter D, Singh A, Fehlings MG, et al. Incidence and prevalence of spinal cord injury in Canada: a national perspective. Neuroepidemiology. 2012;38(4):219–26.
4. Wolf SL, Newton H, Maddy D, Blanton S, Zhang Q, Winstein CJ, et al. The excite trial: relationship of intensity of constraint induced movement therapy to improvement in the wolf motor function test. Restor Neurol Neurosci. 2007;25(5–6):549–62.
5. Taub E, Uswatte G, King DK, Morris D, Crago JE, Chatterjee A. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. Stroke. 2006;37(4):1045–9.
6. Page SJ, Sisto SA, Levine P, Johnston MV, Hughes M. Modified constraint induced therapy: a randomized feasibility and efficacy study. J Rehabil Res Dev. 2001;38(5):583–90.
7. Harris JE, Eng JJ, Miller WC, Dawson AS. A self-administered Graded Repetitive Arm Supplementary Program (GRASP) improves arm function during inpatient stroke rehabilitation: a multi-site randomized controlled trial. Stroke. 2009;40(6):2123–8.
8. Winstein C, Lewthwaite R, Blanton SR, Wolf LB, Wishart L. Infusing motor learning research into neurorehabilitation practice: a historical perspective with case exemplar from the accelerated skill acquisition program. J Neurol Phys Ther. 2014;38(3):190–200.
9. Volpe BT, Huerta PT, Zipse JL, Rykman A, Edwards D, Dipietro L, et al. Robotic devices as therapeutic and diagnostic tools for stroke recovery. Arch Neurol. 2009;66(9):1086–90.
10. Liberson WT, Holmquest HJ, Scot D, Dow M. Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. Arch Phys Med Rehabil. 1961;42:101–5.
11. Vodovnik L. Therapeutic effects of functional electrical stimulation of extremities. Med Biol Eng Comput. 1981;19(4):470–8.
12. Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neurorehabilitation. IEEE Trans Rehabil Eng. 1998;6(1):75–87.

13. Gritsenko V, Chhibber S, Prochazka A. Automated FES-assisted exercise therapy for hemiplegic hand function. Soc Neurosci Abstr. 2001;27:210–20.
14. Reinkensmeyer DJ, Pang CT, Nessler JA, Painter CC. Web-based telerehabilitation for the upper extremity after stroke. IEEE Trans Neural Syst Rehabil Eng. 2002;10(2):102–8.
15. Buick A, Kowalczewski J, Carson R, Prochazka A. Tele-supervised FES-assisted exercise for hemiplegic upper limb. IEEE Trans Neural Syst Rehabil Eng. 2015;24:79–87.
16. Kowalczewski J, Chong SL, Galea M, Prochazka A. In-home tele-rehabilitation improves tetraplegic hand function. Neurorehabil Neural Repair. 2011;25(5):412–22.
17. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. Stroke. 2003;34(9):2181–6.
18. Curt A, Van Hedel HJ, Klaus D, Dietz V. Recovery from a spinal cord injury: significance of compensation, neural plasticity, and repair. J Neurotrauma. 2008;25(6):677–85.
19. Kwakkel G, Veerbeek JM, van Wegen EE, Nijland R, Harmeling-van der Wel BC, Dippel DW. Predictive value of the NIHSS for ADL outcome after ischemic hemispheric stroke: does timing of early assessment matter? J Neurol Sci. 2010;294(1-2):57–61.
20. Stinear C. Prediction of recovery of motor function after stroke. Lancet Neurol. 2010;9(12):1228–32.
21. Riley JD, Le V, Der-Yeghiaian L, See J, Newton JM, Ward NS, et al. Anatomy of stroke injury predicts gains from therapy. Stroke. 2011;42(2):421–6.
22. Houwink A, Nijland RH, Geurts AC, Kwakkel G. Functional recovery of the paretic upper limb after stroke: who regains hand capacity? Arch Phys Med Rehabil. 2013;94(5):839–44.
23. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13–31.
24. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1994;75(4):394–8.
25. Teasell R, Foley N, Richardson M, Allen L, Speechley M. Evidence-based review of stroke rehabilitation. 7. Outpatient stroke rehabilitation. Evidence-based review of stroke rehabilitation. 2013;7:1–41.
26. Fawcett JW, Curt A, Steeves JD, Coleman WP, Tuszynski MH, Lammertse D, et al. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord. 2007;45(3):190–205.
27. Nudo RJ, Jenkins WM, Merzenich MM, Prejean T, Grenda R. Neurophysiological correlates of hand preference in primary motor cortex of adult squirrel monkeys. J Neurosci. 1992;12(8):2918–47.
28. Merzenich MM, Jenkins WM. Reorganization of cortical representations of the hand following alterations of skin inputs induced by nerve injury, skin island transfers, and experience. J Hand Ther. 1993;6:89–104.
29. Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM. Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol. 1984;224:591–605.
30. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. J Neurosci. 1996;16(2):785–807.
31. Barreca S. Management of the post stroke hemiplegic arm and hand: treatment recommendations of the 2001 consensus panel. Heart and Stroke Foundation of Ontario. Toronto; 2001.
32. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Compensation in recovery of upper extremity function after stroke: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1994;75(8):852–7.
33. Michaelsen SM, Dannenbaum R, Levin MF. Task-specific training with trunk restraint on arm recovery in stroke: randomized control trial. Stroke. 2006;37(1):186–92.
34. Michaelsen SM, Luta A, Roby-Brami A, Levin MF. Effect of trunk restraint on the recovery of reaching movements in hemiparetic patients. Stroke. 2001;32(8):1875–83.
35. Taub E, Crago JE, Burgio LD, Groomes TE, Cook 3rd EW, DeLuca SC, et al. An operant approach to rehabilitation medicine: overcoming learned nonuse by shaping. J Exp Anal Behav. 1994;61(2):281–93.
36. van der Lee JH, Snels IA, Beckerman H, Lankhorst GJ, Wagenaar RC, Bouter LM. Exercise therapy for arm function in stroke patients: a systematic review of randomized controlled trials. Clin Rehabil. 2001;15(1):20–31.
37. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil. 2004;18(8):833–62.
38. Lohse KR, Lang CE, Boyd LA. Is more better? Using metadata to explore dose-response relationships in stroke rehabilitation. Stroke. 2014;45(7):2053–8.
39. Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): a single-center RCT. Neurology. 2009;73(3):195–201.
40. Foley N, Mehta S, Jutai J, Staines E, Teasell R. Evidence-based review of stroke rehabilitation. 10. Upper extremity interventions. Evidence-based review of stroke rehabilitation [Internet]. 2013;16:1–163. Available from: http://www.ebrsr.com/modules.html.

41. Barreca S, Wolf SL, Fasoli S, Bohannon R. Treatment interventions for the paretic upper limb of stroke survivors: a critical review. Neurorehabil Neural Repair. 2003;17(4):220–6.
42. Dickstein R, Hocherman S, Pillar T, Shaham R. Stroke rehabilitation. Three exercise therapy approaches. Phys Ther. 1986;66(8):1233–8.
43. Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. Exp Neurol. 1989;104(2):125–32.
44. Taub E. Movement in nonhuman primates deprived of somatosensory feedback. Exerc Sport Sci Rev. 1976;4:335–74.
45. Taub E, Miller NE, Novack TA, Cook 3rd EW, Fleming WC, Nepomuceno CS, et al. Technique to improve chronic motor deficit after stroke. Arch Phys Med Rehabil. 1993;74(4):347–54.
46. Pons TP, Garraghty PE, Ommaya AK, Kaas JH, Taub E, Mishkin M. Massive cortical reorganization after sensory deafferentation in adult macaques. Science. 1991;252(5014):1857–60.
47. Richards LG, Stewart KC, Woodbury ML, Senesac C, Cauraugh JH. Movement-dependent stroke recovery: a systematic review and meta-analysis of TMS and fMRI evidence. Neuropsychologia. 2008;46(1):3–11.
48. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006;296(17):2095–104.
49. Daniel L, Howard W, Braun D, Page SJ. Opinions of constraint-induced movement therapy among therapists in southwestern Ohio. Top Stroke Rehabil. 2012;19(3):268–75.
50. Thrane G, Askim T, Stock R, Indredavik B, Gjone R, Erichsen A, et al. Efficacy of constraint-induced movement therapy in early stroke rehabilitation: a randomized controlled multisite trial. Neurorehabil Neural Repair. 2014. doi:10.1177/1545968314558599.
51. Page SJ, Levine P. Modified constraint-induced therapy in patients with chronic stroke exhibiting minimal movement ability in the affected arm. Phys Ther. 2007;87(7):872–8.
52. Page SJ, Levine P. Modified constraint-induced therapy extension: using remote technologies to improve function. Arch Phys Med Rehabil. 2007;88(7):922–7.
53. Nijland R, Kwakkel G, Bakers J, van Wegen E. Constraint-induced movement therapy for the upper paretic limb in acute or sub-acute stroke: a systematic review. Int J Stroke. 2011;6(5):425–33.
54. Winstein CJ, Wolf SL, Dromerick AW, Lane CJ, Nelsen MA, Lewthwaite R, et al. Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE): a randomized controlled trial protocol. BMC Neurol. 2013;13:5.
55. Whitall J, McCombe Waller S, Silver KH, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. Stroke. 2000;31(10):2390–5.
56. Luft AR, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. JAMA. 2004;292(15):1853–61.
57. Cauraugh JH, Kim SB, Duley A. Coupled bilateral movements and active neuromuscular stimulation: intralimb transfer evidence during bimanual aiming. Neurosci Lett. 2005;382(1–2):39–44.
58. Whitall J, Waller SM, Sorkin JD, Forrester LW, Macko RF, Hanley DF, et al. Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms: a single-blinded randomized controlled trial. Neurorehabil Neural Repair. 2011;25(2):118–29.
59. Summers JJ, Kagerer FA, Garry MI, Hiraga CY, Loftus A, Cauraugh JH. Bilateral and unilateral movement training on upper limb function in chronic stroke patients: a TMS study. J Neurol Sci. 2007;252(1):76–82.
60. Cauraugh JH, Coombes SA, Lodha N, Naik SK, Summers JJ. Upper extremity improvements in chronic stroke: coupled bilateral load training. Restor Neurol Neurosci. 2009;27(1):17–25.
61. Lin KC, Chang YF, Wu CY, Chen YA. Effects of constraint-induced therapy versus bilateral arm training on motor performance, daily functions, and quality of life in stroke survivors. Neurorehabil Neural Repair. 2009;23(5):441–8.
62. Bayona NA, Bitensky J, Salter K, Teasell R. The role of task-specific training in rehabilitation therapies. Top Stroke Rehabil. 2005;12(3):58–65.
63. Salter RB. History of rest and motion and the scientific basis for early continuous passive motion. Hand Clin. 1996;12(1):1–11.
64. Dirette D, Hinojosa J. Effects of continuous passive motion on the edematous hands of two persons with flaccid hemiplegia. Am J Occup Ther. 1994;48(5):403–9.
65. Aisen ML, Krebs HI, Hogan N, McDowell F, Volpe BT. The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. Arch Neurol. 1997;54(4):443–6.
66. Hogan N, Krebs HI, Rohrer B, Palazzolo JJ, Dipietro L, Fasoli SE, et al. Motions or muscles? Some behavioral factors underlying robotic assistance of motor recovery. J Rehabil Res Dev. 2006;43(5):605–18.
67. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362(19):1772–83.
68. Cramer SC. Brain repair after stroke. N Engl J Med. 2010;362(19):1827–9.
69. Semrau JA, Herter TM, Scott SH, Dukelow SP. Robotic identification of kinesthetic deficits after stroke. Stroke. 2013;44(12):3414–21.

70. Tyryshkin K, Coderre AM, Glasgow JI, Herter TM, Bagg SD, Dukelow SP, et al. A robotic object hitting task to quantify sensorimotor impairments in participants with stroke. J Neuroeng Rehabil. 2014;11(1):47.
71. Johnson MJ, Feng X, Johnson LM, Winters JM. Potential of a suite of robot/computer-assisted motivating systems for personalized, home-based, stroke rehabilitation. J Neuroeng Rehabil. 2007;4:6.
72. Ruparel R, Johnson MJ, Strachota E, McGuire J, Tchekanov G. Evaluation of the TheraDrive system for robot/computer assisted motivating rehabilitation after stroke. Conf Proc IEEE Eng Med Biol Soc. 2009;2009:811–4.
73. Nef T, Mihelj M, Riener R. ARMin: a robot for patient-cooperative arm therapy. Med Biol Eng Comput. 2007;45(9):887–900.
74. Nef T, Riener R. Three-dimensional multi-degree-of-freedom Arm therapy robot (ARMin). In: Dietz V, Nef T, Rymer WZ, editors. Neurorehabilitation technology. London: Springer; 2012. p. 141–57.
75. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2):159–66.
76. Popescu VG, Burdea GC, Bouzit M, Hentz VR. A virtual-reality-based telerehabilitation system with force feedback. IEEE Trans Inf Technol Biomed. 2000;4(1):45–51.
77. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau ML. Computerized arm training improves the motor control of the severely affected arm after stroke: a single-blinded randomized trial in two centers. Stroke. 2005;36(9):1960–6.
78. Lambercy O, Dovat L, Gassert R, Burdet E, Teo CL, Milner T. A haptic knob for rehabilitation of hand function. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):356–66.
79. Takahashi CD, Der-Yeghiaian L, Le V, Motiwala RR, Cramer SC. Robot-based hand motor therapy after stroke. Brain. 2008;131(Pt 2):425–37.
80. Maciejasz P, Eschweiler J, Gerlach-Hahn K, Jansen-Troy A, Leonhardt S. A survey on robotic devices for upper limb rehabilitation. J Neuroeng Rehabil. 2014;11:3.
81. Sivan M, O'Connor RJ, Makower S, Levesley M, Bhakta B. Systematic review of outcome measures used in the evaluation of robot-assisted upper limb exercise in stroke. J Rehabil Med. 2011;43(3):181–9.
82. Brokaw EB, Black I, Holley RJ, Lum PS. Hand Spring Operated Movement Enhancer (HandSOME): a portable, passive hand exoskeleton for stroke rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2011;19(4):391–9.
83. Frick EM, Alberts JL. Combined use of repetitive task practice and an assistive robotic device in a patient with subacute stroke. Phys Ther. 2006;86(10):1378–86.
84. Kutner NG, Zhang R, Butler AJ, Wolf SL, Alberts JL. Quality-of-life change associated with robotic-assisted therapy to improve hand motor function in patients with subacute stroke: a randomized clinical trial. Phys Ther. 2010;90(4):493–504.
85. Kahn LE, Lum PS, Rymer WZ, Reinkensmeyer DJ. Robot-assisted movement training for the stroke-impaired arm: does it matter what the robot does? J Rehabil Res Dev. 2006;43(5):619–30.
86. Reinkensmeyer DJ, Akoner O, Ferris DP, Gordon KE. Slacking by the human motor system: computational models and implications for robotic orthoses. Conf Proc IEEE Eng Med Biol Soc. 2009;1:2129–32.
87. Allen D. You're never too old for a Wii. Nurs Older People. 2007;19(8):8.
88. Cowley AD, Minnaar G. New generation computer games: watch out for Wii shoulder. BMJ. 2008;336(7636):110.
89. Deutsch JE, Borbely M, Filler J, Huhn K, Guarrera-Bowlby P. Use of a low-cost, commercially available gaming console (Wii) for rehabilitation of an adolescent with cerebral palsy. Phys Ther. 2008;88(10):1196–207.
90. Graves LE, Ridgers ND, Stratton G. The contribution of upper limb and total body movement to adolescents' energy expenditure whilst playing Nintendo Wii. Eur J Appl Physiol. 2008;104(4):617–23.
91. Robinson RJ, Barron DA, Grainger AJ, Venkatesh R. Wii knee. Emerg Radiol. 2008;15(4):255–7.
92. Saposnik G, Mamdani M, Bayley M, Thorpe KE, Hall J, Cohen LG, et al. Effectiveness of Virtual Reality Exercises in STroke Rehabilitation (EVREST): rationale, design, and protocol of a pilot randomized clinical trial assessing the Wii gaming system. Int J Stroke. 2010;5(1):47–51.
93. Yin CW, Sien NY, Ying LA, Chung SF, Tan May Leng D. Virtual reality for upper extremity rehabilitation in early stroke: a pilot randomized controlled trial. Clin Rehabil. 2014;28(11):1107–14.
94. Lucca LF. Virtual reality and motor rehabilitation of the upper limb after stroke: a generation of progress? J Rehabil Med. 2009;41(12):1003–100.
95. Dobkin BH. Confounders in rehabilitation trials of task-oriented training: lessons from the designs of the EXCITE and SCILT multicenter trials. Neurorehabil Neural Repair. 2007;21(1):3–13.
96. Sanchez RJ, Liu J, Rao S, Shah P, Smith R, Rahman T, et al. Automating arm movement training following severe stroke: functional exercises with quantitative feedback in a gravity-reduced environment. IEEE Trans Neural Syst Rehabil Eng. 2006;14(3):378–89.
97. Housman SJ, Scott KM, Reinkensmeyer DJ. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. Neurorehabil Neural Repair. 2009;23(5):505–14.
98. Colomer C, Baldovi A, Torrome S, Navarro MD, Moliner B, Ferri J, et al. Efficacy of Armeo(R)

Spring during the chronic phase of stroke. Study in mild to moderate cases of hemiparesis. Neurologia. 2013;28(5):261–7.
99. Zariffa J, Kapadia N, Kramer JL, Taylor P, Alizadeh-Meghrazi M, Zivanovic V, et al. Effect of a robotic rehabilitation device on upper limb function in a sub-acute cervical spinal cord injury population. IEEE Int Conf Rehabil Robot. 2011;2011:5975400.
100. Zariffa J, Kapadia N, Kramer JL, Taylor P, Alizadeh-Meghrazi M, Zivanovic V, et al. Feasibility and efficacy of upper limb robotic rehabilitation in a subacute cervical spinal cord injury population. Spinal Cord. 2012;50(3):220–6.
101. Prange GB, Jannink MJ, Stienen AH, van der Kooij H, Ijzerman MJ, Hermens HJ. Influence of gravity compensation on muscle activation patterns during different temporal phases of arm movements of stroke patients. Neurorehabil Neural Repair. 2009;23(5):478–85.
102. Krabben T, Prange GB, Molier BI, Stienen AH, Jannink MJ, Buurke JH, et al. Influence of gravity compensation training on synergistic movement patterns of the upper extremity after stroke, a pilot study. J Neuroeng Rehabil. 2012;9:44.
103. Prange GB, Kottink AI, Buurke JH, Eckhardt MM, van Keulen-Rouweler BJ, Ribbers GM, et al. The effect of arm support combined with rehabilitation games on upper-extremity function in subacute stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2015;29(2):174–82.
104. Lum PS, Taub E, Schwandt D, Postman M, Hardin P, Uswatte G. Automated Constraint-Induced Therapy Extension (AutoCITE) for movement deficits after stroke. J Rehabil Res Dev. 2004;41(3A):249–58.
105. Taub E, Lum PS, Hardin P, Mark VW, Uswatte G. AutoCITE: automated delivery of CI therapy with reduced effort by therapists. Stroke. 2005;36(6):1301–4.
106. Stinear CM, Barber PA, Coxon JP, Fleming MK, Byblow WD. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. Brain. 2008;131(Pt 5):1381–90.
107. Barker RN, Brauer SG, Carson RG. Training of reaching in stroke survivors with severe and chronic upper limb paresis using a novel nonrobotic device: a randomized clinical trial. Stroke. 2008;39(6):1800–7.
108. Friedman N, Chan V, Reinkensmeyer AN, Beroukhim A, Zambrano GJ, Bachman M, et al. Retraining and assessing hand movement after stroke using the MusicGlove: comparison with conventional hand therapy and isometric grip training. J Neuroeng Rehabil. 2014;11:76.
109. Zondervan DK, Augsburger R, Bodenhoefer B, Friedman N, Reinkensmeyer DJ, Cramer SC. Machine-based, self-guided home therapy for individuals with severe arm impairment after stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2015;29(5):395–406.
110. Feys H, De Weerdt W, Verbeke G, Steck GC, Capiau C, Kiekens C, et al. Early and repetitive stimulation of the arm can substantially improve the long-term outcome after stroke: a 5-year follow-up study of a randomized trial. Stroke. 2004;35(4):924–9.
111. Prochazka A, Kowalczewski J. A fully automated, quantitative test of upper limb function. J Mot Behav. 2015;47(1):19–28.
112. Kowalczewski J. Upper extremity neurorehabilitation. Edmonton: University of Alberta; 2009.
113. Buick A, Unterschultz L, Kowalczewski J, Carson RG, Prochazka A, editors. Use of accelerometers and MEPs to assess corticospinal excitability following novel combined therapy in chronic stroke. Society for Neuroscience 42nd annual general meeting; New Orleans; 2012.
114. Foley N, Mehta S, Jutai J, Staines E, Teasell R. Evidence-based review of stroke rehabilitation. 10. Upper extremity interventions. Toronto: Canadian Stroke Network; 2013.
115. Baker L, Yeh C, Wilson D, Waters RL. Electrical stimulation of wrist and fingers for hemiplegic patients. Phys Ther. 1979;59:1495–9.
116. Waters R, Bowman B, Baker L, Benton L, Meadows P. Treatment of hemiplegic upper extremity using electrical stimulation and biofeedback training. In: Advances in external control of human extremities, vol. 7. Belgrade: Yugoslav Committee for Electronics and Automation; 1981. p. 251–66.
117. Taylor PN, Burridge JH, Hagan SA, Chapple P, Swain ID, editors. Improvement in hand function and sensation in chronic stroke patients following electrical stimulation exercises. A retrospective clinical audit. First annual conference of the international FES Society; 1996; Cleveland.
118. Vodovnik L, Bajd T, Kralj A, Gracanin F, Strojnik P. Functional electrical stimulation for control of locomotor systems. CRC Crit Rev Bioeng. 1981;6(2):63–131.
119. Taylor P, Burridge J, Dunkerley A, Wood D, Norton J, Singleton C, et al. Clinical audit of 5 years provision of the Odstock dropped foot stimulator. Artif Organs. 1999;23(5):440–2.
120. Stein RB, Chong S, Everaert DG, Rolf R, Thompson AK, Whittaker M, et al. A multicenter trial of a footdrop stimulator controlled by a tilt sensor. Neurorehabil Neural Repair. 2006;20(3):371–9.
121. Hansen GO. EMG-controlled functional electrical stimulation of the paretic hand. Scand J Rehabil Med. 1979;11:189–93.
122. Heckmann J, Mokrusch T, Kroeckel A, Warnke S, von Stockert T, Neundoerfer B. Electromyogram-triggered neuromuscular stimulation for improving the arm function of acute stroke survivors: a randomized pilot study. Eur J Phys Med Rehabil. 1997;7:138–41.
123. Francisco G, Chae J, Chawla H, Kirshblum S, Zorowitz R, Lewis G, et al. Electromyogram-triggered neuromuscular stimulation for improving the arm function of acute stroke survivors: a randomized pilot study. Arch Phys Med Rehabil. 1998;79(5):570–5.

124. Cauraugh JH, Kim S. Two coupled motor recovery protocols are better than one: electromyogram-triggered neuromuscular stimulation and bilateral movements. Stroke. 2002;33(6):1589–94.
125. Chae J. Neuromuscular electrical stimulation for motor relearning in hemiparesis. Phys Med Rehabil Clin N Am. 2003;14(1 Suppl):S93–109.
126. de Kroon JR, Ijzerman MJ, Chae J, Lankhorst GJ, Zilvold G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. J Rehabil Med. 2005;37(2):65–74.
127. Gritsenko V, Prochazka A. A functional electric stimulation-assisted exercise therapy system for hemiplegic hand function. Arch Phys Med Rehabil. 2004;85(6):881–5.
128. Popovic D, Popovic M, Sinkjaer T, Stefanovic A, Schwirtlich L. Therapy of paretic arm in hemiplegic subjects augmented with a neural prosthesis: a cross-over study. Can J Physiol Pharmacol. 2004;82(8–9):749–56.
129. Popovic M, Thrasher T, Zivanovic V, Takaki J, Hajek V. Neuroprosthesis for retraining reaching and grasping functions in severe hemiplegic patients. Neuromodulation. 2005;8:58–72.
130. Alon G, Levitt AF, McCarthy PA. Functional electrical stimulation enhancement of upper extremity functional recovery during stroke rehabilitation: a pilot study. Neurorehabil Neural Repair. 2007;21(3):207–15.
131. Kowalczewski J, Gritsenko V, Ashworth N, Ellaway P, Prochazka A. Upper-extremity functional electric stimulation-assisted exercises on a workstation in the subacute phase of stroke recovery. Arch Phys Med Rehabil. 2007;88(7):833–9.
132. Kowalczewski JA, Prochazka A, Chong SL, editors. Home based upper extremity rehabilitation in spinal cord injured patients. Society for Neuroscience Abstracts; San Diego; 2007.
133. Weingarden HP, Zeilig G, Heruti R, Shemesh Y, Ohry A, Dar A, et al. Hybrid functional electrical stimulation orthosis system for the upper limb: effects on spasticity in chronic stable hemiplegia. Am J Phys Med Rehabil. 1998;77(4):276–81.
134. Nathan RH. US Patent #5,330,516. Device for generating hand function. US Patent Office. 1994:15 claims, 6 drawing sheets.
135. Prochazka A. Inventor garment having controller that is activated by mechanical impact. Canada, WO 99/190191997.
136. Popovic D, Stojanovic A, Pjanovic A, Radosavljevic S, Popovic M, Jovic S, et al. Clinical evaluation of the bionic glove. Arch Phys Med Rehabil. 1999;80(3):299–304.
137. Kowalczewski J, Chong S, Prochazka A, editors. Improving tetraplegic hand function with FES and in-home tele-rehabilitation. Treatment strategies for SCI: from biology to clinical reality. Banff: University of Alberta; 2010.
138. Prochazka A. Neuroprosthetics. In: Edelle C, Field-Fote P, editors. Spinal cord injury rehabilitation. Philadelphia: FA Davis Company; 2009. p. 87–99.
139. Allington J, Spencer SJ, Klein J, Buell M, Reinkensmeyer DJ, Bobrow J. Supinator Extender (SUE): a pneumatically actuated robot for forearm/wrist rehabilitation after stroke. Conf Proc IEEE Eng Med Biol Soc. 2011;2011:1579–82.
140. Andrews K, Stewart J. Stroke recovery: he can but does he? Rheumatol Rehabil. 1979;18(1):43–8.
141. Kowalczewski J, Prochazka A. Technology improves upper extremity rehabilitation. Prog Brain Res. 2011;192:147–59.
142. Wolf SL, Sahu K, Bay RC, Buchanan S, Reiss A, Linder S, et al. The HAAPI (Home Arm Assistance Progression Initiative) trial: a novel robotics delivery approach in stroke rehabilitation. Neurorehabil Neural Repair. 2015. doi:10.1177/1545968315575612.
143. Cohn ER, editor. Telerehabilitation in 2012: policy and infrastructure challenges to ubiquitous deployment across the United States. RESNA annual conference – 2012; 2012; Baltimore: http://web.resna.org/conference/proceedings/2012/PublicPolicy/TELEREHABILITATIONIN2012.html.
144. Johnston MV, Sherer M, Whyte J. Applying evidence standards to rehabilitation research. Am J Phys Med Rehabil. 2006;85(4):292–309.
145. Wolf SL, Winstein CJ, Miller JP, Blanton S, Clark PC, Nichols-Larsen D. Looking in the rear view mirror when conversing with back seat drivers: the EXCITE trial revisited. Neurorehabil Neural Repair. 2007;21(5):379–87.
146. Seitz RJ, Kammerzell A, Samartzi M, Jander S, Wojtecki L, et al. Monitoring of visuomotor coordination in healthy subjects and patients with stroke and Parkinson's disease: an application study using the PABLO®-device. Int J Neurorehabil. 2014;1:113. doi:10.4172/2376-0281.1000113.

Upper-Extremity Therapy with Spring Orthoses

27

David J. Reinkensmeyer and Daniel K. Zondervan

Abstract

We describe the development of the spring-based orthosis approach (as exemplified by T-WREX and ArmeoSpring) to enhance upper-extremity movement therapy after neurologic injury. This approach is based around the concept of using springs to assist a patient in moving his or her weakened arm as he or she practices computerized movement tasks. This chapter first traces the development of spring orthoses for 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 mechanical assistance, functional exercise, and computer gaming in promoting upper-extremity movement recovery after stroke. This evidence suggests a path forward toward simplified spring-based orthoses for home use. As an example, we discuss the design and initial testing of a simple lever-based spring orthosis, the Resonating Arm Exerciser.

Keywords

Movement rehabilitation • Motor learning • Rehabilitation technology • Stroke • Computer games • Upper-extremity exercise

D.J. Reinkensmeyer, PhD (✉)
Flint Rehabilitation Devices, LLC
18023 Sky Park Circle, STE H2, Irvine, CA 92614, USA

Department of Mechanical and Aerospace Engineering, University of California at Irvine, 4200 Engineering Gateway, Irvine, CA 92697-3975, USA

Department of Biomedical Engineering, University of California at Irvine, 4200 Engineering Gateway, Irvine, CA 92697-3975, USA

Department of Physical Medicine and Rehabilitation, University of California at Irvine, 4200 Engineering Gateway, Irvine, CA 92697-3975, USA

Department of Anatomy and Neurobiology, University of California at Irvine, 4200 Engineering Gateway, Irvine, CA 92697-3975, USA
e-mail: dreinken@uci.edu

D.K. Zondervan, PhD
Department of Mechanical and Aerospace Engineering, University of California at Irvine, 4200 Engineering Gateway, Irvine, CA 92697-3975, USA

D.J. Reinkensmeyer, V. Dietz (eds.), *Neurorehabilitation Technology*,
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Abbreviations

LARA	Lever actuated resonance assistance
RAE	Resonating Arm Exerciser
T-WREX	Therapy-Wilmington robotic exoskeleton
WREX	Wilmington robotic exoskeleton

27.1 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 information 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 that 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 Bi-Manu-Track [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 as InMotion ARM Interactive Therapy System and Bi-Manu-Track). 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 [5–10]. 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 [8–10] or a matched amount of exercise performed with another rehabilitation technology, such as electromyogram-triggered functional electrical stimulation [11] or sensor-based approaches to range of motion exercise [12].

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 our 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 [13]. 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 ther-

apies 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" [14]. 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 mouselike 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 with National Institute of Disability and Rehabilitation Research (NIDRR) support 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 [15]. First, we used a spring orthosis as the basic platform. That is, 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 also with NIDRR support had developed the innovative arm support called WREX to assist children with weakened arms in moving their arms [16] (see Table 27.1 for a summary comparison of the spring orthosis devices discussed in this paper, beginning with WREX and T-WREX). We scaled up the WREX design to be large enough and strong enough to support movements by adults with a stroke (Fig. 27.1). 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. 27.1b). 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. 27.1c).

27.1.1 Clinical Testing with T-WREX

We performed a pilot study with T-WREX at UC Irvine [15]. In this study, we first quantified the

Table 27.1 Examples of spring orthoses for upper-extremity rehabilitation

Device	Advantages	Limitations
WREX [16]	Allows gradable assistance in three dimensions using elastic bands and four bar mechanisms. Can now be 3D printed and worn as an assistive device for children with weak arms	No grip force or joint motion sensing
T-WREX [15, 17]	Based on WREX. Incorporated grip force and joint motion sensing allowing patients to perform rehabilitation exercise by playing task-oriented, therapeutic computer games	Time consuming to adjust link lengths and amount of support
ArmeoSpring [18–25]	Commercial product based on T-WREX. Quickly adjustable for different patient morphologies and assistance level needs	Expensive ($60,000)
FreeBal [26]	Supports the forearm with a simple spring mechanism acting through an overhead boom. Quick and easy to set up	Does not measure individual joint motions
ArmeoBoom [27]	Commercial product based on FreeBal	Does not measure individual joint motions. Still relatively expensive ($15,000)
Resonating Arm Exerciser (RAE, 78, 79)	Attaches to a wheelchair and provides assistance to shoulder/elbow movement using mechanical resonance	Only allows forward/back arm movement in the parasagittal plane
LARA [28]	Based on RAE. Allows individual with weakened arm to propel a wheelchair bimanually	Maneuverability limited

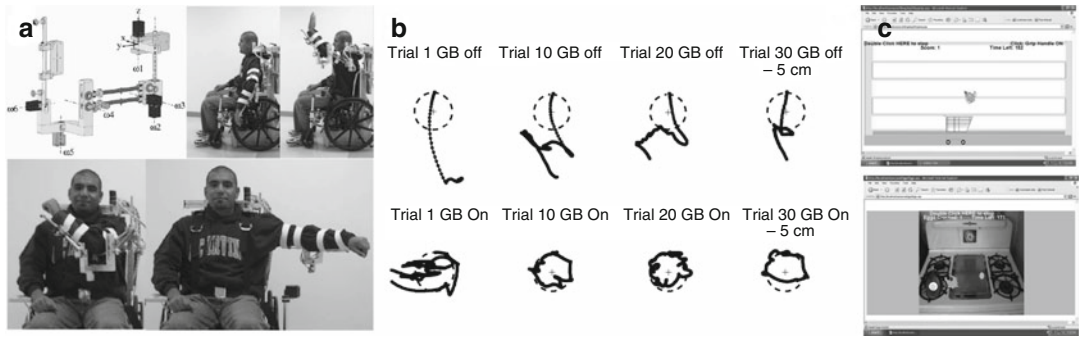

Fig. 27.1 (**a**) The T-WREX arm support exoskeleton was based on WREX and relieves the weight of the arm while allowing a wide range of motion of the arm. (**b**) This sequence of plots shows the hand trajectory when a person with severe paresis after chronic stroke tried to trace a circle in the frontal 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. [15]; © 2006, IEEE; used with permission)

effect of the gravity balance provided by 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 one 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. 27.1b). 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. 27.1b). 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 [29].

We also performed a pilot therapeutic test of T-WREX at UC Irvine [15]. 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. 27.2a). 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 [30]), active reaching range of motion (ROM), and self-reported quality and amount of arm use (Motor Activity Log

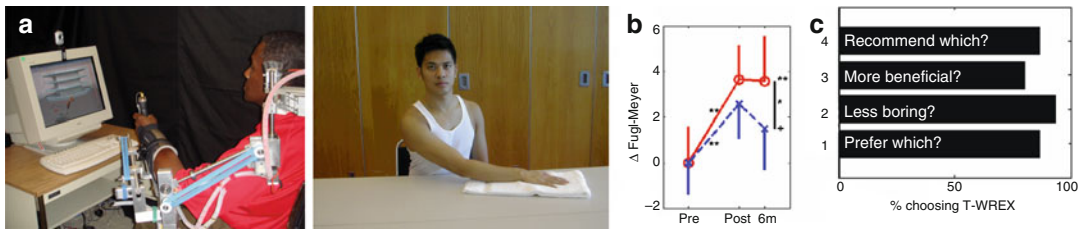

Fig. 27.2 (**a**) In a single-blind randomized controlled trial of T-WREX, we compared training with T-WREX to training of the arm on a tabletop with a towel. (**b**) Improvements in upper-extremity (UE) movement ability as measured with the UE Fugl–Meyer (FM) scale following chronic stroke with 2 months 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)

[31]). 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 ± SD, $p = 0.05$, Fig. 27.2b). The volunteers reported a strong preference for the T-WREX training compared to the tabletop training (Fig. 27.2c). 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 required for a simple form of semiautonomous exercise (tabletop exercise with a towel). Also in support of the general approach, another group showed also that computer game-driven movement practice with the arm supported by a different spring-based arm support, the FreeBal system, could improve arm motor recovery after chronic stroke [26].

27.1.2 Commercialization of T-WREX into ArmeoSpring and Further Testing

Hocoma AG licensed the intellectual property for T-WREX from the University of California at Irvine and then substantially improved the mechanical, electrical, and software designs of T-WREX for usability and manufacturability. The resulting ArmeoSpring device (Fig. 27.3) is as of 2015 being used in over 700 clinics around the world.

Multiple research studies have been conducted with ArmeoSpring measuring its therapeutic effects and expanding its use by other patient populations. Training with ArmeoSpring improved impairment and activity measures in chronic stroke patients with more mild hemiparesis than had been tested in previous studies with T-WREX (average starting Fugl–Meyer Upper-Extremity Score 45.7/66) [18]. Training with ArmeoSpring by individuals in the acute phase after stroke, as opposed to the chronic stage, was found to be about as effective as conventional one-on-one training with a therapist [19, 20]. In one of these studies, the group that trained with ArmeoSpring significantly improved shoulder range of motion and movement smoothness, while the control group did not [20]. The ArmeoSpring group also expressed higher satisfaction with the therapy [20]. ArmeoSpring was also combined with an iterative electrical stimulation system, improving clinical outcomes for individuals with chronic stroke [21].

Fig. 27.3 ArmeoSpring, 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)

Another study used ArmeoSpring to investigate if the weight support provided by the device was in and of itself therapeutically advantageous [22]. This study compared the therapeutic effects of a single computer game, played alone, or with haptic input from a haptic robot, or with arm support from ArmeoSpring. All three groups improved a comparable amount, although the haptic group improved more on the Box and Blocks score. The mechanical constraints inherent to ArmeoSpring appeared to prevent learning of some compensatory movements.

ArmeoSpring has also now been tested with other patient populations besides individuals with stroke. ArmeoSpring was found to increase amount of training while reducing amount of active therapist time required and to have a small therapeutic benefit for individuals with subacute cervical spinal cord injury, but only for individuals with partial hand function at baseline [23].

Training with ArmeoSpring benefited individuals with multiple sclerosis in a pilot study with ten individuals with a high level of disability [24], as well as individuals with proximal humeral fractures [25].

In terms of assessment, ArmeoSpring was shown to provide reliable measurement of active arm workspace for people with cervical spinal cord injury [32]. A variety of kinematic measurements obtained from ArmeoSpring during therapeutic game play accurately predicted clinical scores of upper-extremity movement ability after SCI [33]. Normative values for accuracy, speed, and smoothness for a single exercise using ArmeoSpring were recently established [34].

27.2 Reevaluating the Conceptual Framework for Spring-Based Orthoses: Status of Functional, Assistive, Computer Gaming in Upper-Extremity Motor Recovery

The spring orthosis approach exemplified by T-WREX resulted in a successful, clinically verified product, ArmeoSpring. However, even without robotic actuators, this device is relatively expensive and impractical for widespread home use. There is therefore an apparent need to develop simpler spring orthoses for home use. One approach is the FreeBal device [35–37], which uses an overhead sling and cable/spring system to assist in three-dimensional movement and incorporates computer games. This device is now commercialized as ArmeoBoom. In a recent multisite study with 70 subacute stroke patients, training with ArmeoBoom produced comparable results to conventional training, although the patients rated the therapy as having higher interest and enjoyment than the conventional training [27]. This suggests simpler spring orthoses may indeed retain comparable therapeutic benefit as more complex devices.

With this in mind, in this section, we reexamine the rationale for the spring orthosis approach, with the goal of extracting information to aid in the design of even simpler spring orthoses. As reviewed above, the rationale driving development of T-WREX was that physical assistance (without recourse to robotics), functionally oriented activities, and computer gaming best promote movement recovery of the upper extremity. We review recent research findings that both support and challenge the three components of this rationale and, then in the next section, based on this reasoning, describe development of a very simple spring orthosis device, the Resonating Arm Exerciser.

27.2.1 Is Physical Assistance Beneficial for Promoting Motor Recovery?

Spring-based orthoses provide 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) [38]. 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 [39].

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 [40–42]. As an example, Lotze and colleagues [41] 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 [42]. 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 [43]. 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 [44]. 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 [45]. 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 [46, 47].

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 [48–51]. Weakness following stroke primarily has a neurologic rather than muscular origin, as, for example, electrical stimulation can produce near normal muscle forces after stroke [52]. 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 [53]. 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 [54, 55]. 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 [56–58]. 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 [59]. Thus, when the guidance is removed, learning is reduced, although for some tasks, this may not be true [60–63].

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 a study of a hand training device, HWARD [64], 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 is clearly important for gait 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," and this may increase desire to practice [65–67].

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 [68]; 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. Thus, 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 motivation and self-efficacy. Development of simpler spring orthosis should likely seek to incorporate these same properties as well.

27.2.2 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 Bi-Manu-Track, a device that assists unilateral and bilateral forearm supination/pronation or wrist flexion/extension movements [11]. Robotic training of the forearm and wrist using the Bi-Manu-Track 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 "nonfunctional," involving rotation of the wrist or forearm in order to track computer targets, perhaps making any transfer to functional movement ability surprising.

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 [64]. 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 with MIT-Manus in volunteers with severe-to-moderate chronic stroke [69] 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.

Two other recent studies with the BONES arm movement training robot further illustrate the current ambiguity around the role of functional training in rehabilitation. BONES is a six degrees-of-freedom, backdrivable arm exoskeleton specifically designed to assist in functional training [70]. In a study with unimpaired participants, BONES was used to guide the arm through a complex movement, similar to a tennis backhand stroke [71]. One group practiced only the target backhand movement, receiving guidance from BONES, and then periodically trying to replicate the movement without guidance. Three other groups practiced the backhand movement, but also subcomponents of the backhand movement, broken down into the shoulder component alone and elbow component alone (anatomical decomposition), or four individual joint movements in Euler components (Euler decomposition), or the motion of the elbow tip and hand with respect to the elbow (visual decomposition). Importantly, all groups practiced exactly the same number of movements; thus, the group that practiced only the target movement practiced this target movement in its entirety eight times more, since they did not "waste" time practicing the "nonfunctional" component movements. Yet, despite less experience with the target movement, the individuals who experienced part training learned better, but only when the motion was decomposed into anatomical coordinates. This suggests that breaking down a movement into specific components may aid in motor learning and challenges the idea that one should always practice the target functional movement.

The second study used a crossover design to evaluate the efficacy of functionally oriented training with BONES, compared to individual joint training with BONES, for individuals with a chronic stroke [72]. In this study, 20 participants with a stroke exercised three times per week with one technique for 4 weeks, rested a week, and then crossed over to the other technique for four more weeks. Surprisingly, individual joint training was about as effective as functional, multijoint training, across a broad range of clinical and robotic outcome measures.

These studies suggest that practicing a target functional task is not necessarily the most efficient movement training strategy and seem to call into question the notion of limited transfer in motor training, since training with the part transferred well to learning the whole in both studies. A further key recent study that also challenges the idea of limited transfer is one in which 11 participants with a stroke practiced for 5 days a feeding task with their affected side [73]. The investigators tested whether the improvements in ability to perform this task transferred more to a similar, untrained task than a dissimilar, untrained task. Surprisingly, performance on all three tasks improved, and was not dependent on the degree of similarity to the trained task.

How does this information relate to the spring orthosis approach? It suggests that it may not be necessary to have complex multi-DOF exoskeletons to achieve therapeutic benefits. That is, while the use of high DOF, functionally oriented exoskeletons is not detrimental and allows flexibility in selecting movements to train, it may be possible to design simpler devices with fewer DOF that focus on a reduced set of key component movements required for functional movements. Devices that help train the "part" may contribute to learning the "whole."

27.2.3 Can Computer Games and Quantitative Feedback Improve Recovery?

A third premise of the spring orthosis approach as exemplified by T-WREX, 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 [74]. 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 [75]. 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.

How does this information relate to the spring orthosis approach? At a minimum it suggests that making a task engaging and making feedback available about performance of the task are beneficial for any proposed simpler spring orthosis.

27.3 Toward Simpler Spring Orthoses: The Resonating Arm Exerciser

27.3.1 Design Rationale

While T-WREX, and subsequently ArmeoSpring, as well as FreeBal and ArmeoBoom, demonstrated that it is possible to achieve some of the benefits of robotic assistance without the robot, these devices remain complex on the spectrum of therapeutic technology. Indeed, even though ArmeoSpring and ArmeoBoom are currently being used in hundreds of rehabilitation clinics, therapeutic access to such devices is still limited to a small percentage of the target population. This fact was highlighted by a visit to our laboratory by Dr. Don Schoendorfer, the founder of Free Wheelchair Mission, a nonprofit organization that seeks to provide low-cost wheelchairs to the more than 100 million individuals in developing nations who cannot afford a wheelchair [76]. While Dr. Schoendorfer was enthusiastic about rehabilitation robotic technologies, he challenged us to develop simpler devices that could provide some of the benefits of robotic therapy to individuals who have motor impairment and limited financial resources.

In response to this challenge, we developed a device that focused first on achieving the primary rationale for the spring orthosis approach—physical assistance—but in a much simpler way. We developed the mechanical design from two core concepts. The first was to base the new device on an existing low-cost technology, the $70 manual wheelchairs developed by Free Wheelchair

Mission. The second was to implement a successful arm therapy developed by Dr. Hilde Feys, in which individuals with stroke repetitively rock themselves back and forth in a rocking chair by pushing and pulling with their impaired arm [77]. In a large-scale randomized controlled trial, Feys found that individuals who performed this exercise during the subacute phase of stroke had a significantly greater increase in FM score of 17 points at a 5-year follow-up [78], a notable gain on the order of the largest benefit obtained with a robotic device.

The result of this design approach was RAE (the Resonating Arm Exerciser; see Fig. 27.4) [79]. RAE is simply a lever with a hinged forearm support that can be rigidly attached to the push rim of a manual wheelchair. Elastic bands stretch between the lever and the wheelchair frame, supporting the weight of the arm against gravity, like T-WREX. However, the device also provides another form of assistance because it can be approximated as a linear, second-order system with a resonant mode [79]. If the user moves the lever back and forth at the resonant frequency of the system, the elastic bands assist the user, increasing his or her forward and backward range of motion for a given input force. Thus, while RAE provides arm support against gravity like prior spring orthoses, it also provides active assistance during movement using resonance in a direction roughly orthogonal to gravity. Since RAE is a passive device, the user will not receive this resonance assistance without active involvement in the exercise, achieving the goal of minimizing slacking while providing physical assistance during therapy.

Fig. 27.4 A person using RAE with a "flat-palm" grip in a standard wheelchair. The participant uses RAE by pushing and pulling rhythmically on the lever, moving their shoulder, elbow, and wrist in a coordinated pattern that is a key subcomponent of a reach-and-retrieval task. The elastic bands attached between the RAE lever and the wheelchair frame support the arm against gravity while creating a resonant system that provides active assistance during rhythmic exercise (Adapted from Zondervan et al. [79]; used with permission)

A possible limitation of RAE's simple design is that it only allows repetitive practice of a single, stereotypical back and forth arm movement involving coordinated shoulder and elbow flexion and extension. These movements are arguably nonfunctional in nature. However, they do represent a key subcomponent of a functional reach-and-retrieval task. As reviewed in the previous section, recent studies suggest that practicing appropriate movement components may lead to increased benefit over practice of complete movements alone [71–73, 80, 81]. That is, practicing the "part" with RAE may ultimately benefit the "whole" functional arm movements the user wishes to make.

Finally, as discussed above, several studies involving computer games and feedback in rehabilitation suggest that the rehabilitation task should be engaging and should provide feedback about performance of the task. While the first version of RAE did not incorporate computer games, exercise with RAE is engaging and goal oriented, since a user must move his or her arm with a specific timing to achieve the desired resonance assistance. In addition, when the timing is correct, the user receives feedback because his or her arm moves through a wider range of motion, and he or she experiences a soothing rocking motion like the one provided by a rocking chair.

27.3.2 Therapeutic Testing of the Resonating Arm Exerciser

After developing RAE, we performed several studies to understand the therapeutic efficacy of

exercise with the device after stroke. As a first step, we invited six individuals in the chronic phase of stroke to use RAE in a single laboratory session [79]. We instructed the participants to exercise with RAE at whatever frequency felt most natural. We compared their self-selected movement frequency during exercise to the estimated resonant frequency of the system, determined by measuring the step response of the lever with the participant's arm in the device. We also asked participants to push and pull on the lever with a single, sustained effort, and we measured the maximum range of motion they achieved. We compared this value to the maximum range of motion they achieved during rhythmic exercise. Here, we found that individuals successfully entrained to the resonant frequency of the system during rhythmic exercise without explicit instruction and that this resonance significantly increased their maximum range of motion with RAE by a factor of 1.7 ($p=0.04$). This study verified that even individuals with severe impairment can easily entrain to a resonant system and that a lever-based system using resonance can not only provide weight support but can also provide assistance for movements orthogonal to gravity via the resonance.

Next, we performed a pilot study with eight volunteers in the chronic phase of stroke at the Instituto Nacional de Neurología y Neurocirugía in Mexico City, to determine if exercise with RAE could improve their arm movement ability [79]. Three participants exercised with RAE for eight 45-min sessions spread out over 3 weeks and then rested for 3 weeks. The other five participants rested for 3 weeks and then completed the same 6 h of therapy. We measured each participant's active range of motion in RAE, their Fugl–Meyer score, and their subjective pain levels before and after both the exercise period and the rest period. Individuals in the chronic phase of stroke have reached a well-documented "plateau" in arm recovery; thus, we used the participant's initial assessment as a baseline. The group that rested first ($n=5$) had no significant change in any of the outcome measures after the 3 week rest period, confirming this plateau effect. After the 3-week exercise period, the participants' ($n=8$) range of motion in RAE significantly increased by $66\% \pm 20\%$ ($p=0.003$), and their FM score significantly increased by 8.5 ± 4 points ($p=0.009$). The participants did not report any increase in pain, and the observed gains in arm movement ability were sustained 3 months after treatment.

Encouraged by these initial results, we performed a randomized, controlled study of at-home exercise with RAE [80]. Sixteen participants with a mean initial FM score of 21/66 (i.e., severe levels of arm impairment) in the chronic phase of stroke were randomized to perform either 3 weeks of home-based exercise with RAE for 3 h per week or 3 weeks of conventional home-based exercises for 3 h per week, in the form of a booklet of arm exercises they were instructed to complete. The group that performed conventional exercises also crossed over to perform an additional 3 weeks of exercise with RAE. Both groups had significant increases in FM score immediately after exercise, but these improvements were not sustained at 1 month posttreatment. Notably, exercise with RAE led to a significantly greater increase in distal FM score than conventional exercises at 1 month posttreatment (Fig. 27.5). These results again support the idea of "component-specific therapy" since the stereotypical exercises performed with RAE led to a reduction in impairment important for a wide range of tasks that were not explicitly trained.

While this study successfully demonstrated the therapeutic potential of simpler spring orthoses, participants often remarked that exercise with RAE was boring, and did not hold their attention. Following the model that proved successful for T-WREX, we developed video games for RAE to increase motivation. A key challenge in this effort is the fact that RAE has limited degrees of freedom and requires a user to move at a specific frequency, minimizing the number of inputs that can be extracted during exercise in order to control a video game [28]. We solved this problem by developing a novel algorithm that allows users to control a game by modulating their movement amplitude during rhythmic rocking. We then linked this input system to games that only required a single input to

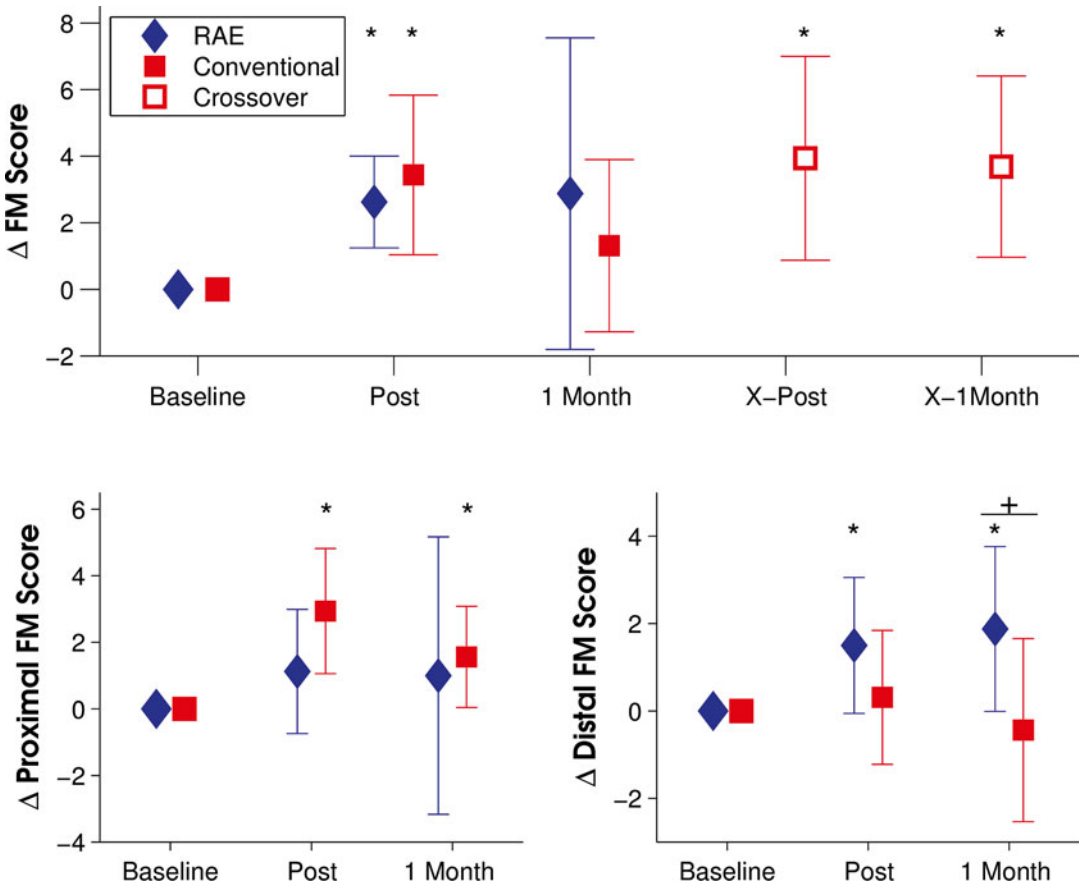

Fig. 27.5 Changes in Fugl–Meyer score after 3 weeks of home-based exercise with RAE and home-based conventional exercises ($n=16$). While both groups had significant improvements immediately after therapy, they were not retained 1 month later. After the conventional group crossed over to receive RAE therapy (*open squares*), they had significantly improvements in FM score compared to baseline both immediately after therapy and at long-term follow-up. Notably, participants who exercised with RAE initially had significantly greater improvements in distal function compared to the conventional group at 1 month posttherapy (*bottom right plot*, $p=0.02$, shown with a '+'). *denotes significant changes compared to baseline at $p<0.05$. *Error bars* denote ±1 standard deviation (From Zondervan et al. [80]. © 2014; reprinted by permission of SAGE Publications)

play, a paradigm that has become increasingly popular in mobile games (e.g., Flappy Bird, Temple Run, Jetman, etc.). In a pilot study, we found that individuals with stroke could successfully use this system to play videogames and that this increased their motivation to exercise with the device.

While video games are well suited to increase motivation and provide quantitative feedback, they are not the only solution to this problem. After observing that RAE gave individuals with even very severe motor impairment after stroke the ability to successfully move themselves back and forth in a wheelchair, we realized that a simple ratchet-like gear would enable them to self-ambulate with the device [28]. We developed a prototype version of this lever-actuated resonance assisted (LARA) wheelchair and demonstrated that individuals with severely impaired upper extremities could use this LARA wheelchair to move themselves over 50 ft in a straight line (Fig. 27.6). In this configuration, the users received quantitative feedback in the form of visually observing their overground speed and driving accuracy and were highly motivated to use the device since it enabled them to obtain

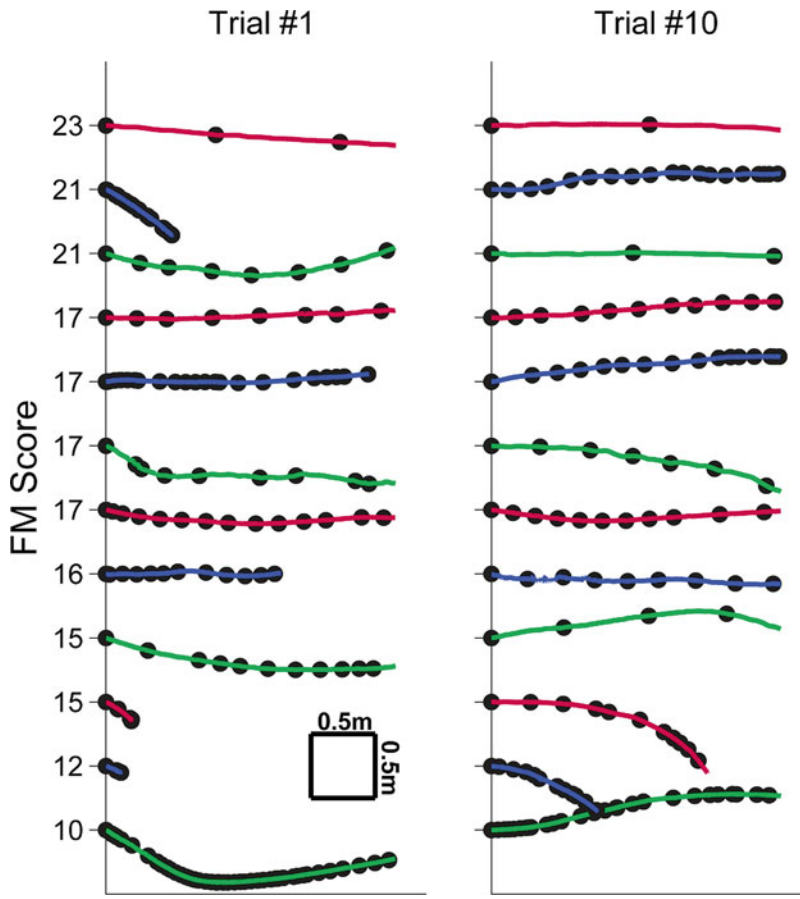

Fig. 27.6 Overhead view of wheelchair paths during self-propulsion by 12 subjects with severe hemiparesis after stroke (mean baseline FM score 17 ± 4 out of 66). The subjects used LARA to bimanually propel themselves in a wheelchair a maximum of 3 m in a straight line, ten times each; the first and tenth trials are shown. Each line represents a different subject as they moved from left to right. The starting y-position for each subject is offset according to their FM scores, with the lowest scores at the bottom and the highest scores at the top. None of the subjects could normally propel a manual wheelchair with their impaired arm, but after 15 min of practice with LARA, 10/12 succeeded in moving 3 m. Paths are flipped for the left-hemiparetic subjects so that the side of the wheelchair controlled by the impaired arm is always shown on the bottom side of the figure. *Dots* indicate 2-s intervals during the trial. The average speed across all subjects increased significantly from the first to the tenth trial, reaching 0.2 ± 0.2 m/s on the tenth trial (paired *t*-test, $p = 0.014$). The subjects found the experience highly significant because they were able to use their "useless" arm in a functional way

independent mobility while using their impaired arm in a very meaningful way, often for the first time in years. We are excited by these results, since we believe use of a LARA wheelchair after stroke can become a standard of practice in stroke rehabilitation, substantially increasing the number of repetitions of meaningful arm exercises that individuals achieve during inpatient rehabilitation while improving motivation, self-efficacy, and independence.

27.4 Conclusion

In this chapter, we traced the development of spring-based orthoses for upper-extremity arm therapy, as exemplified by T-WREX, ArmeoSpring, and the Resonating Arm Exerciser. Although spring-based orthoses are therapeutically efficacious and now one of the most widely used upper-extremity therapy technologies, randomized controlled trials are still needed to com-

pare the spring orthosis approach to alternate technologies for therapy, including robotic devices and motion capture-based devices. The spring-based orthosis approach perhaps can be viewed as a motion capture device that conveys some of the positive benefits of robotic assistance for motivation and self-efficacy, while preventing slacking. Thus, future comparisons of spring orthosis, robotics, and motion capture approaches should likely include measures of their effects on motivation, as well as of their effects on movement ability. Pilot studies now demonstrate that simple spring-based orthoses, such as RAE, are feasible for home use. The extent to which the reduced flexibility of such simpler spring orthoses matters for therapeutic efficacy is a key question. Finally, we predict an increasing trend toward using spring orthoses as assistive devices throughout the day to improve functional activity and, by so doing, to provide therapy. The LARA-based wheelchair, which allows severely impaired hemiparetic individuals to propel themselves bimanually, is an example of this approach. Springs are typically lighter than robotic actuators, and thus spring orthoses will likely become increasingly useful as wearable devices for improving functional activity.

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References

1. Hogan N, Krebs HI, Charnarong J, Sharon A. Interactive robot therapist. US Patent 5,466,213, 1995.
2. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002; 83(7):952–9.
3. Reinkensmeyer DJ, Dewald JPA, Rymer WZ. Guidance-based quantification of arm impairment following brain injury: a pilot study. IEEE Trans Rehabil Eng. 1999;7(1):1–11.
4. Hesse S, Schulte-Tigges G, Konrad M, Bardeleben A, Werner C. Robot-assisted arm trainer for the passive and active practice of bilateral forearm and wrist movements in hemiparetic subjects. Arch Phys Med Rehabil. 2003;84(6):915–20.
5. Prange GB, Jannink MJA, Groothuis CGM, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev. 2006;43(2):171–84.
6. Brewer BR, McDowell SK, Worthen-Chaudhari LC. Poststroke upper extremity rehabilitation: a review of robotic systems and clinical results. Top Stroke Rehabil. 2007;14(6):22–44. United States.
7. Mehrholz J, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving arm function and activities of daily living after stroke. Cochrane Database Syst Rev. 2008;(4):CD006876. England.
8. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362(19):1772–83.
9. Reinkensmeyer DJ, Wolbrecht ET, Chan V, Chou C, Cramer SC, Bobrow JE. Comparison of 3D, assist-as-needed robotic arm/hand movement training provided with Pneu-WREX to conventional table top therapy following chronic stroke. Am J Phys Med Rehabil. 2012;91:S232–41.
10. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, et al. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol. 2014;13(2):159–66.
11. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau ML. Computerized arm training improves the motor control of the severely affected arm after stroke: a single-blinded randomized trial in two centers. Stroke. 2005;36(9):1960–6. Epub 2005 Aug 18.
12. Kahn LE, Zygman ML, Rymer WZ, Reinkensmeyer DJ. Robot-assisted reaching exercise promotes arm movement recovery in chronic hemiparetic stroke: a randomized controlled pilot study. J Neuroeng Neurorehabil. 2006;3:12.
13. Kahn LE, Lum PS, Rymer WZ, Reinkensmeyer DJ. Robot-assisted movement training for the stroke-impaired arm: does it matter what the robot does? J Rehabil Res Dev. 2006;43(5):619–30.
14. Reinkensmeyer DJ, Pang CT, Nessler JA, Painter CC. Web-based telerehabilitation for the upper-extremity after stroke. IEEE Trans Neural Sci Rehabil Eng. 2002;10:1–7.
15. Sanchez RJ, Liu J, Rao S, Shah P, Smith R, Rahman T, et al. Automating arm movement training following severe stroke: functional exercises with quantitative feedback in a gravity-reduced environment. IEEE Trans Neural Syst Rehabil Eng. 2006;14(3):378–89.
16. Rahman T, Sample W, Seliktar R, Alexander M, Scavina M. A body-powered functional upper limb orthosis. J Rehabil Res Dev. 2000;37(6):675–80.
17. Housman SJ, Scott KM, Reinkensmeyer DJ. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with

severe hemiparesis. Neurorehabil Neural Repair. 2009;23(5):505–14.
18. Colomer C, Baldoví A, Torromé S, Navarro MD, Moliner B, Ferri J, et al. Efficacy of Armeo® Spring during the chronic phase of stroke. Study in mild to moderate cases of hemiparesis. Neurologia. 2013;28(5):261–7.
19. Joo M, Park H, Noh S, Kim J, Kim H, Jang C. Effects of robot-assisted arm training in patients with subacute stroke. Brain Neurorehabil. 2014;7(2):111–7.
20. Bartolo M. Arm weight support training improves functional motor outcome and movement smoothness after stroke. Funct Neurol. 2014;29(1):15–22.
21. Meadmore KL, Hughes A-M, Freeman CT, Cai Z, Tong D, Burridge JH, et al. Function electrical stimulation mediated by iterative learning control and 3D robotics reduces motor impairment in chronic stroke. J Neuroeng Rehabil. 2012;9(1):32.
22. Cameirão MS, Badia SB i, Duarte E, Frisoli A, Verschure PFMJ. The combined impact of virtual reality neurorehabilitation and its interfaces on upper extremity functional recovery in patients with chronic stroke. Stroke. 2012;43(10):2720–8.
23. Zariffa J, Kapadia N, Kramer JL, Taylor P, Alizadeh-Meghrazi M, Zivanovic V, et al. Feasibility and efficacy of upper limb robotic rehabilitation in a subacute cervical spinal cord injury population. Spinal Cord. 2012;50(3):220–6.
24. Gijbels D, Lamers I, Kerkhofs L, Alders G, Knippenberg E, Feys P. The Armeo Spring as training tool to improve upper limb functionality in multiple sclerosis: a pilot study. J Neuroeng Rehabil. 2011;8(5):5.
25. Schwickert L, Klenk J, Stähler A, Becker C, Lindemann U. Robotic-assisted rehabilitation of proximal humerus fractures in virtual environments: a pilot study. Z Gerontol Geriatr. 2011;44(6):387–92.
26. Van der Kooij H, Prange GB, Krabben T, Renzenbrink GJ, de Boer J, Hermens HJ, et al. Preliminary results of training with gravity compensation of the arm in chronic stroke survivors. Conference proceedings IEEE engineering medicine biology society. Minneapolis, MN, USA. Piscataway, New Jersey 2009:2426–9
27. Prange GB, Kottink AIR, Buurke JH, Eckhardt MMEM, van Keulen-Rouweler BJ, Ribbers GM, et al. The effect of arm support combined with rehabilitation games on upper-extremity function in subacute stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2015;29(2):174–82.
28. Zondervan DK, Smith B, Reinkensmeyer DJ. Lever-actuated resonance assistance (LARA): a wheelchair-based method for upper extremity therapy and overground ambulation for people with severe arm impairment. IEEE international conference rehabilitation robotics. Seattle, WA, USA; Piscataway, New Jersey. 2013. p. 1–6.
29. Iwamuro BT, Cruz EG, Connelly LL, Fischer HC, Kamper DG. Effect of a gravity-compensating orthosis on reaching after stroke: evaluation of the therapy assistant WREX. Arch Phys Med Rehabil. 2008;89(11):2121–8.
30. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13–31.
31. Van der Lee JH, Beckerman H, Knol DL, de Vet HCW, Bouter LM. Clinimetric properties of the motor activity Log for the assessment of arm use in hemiparetic patients. Stroke. 2004;35(6):1404–10.
32. Rudhe C, Albisser U, Starkey ML, Curt A, Bolliger M. Reliability of movement workspace measurements in a passive arm orthosis used in spinal cord injury rehabilitation. J Neuroeng Rehabil. 2012;9:37.
33. Zariffa J, Kapadia N, Kramer JL, Taylor P, Alizadeh-Meghrazi M, Zivanovic V, et al. Relationship between clinical assessments of function and measurements from an upper-limb robotic rehabilitation device in cervical spinal cord injury. IEEE Trans Neural Syst Rehabil Eng. 2012;20(3):341–50.
34. Merlo A, Longhi M, Giannotti E, Prati P, Giacobbi M, Ruscelli E, et al. Upper limb evaluation with robotic exoskeleton. Normative values for indices of accuracy, speed and smoothness. NeuroRehabilitation. 2013;33(4):523–30.
35. Stienen AHA, Hekman EEG, Van der Helm FCT, Prange GB, Jannink MJA, Aalsma AMM, et al. Freebal: dedicated gravity compensation for the upper extremities. IEEE 10th international conference rehabilitation robotics. Noordwijk, Netherlands, Piscataway, New Jersey 2007. p. 804–8.
36. Prange GB, Jannink MJ, Stienen AH, van der Kooij H, Ijzerman MJ, Hermens HJ. Influence of gravity compensation on muscle activation patterns during different temporal phases of arm movements of stroke patients. Neurorehabil Neural Repair. 2009;23(5):478–85.
37. Stienen A, Hekman E, van der Helm F, van der Kooij H. Self-aligning exoskeleton axes through decoupling of joint rotations and translations. IEEE T Robot. 2009;25(3):628–33.
38. Emken JL, Benitez R, Sideris A, Bobrow JE, Reinkensmeyer DJ. Motor adaptation as a greedy optimization of error and effort. J Neurophysiol. 2007;97(6):3997–4006.
39. Wolbrecht ET, Chan V, Reinkensmeyer DJ, Bobrow JE. Optimizing compliant, model-based robotic assistance to promote neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2008;16(3):286–97.
40. Lippman LG, Rees R. Consequences of error production in a perceptual-motor task. J Gen Psychol. 1997;124(2):133–42.
41. Lotze M, Braun C, Birbaumer N, Anders S, Cohen LG. Motor learning elicited by voluntary drive. Brain. 2003;126(4):866–72.
42. Kaelin-Lang A, Sawaki L, Cohen LG. Role of voluntary drive in encoding an elementary motor memory. J Neurophysiol. 2005;93:1099–103.
43. Van Asseldonk EH, Wessels M, Stienen AH, van der Helm FC, van der Kooij H. Influence of haptic guidance in learning a novel visuomotor task. J Physiol Paris. 2009;103(3–5):276–85.
44. Hu XL, Tong KY, Song R, Zheng XJ, Leung WW. A comparison between electromyography-driven robot and passive motion device on wrist rehabilitation for

chronic stroke. Neurorehabil Neural Repair. 2009;23(8):837–46.
45. Israel JF, Campbell DD, Kahn JH, Hornby TG. Metabolic costs and muscle activity patterns during robotic- and therapist-assisted treadmill walking in individuals with incomplete spinal cord injury. Phys Ther. 2006;86(11):1466–78.
46. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39(6):1786–92.
47. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5–13.
48. Bohannon RW, Warren ME, Cogman KA. Motor variables correlated with the hand-to-mouth maneuver in stroke patients. Arch Phys Med Rehabil. 1991;7:682–4.
49. Canning CG, Ada L, Adams R, O'Dwyer NJ. Loss of strength contributes more to physical disability after stroke than loss of dexterity. Clin Rehabil. 2004;18(3):300–8. England.
50. Lang c, Wagner JM, Edwards DF, Dromerick AW. Upper extremity use in people with hemiparesis in the first few weeks after stroke. J Neurol Phys Ther. 2007;31(2):56–63.
51. Harris JE, Eng JJ. Paretic upper-limb strength best explains arm activity in people with stroke. Phys Ther. 2007;87(1):88–97. United States.
52. Landau WM, Sahrmann SA. Preservation of directly stimulated muscle strength in hemiplegia due to stroke. Arch Neurol. 2002;59(9):1453–7. United States.
53. Enoka RM. Neural adaptations with chronic physical activity. J Biomech. 1997;30(5):447–55. New York: Elsevier.
54. Ada L, Dorsch S, Canning CG. Strengthening interventions increase strength and improve activity after stroke: a systematic review. Aust J Physiother. 2006;52(4):241–8. Australia.
55. Taylor NF, Dodd KJ, Damiano DL. Progressive resistance exercise in physical therapy: a summary of systematic reviews. Phys Ther. 2005;85(11):1208–23. United States.
56. Cai LL, Fong AJ, Otoshi CK, Liang Y, Burdick JW, Roy RR, et al. Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. J Neurosci. 2006;26(41):10564–8.
57. Lewek MD, Cruz TH, Moore JL, Roth HR, Dhaher YY, Hornby TG. Allowing intralimb kinematic variability during locomotor training poststroke improves kinematic consistency: a subgroup analysis from a randomized clinical trial. Phys Ther. 2009;89(8):829–39.
58. Ziegler MD, Zhong H, Roy RR, Edgerton VR. Why variability facilitates spinal learning. J Neurosci. 2010;30(32):10720–6.
59. Winstein CJ, Pohl PS, Lewthwaite R. Effects of physical guidance and knowledge of results on motor learning: support for the guidance hypothesis. Res Q Exerc Sport. 1994;65(4):316–32.
60. Marchal Crespo L, Reinkensmeyer DJ. Haptic guidance can enhance motor learning of a steering task. J Mot Behav. 2008;40(6):545–56.
61. Marchal-Crespo L, Furumasu J, Reinkensmeyer DJ. A robotic wheelchair trainer: design overview and a feasibility study. J Neuroeng Rehabil. 2010;7:40.
62. Marchal-Crespo L, McHughen S, Cramer SC, Reinkensmeyer DJ. The effect of haptic guidance, aging, and initial skill level on motor learning of a steering task. Exp Brain Res. 2009;201(2):209–20.
63. Milot MH, Marchal-Crespo L, Green CS, Cramer SC, Reinkensmeyer DJ. Comparison of error amplification and haptic guidance training techniques for learning of a timing-based motor task by healthy individuals. Exp Brain Res. 2009;201(2):119–31.
64. Takahashi CD, Der-Yeghiaian L, Le V, Motiwala RR, Cramer SC. Robot-based hand motor therapy after stroke. Brain. 2008;131(Pt 2):425–37. England.
65. Reinkensmeyer DJ, Housman SJ. "If I can't do it once, why do it a hundred times?" Connecting volition to movement success in a virtual environment motivates people to exercise the arm after stroke. Proceedings of virtual rehabilitation conference. Venice, Italy; Piscataway, New Jersey 2007. p. 44–8.
66. Duarte JE, Gebrekristos B, Perez S, Rowe JB, Sharp K, Reinkensmeyer DJ. Effort, performance, and motivation: insights from robot-assisted training of human golf putting and rat grip strength. IEEE international conference rehabilitation robotics [proceedings]. Seattle, WA, USA; Piscataway, New Jersey 2013;2013:1–6.
67. Duarte JE, Reinkensmeyer DJ. Effects of robotically modulating kinematic variability on motor skill learning and motivation. J Neurophysiol. 2015;113(7):2682–91.
68. Marchal-Crespo L, Reinkensmeyer DJ. Review of control strategies for robotic movement training after neurologic injury. J Neural Eng Rehabil. 2008;6:20.
69. Krebs HI, Mernoff S, Fasoli SE, Hughes R, Stein J, Hogan N. A comparison of functional and impairment-based robotic training in severe to moderate chronic stroke: a pilot study. NeuroRehabilitation. 2008;23(1):81–7. Netherlands.
70. Klein J, Spencer SJ, Allington J, Bobrow JE, Reinkensmeyer DJ. Optimization of a parallel shoulder mechanism to achieve a high force, low mass, robotic arm exoskeleton. IEEE Trans Robot. 2010;26(4):710–5.
71. Klein J, Spencer SJ, Reinkensmeyer DJ. Breaking it down is better: haptic decomposition of complex movements aids in robot-assisted motor learning. IEEE Trans Neural Syst Rehabil Eng. 2012;20(3):268–75.

72. Milot MH, Spencer SJ, Chan V, Allington JP, Klein J, Chou C, et al. Re-training upper extremity movement with the robotic exoskeleton BONES after chronic stroke: a crossover pilot study evaluating the functional outcomes of more naturalistic robotic movement training. J Neuroeng Rehabil. 2013;10:112.
73. Schaefer SY, Patterson CB, Lang CE. Transfer of training between distinct motor tasks after stroke: implications for task-specific approaches to upper-extremity neurorehabilitation. Neurorehabil Neural Repair. 2013;27:602–12. [Internet], [cited 2013 Apr 9]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/23549521.
74. Mirelman A, Bonato P, Deutsch JE. Effects of training with a robot-virtual reality system compared with a robot alone on the gait of individuals after stroke. Stroke. 2008;40:169–74.
75. Dobkin BH, Plummer-D'Amato P, Elashoff R, Lee J. International randomized clinical trial, stroke inpatient rehabilitation with reinforcement of walking speed (SIRROWS), improves outcomes. Neurorehabil Neural Repair. 2010;24(3):235–42.
76. Shore SL. Use of an economical wheelchair in India and Peru: impact on health and function. Med Sci Monit. 2008;14(12):71–9.
77. Feys HM, De Weerdt WJ, Selz BE, Cox Steck GA, Spichiger R, Vereeck LE, et al. Effect of a therapeutic intervention for the hemiplegic upper limb in the acute phase after stroke: a single-blind, randomized, controlled multicenter trial. Stroke. 1998;29(4):785–92.
78. Feys H, De Weerdt W, Verbeke G, Steck GC, Capiau C, Kiekens C, et al. Early and repetitive stimulation of the arm can substantially improve the long-term outcome after stroke: a 5-year follow-up study of a randomized trial. Stroke. 2004;35(4):924–9.
79. Zondervan DK, Palafox L, Hernandez J, Reinkensmeyer DJ. The resonating arm exerciser: design and pilot testing of a mechanically passive rehabilitation device that mimics robotic active assistance. J Neuroeng Rehabil. 2013;10:39.
80. Zondervan DK, Augsburger R, Bodenhoefer B, Friedman N, Reinkensmeyer DJ, Cramer SC. Machine-based, self-guided home therapy for individuals with severe arm impairment after stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2014;29(5):395–406.
81. Friedman N, Chan V, Reinkensmeyer AN, Beroukhim A, Zambrano G, Bachman M, et al. Retraining and assessing hand movement after stroke using the MusicGlove: comparison with conventional hand therapy and isometric grip training. J Neuroeng Rehabil Res. 2014;11:76.

Virtual Reality for Sensorimotor Rehabilitation Post Stroke: Design Principles and Evidence

28

Sergi Bermúdez i Badia, Gerard G. Fluet, Roberto Llorens, and Judith E. Deutsch

Abstract

In the recent years, the use of virtual reality (VR) to enhance motor skills of persons with activity and participation restriction due to disease or injury has been become an important area of research. In this chapter, we describe the design of such VR systems and their underlying principles, such as experience-dependent neuroplasticity and motor learning. Further, psychological constructs related to motivation including salience, goal setting, and rewards are commonly utilized in VR to optimize motivation during rehabilitation activities. Hence, virtually simulated activities are considered to be ideal for (1) the delivery of specific feedback, (2) the ability to perform large volumes of training, and (3) the presentation of precisely calibrated difficulty levels, which maintain a high level of challenge throughout long training sessions. These underlying principles are contrasted with a growing body of research comparing the efficacy of VR with traditionally presented rehabilitation activities in persons with stroke that demonstrate comparable or better outcomes for VR. In addition, a small body of literature has utilized direct assays of neuroplasticity to evaluate the effects of virtual rehabilitation interventions in persons with stroke. Promising developments and findings also arise from the use of off-the-shelf video game systems for virtual rehabilitation purposes and the integration of VR with robots and brain-computer interfaces. Several

S. Bermúdez i Badia, Eng, PhD (✉)
Madeira Interactive Technologies Institute and Centro de Competências das Ciências Exatas e da Engenharia, Universidade da Madeira, Funchal, Portugal
e-mail: sergi.bermudez@uma.pt

G.G. Fluet, DPT, PhD
Department of Rehabilitation and Movement Sciences, Rutgers – The State University of New Jersey, 65 Bergen Street, Newark, NJ 07101, USA

R. Llorens, PhD
Instituto de Investigación e Innovación en Bioingeniería, Universitat Politècnica de València, Camino de Vera s/n, Valencia, Valencia 46022, Spain

J.E. Deutsch, PT, PhD
Rivers Lab: Department of Rehabilitation and Movement Sciences, Rutgers – The State University of New Jersey, 65 Bergen Street, Newark, NJ 07101, USA

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challenges limiting the translation of virtual rehabilitation into routine rehabilitation practice need to be addressed but the field continues to hold promise to answer key issues faced by modern healthcare.

Keywords
Virtual reality • Stroke • Motor rehabilitation • Neuroplasticity • Motor learning • Motivation • Serious games • Brain-computer interfaces • Haptics

28.1 Principles of Virtual Reality in Stroke Sensorimotor Neurorehabilitation

Virtual reality (VR) is an approach to user-computer interface that involves real-time simulation of an environment, scenario, or activity that allows for user interaction via multiple sensory channels [1]. VR and virtual environments (VEs) are created by using hardware and software that allow users to interact with objects and events that appear and sound, and in some cases feel, like those in the real world [2]. VEs are used in a rehabilitation context as an approach to improve the motor and cognitive ability of persons with activity and participation limitations through the use of interactions with VEs [3].

VR aims to substitute the real-world sensations by computer-generated sensory information and to facilitate natural interaction with the virtual world. These characteristics modulate immersion, which is related to the multimodal nature of the perceptual senses. In this chapter we address the term of immersion in the context of visual presentation, and we describe how VEs leverage immersion and presence to describe the quality of the VE and the user's experience of feeling like they are in the real world [4]. Further, experience-dependent neuroplasticity and motor learning serve as the basis for modern approaches to the rehabilitation of persons with neurologic dysfunction and inform the design of many virtual rehabilitation systems. Brief orientations to these concepts and examples of virtual rehabilitation applications incorporating them will begin this chapter (Sects. 28.1.1 and 28.1.2). Motivation drives several key attributes of behavior consistent with motor learning, including salience, attention, and repetition. The psychology of motivation as it relates to participation in simulated activities will follow in Sect. 28.1.3, and its importance related to the future of virtual rehabilitation will be underscored in the conclusion section. Section 28.2 reviews the literature describing the role of interfaces and sensory presentations in virtual rehabilitation and their impact on the user experience. Sections 28.1 and 28.2 can be used by the reader to inform the design or refinement of newer technology-based rehabilitation systems, virtually simulated, or otherwise. A review of studies examining the efficacy of a wide variety of virtual rehabilitation systems applied to sensorimotor rehabilitation of persons with stroke will complete the chapter. A majority of these studies compare the relative efficacy of virtual rehabilitation to traditional rehabilitation. This type of evidence can be used to evaluate current approaches to virtual rehabilitation and justify further study. The conclusion section that follows will identify several possible next steps for the efficacy literature, proposing a shift in its focus as well as a discussion of the impact of new technologies.

28.1.1 Presence and Embodiment in Virtual Reality

Even though there is no standardized definition for presence, it can be understood as the psychological state in which an individual is unable to acknowledge that an experience is computer generated [5, 6]. There is a consensus to characterize presence as a multicomponent construct [7]. It

has been commonly thought that presence is the key mechanism that makes VR work. Presence may be especially relevant in a neurologic population, since the subjective perception when interacting with VEs elicited in persons with CNS dysfunction has been shown to be different to that of healthy subjects [8]. Characteristics of both the user and what and how sensory information are presented by the VE determine the level of presence in VR. With regard to the user, the demographic (age, sex, educational level, etc.), psychocultural (social habits, interaction, etc.), and also clinical characteristics (motor, cognitive, and psychological condition) modulate the perception of the virtual world and the interaction with it [9]. Likewise, a previous experience with VR systems may influence presence [9].

Like presence, embodiment is a multicomponent psychological construct. It has been defined as the sense of one's own body [10], as the bodily self-consciousness [11], or as corporeal awareness [12]. All the existing evidence seems to indicate that presence and embodiment are innately linked. This relationship is evidenced by studies showing that the sense of presence can be modulated with avatars that accurately represent the users' actual selves (rather than avatars representing their ideal selves), which can facilitate their embodiment [13]. Recent research has focused on unifying aspects of the embodied cognition theories and on identifying its subcomponents, such as body ownership and agency [14]. Agency refers to the sense that one can move and control one's body [15]. Body ownership can be defined as the sense that the body that one inhabits is one's own [15]. Consequently, body ownership is continuous and omnipresent and is not only elicited during the movement but also during passive mobilization and at rest. Body ownership and agency are key mechanisms to facilitate embodiment in VR, which has traditionally been mediated by avatars that represent the user's actions.

Research has shown that specific multisensory stimulation can promote not only illusory ownership of parts of the body, such as rubber hands [16], but of the whole body. Multiple studies report that it is possible to perceive another person's body as one's own [17], but also to induce full-body ownership of a mannequin [18] or a complete virtual body [19]. Embodiment in avatars not only determines the body ownership and agency of the virtual representation but also the user's perception of the world and their behavior. For instance, the illusory ownership of a smaller virtual body (a virtual child) has shown to cause overestimation of object sizes [20], while the ownership of taller avatars has shown to promote confidence [21]. However, the relationship between presence and its influencing factors is not one-to-one. For example, high immersion, that is, the extent to which VR is capable of delivering an illusion of reality to the senses of a human participant [22], does not guarantee high level of presence [23]. In contrast, presence can be elicited by adding emotional valence to the media content, regardless of the media form [7]. In healthy adults the salience of the VE, the hardware used to deliver the VE, and the personal qualities of the participants have been shown to interact in creating a sense of presence and immersion [23]. Complete immersion, however, is not a requirement for presence, as participants post stroke were shown to be present even in semi-immersive environments [24]. Thus, some characteristics of VR systems such as synchronism of stimuli [19], alignment and continuity of the real and virtual bodies [25], and perspective [18], are determinants for inducing a sense of presence and embodiment and consequently are contributing factors in the effectiveness of VR-mediated therapies.

28.1.2 Motor Learning Principles

Motor learning principles are defined as the set of processes associated with practice or experience that lead to relatively permanent changes in the ability to perform actions [26]. Different principles have been postulated to modulate motor learning after stroke. Salient, goal-directed, task-specific movement and practice of sufficient intensity are important determinants in motor learning in human skill motor learning [27]. Even though these principles have rarely been analyzed

in isolation after VR interventions, the role of motor learning principles has been discussed by authors who described their systems [28], in review papers [3, 29–33], as well as book chapters [34]. One can find motor learning principles embedded in VEs for motor rehabilitation [29, 34]. In the following section, we will discuss a number of principles that have become integral to VEs for promoting skill acquisition in the real world such as enriched environments, augmented feedback, practice dosing, adaptation, motivation, and task-oriented experiences.

28.1.2.1 Enriched Environments

Preclinical research on enriched environments serves as the basis for hypothesizing that enriched VR experiences could serve as rehabilitation tools to promote motor learning [35]. Initial findings with animal models have shown that enriched environments promote sensorimotor functions and learning after stroke [36]. The benefits of enriched environments have been also postulated for human subjects. When persons post stroke were exposed to enriched environments that motivated exploration, physical training, and social interaction, they increased activity and decreased their alone time [37]. In this context, VR is a promising tool to create synthetic computer-generated environments that provide augmented stimulation to stroke survivors.

28.1.2.2 Intrinsic and Extrinsic Feedback

Movement performance is informed by both intrinsic and extrinsic feedback. Intrinsic feedback relates to the sensory-perceptual information that is naturally generated during or after a movement. Augmented feedback—also known as extrinsic feedback—is an add-on to the intrinsic feedback with the goal of providing further information, in the form of knowledge of performance (KP) and/or knowledge of results (KR), that can facilitate skill learning [38]. Augmented feedback is provided by an external source and not by the movement itself [39]. VEs can provide augmented feedback through different sensory modalities such as visual and auditory information with audiovisual devices and proprioceptive information through specific interfaces such as a haptic apparatus, further described in Sect. 28.2. Consequently, VR systems capitalize on both intrinsic feedback and augmented feedback [38].

There is preliminary evidence supporting that augmented auditory feedback improves the speed and accuracy of virtually simulated activity performance in healthy participants as well as participants with brain injury [40]. Further, because VEs can track motion of body targets or segments, movement monitoring allows the feedback about movement performance and outcome to be very specific. This fact could be key in the beneficial effect in the recovery of motor function after stroke present in VR approaches [see [41] for review]. In studies comparing real-world performance with comparable VE training, several authors have speculated that the cognitive processing required to process the KP in the VR enhances transfer of training to the real world [42, 43]. It is important to note that feedback from VEs, and in particular from games, can be nonspecific and focus on providing positive feedback to encourage participation. This is especially true with commercial video games that have been applied to rehabilitation [30]. To date, little is known about the impact of augmented feedback on the transfer of motor ability improvements from virtual activity to real-world activity [44].

28.1.2.3 Task Specificity

Task specificity has long been a fundamental requirement for designing recovery of function programs. However, the evidence in virtual rehabilitation is controversial. The principle of specificity suggests that motor learning is more effective when practice includes environmental and movement conditions similar to those required for the execution of the movement [45]. This suggests that the benefit of the practice specificity occurs because motor learning is specific to the information available during the learning process. Therefore, removing a source of information that was present during practice (or adding another that was not present) impacts task performance. The specificity of practice hypothesis posits that motor skill learning can be

enhanced by practice conditions, especially sensorimotor and perceptual information available, performance context characteristics, and cognitive processes involved [46]. Consistent with this hypothesis, VEs can build on the most appropriate available interfaces and feedback modalities to reproduce the relevant context of tasks, such as, haptic feedback to recreate the physics of object manipulation [47], video projections to augment tasks with contextual visual information [48, 49], or combining walking on a treadmill while performing a shopping task [50].

VEs have been also used to recreate meaningful tasks to be performed with the upper limbs. Virtual tasks emulating tasks for independent living have been used for assessing the upper limb motor function after stroke [51], showing correlations with clinical scales. Many different VEs have been successfully used for upper-limb rehabilitation with levels of ecological validity that varied widely [52, 53]. Given the multisensory training in VE, there may be essential task requirements, but perfect congruence with the real-world task may not be required.

Training walking is characteristically done using simulations in which participants walk on a treadmill as they navigate in parks, cityscapes, or corridors [54–56] (Fig. 28.1) or walk over obstacles [58]. However, several investigators have used pre-gait or gait-related activities to train walking [42, 57]. The extent that the task practiced sensorimotor and perceptual feedback is congruent between the VE and real-world situation varies greatly based on the VR system. While both Fung and You [55, 57] sought to improve walking post stroke, each approached it with a different degree of task specificity. For example, in a proof of concept study, Fung had participants post stroke walking in a virtual scene on an actuated treadmill, which allowed changes in path speed as well as orientation, producing a high degree of vestibular and proprioceptive fidelity with the VE. In contrast You had participants performing stepping and pre-gait activities on the ground with a level surface, in which a TheraBand™ was placed on the participants' limbs to augment the proprioceptive input. Fung measured and demonstrated participants' ability to adapt their walking based on the environmental demands, while You measured walking performance and demonstrated improvements after training. Their findings suggest that task specificity may be beneficial but not essential in VE constructions in order to demonstrate transfer of training.

28.1.2.4 Dosing

The dose of the training has been reported as a central factor in motor learning [59]. Dosing depends on three key parameters: training duration and frequency with which the individual per-

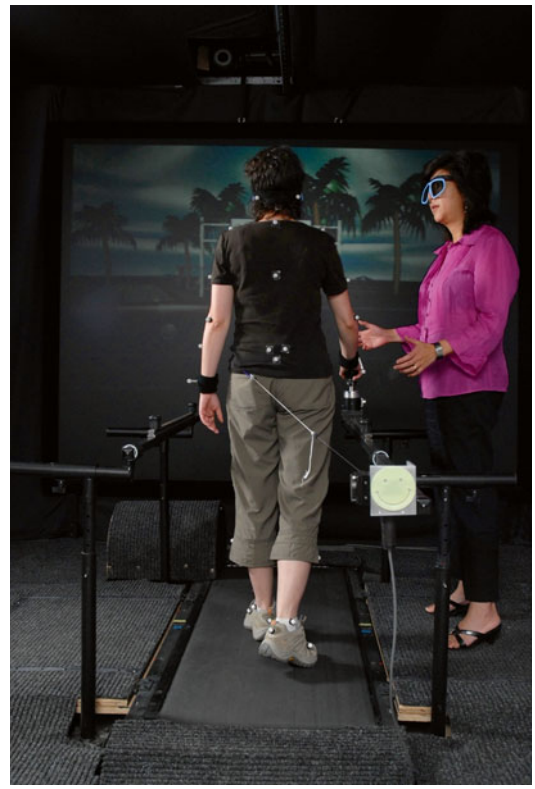

Fig. 28.1 An interactive VR-coupled locomotor system [55] incorporating a self-paced treadmill and dynamic haptics [57] mounted on a 6-degree-of-freedom motion platform. Computer-controlled, synchronized animations are rear projected onto a large screen that can be viewed in 3D with polarized glasses. Such a system can be used to train locomotor adaptation needed to meet demands related to the changing environment (obstruction and surface angle, etc.), tasks (speed requirements, avoiding moving obstacles, dual tasking etc.), and cognitive requirements (attention, planning, etc.) (Reproduced with permission of Joyce Fung)

forms training and the number of repetitions performed during training. It is known that a sufficient dose of practice needs to be performed in order to produce skilled behavior [60] and neuroplastic changes [61]. VEs are designed to promote repetitive task practice that can be tracked and progressed. The number of lower extremity repetitions in VE training has been reported to be comparable to repetitions in animal studies that successfully induced plasticity [28]. Further, work comparing the number of purposeful movements executed with the upper limb of persons post stroke during standard of care was five times lower and slower than when playing Kinect™ [62]. Dose alone, however, is not sufficient for motor learning and neural plasticity (see Sect. 28.3).

28.1.2.5 Adaptability

The repetition of a task is critical for its learning and its refinement. However, the mere repetition of a task has not been shown to induce plastic changes in motor maps. Studies in animals have shown that exposure to a task that requires little or no learning does not produce changes in motor maps or neural morphology [63]. Based on this principle, rehabilitation interventions should involve motor skills with growing difficulty to always pose a motor challenge for poststroke subjects [64]. The benefits of VEs are, on one hand, that they can accurately assess the patients' motor condition and, on the other hand, that they can adapt the motor tasks to match this changing condition. Adaptability of the motor tasks has been integrated in several VEs, from the upper limb [52] to balance [65]. VR systems with built-in calibration capabilities or personalization algorithms to autonomously adjust the intensity of training sessions to each patient have been shown to be more effective as compared to conventional therapy [66–68].

28.1.2.6 Motivation

Motivation can be defined as the set of forces that move an individual to act, which may be extrinsic (prompted by an external reward) or intrinsic (propitiated because the task is inherently pleasurable: curiosity, play, etc.). Research has shown that motivation promotes learning [69]. As shown in the following section, motivation plays a major role in VE because it persuades patients to accomplish a task and facilitates presence in the virtual world.

28.1.3 Motivating Through Gaming Elements in Virtual Environments

There are multiple models of motivation, some of which explore intrinsic motivational factors in which the motivation is derived from the act of participation itself or extrinsic factors in which the person is motivated by the purpose of the activity [70]. In the context of sensorimotor rehabilitation, the goal is to facilitate clients to be self-directed and motivated, both because the activity is interesting in itself and because achieving the outcome is important. There is agreement that gaming elements can improve motivation and that, if paired with other activities, they can be harnessed to engage users and achieve desired outcomes [71]. However, there is no consensus regarding the required essential characteristics of these gaming elements. Many elements have been suggested to be important for the design of a successful game, such as fun, flow, goals, feedback, game balance, pacing, interesting choices, and narrative structure among others [72]. In the following sections, we will discuss some of the intrinsic characteristics of games that can affect motivation and learning [73], and how those are used in the context of motor rehabilitation. While these intrinsic characteristics are discussed as gaming elements in VE, it is important to note that many of them, for example, goal setting, balancing challenge, and reward, overlap with principles of motor learning.

28.1.3.1 Goal Setting

Games generally set multiple goals at different time scales. An appropriate balance of short, medium, and long-term goals has been shown to have a motivating effect in extending game play [72]. Further, goals should be achievable but they should also be attained through a chain of

interesting decisions. That is, when players are presented with choices, no one decision should be obviously correct. Most VEs exclusively designed for motor rehabilitation only consider immediate goals (to perform a specific motor task such as reaching or walking) and long-term goals (to collect a sufficiently high amount of rewards). Instead, VEs integrating both cognitive and motor domains seem to be better suited to pose goals at multiple time scales through non-trivial decisions [50, 74, 75].

28.1.3.2 Rewards

Recent findings suggest that providing appropriate feedback to exercises can stimulate the learning process in rehabilitation therapy [41]. VEs are extremely well suited to provide immediate and specific feedback to users, this feature being essential for sustained attention, learning, motivation, and fun [72]. Actions can be rewarded with positive visual and auditory feedback, scores, and specific KP and KR [76, 77]. Many VR-based rehabilitation activities utilize auditory feedback related to successful task completion via general "celebratory" sounds or appropriate sounds when acquiring a target (i.e., explosions during a shooting task). Comparable negative feedback can be provided for unsuccessful performance (collision with an obstacle) [78]. This approach to feedback provides the participant KR, a modality of feedback associated with rapid, effective motor learning [79]. However, rewards can also have negative effects in high-interest tasks when rewards are predictable and not associated to performance [80]. Consequently, rewards need to be properly manipulated in their number, timing, and quality in order to sustain attention over extended periods of time.

28.1.3.3 Challenge

VEs for motor rehabilitation should be adjusted in terms of movement demands and dynamics, avoiding situations in which patients lose the ability to directly control the task. It has been suggested that players desire a level of challenge that is neither too easy nor too difficult to perform [81], which is consistent with the early findings of Yerkes and Dodson, when the relation between induced stress and task-learning performance was studied in mice [82] and later replicated in humans in multiple domains [83, 84]. Csikszentmihalyi in his flow theory describes that user experience during play (anxiety, boredom, and flow) is modulated through the challenge posed and the level of skills required [85]. Flow, defined as the moment of maximum player engagement, is placed at the right balance between user skills and level of challenge. For this reason, it is necessary that the tasks given as well as the time available to complete them are calibrated to introduce a controlled challenge [86]. Therefore, recent developments in VEs for motor training already incorporate transparent and automated modules for the personalization of training, by adjusting task difficulty depending on patient's success rate or by modifying time available to accomplish a goal [52, 87, 88]. In the cases when VEs are designed to teach complex skills, complex and demanding tasks should be broken down into simpler and more achievable tasks [72]. While simple tasks can be trained by increasing their difficulty in more demanding task settings, complex tasks need to be trained by bringing together previously learned simpler ones, providing a balance of challenge and engagement [89].

28.1.3.4 Narrative Structure

Flat and static training tasks can be monotonous and eventually limit the patient's engagement. Malone and Lepper [81] identified curiosity as one of the principal drivers of user engagement in serious games, being it either interest evoked by novel sensations or the desire for knowledge. Narrative elements can be exploited to build an interesting dramatic arc around the training task to increase the engagement of patients, to facilitate the comprehension of the training objectives, and, most importantly, to deliver a clear sense of progress. Multiple elements can be used to shape a narrative curve, such as, story events, task difficulty, novel environments, new challenges, or skills. VEs designed to realistically simulate activities, such as navigating a virtual city or shopping in a virtual supermarket, generally provide richer narratives than tasks with simpler cognitive demands [50, 90, 91].

28.1.4 Summary

Motor learning and motivation theories have informed the development of virtual environments and serious games (Table 28.1). Recommendations for the use of augmented feedback or rewards, specifically knowledge of results, are consistently found in the VR literature; yet there are few studies to empirically support its use. Rather the assumption has been made that augmented feedback principles apply in real-world practice and should therefore inform VR design. In contrast, there is modest evidence that VEs promote a high degree of repetition, and video games deliver doses that are higher than standard exercises. Motor learning principles dominated the VR landscape, and, more recently, the motivation literature has contributed design principles to guide the appropriate challenge as well as increase the narrative of the game. The assumption that motor learning and motivation are essential for the efficacy of virtual rehabilitation is still an open question.

28.2 The Role of Multisensory Stimuli and Interfaces

VR can be used to present rich complex multisensory information and can elicit a substantial feeling of user presence in the VE as well as a perceived ability to interact with the VE directly [3]. Hence, the way sensory stimulation is provided and how interaction is facilitated through

Table 28.1 Table summarizing some of the key features and their evidence for the design of effective VR systems for motor rehabilitation

		Evidence	References
Motor learning	Enriched environments	Promote activity levels	[37]
	Intrinsic and extrinsic feedback	Knowledge of performance and knowledge of results facilitate skill learning	[38, 41]
		Knowledge of results has been associated with rapid, effective motor learning	[79]
	Task specificity	Virtual tasks emulating ADLs can be used to assess upper limb motor function	[51]
		May be beneficial but not necessary in VR	[45, 55, 57]
	Dosing	The number of repetitions in VR is comparable to animal studies that induced plasticity	[28]
		Purposeful movements in VR are performed faster and with higher frequency	[62]
	Adaptability	VR systems with calibration and/or personalization capabilities are more effective than conventional therapy	[66–68]
Motivation	Goal setting	An appropriate balance of short, medium, and long-term goals has a motivating effect	[72]
		VEs integrating cognitive and motor domains are better suited to pose goals at multiple time scales	[50, 74, 75]
	Rewards	Actions should be rewarded with positive visual and auditory feedback, scores, and specific knowledge of performance and knowledge of results	[76, 77]
	Challenge	Task difficulty and time available to complete them should calibrated to control challenge	[86]
		Complex and demanding tasks should be broken down into simpler and more achievable tasks	[72]
	Narrative	Curiosity is one of the principal drivers of user engagement in serious games	[81]
		VEs designed to realistically simulate activities generally provide richer narratives than motor-only tasks	[50, 90, 91]

interfaces determine the level of immersion. Visual, auditory, and haptic stimuli all contribute important elements to promote user interactivity, while interfaces are required to deliver and augment sensory information. Presence is consequently influenced not only by the stimulation and the interaction mechanisms (and their verisimilitude) but also by the characteristics of the VE.

28.2.1 Visual Presentation

VR systems are frequently classified by the visual presentations they provide to a user and the presence or absence of somatosensory feedback. Visual stimuli are generally grouped by their degree of immersion. Two-dimensional presentations delivered on flat screens are generally considered non-immersive. Three-dimensional presentations utilizing stereoscopic projections or flicker glasses with fixed visual perspectives are considered semi-immersive. Fully immersive systems provide three-dimensional visual information, and perspective is updated with head movements. Full immersion is provided via head-mounted devices or within cave-type environments.

A steadily growing literature has examined the impact of visual presentation on movement kinematics of persons performing reaching movements. Measurable differences in end point and angular measures of upper extremity movement have been noted when comparing two-dimensional simulated movements and comparable real-world activities [93, 94]. Similar differences have been identified in the upper limb when comparing three-dimensional simulated and real-world activities [95–97] as well as differences between two-dimensional and three-dimensional simulated reaching activities [98]. While there are measurable differences in the movements elicited by comparable activities presented in virtual and veridical worlds, multiple authors describing the training of upper extremity reaching and functional activities by persons with stroke in VEs have shown that comparable real-world improvements in motor abilities can be elicited through repetitive practice in a variety of VEs. Most importantly, upper limb studies show that these improvements are comparable to or better than those elicited by real-world training [31, 33, 99].

28.2.2 Point of View

Most immersive and semi-immersive systems, and even some non-immersive systems, present first-person points of view of the workspace during virtual rehabilitation activities. These presentations typically include virtual representations of the participant's limbs or a landscape in which the person might be navigating or acting. However, VR also offers the opportunity to provide users a perspective on movement they may not ordinarily have. For example, video capture-type VR systems present mirror images of the patient as they interact with a VE. These types of augmented reality systems designed for rehabilitation frequently incorporate the ability for the subject to view an image of their own limbs interacting with a VE. One of the reported strengths of this point of view is the high-fidelity feedback regarding patient's posture [100]. This approach presents higher-quality information related to limb movement and reduces the need for the brain to rectify differences in somatosensory and visual information associated with the other approaches to VR. One study describes a superior motor performance on a task using an augmented reality system providing a first-person view of the task with the participants' own arms interacting with the VE when compared to a two-dimensional system requiring incongruent motor actions—horizontal forward reaching to elicit vertical movement—in the VE [101]. Walking simulations have used both the first- [54] and third-person perspectives [42, 58]. Little research regarding comparing the impact of point of view on treatment outcomes has been published to date.

28.2.3 Auditory Stimuli

Auditory information is a key sensory component of most VEs and has broad impact on the participant's experience. It is used to enhance

immersion in the VE by providing sounds consistent with an activity (i.e., automobile-related sounds for a driving game or the sound of liquid hitting a surface during a pouring activity) [78]. Spatial sound rendering can also be used to increase the realism of a VE and aid user navigation within a VE (i.e., volume increasing as the virtual representation of the participant approaches the source of a sound in the VE) [78]. The addition of music and specific attributes such as rhythm and cadence has been shown to have a direct impact on the motor performance of healthy and disabled participants [102], particularly when continuous tasks such as gait are simulated [103]. Friedman et al. also found that the addition of music enhanced hand motor performance as well as motivation in the training of hand functional movements [104].

28.2.4 Haptic, Tactile Stimuli and Their Interfaces

Simple or robotic haptic interfaces have allowed for the addition of tactile information and interaction forces into what was previously an essentially visual and auditory experience. Devices of varying complexity are interfaced with more traditional VE presentations to provide haptic feedback that enriches the sensory experience, add physical task parameters, and provide forces that produce biomechanical and neuromuscular interactions with the VE that approximate real-world movement more accurately than visual-only VEs. Simple haptic feedback has been utilized to add the perception of contact to skills like kicking a soccer ball or striking a piano key [105, 106] (Fig. 28.2). Collisions with virtual world obstacles can be used to teach normal movement trajectories such as to place an object on a shelf or the action required to step over a curb [58, 67, 107] (Fig. 28.3). Haptic forces can also be synchronized with visual feedback to improve a users' sense of agency in the virtual world. In two small studies involving healthy subjects, this feedback combination was found to be more effective for skill learning than visual-only

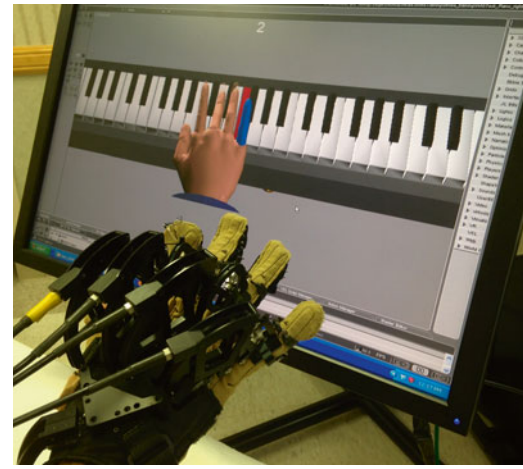

Fig. 28.2 The NJIT-TrackGlove system utilizes a 6-degree-of-freedom magnetic tracker, the TrakStar (Ascension Technology Corporation, USA) and a 22-DOF Cyberglove (Cyberglove Systems, USA). The simulation pictured also utilizes the Cybergrasp, a cable-actuated robotic exoskeleton. In the pictured simulation, the Virtual Piano Trainer, the magnetic tracker allows the participant to position their hand over the virtual keyboard and the Cyberglove allows them to strike keys with a specific finger. The Cybergrasp can be programmed to provide haptically rendered collisions when keys are pressed or assistance in maintaining extension of non-cued fingers for more impaired subjects [106]

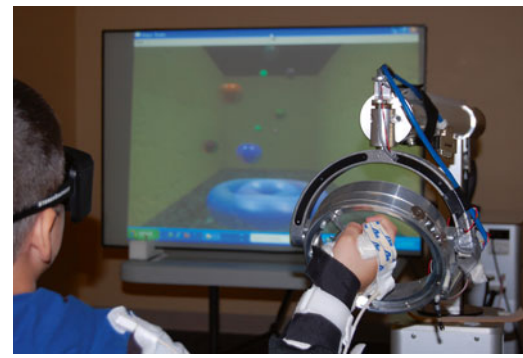

Fig. 28.3 The NJIT-RAVR system utilizes a 3-degree-of-freedom robotic (DOF) interface, the Haptic Master (Moog, The Netherlands), three additional passive DOF via a ring gimbal and a 22-DOF Cyberglove (Cyberglove Systems, USA). The Haptic Master is used to provide haptic rendering of virtual workspaces and adds global forces such as gravity to the virtual environments. The ring gimbal allows for normal positioning of the hand during simulated tasks, and the Cyberglove collects data related to finger position. These interfaces are integrated with a suite of complex, virtually simulated tasks to allow for task-based sensorimotor training for persons with upper extremity hemiparesis [67]

feedback in healthy subjects [108, 109]. Simulations that aim to shape the behavior of the upper limb have successfully combined haptic feedback with KP to improve upper limb trajectories as poststroke individuals placed virtual cups on a cupboard [92]. Participants placed their limbs in the haptic master, which augmented the intrinsic feedback with proprioceptive cues, and the simulation provided information on the trajectory. The coupling of the feedback smoothed out the movement trajectories. Further, haptics has been also used to simulate the interaction forces produced by tools in VEs [3], which increase the sense of immersion and activate neural networks involved with tool manipulation [110]. In a lower extremity application, the addition of haptics improved the accuracy of the limb movement in the VE [28].

28.2.5 Brain-Computer Interfaces

The combination of brain-computer interfaces (BCIs) and VR for stroke rehabilitation is increasing in popularity and acceptance [111, 112] (Fig. 28.4). BCIs are systems that detect changes in brain signals and translate them into control commands [114]. Such systems exploit the relationships between users' mental state and corresponding electrophysiological signals. In noninvasive BCIs, electroencephalography is commonly used for measuring brain activity. BCI technology has been used to support mental practice of motor actions [113]. Motor imagery (MI), the mental practice of motor actions, has been the basis of most BCI approaches to stroke rehabilitation, with a focus on hand and arm training and always relying—at least—on visual feedback [see [111] for review]. Recent findings of an RCT corroborate that the benefits of MI-based poststroke rehabilitation are boosted when trained in the context of a BCI paradigm that provides online visual feedback by means of a VR presentation of the patient's hands [49].

28.2.6 Summary

Research into the impact of visual, auditory, and tactile information on virtual rehabilitation activity has started to establish a tentative set of best practices for virtual rehabilitation in terms of the user experience to varying degrees (Table 28.2). The impact of auditory feedback

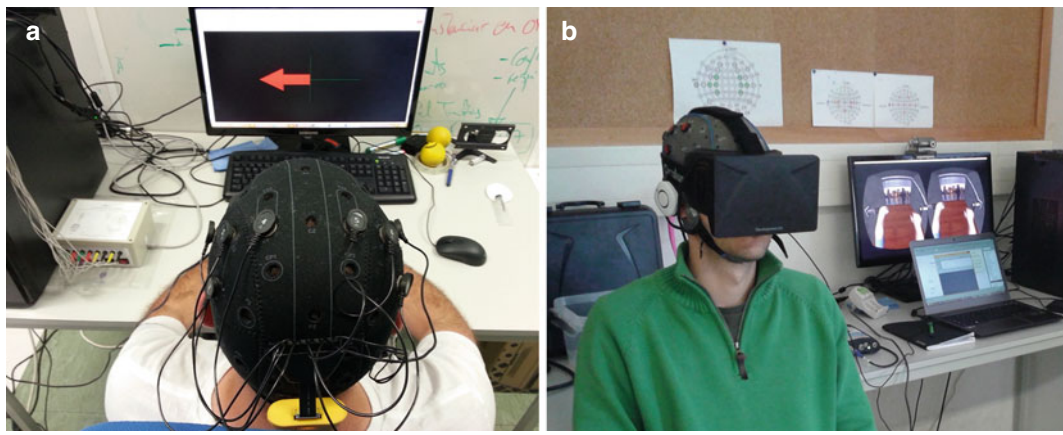

Fig. 28.4 The RehabNet system interfaces a large number of BCI technologies (g.mobiLab, Enobio, OpenBCI, EPOC, NeuroSky) and tracking devices (Kinect v1 and v2, Leap Motion, Wii controllers, android phones) with VEs to deliver immersive VR experiences. The RehabNet system is flexible and can work in multiple configurations: (**a**) MI-BCI neurofeedback training using standard Graz visualization feedback with an eight-channel Enobio acquisition system (Neuroelectrics, Spain); (**b**) MI-BCI VR training with the virtual representation of the upper limbs in a goal-oriented task presented through a head-mounted display and an eight-channel g.mobiLab acquisition system (g.tec, Austria) [113]

Table 28.2 Table summarizing key evidence on the role of multisensory information for poststroke rehabilitation

		Evidence	References
Visual information	2D and 3D simulations	Exist differences in end point and angular measures with real-world activities	2D: [93, 94] 3D: [95–97]
		Improvements are comparable to real-world training	[31, 33, 99]
	Video capture	Provides high-fidelity feedback on patient's posture	[100]
	First-person view	Superior task performance	[101]
		Boosts the effects of motor imagery training supported with online BCI feedback	[49]
Auditory information	Spatial sound	Increases realism and aids navigation	[78]
	Music	Rhythm has a direct impact in performance of motor tasks	[102–104]
Haptic and tactile information	Collisions	Can be used to teach normal movement trajectories	[58, 67, 107]
	Haptic guidance	Is more effective for skill learning than visual information only	[108, 109]
		Augments intrinsic feedback with knowledge of performance	[92]
		Improves accuracy of movements	[28]
	Interaction forces with tools	Increase immersion and brain activation	[110]

on virtual rehabilitation is at an early stage of development but preliminary work supports the additive effects of rhythm and auditory rendering to the overall effectiveness of virtual activity. There is a larger body of evidence supporting that the visual stimulus has a direct, predictable impact on the motor output elicited during simulated activities. However, there is no evidence supporting the notion that higher-fidelity visual presentations during virtual rehabilitation translate into larger improvements in the ability of persons with disability to function in the real world. This mismatch between user experience and effectiveness needs to be considered, because higher-fidelity, fully immersive visual presentations currently require more expensive equipment and more challenging programming to produce. A similar dichotomy exists between VR simulations interfaced with robots to provide tactile feedback and add global forces. Research supports that motor skill learning within the VE is more efficient with these additions. However this benefit comes at the cost of greater complexity and expense for these integrated systems. These two factors are frequently cited as reasons for the slow adoption of integrated VR-robotic systems into routine clinical practice.

28.3 Neuroscience of Virtual Reality

Knowledge of the neural processes occurring after the central nervous system damage as well as the nervous system's response to activity is necessary to understand the impact of virtual rehabilitation on neural recovery. True recovery is based on behavioral change associated with brain plasticity or neuroplastic changes. After stroke, it is known that perilesional and contralesional brain networks become more excitable, facilitating their reorganization [64, 115]. Research has shown that the recruitment of contralateral or ipsilateral networks largely depends on the integrity of the remaining cortical, subcortical, and corticospinal tracts [116]. As recovery progresses, brain activation patterns of stroke patients become more similar with those of healthy individuals [117, 118], showing that restoration to normal activity patterns correlates with restoration of motor function.

28.3.1 Brain Plasticity

VR is a particularly interesting research field as it allows creating computer-generated environments

that provide customized experiences involving different sensory channels. The motivation of using VR in sensorimotor rehabilitation after a brain lesion is the administration of specific experiences that drive cortical reorganization to support the reacquisition of motor skills. Consequently, neural plasticity is commonly used as an efficacy measure of VR training. Neurophysiological adaptations to training in virtual and real-world environments by people with stroke have been shown to rely on similar neural reorganization processes [3]. To date four studies have used functional magnetic resonance imaging (fMRI) to describe neuroplastic responses to virtually simulated rehabilitation programs in persons with stroke. Two early studies were done by You and Jang et al. on locomotor and upper extremity interventions, respectively [57, 119]. Subjects in both studies demonstrated decreased activation of the non-lesioned primary motor cortex and increased activation of the lesioned cortex following intervention. Newer studies by Saleh et al. and Orihuela et al. described more complex and less consistent responses. Both described changes in connectivity between lesioned and non-lesioned hemispheres with some subjects demonstrating decreases in lesioned hemispheric activation and other demonstrating increases [120, 121]. Despite inconsistent findings, subjects in all four of these studies demonstrated changes in neural activation subsequent to training and positive improvements in motor function.

28.3.2 Visuomotor Representations

It is known that cortical areas involved in the preparation and execution of motor actions undergo plastic changes [122] either due to repeated sessions of proprioceptive stimulation through passive physical training [123] or as a result of task-oriented physical training [124]. Motor deficits do not only arise from the directly damaged tracts by stroke but the networks they disrupt. Hence, its recovery also depends on the intra- and interhemispheric interactions among motor regions [125]. For instance, bilateral recruitment of motor networks can result from unilateral motor movements in hemiparetic stroke patients [125, 126]. Motor training through VE interaction may involve different elements such as object-oriented action planning, action observation, and feedback of the performed action. Unfortunately, there are no standardized protocols for VR motor rehabilitation after stroke, and different interventions have produced distinct effects in both neural reorganization and motor recovery [see [33] for review]. To deliver an optimal rehabilitation process, it becomes essential to identify and understand the neural systems and cerebral processes engaged during motor training mediated by VR.

One of these candidate systems is the human mirror neuron system (MNS), which is primarily composed of neurons located in the inferior parietal lobe, the ventral premotor cortex, and the caudal part of the inferior frontal gyrus [127]. These are candidate areas for sensory control of action, movement imagery, and imitation [127, 128]. The MNS is of great relevance because it has been shown to be active during performance of goal-directed actions, their passive observation and their mental simulation [129]. The MNS has been hypothesized to be involved in action understanding and imitation [130], and, as such, it may represent an important neurophysiological substrate for regaining impaired motor function after stroke [131, 132]. Recently, it was suggested that the mere observation of goal-oriented motor actions can be used as a driver [133], and findings corroborate that the use of passive observation of goal-oriented actions can have a positive effect in motor recovery after stroke [134, 135].

From these findings, it is clear that the manipulation of the visual feedback for motor rehabilitation purposes can be an effective ingredient of VR systems. Maeda et al. [136] showed that movement observation can directly enhance and facilitate the motor outcome of the muscles involved in the observed action. In addition, the MNS has been shown to respond to biological as well as robotic effectors [137] and to the manipulation of tools in the real world [138] and VR [139]. Consequently, there is strong evidence

supporting that VE interaction can be effective in engaging primary and secondary motor areas for upper extremities [140], locomotion [57], as well as the mirror mechanisms [139, 141].

Consistent with the above findings, the activation of the human MNS has been also documented during the imagination of motor actions [132, 141]. As discussed in Sect. 28.2.5, MI-based BCIs rely on the detection of sensorimotor rhythms, an oscillatory rhythm of synchronized neural brain activity in the alpha and lower beta frequency bands that is measured in sensorimotor brain areas. It has been shown that sensorimotor rhythms can be enhanced by means of BCI training and that they correlate with motor recovery [49]. Restorative BCIs relying on MI aim at mobilizing neuroplastic changes of the brain in order to achieve reorganization of motor networks and enhance motor recovery [142, 143]. In addition, imaging studies have shown that the combination of first-person observation VR and motor imagery is more effective at recruiting more task-related networks than other conditions for both lower limb [144] and upper limb [145] movements.

The ability to distort visual feedback is an area of inquiry that has been investigated as a possible method to optimize motor adaptations to VR-based rehabilitation activities as well. Preliminary investigations into the visual "augmentation" of small errors during virtual rehabilitation activities performed by persons with stroke have suggested that this approach might enhance motor training outcomes in this population [146]. One possible mechanism for this effect might be an increased level of cortical activity necessary for the brain to rectify virtual movement amplitude that is not scaled to participant movement [147]. One distortion of visual feedback that has been associated with poor responses has been temporal lags between participant movement and corresponding movement within the VE. This may interfere with feedforward/feedback control of movement making delayed visual feedback confusing [148]. Recent findings of an RCT also suggest that the visual amplification of upper limb movements can be used to counteract the acquired nonuse of the hemiparetic limb in stroke patients [149].

28.3.3 Summary

After stroke, relearning of motor function is mediated by neuroplasticity. Evidence shows that VR can be a valid tool to drive motor networks, brain plasticity, and functional recovery (Table 28.3). Research has shown that after stroke, a window opens when networks become more excitable, and VR has revealed as an effective tool to engage visuomotor processes such as the ones related to action execution, observation, understanding, and mental simulation. In fact, the manipulation of visual representations has been shown to engage motor networks during passive observation and mental simulation and facilitate the movement of muscles. Thus, the manipulation of these processes through VR not only can enhance neural activation but improve motor outcomes as well.

28.4 Evidence Base: Impact of VR

28.4.1 Upper Extremities

28.4.1.1 Custom Systems

A large majority of the research examining the effectiveness of simulated rehabilitation activities done prior to 2010 utilized custom developed systems of sensors and software designed specifically for rehabilitation and were not commercially available. These systems frequently utilized powerful computers that provided substantial flexibility. This flexibility allowed researchers to engineer and reengineer VEs to answer research questions and test hypotheses based on observation of subjects interacting with the systems and emerging knowledge from the fields of neuroscience and motor control. Studies examining custom-designed VR-based interventions targeting the upper extremity of persons with stroke make up the largest and most mature evidence base related to virtual rehabilitation. Several reviews of early pilots and controlled trials describe the ability of VR-based interventions to elicit measurable activity level improvements, comparable to those of traditionally presented training, mostly in persons with chronic upper

Table 28.3 Table summarizing evidence supporting the use of VR to drive neural processes involved in motor recovery

	Evidence	References
Brain plasticity	After stroke perilesional and contralesional networks become more excitable	[64, 115]
	Restoration of motor function parallels restoration of normal brain activity patterns	[117, 118]
	Training adaptations to VR and real-world training rely on similar reorganization processes	[3]
	fMRI studies demonstrate changes in neural activation and improved motor function in response to VR training	[57, 119–121]
Visuomotor representations	Bilateral recruitment of motor networks can result from unimanual motor actions	[125, 126]
	MNS is active during motor action execution, motor observation, and mental simulation of motor actions	[129, 132, 141]
	MNS could be involved in action understanding and imitation	[130]
	MNS responds to biological VR, tools, and robotic effectors	[137–139]
	Movement observation facilitates movement of the muscles involved in the observed action	[136]
	Passive observation of motor actions has a positive effect in motor recovery after stroke	[134, 135]
	Motor imagery BCI training enhances motor recovery	[49, 142, 143]
	First-person VR combined with motor imagery is more effective at recruiting task-related networks	[144, 145]
	Visual amplification of movements and/or errors in VR might enhance motor training outcomes	[146, 149]

extremity hemiparesis due to stroke [3, 31, 150, 151]. More recently, a Cochrane review by Laver et al. considered the impact of a set of twelve protocols of simulated rehabilitation activities used in RCT on upper extremity function and activity [33]. The studies all had control groups employing a traditionally presented rehabilitation intervention. The sample size across these twelve studies was 397 persons with stroke. A small significant effect favoring VR-based intervention over traditionally presented interventions for the improvement of upper extremity function and activity performance ability was identified. When pooled, studies with VR interventions totaling more than 15 h of training and studies with subjects in the acute and subacute stages of recovery demonstrated significant improvements in upper extremity function. Studies with less than 15 h of intervention and studies with subjects in the chronic stage did not. The balance of this discussion will focus on evidence examining the impact of the effectors trained, interfaces utilized, and the severity of the impairment of participants. In addition some key studies that were not included in these meta-analyses for methodological reasons and papers published following the Cochrane review by Laver will be discussed.

A large majority of the evidence examining simulated interventions for the upper extremity of persons with stroke focuses on gross movements of the upper extremity. Evidence supporting the efficacy of VR-based interventions targeting the fingers and hand has developed more slowly, but a similar pattern of activity level improvement that is comparable to real-world training is emerging [152–154]. VR-based integrated training of the hand and arm is a newer area of study with a smaller body of evidence that tentatively supports a similar level of efficacy [155, 156].

A wide variety of interfaces have been utilized to translate participant movement from the veridical environment into the VE. A majority of the most recent studies of custom systems have utilized camera-based interfaces [52, 157–159] or systems with robotic interfaces [152, 153]. The

only study comparing the relative effectiveness of these two approaches did not identify a substantial difference in outcomes [160]. As the options for utilizing robotic interfaces grow in number, it will be important to revisit this comparison because of the cost impact related to robotic technology.

The initial study of simulated rehabilitation of the upper extremity focused on persons in the chronic stage of impairment. The completion of the most intense period of spontaneous neural recovery in the subjects of these studies allowed for more clear determinations of the relative contribution of simulated rehabilitation activities to functional motor recovery. A trend toward the examination of intervention during the acute stage of rehabilitation began with a study by Cameirão et al. who described earlier recovery of the upper extremity of motor function in persons performing additional simulated training targeted at the upper extremity than persons performing traditionally presented training or nonspecific simulations. Subjects began this study in the first few weeks following their strokes [66]. VR and control group subjects demonstrated comparable levels of upper extremity motor performance at long-term follow-up. In contrast, a more recent and larger study by Turolla et al. detected improvements in upper extremity Fugl-Meyer Assessment (FMA) test scores as well as Functional Independence Measure scores that persisted at long-term follow-up [158]. The size of the study by Turolla et al. allowed for the examination of subjects' adaptation to VR-based and real-world training and controlled for severity of impairment. Interestingly, moderately and severely impaired subjects made larger magnitude improvements from the same intervention than mildly impaired subjects. Intervention studies of more impaired subjects should be an area of focus for ongoing studies of VR-based intervention utilizing custom systems.

So far, the combination of BCIs and VEs has gained popularity and has been proven useful to train functional upper extremity movements, with a focus on the hand, upper limb, and limited work in ankle MI training [see [111] for review]. Unfortunately, the use of this approach in clinical environment is limited and hardly used outside laboratory environments. Most of the BCI studies involved a limited number of patients (<10) with few notable exceptions [161, 162], and only few RCT trials exist. Ang et al. and Varkuti et al. performed RCTs combining an EEG-based BCI-MI task with visual feedback and a robotic device [163–165]. Group sizes of these trials were small and dissimilar (from 2 to 14 patients) and results were inconclusive. Most studies found clinical improvements as assessed by the FMA after BCI-MI training, but no differences with the control condition. A recent RCT involving 28 stroke survivors compared the effect of BCI VR feedback on hand MI training as compared to MI alone. The BCI group showed changes in EEG modulation during MI, which correlated with significant clinical improvements in FMA [49]. These findings are consistent with research indicating that BCI-triggered changes in functional connectivity in stroke population correlate with clinical improvements [165]. Despite the lack of large RCTs and the discrepancy between interfaces used, the specifics of BCI-MI paradigms, and setups, findings are encouraging and suggest that the combination of VR with a BCI-MI paradigm can be effective in producing changes in brain activation patterns that correlate with gains in motor function.

28.4.1.2 Off-the-Shelf Systems

As with many other fields, consumer communications and entertainment technology have spurred disruptive development in the field of virtual rehabilitation. The Sony® EyeToy®, a camera-based motion capture systems designed to be compatible with the PlayStation™ two-entertainment system, was initially released in 2003. A majority of the initial studies examining rehabilitation applications of this system involved balance activities or gross reaching movements [166]. In an RCT by Yavuzer et al., subjects performing an EyeToy®-based intervention made better improvements in upper extremity function than a group of subjects performing a conventional training program [167]. Two subsequent systems have been released more broadly and have had more substantial impact on the field of

rehabilitation, the Wii™ manufactured by Nintendo® and the Kinect™ manufactured by Microsoft®.

The Nintendo® Wii™, which features two accelerometer-based controllers in addition to infrared motion capture capabilities, initially became available in 2006. In 2012, the Wii™ fit game became available. This game was bundled with the Wii™ Balance Board, a force sensor that interfaces with the Wii™ console. These systems have been widely adopted in rehabilitation facilities and nursing homes without modification as a recreation and rehabilitation modality [168]. Several studies of upper extremity rehabilitation have utilized the Wii™ system in patients with stroke. Subjects in several pilot studies of persons with stroke using the Wii™ have demonstrated statistically significant improvements in motor function and activity level clinical tests [169–171]. In spite of the fact that the Wii™ interface does not collect individual finger movement or grip force data, subjects in another pilot study demonstrated fine motor improvements in persons with stroke following a Wii™-based intervention [172]. Two controlled studies comparing Wii™-based upper extremity interventions and a dose matched traditionally presented upper extremity intervention demonstrated statistically significant improvements at the function and activity levels. Improvements demonstrated by the two groups in both studies did not differ [168, 173]. The Wii™ training group in a third controlled trial made larger improvements on the upper extremity FMA and Box and Blocks test than a dose-matched traditional training group [174]. The Cochrane review by Laver et al. in 2015 identified only 1 RCT utilizing an off-the-shelf gaming system [173] compared to six RCTs with upper extremity simulated interventions using custom VR systems in persons with stroke that were methodologically suitable for comparison. Both groups of studies demonstrated significant effects but further research is needed to determine impact differences between the two approaches [33].

The Microsoft® Kinect™, a peripheral for the Xbox series that detects user's movements through a depth-sensing camera, was released to interface with the Xbox 360 in 2010. A substantial body of research related to the validity of measurements of human movement with the Kinect™ has been developed [see [175] for a detailed review]. However, few studies of the clinical effectiveness of Kinect™-based rehabilitation programs for persons with upper extremity impairments have been published to date. A case/feasibility study with a severely impaired subject demonstrated increased upper extremity active range of motion, but no improvements in upper extremity FMA score after a 10-session training program [176]. This subject was severely impaired which may underestimate the potential of this intervention for less impaired subjects. A case series of five subjects with moderate impairments demonstrated improvements in upper extremity FMA and Wolf Motor Function Test (WMFT) scores that corresponded to increases in cortical activation of the lesioned hemisphere [177]. The changes in clinical test scores and cortical activation demonstrated by subjects in this case series were comparable to those demonstrated by subjects in studies of custom VR systems [120]. Two studies have examined the addition of Kinect™-based upper extremity rehabilitation activities to a program of traditionally presented therapy [53, 178]. Control groups for both of these studies performed the same volume of traditionally presented therapy as the experimental group. As would be expected, the subjects performing the additional Kinect™-based therapy demonstrated larger changes in active range of motion, ADL ability, and larger improvements in upper extremity FMA, WMFT, and Motor Activity Log (MAL) tests. More rigorous testing of Kinect™-based rehabilitation activities will be necessary to evaluate their value relative to custom VR or traditionally presented therapy.

28.4.2 Balance and Gait

28.4.2.1 Custom Systems

Historically, the development and application of VR systems for neurorehabilitation focused on the upper limbs. This may have been motivated by two main factors. First, relative to upper limb

use, balance and walking skills are more commonly and extensively recovered after a stroke. Second, building balance and walking VR-based systems require greater technical and space requirements to meet the special physical and safety challenges. In contrast to most upper limb systems, which allow patients to be seated while performing movements with the upper extremities, balance and walking skills, for the most part, require patients to be upright or to walk. There exists a modest body of work on the development and use of customized VEs for walking recovery and balance, which is reported in several topic specific reviews [179–181] as well as in overview reviews [31, 33]. In contrast to the 397 participants who participated in the upper extremity studies included in Laver's Cochrane Review of Stroke Rehabilitation, there were only 58 persons involved in balance and mobility training, with only 30 participants in the three studies where gait speed was measured [33]. In the three studies represented in the Cochrane review, participants either stepped over virtual objects and landscapes (displayed on an HMD or a screen) while walking on a treadmill [54, 58] or used their affected lower extremities to navigate a plane in a skyscape [42]. Balance was not a primary outcome measure assessed in the Cochrane review, but has been an area of study in VE.

Visual feedback is a common element in evidence-based interventions for balance training post stroke [182]. It is used to provide participants information about the verticality of their posture, which may be impaired due to sensory and perceptual deficits, as well as their weight distribution. Both of these attributes are incorporated into VEs for balance rehabilitation. The GestureTek® IREX® video capture system based on chroma key technology was first used in studies involving individuals who had sustained a TBI, where slight improvements were detected in balance [183, 184], confidence [185], and reaction time [184], compared to conventional training protocols. The system has also been used with persons post stroke, providing benefits to the sensory organization, motor function, and balance. In general, training with the system provided benefits that were detected in scales related to balance but not to gait.

Force platforms have been used to estimate and visualize participants' center of pressure providing visual feedback during displacements toward the targets [182]. The use of force platforms in combination with customized virtual exercises has also been explored. The training of the ankle and hip strategies during weight-shifting exercises adapted to the particular limits of stability of each subject provided benefits to conventional physical therapy interventions in the general balance condition and in the maximum reachable distance [186] (Fig. 28.5). Interestingly, these effects were retained at follow-up after the intervention [187]. Similar to balance platforms, standing frames equipped with gyroscopes can detect postural tilts, enabling interaction with the VE through weight transferences. These systems have been used in home-based interventions with individuals post stroke, reporting improvements in balance and gait [188, 189]. However, the use of VR did not provide significant benefits to the training with the standing frame alone.

Walking on a treadmill interfaced with VE has been used to promote recovery of walking for persons post stroke. The inclusion of visual and vibrotactile augmentation while stepping over virtual objects during walking on a treadmill improved walking better than stepping over real-world objects [58]. Several studies have reported the combined use of treadmills and VR and its effects on the gait of stroke survivors. Users commonly walk in the treadmill while the VE is displayed by projectors [54, 190, 191] or TV screens [192, 193], showing real-world video recording [190] or virtual scenarios [191–193], where subjects are required to avoid obstacles while walking. The use of feedback provided by VR not only favored gait [54, 190] but also static balance, sit-to-stand movements, and the use of the paretic limb [190, 192].

In addition to treadmill walking simulations, several investigators have used stepping, pre-gait activities and even training of the lower extremity in sitting to improve walking

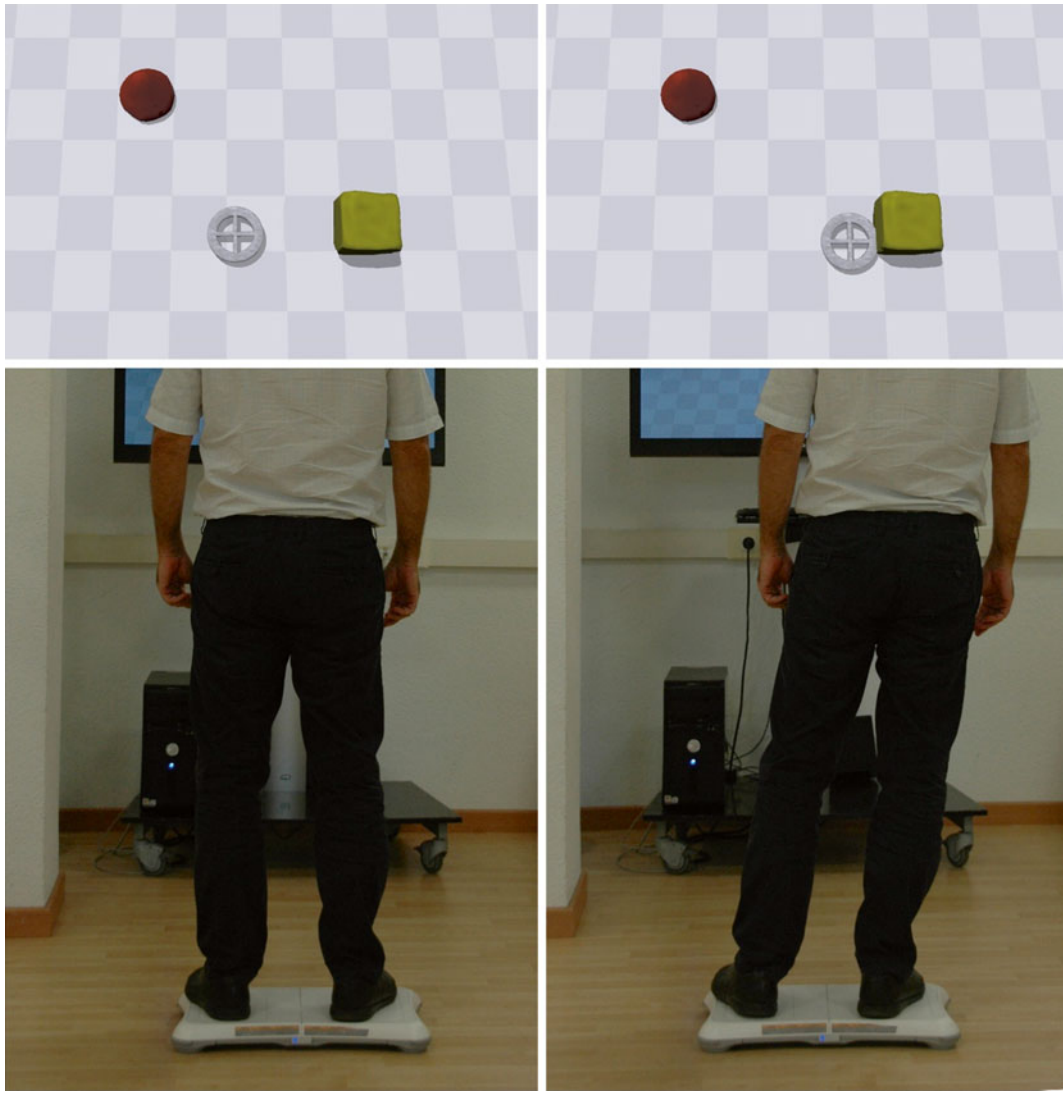

Fig. 28.5 In the system by Llorens et al., after registering their maximum excursion in the mediolateral and anterior-posterior plane, exercises are adapted to each client's particular motor limitations [186]. Exercises require participants to perform postural adjustments involving the ankle and hip strategies to displace their center of pressure toward different targets

for persons in the chronic phase post stroke [42, 57, 194]. Llorens et al. reported that the training through virtual stepping exercises promoted improvement in balance when compared to conventional interventions [194] (Fig. 28.6). Individuals were required to step on items that appeared around a circle with the closest foot while maintaining the other foot inside the circle. This intervention also promoted improvements in gait speed, which could be derived from the training of movements similar to those used in the stance phase of the gait cycle. The system was also used in a home-based intervention with similar results to those obtained in in-clinic interventions [65]. Mirelman et al. coupled VR with a robot-based training of the lower extremity, where participants were required to perform movements with the ankle while sitting to navigate a plane or a boat through a VE. When compared to the

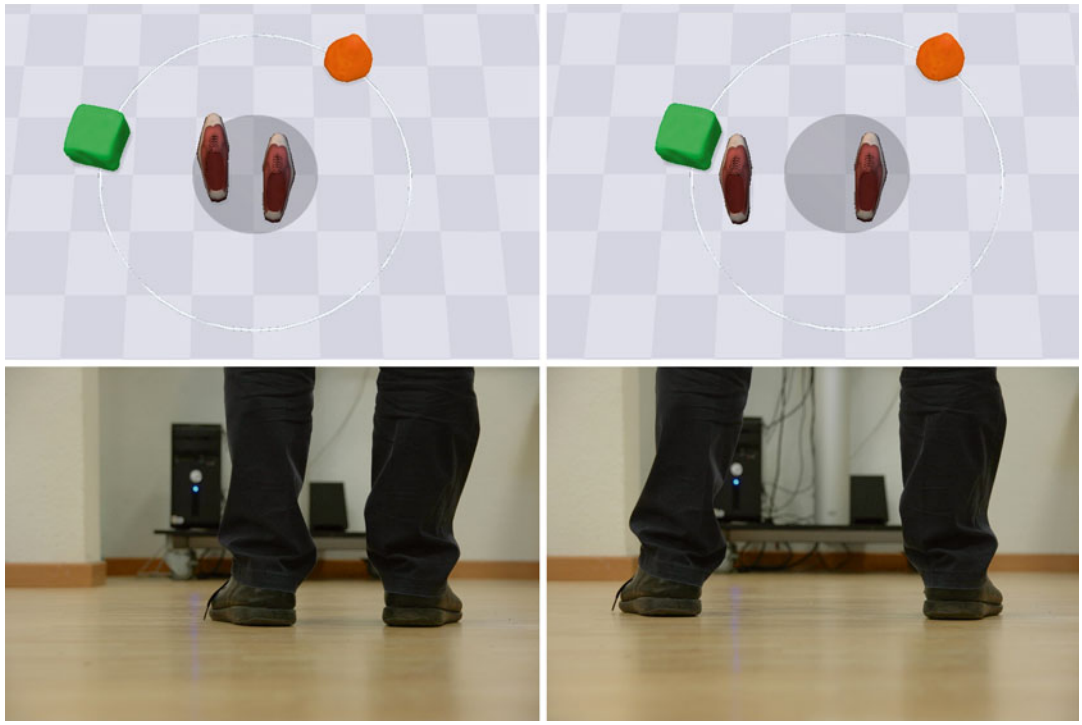

Fig. 28.6 In the system by Llorens et al., the virtual environment consisted of a checkered floor, whose center was indicated by a *darkened circle*, and jelly items that rose from the ground around the circle [194]. The goal of the exercise was to reach the items with the nearest feet while maintaining the supporting foot within the circle. After reaching the item, the extended extremity had to be recruited to the body within the boundaries of the circle. Otherwise the exercise did not allow new items to be reached

robot alone, the VR-robot combination was superior in improving walking velocity and distance in laboratory, clinical, and community-based tests [42]. You and colleagues used the IREX® system to promote functional ambulation and waking through the training of stepping movements, side-to-side weight shifting, and sideways navigation. Interestingly, the locomotor recovery was associated with cortical reorganization from aberrant ipsilateral to more normal contralateral activation of the sensorimotor cortex [57].

28.4.2.2 Off-the-Shelf Systems

The number of studies that employed off-the-shelf systems for balance and mobility training of people post stroke is slowly increasing. Early on there were several case reports of people in the chronic phase post stroke, which reported positive outcomes for balance and mobility interventions [195, 196]. More recently, eight pilot clinical trials using video games to improve balance and mobility have been reported. They have predominantly been conducted with subjects in the chronic phase post stroke [197–201], but there is now some support for application to persons in the subacute [202] and acute phases of recovery [203, 204].

The quality of the research is improving as more of the trials have active control groups and follow-up measurements [200–204]. However, comparing among studies is complicated based on substantial differences in dose and acuity. Several studies had unequal doses and did not use active controls [198, 199]. Studies conducted in the acute and subacute care setting using active controls showed a positive effect for balance and functional ambulation tests favoring the games [202, 204]. In contrast, studies with active controls and balanced doses of persons with chronic strokes favored

standard of care [201] or showed no difference for balance and mobility measures, but favored the VR group for enjoyment measures [200]. As with the upper limb studies, a better understanding about how acuity modifies the benefits of VE training will guide the future clinical application.

Off-the-shelf systems have used similar technologies as the customized VR systems. PlayStation® two EyeToy: Play™ is similar to the IREX® system [205] and was tested at home in a case study with an individual 2 years post stroke [195]. The training of postural adaptations during bilateral stance in subjects post stroke has been mainly facilitated by the Nintendo® Wii™ Balance Board, a force platform peripheral device for the Nintendo® Wii™, which allows interaction through displacements of the center of pressure, it is, through weight shifting [198–200, 202, 204]. Interestingly, some studies have analyzed the combination of static exercises using the Wii™ Balance Board with more dynamic exercises. Deutsch et al. compared standard of care with the Nintendo® Wii™ games and reported no between group differences, but a greater number of within group improvements for balance and mobility measures for the standard of care group [201]. Fritz et al. added EyeToy: Play™ games reporting small positive effects of this training in comparison with traditional therapy [197]. The combined training of weight transferences using the Wii™ Balance Board with dynamic balance exercises with the Microsoft® Kinect™ promoted improvement in the maximum reachable distance in acute subjects post stroke [203], but were equally effective as conventional physical therapy in maintaining physical function outcomes and ADLs in chronic population [206].

28.4.3 Activity Promotion

Movement-based VR systems have focused on sensorimotor rehabilitation, but there is an emerging application to fitness promotion in persons post stroke. Given the importance of physical activity [207] and the barriers to exercise encountered by people post stroke [208], VR is proposed as a facilitator of activity. A group has developed a VR-augmented cycling system that uses heart rate as an input to the VE [209] (Fig. 28.7). In a pilot study, participants post stroke who trained on the system had significant improvements in VO_2 sub-max bicycle test and mobility outcomes [210].

In addition to their use as movement reeducation tools, the off-the-shelf games that are designed to promote activity, also called exergames or active video games (AVGs), have been explored for people post stroke. The ability of persons post stroke to increase their exercise intensity using AVGs has been reported by two groups [211, 212]. Hurkmans et al. characterized two predominantly upper limb Nintendo® Wii™ games and reported that they produced moderate (three to five metabolic equivalents) exercise intensity [212]. Kafri and colleagues in a case-control series compared the energy expenditure and exercise intensity between individuals post stroke with moderate mobility limitations to semi-active healthy matched controls while playing both Kinect™ and Wii™ games in sitting and standing [211]. The games were categorized as a standing balance task to upper limb predominant (boxing) and lower limb predominant (running). Generally individuals post stroke had lower energy expenditure (at the low end of moderate) compared to the healthy controls (moderate to low end of vigorous), at similar exercise intensity. This range of intensity may be used for wellness rather than fitness. Games may be a valid tool for activity promotion, given their potential to increase motivation for exercise and to promote adherence. Future studies that use video games as a tool to improve wellness and fitness will better address these potential applications for stroke survivors.

28.4.4 Summary

A steady proliferation of studies comparing virtual rehabilitation interventions to traditionally presented rehabilitation in persons with stroke has developed over the past 15–20 years. A small

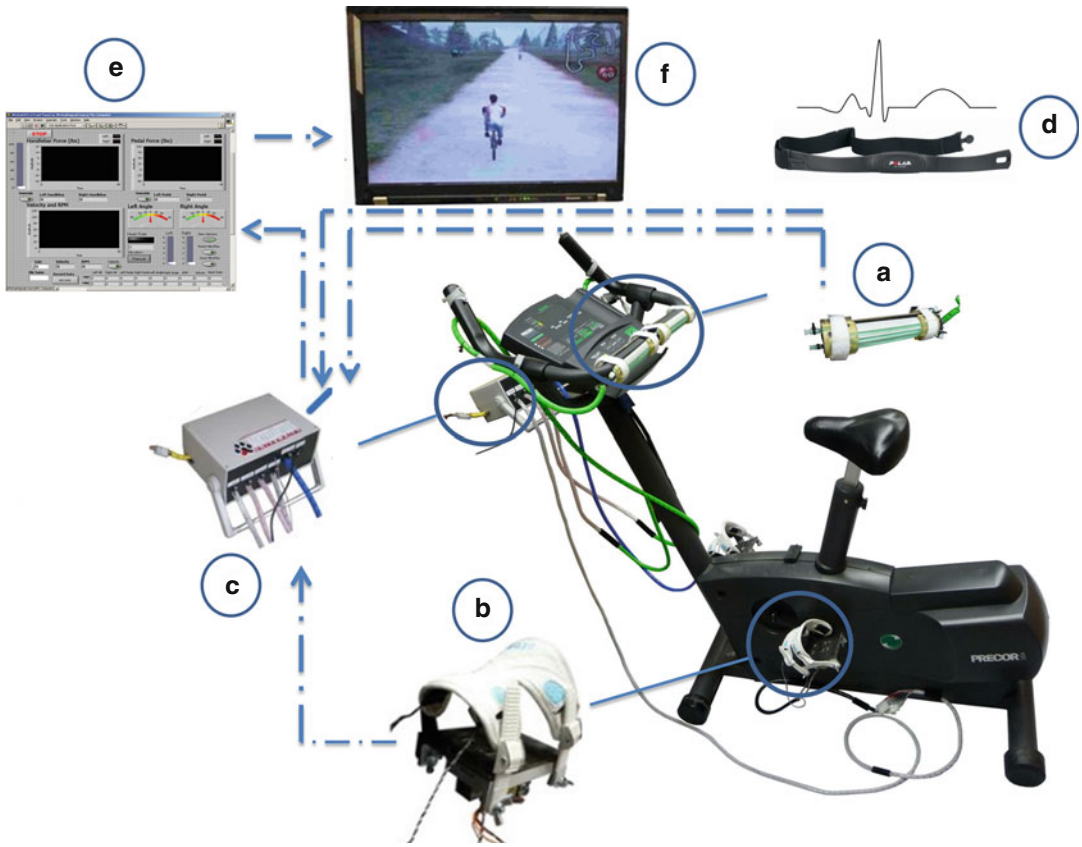

Fig. 28.7 VRACK system complete overview: (**a**) handlebar module; (**b**) smart pedal; (**c**) power supply, preamplifier, and the data acquisition board; (**d**) heart rate monitor, (**e**) practitioner interface; (**f**) virtual reality environment [209] (Reproduced with permission of the Rivers Lab)

group of studies have utilized off-the-shelf commercial gaming systems for the virtual rehabilitation intervention. As a group, comparable outcomes for off-the-shelf virtual interventions and traditionally presented interventions are reported. Similarly, comparable outcomes have been reported when comparing virtual and real-world upper extremity training in subjects with more acute strokes. The best developed area of this literature examines upper extremity interventions in subjects with chronic strokes using customized lab-based systems. These comparisons describe slightly better outcomes for virtual rehabilitation interventions. This advantage is more pronounced in mildly impaired subjects. More, larger, and better controlled studies are required to draw definitive conclusions along these two lines of inquiry.

A substantially smaller literature has examined the relative efficacy of a VR-based rehabilitation on walking ability (as measured by gait speed) in persons with stroke. A nonsignificant trend toward better outcomes for virtual reality-based training as compared to real-world gait training has been identified. The balance of studies comparing the impact of these two training approaches considers the kinetics and kinematics of gait. Neither approach to training has been associated with significant advantages across multiple studies. Similarly, balance interventions presented in virtual environments have been associated with comparable, but not significantly better outcomes than traditionally presented balance training across a wide range of balance measures. An expansion of the size and number of studies and a focus on a smaller set of

outcome measures will be necessary to identify an additive effect for virtual environments on gait and balance training if one exists.

Conclusions

A review of this chapter should leave the reader with the impression that (1) there is a science underpinning virtual rehabilitation and (2) the evidence base related to the efficacy of virtual rehabilitation has confirmed that it can be a viable and, for the upper limb, a superior alternative to traditionally presented activities. While these impressions are validating on one hand, they also identify a need for continued improvement. This said, trends also emerge, indicating opportunities for optimizing virtual rehabilitation and expanding the populations and areas in which it is practiced.

While there is consensus that neuroplasticity is central to the motor recovery process, there is a relatively small literature examining the impact of VR interventions on positive, neuroplastic adaptations in persons with neurologic injuries. Some pioneering investigations utilizing neuroimaging have been conducted. An expansion of this area of inquiry could optimize and accelerate both the design and implementation of VR-based rehabilitation interventions. However, the cost and need for large transdisciplinary teams to perform studies of this type have kept progress in this area slow.

There is also consensus that motor learning is central to the process of neuroplasticity, and VR-based rehabilitation interventions are typically constructed with attention paid to accepted principles of motor learning. Examinations of the motor learning accomplished by virtual interventions have predominantly focused on transfer of motor skills learned in VEs to veridical world motor skills and performance improvements achieved during virtual interventions to a lesser extent, both with favorable results. A broader implementation of formal motor learning paradigms to the study of virtual rehabilitation might offer a more efficient and cost-effective approach to the optimization of virtual rehabilitation. By their nature, interfaces designed for VE-based activities are well suited to collect the necessary data. In addition, simulated activities are easily presented in the systematic, reproducible fashion necessary for the study of within and between session learning.

Science related to motivation may, first, enhance the volume of motor practice performed independently by patients in their homes. Home practice is critical in areas with limited access to therapist due to availability or reimbursement issues, and compliance with home practice schedules is typically poor. Second, motivation science may enhance the frequency and duration of the performance of fitness-oriented activities in persons with disabilities. Motivation and access are primary obstacles to the regular performance of fitness activities with a wide variety of disabilities, both of which can be overcome with well-designed, simulated exercise programs.

Two important trends will be critical for shaping the future development of virtual reality. One key to the transition of virtual rehabilitation to the home environment has been the development of lower cost, but effective interfaces. The ability to customize the application of Kinect™ sensors should prove to accelerate this transition, allowing for the use of off-the-shelf equipment to access simulations designed specifically for rehabilitation. Affordable sensing technology will also have an important impact on broadening the rehabilitation opportunities available to a wide set of populations with divergent rehabilitation goal interests. Patients with rehabilitation goals on the opposite end of the movement ability spectrum could utilize arrays of wearable sensors to interface with complex, challenging environments (e.g., firefighting or city street crossing) that would not be possible in a veridical presentation due to safety or logistical reasons. Another future trend is the development of brain-computer interfaces, which rely on the recruitment of brain networks to transform an intention to move to virtual world movement for a person with profound

motor impairments that would not be able to move in another fashion.

Clearly, virtual rehabilitation is an expanding area in the field of technology-based rehabilitation and has an evidence base that is growing in terms of size and quality. Several challenges described above need to be addressed but the field continues to hold promise to answer key issues faced by modern healthcare.

References

1. Burdea GC, Coiffet P. Virtual reality technology. Presence. 2003;12(6):663–4.
2. Wilson PN, Foreman N, Stanton D. Virtual reality, disability and rehabilitation. Disabil Rehabil. 1997;19(6):213–20.
3. Adamovich SV, Fluet GG, Tunik E, Merians AS. Sensorimotor training in virtual reality: a review. Neurorehabilitation. 2009;25(1):29–44.
4. Slater M, Wilbur S. A framework for immersive virtual environments (FIVE): speculations on the role of presence in virtual environments. Presence. 1997;6(6):603–16.
5. Lee KM. Presence, explicated. Commun Theory. 2004;14(1):27–50.
6. Riva G. Is presence a technology issue? Some insights from cognitive sciences. Virtual Reality. 2009;13(3):159–69.
7. Baños RM, Botella C, Alcañiz M, Liaño V, Guerrero B, Rey B. Immersion and emotion: their impact on the sense of presence. Cyberpsychol Behav. 2004;7(6):734–41.
8. Llorens R, Noe E, Naranjo V, Borrego A, Latorre J, Alcaniz M. Tracking systems for virtual rehabilitation: objective performance vs. subjective experience. A practical scenario. Sensors. 2015;15(3):6586–606.
9. Stanney KM, Mourant RR, Kennedy RS. Human factors issues in virtual environments: a review of the literature. Presence. 1998;7(4):327–51.
10. Arzy S, Overney LS, Landis T, Blanke O. Neural mechanisms of embodiment: asomatognosia due to premotor cortex damage. Arch Neurol. 2006;63(7):1022–5.
11. Legrand D. The bodily self: the sensorimotor roots of pre-reflective self-consciousness. Phenom Cogn Sci. 2006;5(1):89–118.
12. Berlucchi G, Aglioti S. The body in the brain: neural bases of corporeal awareness. Trends Neurosci. 1997;20(12):560–4.
13. Schultze U. Embodiment and presence in virtual worlds: a review. J Inf Technol. 2010;25(4):434–49.
14. Longo MR, Schüür F, Kammers MPM, Tsakiris M, Haggard P. What is embodiment? A psychometric approach. Cognition. 2008;107(3):978–98.
15. Tsakiris M. My body in the brain: a neurocognitive model of body-ownership. Neuropsychologia. 2010;48(3):703–12.
16. Botvinick M, Cohen J. Rubber hands /'feel/' touch that eyes see. Nature. 1998;391(6669):756.
17. Petkova VI, Ehrsson HH. If I were you: perceptual illusion of body swapping. PLoS ONE. 2008;3(12), e3832.
18. Petkova VI, Khoshnevis M, Ehrsson HH. The perspective matters! Multisensory integration in egocentric reference frames determines full body ownership. Front Psychol. 2011;2:35.
19. Slater M, Perez-Marcos D, Ehrsson HH, Sanchez-Vives MV. Inducing illusory ownership of a virtual body. Front Neurosci. 2009;3(2):214–20.
20. Banakou D, Groten R, Slater M. Illusory ownership of a virtual child body causes overestimation of object sizes and implicit attitude changes. Proc Natl Acad Sci U S A. 2013;110(31):12846–51.
21. Yee N, Bailenson J. The proteus effect: the effect of transformed self-representation on behavior. Human Commun Res. 2007;33(3):271–90.
22. Slater M. Measuring presence: a response to the witmer and singer presence questionnaire. Presence. 1999;8(5):560–5.
23. Rand D, Kizony R, Feintuch U, Katz N, Josman N, Rizzo A, et al. Comparison of two VR platforms for rehabilitation: video capture versus HMD. Presence. 2005;14(2):147–60.
24. Rand D, Kizony R, Weiss PT. The Sony PlayStation II EyeToy: low-cost virtual reality for use in rehabilitation. J Neurol Phys Ther. 2008;32(4):155–63.
25. Perez-Marcos D, Sanchez-Vives M, Slater M. Is my hand connected to my body? The impact of body continuity and arm alignment on the virtual hand illusion. Cogn Neurodyn. 2012;6(4):295–305.
26. Schmidt RA, editor. Motor learning principles for physical therapy. Contemporary management of motor control problems: proceedings of the II STEP conference. Alexandria: Foundation for Physical Therapy; 1991.
27. Wulf G, Shea C, Lewthwaite R. Motor skill learning and performance: a review of influential factors. Med Educ. 2010;44(1):75–84.
28. Deutsch JE, Merians AS, Adamovich S, Poizner H, Burdea GC. Development and application of virtual reality technology to improve hand use and gait of individuals post-stroke. Restor Neurol Neurosci. 2004;22(3–5):371–86.
29. Holden MK. Virtual environments for motor rehabilitation: review. Cyberpsychol Behav. 2005;8(3):187–211.
30. Deutsch JE, Brettler A, Smith C, Welsh J, John R, Guarrera-Bowlby P, et al. Nintendo wii sports and wii fit game analysis, validation, and application to stroke rehabilitation. Top Stroke Rehabil. 2011;18(6):701–19.
31. Fluet GG, Deutsch JE. Virtual reality for sensorimotor rehabilitation post-stroke: the promise and

current state of the field. Curr Phys Med Rehabil Rep. 2013;1(1):9–20.
32. Levin MF, Weiss PL, Keshner EA. Emergence of virtual reality as a tool for upper limb rehabilitation: incorporation of motor control and motor learning principles. Phys Ther. 2015;95(3):415–25.
33. Laver KE, George S, Thomas S, Deutsch JE, Crotty M. Virtual reality for stroke rehabilitation. Cochrane Database Syst Rev. 2015;2:523–30.
34. Levac D, Sveistrup H. Motor learning and virtual reality. In: Weiss PL, Keshner EA, Levin MF, editors. Virtual reality for physical and motor rehabilitation. New York: Springer; 2014.
35. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. J Neurophysiol. 1998;80(6):3321–5.
36. Janssen H, Bernhardt J, Collier JM, Sena ES, McElduff P, Attia J, et al. An enriched environment improves sensorimotor function post-ischemic stroke. Neurorehabil Neural Repair. 2010;24(9):802–13.
37. Janssen H, Ada L, Bernhardt J, McElduff P, Pollack M, Nilsson M, et al. An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: a pilot non-randomized controlled trial. Disabil Rehabil. 2014;36(3):255–62.
38. Sigrist R, Rauter G, Riener R, Wolf P. Augmented visual, auditory, haptic, and multimodal feedback in motor learning: a review. Psychon Bull Rev. 2013;20(1):21–53.
39. Winstein CJ. Knowledge of results and motor learning – implications for physical therapy. Phys Ther. 1991;71(2):140–9.
40. Klinger E, Cherni H, Joseph P-A. Impact of contextual additional stimuli on the performance in a virtual activity of daily living (vADL) among patients with brain injury and controls. Int J Disabil Human Dev. 2014;13(3):377–82.
41. Molier BI, Van Asseldonk EH, Hermens HJ, Jannink MJ. Nature, timing, frequency and type of augmented feedback; does it influence motor relearning of the hemiparetic arm after stroke? A systematic review. Disabil Rehabil. 2010;32(22):1799–809.
42. Mirelman A, Bonato P, Deutsch JE. Effects of training with a robot-virtual reality system compared with a robot alone on the gait of individuals after stroke. Stroke. 2009;40(1):169–74.
43. Subramanian SK, Lourenco CB, Chilingaryan G, Sveistrup H, Levin MF. Arm motor recovery using a virtual reality intervention in chronic stroke: randomized control trial. Neurorehabil Neural Repair. 2013;27(1):13–23.
44. Holden M, Todorov E, Callahan J, Bizzi E. Virtual environment training improves motor performance in two patients with stroke: case report. J Neurol Phys Ther. 1999;23(2):57–67.
45. Schmidt RA. Motor learning and performance: a situation-based learning approach. Champaign: Human Kinetics; 2008.
46. Magill RA. Motor learning and control: current concepts and applications. 9th ed. New York: McGraw Hill; 2007. 466 p.
47. Lam P, Hebert D, Boger J, Lacheray H, Gardner D, Apkarian J, et al. A haptic-robotic platform for upper-limb reaching stroke therapy: preliminary design and evaluation results. J Neuroeng Rehabil. 2008;5(1):15.
48. Colomer C, Llorens R, Noé E, Alcañiz M. Effect of a mixed reality-based intervention on arm, hand, and finger function on chronic stroke. J Neuroeng Rehabil. 2016;13:45.
49. Pichiorri F, Morone G, Petti M, Toppi J, Pisotta I, Molinari M, et al. Brain–computer interface boosts motor imagery practice during stroke recovery. Ann Neurol. 2015;77(5):851–65.
50. Kizony R, Levin MF, Hughey L, Perez C, Fung J. Cognitive load and dual-task performance during locomotion poststroke: a feasibility study using a functional virtual environment. Phys Ther. 2010;90(2):252–60.
51. Adams RJ, Lichter MD, Krepkovich ET, Ellington A, White M, Diamond PT. Assessing upper extremity motor function in practice of virtual activities of daily living. IEEE Trans Neural Syst Rehabil Eng. 2015;23(2):287–96.
52. Cameirão MS, Bermúdez i Badia S, Duarte E, Verschure P. Neurorehabilitation using the virtual reality based rehabilitation gaming system: methodology, design, psychometrics, usability and validation. J Neuroeng Rehabil. 2010;7:48.
53. Shin J-H, Ryu H, Jang SH. A task-specific interactive game-based virtual reality rehabilitation system for patients with stroke: a usability test and two clinical experiments. J Neuroreng Rehabil. 2014;11(1):32.
54. Yang YR, Tsai MP, Chuang TY, Sung WH, Wang RY. Virtual reality-based training improves community ambulation in individuals with stroke: a randomized controlled trial. Gait Posture. 2008;28(2):201–6.
55. Fung J, Richards CL, Malouin F, McFadyen BJ, Lamontagne A. A treadmill and motion coupled virtual reality system for gait training post-stroke. Cyberpsychol Behav. 2006;9(2):157–62.
56. Fung J, Perez CF, editors. Sensorimotor enhancement with a mixed reality system for balance and mobility rehabilitation. Engineering in medicine and biology society, EMBC, 2011 annual international conference of the IEEE, IEEE, Boston, MA, 2011.
57. You SH, Jang SH, Kim Y-H, Hallett M, Ahn SH, Kwon Y-H, et al. Virtual reality–induced cortical reorganization and associated locomotor recovery in chronic stroke an experimenter-blind randomized study. Stroke. 2005;36(6):1166–71.
58. Jaffe DL, Brown DA, Pierson-Carey CD, Buckley EL, Lew HL. Stepping over obstacles to improve walking in individuals with poststroke hemiplegia. J Rehabil Res Dev. 2004;41(3A):283–92.
59. Kwakkel G, van Peppen R, Wagenaar RC, Wood Dauphinee S, Richards C, Ashburn A, et al. Effects

of augmented exercise therapy time after stroke: a meta-analysis. Stroke. 2004;35(11):2529–39.
60. Schmidt RA, Lee T. Motor control and learning. 5th Revised edition. Champaign: Human Kinetics Ltd; 2011.
61. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res. 2008;51(1):S225–39.
62. Rand D, Givon N, Weingarden H, Nota A, Zeilig G. Eliciting upper extremity purposeful movements using video games: a comparison with traditional therapy for stroke rehabilitation. Neurorehabil Neural Repair. 2014;28(8):733–9.
63. Remple MS, Bruneau RM, VandenBerg PM, Goertzen C, Kleim JA. Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. Behav Brain Res. 2001;123(2): 133–41.
64. Dancause N, Nudo RJ. Shaping plasticity to enhance recovery after injury. Prog Brain Res. 2011;192: 273–95.
65. Llorens R, Noe E, Colomer C, Alcaniz M. Effectiveness, usability, and cost-benefit of a virtual reality-based telerehabilitation program for balance recovery after stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2015;96(3):418–25.
66. Cameirão M, Bermúdez i Badia S, Duarte E, Verschure PF. Virtual reality based rehabilitation speeds up functional recovery of the upper extremities after stroke: a randomized controlled pilot study in the acute phase of stroke using the rehabilitation gaming system. Restor Neurol Neurosci. 2011;29(5):287–98.
67. Adamovich SV, Fluet GG, Merians AS, Mathai A, Qiu Q. Incorporating haptic effects into three-dimensional virtual environments to train the hemiparetic upper extremity. IEEE Trans Neural Syst Rehabil Eng. 2009;17(5):512–20.
68. Fluet GG, Merians AS, Qiu Q, Lafond I, Saleh S, Ruano V, et al. Robots integrated with virtual reality simulations for customized motor training in a person with upper extremity hemiparesis: a case report. J Neurol Phys Ther. 2012;36(2):79–86.
69. Homberg V. Evidence based medicine in neurological rehabilitation – a critical review. Acta Neurochir Suppl. 2005;93:3–14.
70. Ryan RM, Deci EL. Intrinsic and extrinsic motivations: classic definitions and new directions. Contemp Educ Psychol. 2000;25(1):54–67.
71. Wouters P, Van Nimwegen C, Van Oostendorp H, Van Der Spek ED. A meta-analysis of the cognitive and motivational effects of serious games. J Educ Psychol. 2013;105(2):249.
72. Linehan C, Kirman B, Lawson S, Chan G, editors. Practical, appropriate, empirically-validated guidelines for designing educational games. Proceedings of the SIGCHI conference on human factors in computing systems; ACM; New York, NY, 2011.
73. Garris R, Ahlers R, Driskell JE. Games, motivation, and learning: a research and practice model. Simul Gaming. 2002;33(4):441–67.
74. Faria A, Vourvopoulos A, Cameirão M, Fernandes J, i Badia SB, editors. An integrative virtual reality cognitive-motor intervention approach in stroke rehabilitation: a pilot study. 10th international conference disability, virtual reality & associated technologies, Gothenburg, Sweden, 2014.
75. Rabin BA, Burdea GC, Roll DT, Hundal JS, Damiani F, Pollack S. Integrative rehabilitation of elderly stroke survivors: the design and evaluation of the BrightArm™. Disabil Rehabil Assist Technol. 2012;7(4):323–35.
76. Cirstea CM, Ptito A, Levin MF. Feedback and cognition in arm motor skill reacquisition after stroke. Stroke. 2006;37(5):1237–42.
77. Kilduski NC, Rice MS. Qualitative and quantitative knowledge of results: effects on motor learning. Am J Occup Ther. 2003;57(3):329–36.
78. Rosati G, Rodà A, Avanzini F, Masiero S. On the role of auditory feedback in robot-assisted movement training after stroke: review of the literature. Comp Int Neurosci. 2013;2013:11.
79. Lauber B, Keller M. Improving motor performance: selected aspects of augmented feedback in exercise and health. Eur J Sport Sci. 2014;14(1):36–43.
80. Cameron J, Banko KM, Pierce WD. Pervasive negative effects of rewards on intrinsic motivation: the myth continues. Behav Anal. 2001;24(1):1.
81. Malone T, Lepper M. Making Learning Fun: A Taxonomy of Intrinsic Motivation for Learning in Snow, RE, and Farr, MJ (eds.) Aptitude. Learning, and Instruction (Hillsdale, NJ: Lawrence Earlbaum, 1987), 1987;3:223–53.
82. Yerkes RM, Dodson JD. The relation of strength of stimulus to rapidity of habit-formation. J Comp Neurol Psychol. 1908;18(5):459–82.
83. Duffy E. Activation and behavior. New York: Wiley; 1962.
84. Malmo RB. Activation: a neuropsychological dimension. Psychol Rev. 1959;66(6):367.
85. Csikszentmihalyi M. In: Jossey-Bass, editor. Beyond boredom and anxiety: experiencing flow in work and play. San Francisco: Jossey-Bass; 1975.
86. Von Ahn L, Dabbish L. Designing games with a purpose. Commun ACM. 2008;51(8):58–67.
87. Bermúdez i Badia S, Cameirao M. The Neurorehabilitation Training Toolkit (NTT): a novel worldwide accessible motor training approach for at-home rehabilitation after stroke. Stroke Res Treat, vol. 2012, Article ID 802157, 13 pages, 2012. doi:10.1155/2012/802157.
88. Borghese NA, Pirovano M, Lanzi PL, Wüest S, de Bruin ED. Computational intelligence and game design for effective at-home stroke rehabilitation. Game Health. 2013;2(2):81–8.
89. Bronner S, Pinsker R, Noah JA. Physiological and psychophysiological responses in experienced players while playing different dance exer-games. Comput Hum Behav. 2015;51:34–41.

90. Gamito P, Oliveira J, Coelho C, Morais D, Lopes P, Pacheco J, et al. Cognitive training on stroke patients via virtual reality-based serious games. Disabil Rehabil. 2015:1–4.
91. Vourvopoulos A, Faria AL, Ponnam K, Bermudez i Badia S, editors. Rehab City: design and validation of a cognitive assessment and rehabilitation tool through gamified simulations of activities of daily living. Proceedings of the 11th conference on advances in computer entertainment technology; ACM; New York, NY, 2014.
92. Merians AS, Fluet GG, Qiu Q, Saleh S, Lafond I, Davidow A, et al. Robotically facilitated virtual rehabilitation of arm transport integrated with finger movement in persons with hemiparesis. J Neuroeng Rehabil. 2011;8:27.
93. Ada L, Canning C, Carr J, Kilbreath S, Shepherd R. Task-specific training of reaching and manipulation. Adv Psychol. 1994;105:239–65.
94. Viau A, Feldman AG, McFadyen BJ, Levin MF. Reaching in reality and virtual reality: a comparison of movement kinematics in healthy subjects and in adults with hemiparesis. J Neuroeng Rehabil. 2004;1(1):11.
95. Subramanian S, Knaut LA, Beaudoin C, McFadyen BJ, Feldman AG, Levin MF. Virtual reality environments for post-stroke arm rehabilitation. J Neuroeng Rehabil. 2007;4:20.
96. Knaut LA, Subramanian SK, McFadyen BJ, Bourbonnais D, Levin MF. Kinematics of pointing movements made in a virtual versus a physical 3-dimensional environment in healthy and stroke subjects. Arch Phys Med Rehabil. 2009;90(5): 793–802.
97. Levin MF, Magdalon EC, Michaelsen SM, Quevedo A. Quality of grasping and the role of haptics in a 3D immersive virtual reality environment in individuals with stroke. IEEE Trans Neural Syst Rehabil Eng. 2015;23:1047–55; PP(99):1.
98. van den Hoogen W, Feys P, Lamers I, Coninx K, Notelaers S, Kerkhofs L, et al. Visualizing the third dimension in virtual training environments for neurologically impaired persons: beneficial or disruptive? J Neuroeng Rehabil. 2012;9(1):73.
99. Fluet G, Merians A, Qiu Q, Adamovich S, editors. Sensorimotor training in virtual environments produces similar outcomes to real world training with greater efficiency. Virtual Rehabilitation (ICVR), 2013 international conference on; IEEE; Philadelphia, PA, 2013.
100. Weiss PL, Rand D, Katz N, Kizony R. Video capture virtual reality as a flexible and effective rehabilitation tool. J Neuroeng Rehabil. 2004;1(1):12.
101. Hondori HM, Khademi M, McKenzie A, Dodakian L, Lopes CV, Cramer SC. Utility of augmented reality in relation to virtual reality in stroke rehabilitation. Stroke. 2014;45:1.
102. Thaut MH, McIntosh GC, Hoemberg V. Neurobiological foundations of neurologic music therapy: rhythmic entrainment and the motor system. Front Psychol. 2014;5:1185–95.
103. Powell W. Virtually walking: factors influencing walking and perception of walking in treadmill-mediated virtual reality to support rehabilitation. University of Portsmouth; Portsmouth, UK, 2011.
104. Friedman N, Chan V, Zondervan D, Bachman M, Reinkensmeyer DJ, editors. MusicGlove: motivating and quantifying hand movement rehabilitation by using functional grips to play music. Engineering in medicine and biology society, EMBC, 2011 annual international conference of the IEEE, IEEE, Boston, MA, 2011.
105. Brütsch K, Koenig A, Zimmerli L, Mérillat-Koeneke S, Riener R, Jäncke L, et al. Virtual reality for enhancement of robot-assisted gait training in children with neurological gait disorders. J Rehabil Med. 2011;43(6):493–9.
106. Adamovich S, Fluet G, Mathai A, Qiu Q, Lewis J, Merians A. Design of a complex virtual reality simulation to train finger motion for persons with hemiparesis: a proof of concept study. J Neuroeng Rehabil. 2009;6:28.
107. Wellner M, Thüring T, Smajic E, von Zitzewitz J, Duschau-Wicke A, Riener R. Obstacle crossing in a virtual environment with the rehabilitation gait robot LOKOMAT. Stud Health Technol Inform. 2006;125:497–9.
108. Huegel JC, O'Malley MK, editors. Progressive haptic and visual guidance for training in a virtual dynamic task. Haptics symposium, 2010 IEEE, Waltham, MA, 25–26 Mar 2010.
109. Huang FC, Gillespie RB, Kuo AD. Visual and haptic feedback contribute to tuning and online control during object manipulation. J Mot Behav. 2007;39(3):179–93.
110. Schweighofer N, Choi Y, Winstein C, Gordon J. Task-oriented rehabilitation robotics. Am J Phys Med Rehabil. 2012;91(11):S270–9.
111. Ang KK, Guan C. Brain-computer interface in stroke rehabilitation. J Comp Sci Eng. 2013;7(2):139–46.
112. Vourvopoulos A, Muñoz J, Bermúdez i Badia S, editors. Optimizing motor imagery neurofeedback through the use of multimodal immersive virtual reality and motor priming. Virtual rehabilitation (ICVR), 2015 international conference on IEEE, Valencia, Spain, 2015.
113. Prasad G, Herman P, Coyle D, McDonough S, Crosbie J. Applying a brain-computer interface to support motor imagery practice in people with stroke for upper limb recovery: a feasibility study. J Neuroeng Rehabil. 2010;7(1):60.
114. Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain–computer interfaces for communication and control. Clin Neurophysiol. 2002;113(6):767–91.
115. Bütefisch CM, Netz J, Weßling M, Seitz RJ, Hömberg V. Remote changes in cortical excitability after stroke. Brain. 2003;126(2):470–81.
116. Ward NS, Newton JM, Swayne OB, Lee L, Thompson AJ, Greenwood RJ, et al. Motor system

activation after subcortical stroke depends on corticospinal system integrity. Brain. 2006;129(3): 809–19.
117. Ward N, Brown M, Thompson A, Frackowiak R. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain. 2003;126(11):2476–96.
118. Carey LM, Abbott DF, Egan GF, O'Keefe GJ, Jackson GD, Bernhardt J, et al. Evolution of brain activation with good and poor motor recovery after stroke. Neurorehabil Neural Repair. 2006;20(1):24–41.
119. Jang SH, You SH, Hallett M, Cho YW, Park C-M, Cho S-H, et al. Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study. Arch Phys Med Rehabil. 2005;86(11):2218–23.
120. Saleh S, Bagce H, Qiu Q, Fluet G, Merians A, Adamovich S, et al. Mechanisms of neural reorganization in chronic stroke subjects after virtual reality training. Conf Proc IEEE Eng Med Biol Soc. 2011;2011:8118–21.
121. Orihuela-Espina F, Fernandez del Castillo I, Palafox L, Pasaye E, Sanchez-Villavicencio I, Leder R. Neural reorganization accompanying upper limb motor rehabilitation from stroke with virtual reality-based gesture therapy. Top Stroke Rehabil. 2013;20(3):197–209.
122. Richards LG, Stewart KC, Woodbury ML, Senesac C, Cauraugh JH. Movement-dependent stroke recovery: a systematic review and meta-analysis of TMS and fMRI evidence. Neuropsychologia. 2008; 46(1):3–11.
123. Carel C, Loubinoux I, Boulanouar K, Manelfe C, Rascol O, Celsis P, et al. Neural substrate for the effects of passive training on sensorimotor cortical representation: a study with functional magnetic resonance imaging in healthy subjects. J Cereb Blood Flow Metab. 2000;20(3):478–84.
124. Jang SH, Kim Y-H, Cho S-H, Lee J-H, Park J-W, Kwon Y-H. Cortical reorganization induced by task-oriented training in chronic hemiplegic stroke patients. Neuroreport. 2003;14(1):137–41.
125. Grefkes C, Fink GR. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. Brain. 2011;134: 1264–76.
126. Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. Ann Neurol. 2008;63(3):272–87.
127. Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G. Cortical mechanisms of human imitation. Science. 1999;286(5449):2526–8.
128. Gallese V, Fadiga L, Fogassi L, Rizzolatti G. Action recognition in the premotor cortex. Brain. 1996;119(2):593–609.
129. Grezes J, Decety J. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum Brain Mapp. 2001;12(1):1–19.
130. Rizzolatti G, Craighero L. The mirror-neuron system. Annu Rev Neurosci. 2004;27:169–92.
131. Buccino G, Solodkin A, Small SL. Functions of the mirror neuron system: implications for neurorehabilitation. Cogn Behav Neurol. 2006;19(1):55–63.
132. Garrison KA, Winstein CJ, Aziz-Zadeh L. The mirror neuron system: a neural substrate for methods in stroke rehabilitation. Neurorehabil Neural Repair. 2010;24(5):404–12.
133. Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, et al. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur J Neurosci. 2001;13(2):400–4.
134. Sale P, Franceschini M. Action observation and mirror neuron network: a tool for motor stroke rehabilitation. Eur J Phys Rehabil Med. 2012;48(2):313–8.
135. Ertelt D, Small S, Solodkin A, Dettmers C, McNamara A, Binkofski F, et al. Action observation has a positive impact on rehabilitation of motor deficits after stroke. Neuroimaging. 2007;36:164–73.
136. Maeda F, Kleiner-Fisman G, Pascual-Leone A. Motor facilitation while observing hand actions: specificity of the effect and role of observer's orientation. J Neurophysiol. 2002;87(3):1329–35.
137. Gazzola V, Rizzolatti G, Wicker B, Keysers C. The anthropomorphic brain: the mirror neuron system responds to human and robotic actions. Neuroimage. 2007;35(4):1674–84.
138. Ferrari PF, Rozzi S, Fogassi L. Mirror neurons responding to observation of actions made with tools in monkey ventral premotor cortex. J Cogn Neurosci. 2005;17(2):212–26.
139. Modrono C, Navarrete G, Rodríguez-Hernández AF, González-Mora JL. Activation of the human mirror neuron system during the observation of the manipulation of virtual tools in the absence of a visible effector limb. Neurosci Lett. 2013;555:220–4.
140. August K, Lewis J, Chandar G, Merians A, Biswal B, Adamovich S, editors. FMRI analysis of neural mechanisms underlying rehabilitation in virtual reality: activating secondary motor areas. Engineering in medicine and biology society, 2006. EMBS'06. 28th annual international conference of the IEEE, IEEE, New York, NY, 2006.
141. Prochnow D, Bermúdez i Badia S, Schmidt J, Duff A, Brunheim S, Kleiser R, et al. A functional magnetic resonance imaging study of visuomotor processing in a virtual reality-based paradigm: rehabilitation gaming system. Eur J Neurosci. 2013;37(9):1441–7.
142. Dobkin BH. Brain–computer interface technology as a tool to augment plasticity and outcomes for neurological rehabilitation. J Physiol. 2007;579(3): 637–42.
143. Grosse-Wentrup M, Mattia D, Oweiss K. Using brain–computer interfaces to induce neural plasticity and restore function. J Neural Eng. 2011;8(2): 025004.
144. Villiger M, Estévez N, Hepp-Reymond M-C, Kiper D, Kollias SS, Eng K, et al. Enhanced activation of

motor execution networks using action observation combined with imagination of lower limb movements. PLoS ONE. 2013;8(8):e72403.
145. Bermúdez i Badia S, Garcia Morgade A, Samaha H, Verschure P. Using a hybrid brain computer interface and virtual reality system to monitor and promote cortical reorganization through motor activity and motor imagery training. IEEE Trans Neural Syst Rehabil Eng. 2013;21(2):174–81.
146. Abdollahi F, Rozario SV, Kenyon RV, Patton JL, Case E, Kovic M, et al. Arm control recovery enhanced by error augmentation. IEEE international conference rehabilitation robotics, Zurich, Switzerland, Jun 29–Jul 1 2011;1–6.
147. Tunik E, Saleh S, Adamovich SV. Visuomotor discordance during visually-guided hand movement in virtual reality modulates sensorimotor cortical activity in healthy and hemiparetic subjects. IEEE Trans Neural Syst Rehabil Eng. 2013;21(2):198–207.
148. Lewis CH, Griffin MJ. Human factors consideration in clinical applications of virtual reality in virtual reality in Neuro-Psycho-Physiology. GIUSEPPE RIVA (Ed.) 1997, 1998 'Ios Press: Amsterdam, Netherlands, 1997;35–58.
149. Ballester BR, Nirme J, Duarte E, Cuxart A, Rodriguez S, Verschure P, et al. The visual amplification of goal-oriented movements counteracts acquired non-use in hemiparetic stroke patients. J Neuroeng Rehabil. 2015;12:50.
150. Saposnik G, Levin M. Virtual reality in stroke rehabilitation a meta-analysis and implications for clinicians. Stroke. 2011;42(5):1380–6.
151. Henderson A, Korner-Bitensky N, Levin M. Virtual reality in stroke rehabilitation: a systematic review of its effectiveness for upper limb motor recovery. Top Stroke Rehabil. 2007;14(2):52–61.
152. Byl NN, Abrams GM, Pitsch E, Fedulow I, Kim H, Simkins M, et al. Chronic stroke survivors achieve comparable outcomes following virtual task specific repetitive training guided by a wearable robotic orthosis (UL-EXO7) and actual task specific repetitive training guided by a physical therapist. J Hand Ther. 2013;26(4):343–52.
153. Fluet GG, Merians AS, Qiu Q, Rohafaza M, VanWingerden AM, Adamovich S. Does training with traditionally presented and virtually simulated tasks elicit differing changes in object interaction kinematics in persons with upper extremity hemiparesis? Top Stroke Rehabil. 2015;22(3):176–84.
154. Turolla A, Daud Albasini OA, Oboe R, Agostini M, Tonin P, Paolucci S, et al. Haptic-based neurorehabilitation in poststroke patients: a feasibility prospective multicentre trial for robotics hand rehabilitation. Comput Math Methods Med. 2013: pp 1–12.
155. Fluet GG, Merians AS, Qiu Q, Davidow A, Adamovich SV. Comparing integrated training of the hand and arm with isolated training of the same effectors in persons with stroke using haptically rendered virtual environments, a randomized clinical trial. J Neuroeng Rehabil. 2014;11(1):126.
156. In TS, Jung KS, Lee SW, Song CH. Virtual reality reflection therapy improves motor recovery and motor function in the upper extremities of people with chronic stroke. J Phys Ther Sci. 2012;24(4):339–43.
157. Kottink AI, Prange GB, Krabben T, Rietman JS, Buurke JH. Gaming and conventional exercises for improvement of arm function after stroke: a randomized controlled pilot study. Games Health. 2014;3(3):184–91.
158. Turolla A, Dam M, Ventura L, Tonin P, Agostini M, Zucconi C, et al. Virtual reality for the rehabilitation of the upper limb motor function after stroke: a prospective controlled trial. J Neuroeng Rehabil. 2013;10:85.
159. Lee SJ, Chun MH. Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. Arch Phys Med Rehabil. 2014;95(3):431–8.
160. Cameirão MS, Bermúdez i Badia S, Duarte E, Frisoli A, Verschure PF. The combined impact of virtual reality neurorehabilitation and its interfaces on upper extremity functional recovery in patients with chronic stroke. Stroke. 2012;43(10):2720–8.
161. Ang KK, Guan C, Chua KSG, Ang BT, Kuah CWK, Wang C, et al. A large clinical study on the ability of stroke patients to use an EEG-based motor imagery brain-computer interface. Clin EEG Neurosci. 2011;42(4):253–8.
162. Cincotti F, Pichiorri F, Arico P, Aloise F, Leotta F, de Vico Fallani F, et al., editors. EEG-based brain-computer interface to support post-stroke motor rehabilitation of the upper limb. Engineering in medicine and biology society (EMBC), 2012 annual international conference of the IEEE, IEEE, San Diego, CA, 2012.
163. Ang KK, Guan C, Sui Geok Chua K, Ang BT, Kuah C, Wang C, et al., editors. A clinical study of motor imagery-based brain-computer interface for upper limb robotic rehabilitation. Engineering in medicine and biology society, 2009. EMBC 2009. annual international conference of the IEEE, IEEE, Minneapolis, MN, 2009.
164. Ang KK, Guan C, Sui Geok Chua K, Ang BT, Kuah C, Wang C, et al., editors. Clinical study of neurorehabilitation in stroke using EEG-based motor imagery brain-computer interface with robotic feedback. Engineering in medicine and biology society (EMBC), 2010 annual international conference of the IEEE, IEEE, Buenos Aires, 2010.
165. Varkuti B, Guan C, Pan Y, Phua KS, Ang KK, Kuah CWK, et al. Resting state changes in functional connectivity correlate with movement recovery for BCI and robot-assisted upper-extremity training after stroke. Neurorehabil Neural Repair. 2013;27(1):53–62.
166. Weiss PL, Sveistrup H, Rand D, Kizony R. Video capture virtual reality: a decade of rehabilitation

assessment and intervention. Phys Ther Rev. 2009;14(5):307–21.
167. Yavuzer G, Senel A, Atay M, Stam H. "Playstation eyetoy games" improve upper extremity-related motor functioning in subacute stroke: a randomized controlled clinical trial. Eur J Phys Rehabil Med. 2008;44(3):237–44.
168. da Silva Ribeiro NM, Ferraz DD, Pedreira É, Mascarenha Í, da Silva Pinto AC, Neto MG, et al. Virtual rehabilitation via Nintendo Wii® and conventional physical therapy effectively treat post-stroke hemiparetic patients. Top Stroke Rehabil. 2015;22(4):299–305.
169. Shiner CT, Byblow WD, McNulty PA. Bilateral priming before wii-based movement therapy enhances upper limb rehabilitation and its retention after stroke a case-controlled study. Neurorehabil Neural Repair. 2014;28(9):828–38.
170. Joo LY, Yin TS, Xu D, Thia E, Chia PF, Kuah CWK, et al. A feasibility study using interactive commercial off-the-shelf computer gaming in upper limb rehabilitation in patients after stroke. J Rehabil Med. 2010;42(5):437–41.
171. Mouawad MR, Doust CG, Max MD, McNulty PA. Wii-based movement therapy to promote improved upper extremity function post-stroke: a pilot study. J Rehabil Med. 2011;43(6):527–33.
172. Paquin K, Ali S, Carr K, Crawley J, McGowan C, Horton S. Effectiveness of commercial video gaming on fine motor control in chronic stroke within community-level rehabilitation. Disabil Rehabil. 2015:1–8.
173. Saposnik G, Teasell R, Mamdani M, Hall J, McIlroy W, Cheung D, et al. Effectiveness of virtual reality using wii gaming technology in stroke rehabilitation a pilot randomized clinical trial and proof of principle. Stroke. 2010;41(7):1477–84.
174. Chen M-H, Huang L-L, Lee C-F, Hsieh C-L, Lin Y-C, Liu H, et al. A controlled pilot trial of two commercial video games for rehabilitation of arm function after stroke. Clin Rehabili. 2014:1–9.
175. Webster D, Celik O. Systematic review of Kinect applications in elderly care and stroke rehabilitation. J Neuroeng Rehabil. 2014;11(1):108.
176. Pastor I, Hayes HA, Bamberg SJM, editors. A feasibility study of an upper limb rehabilitation system using kinect and computer games. Engineering in medicine and biology society (EMBC), 2012 annual international conference of the IEEE, San Diego, CA, Aug 28–Sept 1 2012.
177. Bao X, Mao Y, Lin Q, Qiu Y, Chen S, Li L, et al. Mechanism of Kinect-based virtual reality training for motor functional recovery of upper limbs after subacute stroke. Neural Regen Res. 2013;8(31):2904–13.
178. Lee G. Effects of training using video games on the muscle strength, muscle tone, and activities of daily living of chronic stroke patients. J Phys Ther Sci. 2013;25(5):595.
179. Booth V, Masud T, Connell L, Bath-Hextall F. The effectiveness of virtual reality interventions in improving balance in adults with impaired balance compared with standard or no treatment: a systematic review and meta-analysis. Clin Rehabil. 2013;7:1319–28.
180. Deutsch JE, Mirelman A. Virtual reality-based approaches to enable walking for people poststroke. Top Stroke Rehabil. 2007;14(6):45–53.
181. Darekar A, McFadyen BJ, Lamontagne A, Fung J. Efficacy of virtual reality-based intervention on balance and mobility disorders post-stroke: a scoping review. J Neuroeng Rehabil. 2015;12(1):46.
182. Barclay-Goddard R, Stevenson T, Poluha W, Moffatt ME, Taback SP. Force platform feedback for standing balance training after stroke. Cochrane Database Syst Rev. 2004;(4):CD004129.
183. Sveistrup H, McComas J, Thornton M, Marshall S, Finestone H, McCormick A, et al. Experimental studies of virtual reality-delivered compared to conventional exercise programs for rehabilitation. Cyberpsychol Behav. 2003;6(3):245–9.
184. Bisson E, Contant B, Sveistrup H, Lajoie Y. Functional balance and dual-task reaction times in older adults are improved by virtual reality and biofeedback training. Cyberpsychol Behav. 2007;10(1):16–23.
185. Thornton M, Marshall S, McComas J, Finestone H, McCormick A, Sveistrup H. Benefits of activity and virtual reality based balance exercise programmes for adults with traumatic brain injury: perceptions of participants and their caregivers. Brain Inj. 2005;19(12):989–1000.
186. Gil-Gomez JA, Llorens R, Alcaniz M, Colomer C. Effectiveness of a wii balance board-based system (eBaViR) for balance rehabilitation: a pilot randomized clinical trial in patients with acquired brain injury. J Neuroeng Rehabil. 2011;8:30.
187. Lloréns R, Albiol S, Gil-Gómez J-A, Alcañiz M, Colomer C, Noé E. Balance rehabilitation using custom-made Wii Balance Board exercises: clinical effectiveness and maintenance of gains in an acquired brain injury population. Int J Disabil Human Dev. 2014;3:327–32.
188. Cikajlo I, Rudolf M, Goljar N, Burger H, Matjačić Z. Telerehabilitation using virtual reality task can improve balance in patients with stroke. Disabil Rehabil. 2012;34(1):13–8.
189. Krpic A, Savanovic A, Cikajlo I. Telerehabilitation: remote multimedia-supported assistance and mobile monitoring of balance training outcomes can facilitate the clinical staff's effort. Int J Rehabil Res. 2013;36(2):162–71.
190. Cho KH, Lee WH. Virtual walking training program using a real-world video recording for patients with chronic stroke: a pilot study. Am J Phys Med Rehabil. 2013;92(5):371–84.
191. Darter BJ, Wilken JM. Gait training with virtual reality-based real-time feedback: improving gait

performance following transfemoral amputation. Phys Ther. 2011;91(9):1385–94.
192. Yang S, Hwang WH, Tsai YC, Liu FK, Hsieh LF, Chern JS. Improving balance skills in patients who had stroke through virtual reality treadmill training. Am J Phys Med Rehabil. 2011;90(12):969–78.
193. Walker ML, Ringleb SI, Maihafer GC, Walker R, Crouch JR, Van Lunen B, et al. Virtual reality-enhanced partial body weight-supported treadmill training post-stroke: feasibility and effectiveness in 6 subjects. Arch Phys Med Rehabil. 2010;91(1):115–22.
194. Llorens R, Gil-Gomez JA, Alcaniz M, Colomer C, Noe E. Improvement in balance using a virtual reality-based stepping exercise: a randomized controlled trial involving individuals with chronic stroke. Clin Rehabil. 2015;29(3):261–8.
195. Flynn S, Palma P, Bender A. Feasibility of using the Sony PlayStation 2 gaming platform for an individual poststroke: a case report. J Neurol Phys Ther. 2007;31(4):180–9.
196. Deutsch JE, Robbins D, Morrison J, Bowlby PG. Wii-based compared to standard of care balance and mobility rehabilitation for two individuals post-stroke. 2009 virtual rehabilitation international conference 2009. Haifa, Israel, p. 117–20.
197. Fritz SL, Peters DM, Merlo AM, Donley J. Active video-gaming effects on balance and mobility in individuals with chronic stroke: a randomized controlled trial. Top Stroke Rehabil. 2013;20(3):218–25.
198. Cho KH, Lee KJ, Song CH. Virtual-reality balance training with a video-game system improves dynamic balance in chronic stroke patients. Tohoku J Exp Med. 2012;228(1):69–74.
199. Barcala L, Grecco LA, Colella F, Lucareli PR, Salgado AS, Oliveira CS. Visual biofeedback balance training using wii fit after stroke: a randomized controlled trial. J Phys Ther Sci. 2013;25(8):1027–32.
200. Hung JW, Chou CX, Hsieh YW, Wu WC, Yu MY, Chen PC, et al. Randomized comparison trial of balance training by using exergaming and conventional weight-shift therapy in patients with chronic stroke. Arch Phys Med Rehabil. 2014;95(9):1629–37.
201. Deutsch JE, Bowlby PG, Kafri M, editors. Effects of optimal standard of care compared with interactive video gaming-based balance and mobility training for individuals post-stroke. World congress of physical therapy, Amsterdam, 2011.
202. Morone G, Tramontano M, Iosa M, Shofany J, Iemma A, Musicco M, et al. The efficacy of balance training with video game-based therapy in subacute stroke patients: a randomized controlled trial. Biomed Res Int, vol. 2014, Article ID 580861, 6 pages, 2014. doi:10.1155/2014/580861.
203. Rajaratnam B, Gui KaiEn J, Lee JiaLin K, SweeSin K, Sim FenRu S, Enting L, et al. Does the inclusion of virtual reality games within conventional rehabilitation enhance balance retraining after a recent episode of stroke? Rehabil Res Pract, vol. 2013, Article ID 649561, 6 pages, 2013. doi:10.1155/2013/649561.
204. Bower KJ, Clark RA, McGinley JL, Martin CL, Miller KJ. Clinical feasibility of the nintendo wii for balance training post-stroke: a phase II randomized controlled trial in an inpatient setting. Clin Rehabil. 2014;28(9):912–23.
205. Kizony R, Weiss PL. Virtual reality rehabilitation for all: vivid GX versus Sony PlayStation II EyeToy. 5th international conference on disability, virtual reality and associated technologies, Oxford, 2004. p. 87–94.
206. Singh DK, Mohd Nordin NA, Abd Aziz NA, Lim BK, Soh LC. Effects of substituting a portion of standard physiotherapy time with virtual reality games among community-dwelling stroke survivors. BMC Neurol. 2013;13:199.
207. Gordon NF, Gulanick M, Costa F, Fletcher G, Franklin BA, Roth EJ, et al. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. Circulation. 2004;109(16):2031–41.
208. Rimmer JH, Wang E, Smith D. Barriers associated with exercise and community access for individuals with stroke. J Rehabil Res Dev. 2008;45(2):315–22.
209. Ranky RG, Sivak ML, Lewis JA, Gade VK, Deutsch JE, Mavroidis C. Modular mechatronic system for stationary bicycles interfaced with virtual environment for rehabilitation. J Neuroeng Rehabil. 2014;11:93.
210. Deutsch JE, Myslinski MJ, Kafri M, Ranky R, Sivak M, Mavroidis C, et al. Feasibility of virtual reality augmented cycling for health promotion of people poststroke. J Neurol Phys Ther. 2013;37(3):118–24.
211. Kafri M, Myslinski MJ, Gade VK, Deutsch JE. Energy expenditure and exercise intensity of interactive video gaming in individuals post-stroke. Neurorehabil Neural Repair. 2014;28(1):56–65.
212. Hurkmans HL, Ribbers GM, Streur-Kranenburg MF, Stam HJ, van den Berg-Emons RJ. Energy expenditure in chronic stroke patients playing Wii sports: a pilot study. J Neuroeng Rehabil. 2011;8:38.

Wearable Wireless Sensors for Rehabilitation

29

Andrew K. Dorsch, Christine E. King, and Bruce H. Dobkin

Abstract

Advances in microprocessors, fabrication techniques, communication protocols, and machine learning algorithms have resulted in the development of wearable wireless sensors and allowed investigators to begin addressing an unmet need in clinical rehabilitation: remote monitoring of skills practice. Wearable sensor systems provide the opportunity to not only evaluate the behavior of disabled persons as it occurs in the course of daily life activities but also to provide timely, meaningful feedback to patients and their therapists that can guide and motivate progressive skills practice aimed at maximizing the recovery of motor function. While the technology of wearable sensors continues to improve, additional clinical trials are needed to generate the evidence base demonstrating the utility and efficacy of remote monitoring for clinical care and research in rehabilitation. Promising approaches to the challenges of monitoring gait and reaching movements in disabled persons are highlighted. Practical issues affecting compliance with the sensor use, the data collection, and the analysis of sensor data are discussed. The research infrastructure, sensor components, and feedback protocols necessary to support telerehabilitation will be reviewed.

Keywords

Rehabilitation • Wireless sensor • Telemedicine • Outcome measure • Self-efficacy • Gait • Instrumental activities of daily living

A.K. Dorsch, MD
Department of Neurology, UCLA Geffen School of Medicine, Los Angeles, CA, USA

C.E. King, PhD
Department of Computer Science, University of California Los Angeles, Los Angeles, CA, USA

B.H. Dobkin, MD (✉)
Department of Neurology, Geffen School of Medicine, University of California Los Angeles, 710 Westwood Plaza RNRC 1-138, Los Angeles, CA 90095, USA
e-mail: bdobkin@mednet.ucla.edu

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29.1 Introduction

Wearable sensor systems, a branch of mobile/wireless health, are the latest iteration in the attempt to monitor the behavior of disabled persons. Current systems leverage advances in microprocessors to collect laboratory-quality data about physical activity and physiology from unobtrusive sensors, while modern communication protocols transmit data via the Internet using platforms including smartphones, tablets, and the sensors themselves. What separates the wireless systems of today from the electromechanical foot switches and pedometers of decades past is their ability not only to record movements as they occur, but, more importantly, to provide meaningful feedback directly to the user. In neurorehabilitation, where the majority of functional recovery results from practice performed away from direct clinical supervision, wireless sensing affords clinicians the opportunity to monitor and assist patients in modifying their behavior to maximize both functional recovery and participation in daily life.

29.2 The Potential Role for Wearable Sensors in Neurorehabilitation

The most obvious role for sensing technologies is to serve as a virtual "fly on the wall" that provides an objective assessment of the amount of skills practice in which patients participate, whether that be in the acute hospital, rehabilitation unit, or home environment. Audits of patient activity could measure compliance with prescribed therapies and be used to derive dose-response curves associating the amount of practice with the degree of functional recovery. In clinical trial settings, sensors could be used to control for the amount of activity and skills practice that occurs outside of the formal treatment period, thereby improving the validity of an intervention's effectiveness.

Modern sensor systems are sensitive to changes in the quality with which movements are performed; such information could previously be obtained only in formal motion laboratories. Quantity and quality metrics derived from sensor data may serve as ecologically valid outcome measures of motor performance in real-life situations, complementing the information available from laboratory- or clinically based outcome measures and patient self-report. The combination of sensor with other clinical data may provide a more comprehensive natural history of disease progression and recovery, the results of which could be used to tailor rehabilitative therapies to the unique needs of a given patient or to identify the patient population most likely to respond to a novel clinical trial intervention.

The potential greatest impact of wearable sensor systems is the feedback that can be provided to therapists and patients. Compared to standard clinical practice, in which patients receive feedback on a scale of days to weeks, sensor systems enable real-time or just-in-time assessments and interventions. Using sensors, maladaptive or insufficient amounts of skills practice could be identified and corrected before these patterns of behavior become set. Theories of behavior change that employ different delivery methods and frequencies of feedback can be tested to discover what works best for a given patient population and treatment setting.

It should be noted that, despite the undeniable potential of wireless wearable sensing to impact the practice of medicine in general and rehabilitation in particular, the evidence of its efficacy at improving outcomes remains scant [1, 2]. Most sensor systems undergo basic feasibility testing in healthy volunteers or in small groups of patients. Few such systems mature beyond the pilot or proof-of-concept stage of development. Only recently have clinical trials demonstrated the feasibility of deploying wireless sensors into clinical care environments to monitor activity and provide feedback to patients and therapists to modify behavior [3, 4]. Studies currently underway are deploying sensors into the homes of disabled persons to demonstrate their utility for facilitating long-term changes in behavior and health outcomes.

29.3 State of the Art in Wearable Sensing

An ever-expanding number of sensor systems designed to monitor movement, each of which enables assessment at a different level of granularity, are commercially available to the interested clinician. As an example, Table 29.1 presents but a partial list of sensors that can be deployed to evaluate gait.

Table 29.1 Examples of commercially available wearable sensor systems for gait assessment

Step counters
FitBit (FitBit Inc.)
SenseWear (BodyMedia Inc.)
Activity monitors
ActiGraph (ActiGraph LLC)
StepWatch (Modus Health LLC)
Laboratory-quality gait assessment
APDM (APDM Inc.)
BioSensics (BioSensics LLC)
IDEEA (Minisun)
Xsens (Xsens Technologies)

Rather than engage in an exhaustive comparison between individual devices, common approaches that hold promise in addressing the challenges of assessing goal-directed movements (e.g., gait, reaching) made by patients with disease states commonly encountered during clinical care and research in neurorehabilitation will be presented.

29.3.1 Gait

Most commercially available sensor systems as well as many of those developed in research settings provide an estimate of the time people spend walking. The simplest estimates are derived from step or activity counts recorded by a sensor worn at the wrist, hip, or ankle that contains at minimum a uni- or biaxial accelerometer. Though they can be prone to error when used by more disabled persons (see below), these devices have utility in certain clinical contexts. For example, these devices are able to summarize the overall physical activity and sedentary time of patients after stroke [5, 6] or in those with multiple sclerosis [7], as long as walking speed is greater than 0.5 m/s. Depending upon the patient population under study, similar information can be obtained from a smartphone kept in the pocket or worn on the hip [8].

Of greater utility to neurorehabilitation are more complex sensor systems employing triaxial accelerometers and gyroscopes worn on each ankle. With these more sensitive modules and the classification algorithms that process their data, it is possible to identify steps as well as delimit the alternating phases of the gait cycle (Fig. 29.1). Not only can these systems quantify differences between the walking of disabled and healthy persons (e.g., slower gait speed, decreased magnitude of acceleration during leg swing), the spatiotemporal gait parameters they calculate can be used to evaluate differences in gait quality [9]. Clinically important gait patterns that occur intermittently, such as freezing of gait in patients with Parkinson's disease, can also be identified and characterized using these more advanced sensor systems [10]. Promisingly, data from sensors containing gyroscopes have been used to reconstruct limb trajectories for motion quality analysis [11].

Independent of their ability to classify gait, sensor systems can also evaluate transitions between activities (e.g., sit-to-stand) and provide a quantitative assessment of balance function. One such widely utilized test is the iTUG, an instrumented form of the timed-up-and-go test in which wearable sensors evaluate transitions from sitting to standing as well as spatiotemporal gait parameters during a brief walk [12]. Variations in postural sway can be identified easily from inertial sensor data and are being explored as objective outcome measures for patients with multiple sclerosis and Parkinson's disease [13, 14].

29.3.2 Upper Extremity Movements

Due to the greater degrees of freedom, potential for variations in sensor placement, and number of behaviors to classify, sensor systems for upper extremity motion are less well developed than those used to assess gait. Indeed, many early sensor systems were designed to recreate existing outcome measures such as the NIH Stroke Scale [15], Action Research Arm Test [16], Fugl-Meyer [17], and Wolf Motor Function Test [18]. While restricting the number of tasks to be recognized simplifies the problem of classification, this approach in turn falls prey to the problems of the original outcome measures, namely, that ordinal scales are incomplete summaries of behavior [19]. The utility of recreating an outcome scale is even less certain when the scale under consideration is relatively subjective, such as the case with the modified Ashworth scale [20]. More recent validation testing comparing human and sensor-based evaluations of function has demonstrated the greater sensitivity of sensors to

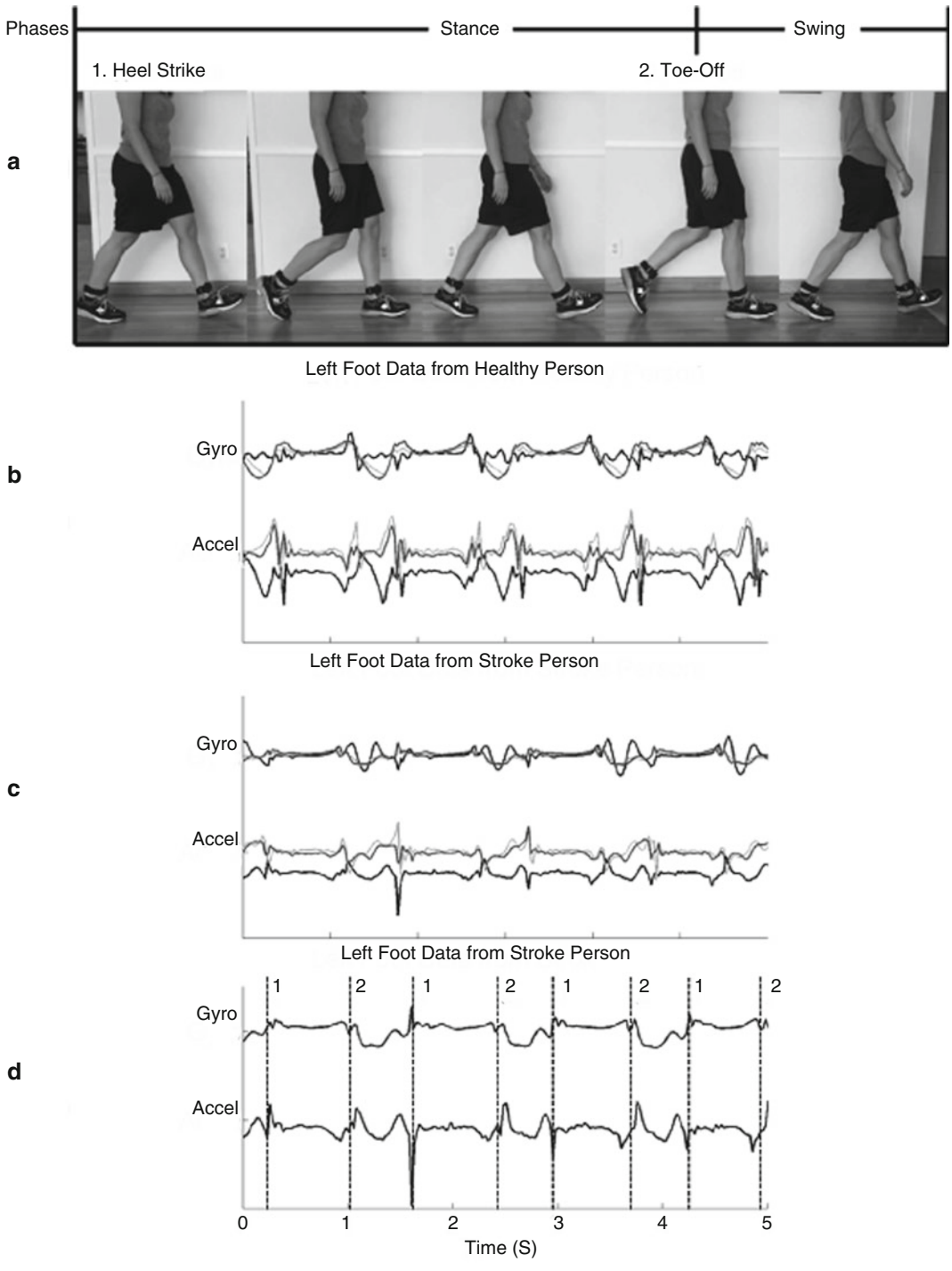

Fig. 29.1 Gait analysis using ankle-worn wireless sensors containing a gyroscope and triaxial accelerometer. (**a**) The gait cycle consists of stance and swing phases delimited by heel strike and toe off, respectively. Events for the left foot are marked. (**b**) Sample of gyroscope (*top* traces) and accelerometer (*bottom* traces) data from a healthy person during casual gait. *Black* traces = superior/inferior axis, *thin gray* traces = anterior/posterior axis, *thick gray* traces = medial/lateral axis; (**c**) corresponding data tracings from a person with hemiparetic stroke; (**d**) accelerometer trace (superior/inferior axis) and gyroscope trace (medial/lateral axis) of person with stroke. Numbers and *dashed lines* correspond to heel strike and toe-off events as in (**a**)

changes in motor function [21], lending support to the argument that sensors should be used to develop new outcome measures.

Current rehabilitation engineering approaches to the problem of activity classification in the upper extremity typically follow two approaches. The first is to have patients perform movements in a physically constrained environment in which video [22] or radio-tagged objects [23] can be used to quantify movement. Similar to the outcome measures described above, certain aspects of a movement can be well described; however, these systems are not close to measuring how people's disabilities modulate interactions with their environments. The alternate approach is to forgo classification in favor of evaluating the quality with which natural movements are made. Metrics derived from prior video-based kinematic evaluations of limb motion including duration, trajectory, length, and smoothness of movement can be measured [24, 25]. Alternate methods of evaluating reach-to-grasp motions, including spectral analysis [26], require further testing and clinical validation.

As compared to movements made with the entire arm, those involving the wrist and fingers present separate challenges for wearable sensors, in particular the relationship between sensor size and the joint displacements under study. One investigational approach has been to design wearable gloves containing goniometers or piezoelectric fabric that can detect subtle movements [27], while another leverage variations in magnetic field strength between a wrist-worn sensor and a magnetic ring worn on the finger during wrist and finger movements [28]. In contrast, the identification and characterization of a single aspect of movement, upper extremity tremor, are more advanced [29, 30], and several sensor systems that monitor tremor are commercially available.

29.4 Choosing a Wearable Sensor System

The ideal sensor system for use in clinical care and research in neurorehabilitation should be low cost, unobtrusive, comfortable, user friendly, and stream to an appropriate healthcare database for review by a patient or clinician. In truth, there is no one-size-fits-all wearable sensor system. A system should be selected based upon its fit to the patients (e.g., active, disabled) and setting (e.g., hospital, clinic, home) in which it is to be used. Its level of sophistication should be proportional to the minimum amount of information required to fully characterize and intervene upon a behavior of interest. For example, a multisensor system that recreates limb trajectories is unnecessary when step counts derived from a single sensor would be sufficient.

29.4.1 End-User Considerations

The factors unique to people participating in rehabilitation should be considered when selecting a wearable sensor system. First, their limb movements are often slower and less symmetric when compared to age-matched healthy persons. Sensors designed for fitness tracking and health promotion in the general population have differing levels of sensitivity [31–34], meaning that they may not be able to accurately characterize movements made at the slow speeds typical of disabled persons [35, 36]. Similar to choosing an outcome measure for a clinical trial, it is essential to select a sensor system that has undergone validation testing in persons with similar functional disabilities to those who are being studied [37, 38].

Concomitant deficits in sensation, vision, language, and cognition should be taken into account when selecting a sensor system, as they can interfere with sensor use as well as the comprehension of instructions and feedback. For example, a sensor that can be attached without the assistance of another person would be most appropriate for a person with limb paresis. Similarly, small buttons may be difficult to push for persons suffering from a loss of dexterity or impaired vision.

Finally, both system aesthetics and the familiarity of potential sensor users with mobile technologies should be considered. Potential users may not be familiar with smartphones, text messaging, or the

Internet [39, 40], in which case a plug-and-play system requiring little user intervention would be most appropriate. Incorporating user preferences into the choice of sensor prior to deployment will help ensure compliance with sensor use over time [41].

29.4.2 Hardware Considerations

A variety of sensing modules (Table 29.2) [28, 42–51] can be built into an existing assistive device (e.g., cane, walker) or worn individually or in combination on the body. The acceleration and force data collected by accelerometers and pressure sensors can quantify limb trajectory, movement, and balance. Physiologic data including heart rate, oxygen saturation, and cortical activity can be collected from passively worn sensors. Sampling of sweat, saliva, or blood by biochemical sensors can track changes in body chemistry before, during, and after activity. The choice of sensor components, number of sensors, body location where sensors are to be worn, data storage capability, and battery life during regular daily use must all be optimized for a given patient population to ensure ease of use.

Wireless systems typically utilize a smartphone or tablet to communicate with sensors, route data to a central database for storage and analysis, and serve as a user interface for providing instructions and feedback. Current communication protocols including ANT/ANT+ (ANT Wireless, Dynastream Innovations Inc., Cochrane, Alberta, Canada) and Bluetooth (Bluetooth SIG, Kirkland, WA) enable rapid upload of data from sensors, while 4G data networks and pervasive Wi-Fi facilitate transmission to a central server. When deploying sensor systems into the homes and communities of patients, especially those who live in remote areas, it is important to consider how data will be collected and feedback provided (e.g., the availability of 4G data coverage in the region). Alternate methods of transmitting data, such as Wi-Fi, use of a mobile hot spot, or even shipping of sensors in the mail, may need to be identified.

29.4.3 Software Considerations

Accurate classification algorithms ensure the validity of the behavioral assessments derived from sensor data. Numerous methodologies developed for the classification of goal-directed movements in healthy persons [52–56] have been applied to the characterization of movements made by persons with hemiparesis, ataxia, poor reach/grasp, and abnormal gait [42, 57–61]. At minimum, a wireless system should be able to filter out artifacts when transforming sensor signals into recognizable movement patterns.

Table 29.2 Examples of sensor modules and the variables they can measure for mobile health and rehabilitation applications

Sensor Module	Variables Measured
Accelerometer	Accelerations/decelerations, velocity, displacement of body segment
Gyroscope	Angular accelerations/decelerations, angular velocity, angular rotation [42]
Magnetometer	Directional vectors of spatial orientation [28]
Electrogoniometer	Joint angle range of motion [43]
Electromyography (EMG)	Timing and amount of muscle activation measured from the surface of the skin [44]
Mechanomyogram (MMG)	Timing and amount of muscle contraction in deeper muscle tissue measured from the surface of the skin [45]
Electroencephalography (EEG)	Neuronal activity measured from the scalp [46]
Electrocardiography (ECG)	Heart rate, heart rate variability [47]
Electrochemistry	Measure chemistry of sweat, tears, other body fluids [48]
Global positioning system (GPS), Wi-Fi	Location [49, 50]
Camera	Ambient sound, light, motion-activated video [51]

Despite the inclusion of common sensing modules, the outputs of sensor systems vary in that some provide full access to the collected raw data while those running more proprietary software may only output general summaries of activity. Additionally, depending upon the system used, different types and amounts of metadata (e.g., sensor type, placement of sensors on the body, duration of data recording) are included with outputs from the sensing modules. Regardless of the system selected, the collection of personal data requires plans to secure that data at each stage of collection, transmission, and storage to ensure patient privacy and compliance with healthcare security regulations [62].

29.5 The Future of Wearable Sensing in Rehabilitation

29.5.1 Telerehabilitation

In the future, patients recovering from neurologic disease will be monitored starting in acute inpatient rehabilitation and then followed after discharge to the home. Wearable sensors and instrumented assistive devices will record purposeful movements and episodes of skills practice, summaries of which will be used by a remote supervising therapist to formulate an individualized rehabilitative treatment plan. Telerehabilitation will enable the provision of services to persons living in remote areas, those with poor access to formal therapy services, and people requiring additional therapies beyond those covered by insurance.

Achieving a clinically meaningful telerehabilitation program will require not only the infrastructure and sensor components to enable remote monitoring but also optimized forms of feedback. In its current form, telerehabilitation consists of intermittent one-on-one video and/or telephone communication between the therapist and patient. Though midsized clinical trials with stroke patients have proved efficacious at increasing physical activity [63], factors including poor compliance with remotely monitored therapies [64], variations in the amount of supervision and feedback [65], and behavioral effects due to financial compensation [66] have confounded results with little systematic evidence for a clinical benefit from telerehabilitation being identified by meta-analysis [67, 68]. Studies utilizing more simplistic step counters have reported better success at establishing changes in and maintenance of physical activity through the use of personalized goal setting as part of a formal behavior change process [69, 70].

29.5.2 Sensor Systems of the Future

The rate of change in wireless health technologies far outpaces that seen in the delivery of clinical care, resulting in a lag between the development of a technology and the demonstration of its clinical utility in randomized trials [71]. Already, wearable sensors consisting of individual sensing modules attached to a flexible substrate can be worn on the skin as a temporary patch to monitor movement [72] or sample cortical activity [73]. Refinements in flexible sensors will enable the remote assessment of swallow performance, opening up new avenues of dysphagia treatment [74, 75]. The instrumentation of therapy equipment (e.g., exercise cycle [76]), orthotics, and prostheses will have the potential to provide additional insights into aspects of skilled motor practice.

The infrastructure supporting the use of wearable sensing in daily care and clinical trials for rehabilitation will evolve due to formal collaborations between research groups that establish interoperable sensor platforms and standard formats for the storage and annotation of sensor data. In the United States, initial efforts to consolidate research resources under the aegis of the National Center for Medical Rehabilitation Research of the NIH are underway. Future advances in algorithms to classify and characterize aspects of goal-directed behavior will be based upon the fusion of data from different modules in sensors and orthotics. The initial efforts in this direction have included the use of an accelerometer and heart rate sensor to quantify the intensity of walking performance by stroke patients [77] and the fusion of inertial sen-

sor data with ambient environmental data collected by a smartphone [78].

29.6 Conclusions

Wearable sensor systems offer the promise of remote monitoring with a degree of precision previously obtainable only in formalized motion analysis laboratories. The development of novel outcome measures that reflect behavior as it is performed in the homes and communities of disabled persons during daily life has the potential to change evaluation of the recovery process as well as the delivery of care for patients recovering from neurologic disease. To become a viable intervention, telerehabilitation will require the selection of appropriate sensor systems, optimization of feedback methodologies, and expansion of the evidence base, demonstrating the efficacy of remote interventions based upon sensor data.

References

1. Kumar S, Nilsen WJ, Abernethy A, Atienza A, Patrick K, Pavel M, Riley WT, Shar A, Spring B, Spruijt-Metz D, Hedeker D, Honavar V, Kravitz R, Lefebvre RC, Mohr DC, Murphy SA, Quinn C, Shusterman V, Swendeman D. Mobile health technology evaluation: the mHealth evidence workshop. Am J Prev Med. 2013;45(2):228–36.
2. Tomlinson M, Rotheram-Borus MJ, Swartz L, Tsai AC. Scaling up mHealth: where is the evidence? PLoS Med. 2013;10(2), e1001382.
3. Dorsch AK, Thomas S, Xu X, Kaiser W, Dobkin BH. SIRRACT: an international randomized clinical trial of activity feedback during inpatient stroke rehabilitation enabled by wireless sensing. Neurorehab Neural Repair. 2015;29:407–15.
4. Mansfield A, Wong JS, Bryce J, Brunton K, Inness EL, Knorr S, Jones S, Taati B, McIlroy WE. Use of accelerometer-based feedback of walking activity for appraising progress with walking-related goals in inpatient stroke rehabilitation: a randomized controlled trial. Neurorehab Neural Repair. Forthcoming 2015.
5. Rand D, Eng JJ, Tang PF, Jeng JS, Hung CY. How active are people with stroke? Use of accelerometers to assess physical activity. Stroke. 2009;40:163–8.
6. Tieges Z, Mead G, Allerhand M, Duncan F, van Wijck F, Fitzsimons C, Greig C, Chastin S. Sedentary behavior in the first year after stroke: a longitudinal cohort study with objective measures. Arch Phys Med Rehabil. 2015;96(1):15–23.
7. Rietberg MB, van Wegen EE, Kollen BJ, Kwakkel G. Do patients with multiple sclerosis show different daily physical activity patterns from healthy individuals? Neurorehabil Neural Repair. 2014;28(6):516–23.
8. Hekler EB, Buman MP, Grieco L, Rosenberger M, Winter SJ, Haskell W, King AC. Validation of physical activity tracking via Android smartphones compared to ActiGraph accelerometer: laboratory-based and free-living validation studies. JMIR Mhealth Uhealth. 2015;3(2):e36.
9. Saremi K, Marehbian J, Yan X, Regnaux JP, Elashoff R, Bussel B, Dobkin BH. Reliability and validity of bilateral thigh and foot accelerometry measures of walking in healthy and hemiparetic subjects. Neurorehabil Neural Repair. 2006;20(2):297–305.
10. Moore ST, Yungher DA, Morris TR, Dilda V, MacDougall HG, Shine JM, Naismith SL, Lewis SJ. Autonomous identification of freezing of gait in Parkinson's disease from lower-body segmental accelerometry. J Neuroeng Rehabil. 2013;10:19.
11. Sabatini AM. Quaternion-based strap-down integration method for applications of inertial sensing to gait analysis. Med Biol Eng Comput. 2005;43(1):94–101.
12. Salarian A, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Aminian K. iTUG, a sensitive and reliable measure of mobility. IEEE Trans Neural Syst Rehabil Eng. 2010;18(3):303–10.
13. Spain RI, Mancini M, Horak FB, Bourdette D. Body-worn sensors capture variability, but not decline, of gait and balance measures in multiple sclerosis over 18 months. Gait Posture. 2014;39(3):958–64.
14. Rocchi L, Palmerini L, Weiss A, Herman T, Hausdorff JM. Balance testing with inertial sensors in patients with Parkinson's disease: assessment of motor subtypes. IEEE Trans Neural Syst Rehabil Eng. 2014;22(5):1064–71.
15. Gubbi J, Rao AS, Fang K, Yan B, Palaniswami M. Motor recovery monitoring using acceleration measurements in post acute stroke patients. Biomed Eng Online. 2013;12:33.
16. Carpinella I, Cattaneo D, Ferrarin M. Quantitative assessment of upper limb motor function in Multiple Sclerosis using an instrumented Action Research Arm Test. J Neuroeng Rehabil. 2014;11(1):67.
17. Del Din S, Patel S, Cobelli C, Bonato P. Estimating Fugl-Meyer clinical scores in stroke survivors using wearable sensors. In: Lovell N, editor. Engineering in medicine and biology society (EMBS) conference; Aug 30–Sep 3 2011; Boston/Piscataway: EMBS; 2011. p. 5839–42.
18. Patel S, Hughes R, Hester T, Stein J, Akay M, Dy J, Bonato P. Tracking motor recovery in stroke survivors undergoing rehabilitation using wearable technology. In: Lovell N, editor. Engineering in medicine and biology society (EMBS) conference; Aug 31–Sep 4 2010; Buenos Aires/Piscataway: EMBS; 2010. p. 6858–61.

19. Hobart JC, Cano SJ, Zajicek JP, Thompson AJ. Rating scales as outcome measures for clinical trials in neurology: problems, solutions, and recommendations. Lancet Neurol. 2007;6(12):1094–105.
20. McGibbon CA, Sexton A, Jones M, O'Connell C. Elbow spasticity during passive stretch-reflex: clinical evaluation using a wearable sensor system. J Neuroeng Rehabil. 2013;10(1):61.
21. Heldman DA, Espay AJ, LeWitt PA, Giuffrida JP. Clinician versus machine: reliability and responsiveness of motor endpoints in Parkinson's disease. Parkinsonism Relat Disord. 2014;20(6):590–5.
22. Lehrer N, Chen Y, Duff ML, Wolf S, Rikakis T. Exploring the bases for a mixed reality stroke rehabilitation system, part II: design of interactive feedback for upper limb rehabilitation. J Neuroeng Rehabil. 2011;8:54.
23. Barman J, Uswatte G, Ghaffari T, Sokal B, Byrom E, Trinh E, Brewer M, Varghese C, Sarkar N. Sensor-enabled RFID system for monitoring arm activity: reliability and validity. IEEE Trans Neural Syst Rehabil Eng. 2012;20(6):771–7.
24. van Dokkum L, Hauret I, Mottet D, Froger J, Métrot J, Laffont I. The contribution of kinematics in the assessment of upper limb motor recovery early after stroke. Neurorehabil Neural Repair. 2014;28(1):4–12.
25. van Kordelaar J, van Wegen E, Kwakkel G. Impact of time on quality of motor control of the paretic upper limb after stroke. Arch Phys Med Rehabil. 2014;95(2):338–44.
26. Wade E, Chen C, Winstein CJ. Spectral analyses of wrist motion in individuals poststroke: the development of a performance measure with promise for unsupervised settings. Neurorehabil Neural Repair. 2014;28(2):169–78.
27. Carbonaro N, Dalle Mura G, Lorussi F, Paradiso R, De Rossi D, Tognetti A. Exploiting wearable goniometer technology for motion sensing gloves. IEEE J Biomed Health Inform. 2014;18(6):1788–95.
28. Friedman N, Rowe JB, Reinkensmeyer DJ, Bachman M. The manometer: a wearable device for monitoring daily use of the wrist and fingers. IEEE J Biomed Health Inform. 2014;18(6):1804–12.
29. Chen BR, Patel S, Buckley T, Rednic R, McClure DJ, Shih L, Tarsy D, Welsh M, Bonato P. A web-based system for home monitoring of patients with Parkinson's disease using wearable sensors. IEEE Trans Biomed Eng. 2011;58(3):831–6.
30. Cole BT, Roy SH, De Luca CJ, Nawab SH. Dynamical learning and tracking of tremor and dyskinesia from wearable sensors. IEEE Trans Neural Syst Rehabil Eng. 2014;22(5):982–91.
31. Welch WA, Bassett DR, Thompson DL, Freedson PS, Staudenmayer JW, John D, Steeves JA, Conger SA, Ceaser T, Howe CA, Sasaki JE, Fitzhugh EC. Classification accuracy of the wrist-worn gravity estimator of normal everyday activity accelerometer. Med Sci Sports Exerc. 2013;45(10):2012–9.
32. Fortune E, Lugade V, Morrow M, Kaufman K. Validity of using tri-axial accelerometers to measure human movement—part II: step counts at a wide range of gait velocities. Med Eng Phys. 2014;36(6):659–69.
33. Tully MA, McBride C, Heron L, Hunter RF. The validation of Fitbit ZipTM physical activity monitor as a measure of free-living physical activity. BMC Research Notes. 2014;7(952).
34. Storm FA, Heller BW, Mazzà C. Step detection and activity recognition accuracy of seven physical activity monitors. PLoS One. 2015;10(3):e0118723.
35. Carroll SL, Greig CA, Lewis SJ, McMurdo ME, Sniehotta FF, Johnston M, Johnston DW, Scopes J, Mead GE. The use of pedometers in stroke survivors: are they feasible and how well do they detect steps? Arch Phys Med Rehabil. 2012;93:466–70.
36. Fulk GD, Combs SA, Danks KA, Nirider CD, Raja B, Reisman DS. Accuracy of 2 activity monitors in detecting steps in people with stroke and traumatic brain injury. Phys Ther. 2014;94(2):222–9.
37. Dobkin BH, Xu X, Batalin M, Thomas S, Kaiser W. Reliability and validity of bilateral ankle accelerometer algorithms for activity recognition and walking speed after stroke. Stroke. 2011;42:2246–50.
38. Motl RW, Weikert M, Suh Y, Sosnoff JJ, Pula J, Soaz C, Schimpl M, Lederer C, Daumer M. Accuracy of the actibelt(®) accelerometer for measuring walking speed in a controlled environment among persons with multiple sclerosis. Gait Posture. 2012;35(2):192–6.
39. Choi NG, DiNitto DM. The digital divide among low-income homebound older adults: internet use patterns, eHealth literacy, and attitudes toward computer/internet use. J Med Internet Res. 2013;15(5):e93.
40. Wu YH, Damnée S, Kerhervé H, Ware C, Rigaud AS. Bridging the digital divide in older adults: a study from an initiative to inform older adults about new technologies. Clin Interv Aging. 2015;10:193–200.
41. Bergmann JH, McGregor AH. Body-worn sensor design: what do patients and clinicians want? Ann Biomed Eng. 2011;39(9):2299–312.
42. Yang S, Zhang JT, Novak AC, Brouwer B, Li Q. Estimation of spatio-temporal parameters for post-stroke hemiparetic gait using inertial sensors. Gait Posture. 2013;37(3):354–8.
43. Wang PT, King CE, Do AH, Nenadic Z. A durable, low-cost electrogoniometer for dynamic measurement of joint trajectories. Med Eng Phys. 2011;33(5):546–52.
44. Roy SH, Cheng MS, Chang SS, Moore J, De Luca G, Nawab SH, De Luca CJ. A combined sEMG and accelerometer system for monitoring functional activity in stroke. IEEE Trans Neural Syst Rehabil Eng. 2009;17:585–94.
45. Hu XL, Tong KY, Li L. The mechanomyography of persons after stroke during isometric voluntary contractions. J Electromyogr Kinesiol. 2007;17(4):473–83.
46. Bertrand A. Distributed signal processing for wireless EEG sensor networks. IEEE Trans Neural Syst Rehabil Eng. 2015;23(6):923–35.

47. Baig MM, Gholamhosseini H, Connolly MJ. A comprehensive survey of wearable and wireless ECG monitoring systems for older adults. Med Biol Eng Comput. 2013;51(5):485–95.
48. Bandodkar AJ, Wang J. Non-invasive wearable electrochemical sensors: a review. Trends Biotechnol. 2014;32(7):363–71.
49. Neven A, Janssens D, Alders G, Wets G, Van Wijmeersch B, Feys P. Documenting outdoor activity and travel behaviour in persons with neurological conditions using travel diaries and GPS tracking technology: a pilot study in multiple sclerosis. Disabil Rehabil. 2013;35(20):1718–25.
50. Chen Z, Zou H, Jiang H, Zhu Q, Soh YC, Xie L. Fusion of WiFi, smartphone sensors and landmarks using the Kalman filter for indoor localization. Sensors (Basel). 2015;15(1):715–32.
51. McNaney R, Vines J, Roggen D, Balaam M, Zhang P, Poliakov I, Olivier P. Exploring the acceptability of Google Glass as an everyday assistive device for people with Parkinson's. In: Jones M, Palanque P, editors. CHI conference on human factors in computing systems; Apr 26–May 1 2014; Toronto. New York: ACS; 2014. p. 2551–4.
52. Yun X, Bachmann ER. Design, implementation, and experimental results of a quaternion-based kalman filter for human body motion tracking. IEEE Trans Robot. 2006;22(6):1216–27.
53. Mannini A, Sabatini A. Accelerometry-based classification of human activities using Markov modeling. Comput Intell Neurosci. 2011;647858.
54. Dalton A, O'Laighin G. Comparing supervised learning techniques on the task of physical activity recognition. IEEE J Biomed Health Inform. 2013;17(1):46–52.
55. Biswas D, Cranny A, Gupta N, Maharatna K, Achner J, Klemke J, Jöbges M, Ortmann S. Recognizing upper limb movements with wrist worn inertial sensors using k-means clustering classification. Hum Mov Sci. 2015;40:59–76.
56. Lemmens RJ, Janssen-Potten YJ, Timmermans AA, Smeets RJ, Seelen HA. Recognizing complex upper extremity activities using body worn sensors. PLoS One. 2015;10(3):e0118642.
57. Sant'Anna A, Salarian A, Wickström N. A new measure of movement symmetry in early Parkinson's disease patients using symbolic processing of inertial sensor data. IEEE Trans Biomed Eng. 2011;58(7):2127–35.
58. Xu X, Batalin MA, Kaiser WJ, Dobkin B. Robust hierarchical system for classification of complex human mobility characteristics in the presence of neurological disorders. International Conference on Body Sensor Networks (BSN 2011); 2011 May 23–5; Dallas/Los Alamitos: IEEE Computer Society; 2011. p. 65–70.
59. Hiremath SV, Ding D, Farringdon J, Vyas N, Cooper RA. Physical activity classification utilizing SenseWear activity monitor in manual wheelchair users with spinal cord injury. Spinal Cord. 2013;51(9):705–9.
60. Lin JFS, Kulić D. Online segmentation of human motion for automated rehabilitation exercise analysis. IEEE Trans Neural Syst Rehabil Eng. 2014;22(1):168–80.
61. Bailey RR, Klaesner JW, Lang CE. Quantifying real-world upper-limb activity in nondisabled adults and adults with chronic stroke. Neurorehabil Neural Repair. Forthcoming 2015.
62. Kumar P, Lee HJ. Security issues in healthcare applications using wireless medical sensor networks: a survey. Sensors (Basel). 2012;12(1):55–91.
63. Chumbler NR, Quigley P, Li X, Morey M, Rose D, Sanford J, Griffiths P, Hoenig H. Effects of telerehabilitation on physical function and disability for stroke patients: a randomized, controlled trial. Stroke. 2012;43(8):2168–74.
64. Benvenuti F, Stuart M, Cappena V, Gabella S, Corsi S, Taviani A, Albino A, Scattareggia Marchese S, Weinrich M. Community-based exercise for upper limb paresis: a controlled trial with telerehabilitation. Neurorehabil Neural Repair. 2014;28(7):611–20.
65. Morris JH, Macgillivray S, McFarlane S. Interventions to promote long-term participation in physical activity after stroke: a systematic review of the literature. Arch Phys Med Rehabil. 2014;95(5):956–67.
66. Spring B, Schneider K, McFadden HG, Vaughn J, Kozak AT, Smith M, Moller AC, Epstein LH, Demott A, Hedeker D, Siddique J, Lloyd-Jones DM. Multiple behavior changes in diet and activity: a randomized controlled trial using mobile technology. Arch Intern Med. 2012;172(10):789–96.
67. Laver KE, Schoene D, Crotty M, George S, Lannin NA, Sherrington C. Telerehabilitation services for stroke. Cochrane Database Syst Rev. 2013(12):CD010255.
68. Khan F, Amatya B, Kesselring J, Galea M. Telerehabilitation for persons with multiple sclerosis. Cochrane Database Syst Rev. 2015;(4):CD010508.
69. Fitzsimons CF, Baker G, Gray SR, Nimmo MA, Mutrie N, Scottish Physical Activity Research Collaboration (SPARColl). Does physical activity counselling enhance the effects of a pedometer-based intervention over the long-term: 12-month findings from the Walking for Wellbeing in the west study. BMC Public Health. 2012;12:206.
70. Harris T, Kerry SM, Victor CR, Ekelund U, Woodcock A, Iliffe S, Whincup PH, Beighton C, Ussher M, Limb ES, David L, Brewin D, Adams F, Rogers A, Cook DG. A primary care nurse-delivered walking intervention in older adults: PACE (pedometer accelerometer consultation evaluation)-Lift cluster randomised controlled trial. PLoS Med. 2015;12(2):e1001783.
71. Riley WT, Glasgow RE, Etheredge L, Abernethy AP. Rapid, responsive, relevant (R3) research: a call for a rapid learning health research enterprise. Clin Transl Med. 2013;2(1):10.
72. Xu S, Zhang Y, Jia L, Mathewson KE, Jang KI, Kim J, Fu H, Huang X, Chava P, Wang R, Bhole S, Wang L, Na

YJ, Guan Y, Flavin M, Han Z, Huang Y, Rogers JA. Soft microfluidic assemblies of sensors, circuits, and radios for the skin. Science. 2014;344(6179):70–4.
73. Norton JJS, Lee DS, Lee JW, Lee W, Kwon O, Won P, Jung SY, Cheng H, Jeong JW, Akce A, Umunna S, Na I, Kwon YH, Wang XQ, Liu Z, Paik U, Huang Y, Bretl T, Yeo WH, Rogers JA. Soft, curved electrode systems capable of integration on the auricle as a persistent brain-computer interface. Proc Natl Acad Sci U S A. 2015;112(13):3920–5.
74. Sejdić E, Steele CM, Chau T. Classification of penetration—aspiration versus healthy swallows using dual-axis swallowing accelerometry signals in dysphagic subjects. IEEE Trans Biomed Eng. 2013;60(7):1859–66.
75. McCormack J, Casey V, Conway R, Saunders J, Perry A. OroPress a new wireless tool for measuring orolingual pressures: a pilot study in healthy adults. J Neuroeng Rehabil. 12(1):32. Forthcoming 2015.
76. Xu JY, Nan X, Ebken V, Wang Y, Pottie GJ, Kaiser WJ. Integrated inertial sensors and mobile computing for real-time cycling performance guidance via pedaling profile classification. IEEE J Biomed Health Inform. 2015;19(2):440–5.
77. Prajapati SK, Mansfield A, Gage WH, Brooks D, McIlroy WE. Cardiovascular responses associated with daily walking in subacute stroke. Stroke Res Treat. 2013; 612458.
78. Xu J, Wang Y, Barrett M, Dobkin B, Pottie GJ, Kaiser W. Personalized, multi-layer daily life profiling through context enabled activity classification and motion reconstruction: an integrated systems approach. IEEE J Biomed Health Inform. 2016;20(1):177–88.

BCI-Based Neuroprostheses and Physiotherapies for Stroke Motor Rehabilitation

30

Colin M. McCrimmon, Po T. Wang, Zoran Nenadic, and An H. Do

Abstract

Despite best available physiotherapy, the stroke survivor population remains affected by significant motor impairment in both upper and lower extremities. Many emerging rehabilitative approaches have ultimately proven to be no better than standard physiotherapy. Hence, there is still a great need for novel methods that can help improve motor outcomes beyond conventional physiotherapy. Brain-computer interfaces (BCIs) may be one such approach. BCIs translate brain signals into control commands for external devices using decoding algorithms. They can be applied to allow those with irreversible paralysis, due to stroke, to directly control prosthetic devices with their brain. Alternatively, they can be applied as novel rehabilitative tools to help improve motor recovery after stroke. However, utilizing BCIs for stroke rehabilitation is a nascent field. While many preliminary clinical studies suggest that BCIs are promising as either neuroprostheses or as rehabilitative tools, there have not been any definitive clinical trials to demonstrate their effectiveness in improving functional or neurological outcomes. Hence, no current practice recommendations can be made regarding BCIs for stroke rehabilitation.

Keywords

Neuroprostheses • Stroke motor rehabilitation • Brain-computer interface • Stroke rehabilitation • Irreversible paralysis

C.M. McCrimmon (✉) • P.T. Wang, PhD
Z. Nenadic, DSc
Department of Biomedical Engineering, University of California Irvine, 3120 Natural Sciences II, Irvine, CA 92697-2715, USA
e-mail: cmccrimm@uci.edu

A.H. Do, MD
Department of Neurology, University of California Irvine, 101 The City Drive, Orange, CA 92686, USA

30.1 Introduction

There are >7 million stroke survivors in the USA alone, with approximately 795,000 new cases annually [1]. Despite spontaneous recovery and intensive physiotherapy [2], ~54 % of stroke survivors remain affected by significant motor impairment [3], such as upper (21 % [4]) and

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lower (50–60 % [5]) extremity deficits. Poststroke motor impairment is directly associated with decreased independence and lost productivity. Gait impairment, in particular, is associated with significant disability and reduced physical activity and is one of the few impairments that is directly linked to poor social reintegration [6, 7]. These problems lead to an increased risk of medical complications and raise a major public health concern in the form of increased healthcare, caregiving, and lost productivity costs. These costs are anticipated to increase as the aging population grows and as acute stroke survival rates improve.

For decades clinicians have utilized assistive devices such as orthoses and functional electrical stimulation (FES) systems to mitigate poststroke motor impairments. However, these devices are cumbersome and may cause discomfort, and their benefits disappear upon removal. Significant effort has been invested to develop new technologies and methodologies to enhance stroke rehabilitation outcomes. However, some of these emerging rehabilitation approaches, such as robotic-assisted therapy, or body weight-supported treadmill training have proven to be no better than conventional physiotherapies [2, 8]. Alternatives, such as brain-computer interface (BCI) technology, may provide functional improvements beyond conventional therapies.

BCIs enable direct brain control of assistive devices and prostheses [9]. They employ decoding algorithms to translate electrophysiological signals acquired from the brain (e.g., electroencephalogram [EEG]) into control commands for assistive devices [9]. When integrated with functional electrical stimulators (FES) or robotic orthoses, BCIs enable the direct brain control of these assistive devices (see Fig. 30.1). Such integrated systems can be applied as neuroprostheses or as novel physiotherapies to restore or improve motor function after stroke. These neuroprosthetic BCI systems are designed to replace motor functions that have been completely lost due to

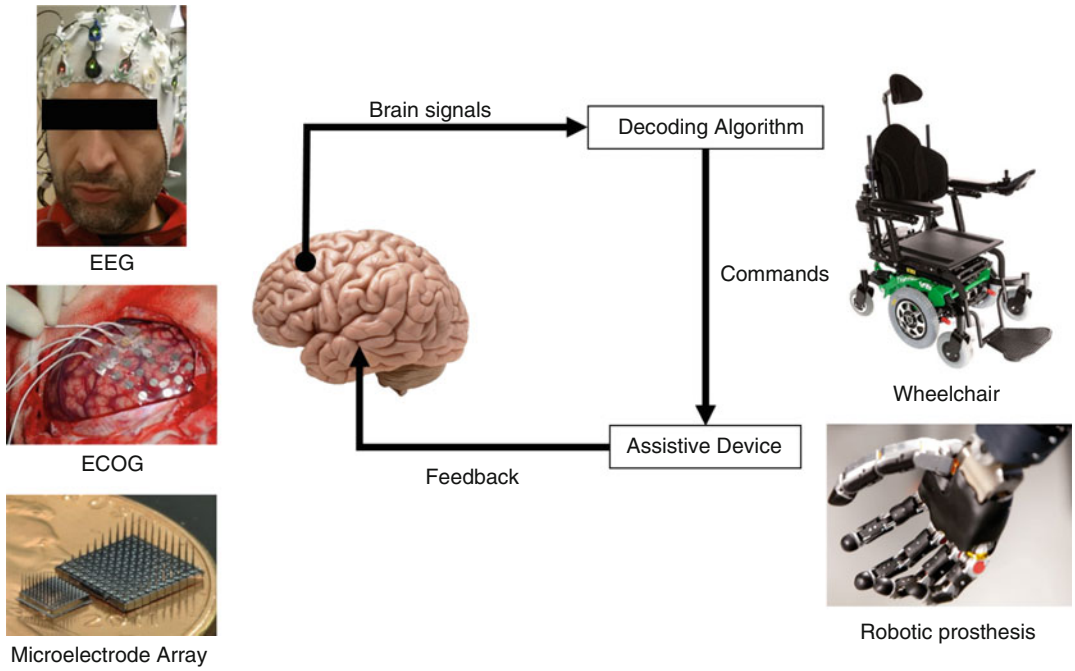

Fig. 30.1 Diagram describing the operation of a typical BCI system. Brain signals are first acquired via EEG, ECoG, or intracortical microelectrodes (local field and action potentials). These signals are analyzed in real time using decoding algorithms. The outputs of these algorithms are commands for external assistive devices. Their response to the brain-derived commands provides feedback to the user so that adjustments can be made as necessary

stroke. When applied in physiotherapy, BCIs are hypothesized to stimulate a Hebbian plasticity process (where "neurons that fire together, wire together"). This approach could be used synergistically with other rehabilitative options and may ultimately facilitate functional recovery beyond that of conventional physiotherapies. This chapter will explore the emerging use of BCI technology in clinical stroke rehabilitation.

30.2 How BCIs Work

BCIs exploit predictable changes in neural signals to enable brain control of external devices. Brain signals such as EEG, electrocorticogram (ECoG), as well as local field and action potentials exhibit predictable changes with various motor behaviors. Typically, BCIs use motor imagery (MI) or even attempted motor execution (ME) to elicit these changes (see Fig. 30.2). For example, the sensorimotor rhythms (SMRs), defined as the 8–30 Hz brain waves from sensory and motor areas [10], are known to be attenuated when an individual initiates movement. This phenomenon is known as event-related desynchronization (ERD). The attenuation of these signals stops with movement cessation, in a process known as event-related synchronization (ERS). In addition to these low frequency modulations, brain waves in the high-gamma band (>70 Hz), which can be acquired from subdural ECoG elec-

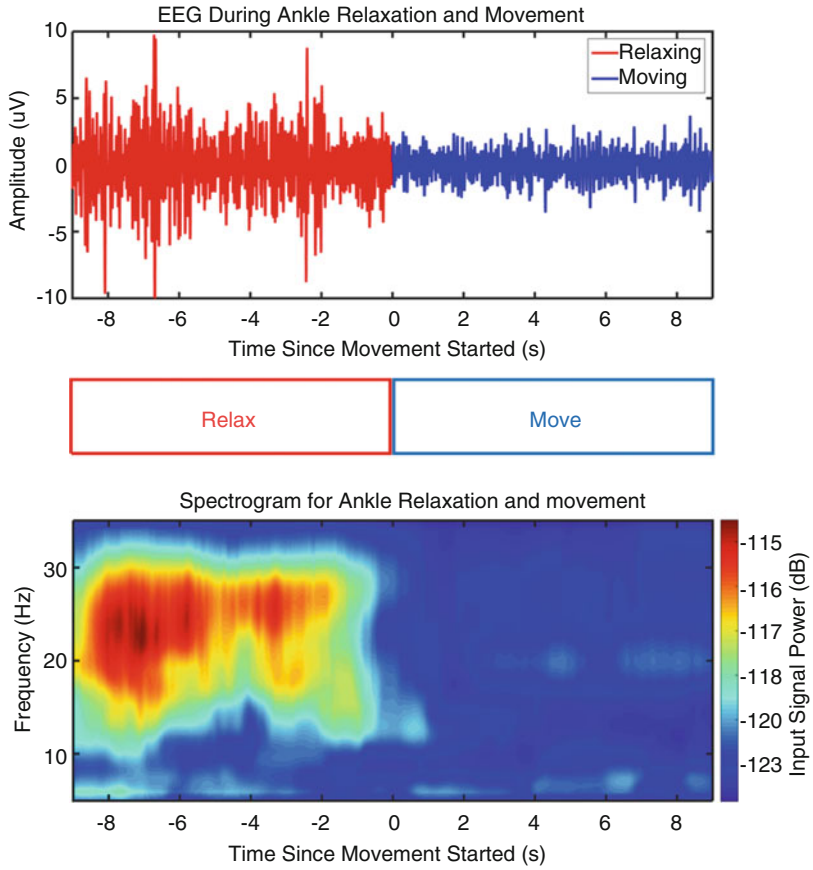

Fig. 30.2 Diagram showing movement-related EEG modulation from the relevant electrode (Cz from the International 10–20 system). When the stroke survivor relaxes the ankle, high-amplitude oscillations (5–35 Hz) are seen in the time series data (*top*) and the time-frequency spectrogram (*bottom*). When the individual moves his paretic ankle, these waves become desynchronized

trodes, also exhibit ERS during movement [11, 12]. Lastly, local populations of neurons have been shown to exhibit increased spiking activity for specific movement directions [13–15].

Decoding algorithms can utilize a variety of statistical analysis techniques to distinguish an individual's intentions based on changes in the neural signals. Typically, this is performed by classifying neural signals into discrete states, such as a movement class (where the individual intends movement via MI or ME) and an idling class (where no movement is intended). This type of discrete classification can be robustly achieved with EEG signals. To predict limb movement trajectories, higher resolution signals, such as ECoG or neuronal action potentials, are required. Upon decoding the movement intention (into either discrete states or continuous trajectories), a computer command is sent to an output device. Common output devices include functional electrical stimulation (FES) systems, robotic limbs or exoskeletons, wheelchairs, and virtual keyboard/mouse. The operation of the device also provides feedback, usually visual, to the user so that adjustments can be made.

30.3 Neuroprosthetic BCI Systems

Historically, BCI systems were developed to target severe forms of motor diseases such as amyotrophic lateral sclerosis (ALS), where they could provide a means of communication with the outside world. Similar BCI systems have since been applied to other neurological diseases, such as high cervical spinal cord injury (SCI), where they are intended to provide the user with volitional and natural upper extremity control. In general, neuroprosthetic BCI systems can be used to acquire movement intention signals from intact brain cortex and subsequently translate them into control commands for devices such as a robotic exoskeletons and FES systems, thereby providing a means to restore brain-controlled manipulation of the environment. Even though the original BCI systems were designed for ALS and SCI, this technology can also be utilized in stroke rehabilitation. More specifically, the ideal post-stroke candidates for such BCI systems would be those with complete or near-complete paralysis due to subcortical strokes (e.g., lesions in the internal capsule) who are unlikely to regain further motor function.

To date, a number of BCI systems have successfully demonstrated that brain signals acquired either noninvasively (typically EEG) or invasively (typically ECoG or intracortical microelectrode arrays) can be exploited to enable brain control of both upper and lower extremity prostheses. For example, Pfurtscheller et al. [16] utilized an EEG-based BCI to enable FES-mediated hand grasping in an individual with C6 SCI. Do et al. [17] also implemented an EEG-based BCI system which enabled an individual with paraplegia to walk using a robotic exoskeleton system. Similarly, King et al. extended this concept to restoration of overground walking in a person with paraplegia due to SCI [18]. Invasive BCIs are able to achieve control of more degrees of freedom (DOF) than existing noninvasive BCI systems and non-BCI technologies (e.g., a mouth joystick). For example, in the BrainGate clinical trials, intracortical microelectrode arrays implanted in tetraplegic individuals enabled control of a 6-DOF robotic arm [19, 20]. Collinger et al. [21] utilized two microelectrode arrays implanted into the motor cortex of a patient with severe tetraparesis due to spinocerebellar degeneration to successfully control a 7-DOF robotic arm. More recently, Aflalo et al. [22] utilized a microelectrode array to record movement trajectory intention in the posterior parietal cortex and enable a person with tetraplegia to control a robotic arm. Although not as robust in function as the microelectrode-based BCIs above, Wang et al. [23] demonstrated that ECoG signals could be used by an individual with tetraplegia to control a robotic arm. Since BCI systems do not monopolize residual motor functions, such as mouth movements, they allow the user to maintain BCI control while talking, drinking, etc.

It is envisioned that the function of the aforementioned systems can be extended to those with hemiplegia due to stroke. For example, distal upper extremity weakness is a common clinical outcome of stroke, and systems such as those by Pfurtscheller et al. [16] may help restore hand movement in stroke survivors. In addition, since

as many as 15 % of stroke survivors lose their ability to ambulate, BCI-controlled lower extremity prostheses could help restore walking. At the time of publication, there are no BCI-controlled neuroprostheses that have undergone definitive clinical trials for safety and efficacy. In addition, none have been FDA approved for marketing, and hence no clinical recommendations can be made regarding the application of neuroprosthetic BCIs for stroke.

Before these devices reach the point where they can be widely used and adopted, several outstanding problems must be addressed. First, these systems are not yet sufficiently accurate to robustly restore movement to paralyzed limbs. For example, the best BCIs, which simply differentiate between movement and idling states, can only reach <95 % accuracy, and this may translate into operation errors that are frustrating or dangerous to the user. Second, they typically require full-sized computers and bulky amplifier arrays, which limit their portability. Significant engineering effort will need to be invested in order to miniaturize the requisite electronic components such that they are wearable, aesthetically acceptable, as well as constantly available and easy to use. Lastly, noninvasive systems require EEG caps which are tedious and time consuming to don and doff. In order to address these challenges, it may be necessary to develop implantable BCI systems, including electrodes, amplifiers, and special purpose microcomputers. Ultimately, clinical trials will need to be conducted to determine whether these systems are safe (e.g., do not cause seizures or nervous tissue injuries) and effective (reduce disability).

30.4 BCI Systems for Physiotherapy

30.4.1 Review of Existing BCI Systems for Stroke Rehabilitation and Underlying Mechanisms

The general consensus in stroke motor rehabilitation is that the most effective practices employ repetitive, high-intensity, goal-oriented movement of the impaired limb (such as constraint-induced movement therapy) to overcome learned disuse [24]. Additionally, it is recommended that patients execute these movements as naturally as possible [25, 26]. However, severely disabled individuals may be unable to participate in active movement therapies, and hence BCIs may be applied as novel therapies to facilitate compliance to these rehabilitative guidelines. It can be hypothesized that BCI therapy, when used in conjunction with conventional physiotherapies, may also improve motor function in those with moderate or mild impairment due to stroke. Stroke survivors are still able to modulate EEG without performing any physical movement [25, 27–32], and this can be exploited by BCIs for stroke rehabilitation. Moreover, MI- and ME-based BCI therapies can be carried out in a repetitive [30] and goal-oriented [24] manner that ensures intense focus on the motor function task [25, 28, 33, 34]. These BCIs may facilitate neuroplastic cortical changes similar to repetitive movement practice [26], possibly through operant conditioning. For example, the BCI output could provide feedback to the user about his/her cortical state, and the user could then attempt to modulate his/her SMRs to achieve maximum control of the BCI. This learning process may lead to subsequent beneficial neural changes [27, 31–33, 35–38] and, in turn, to improved motor function (see Fig. 30.3). For example, MI and ME have been shown to strengthen visuospatial [39], primary/associated motor [26, 30, 38–40], and primary somatosensory [25] networks.

Many previous studies have demonstrated that MI and ME generate robust changes in EEG signals that are suitable for BCIs, even in the post-stroke cortex, making BCI-based stroke rehabilitation a possibility. Mohapp et al. [41] used MI and ME on ten stroke patients with an average BCI classification accuracy between 61.5 % and 79.0 % (depending on which limb and hemisphere were used). Bai et al. [42] investigated both MI and ME tasks with a BCI that utilized beta-rhythm SMR and found that, without extensive training, the classification accuracy in stroke subjects was comparable to healthy subjects (≥80 %). Buch et al. [43] reported successful control of a MEG-based BCI by eight stroke

patients who utilized mu-rhythm ERD during both ME and MI tasks to control an orthosis attached to the plegic hand. Six out of the eight patients achieved a significant increase in BCI classification accuracy by the 20th session, with a median accuracy of 72.48 % across subjects at the final session. Prasad et al. [44] evaluated five chronic stroke patients undergoing combined physical practice and MI-based BCI and found that BCI classification accuracy was ~70 % on average. McCrimmon et al. [45] investigated an ME-based FES therapy in nine chronic stroke patients and found that the average classification accuracy for these subjects was ~80 %. From these studies, it is clear that stroke survivors can successfully control MI- and ME-based BCIs.

Adding a proprioceptive feedback mechanism to MI- and ME-based BCIs may further enhance functional recovery in stroke survivors (see Fig. 30.3). More specifically, proprioceptive BCIs pair motor intention (motor and visuomotor activation) with movement of the paretic limb (e.g., through robotic assistance). This may facilitate Hebbian-like learning and neural reorganization [26, 30, 31, 46] and ultimately improve motor recovery [32, 33, 47]. It is likely that these plastic changes occur at the level of the cortex and primarily affect motor planning and initiation, since synaptic changes directly between upper motor neurons and sensory fibers are unlikely to occur. Additionally, any improvement in motor function results in a subsequent increase in proprioceptive feedback, creating a positive feedback loop of further CNS changes [26].

This proprioceptive BCI concept has been successfully realized in several studies. For example, Broetz et al. [36] and Caria et al. [46] trained a hemiplegic patient with no active finger extension with a BCI that drove an orthosis attached to his paralyzed arm. The patient used mu-rhythm modulation to control the orthosis and underwent goal-directed physiotherapy training over the course of 1 year. Gomez-Rodriguez et al. [47] evaluated BCI-robotic arm-assisted

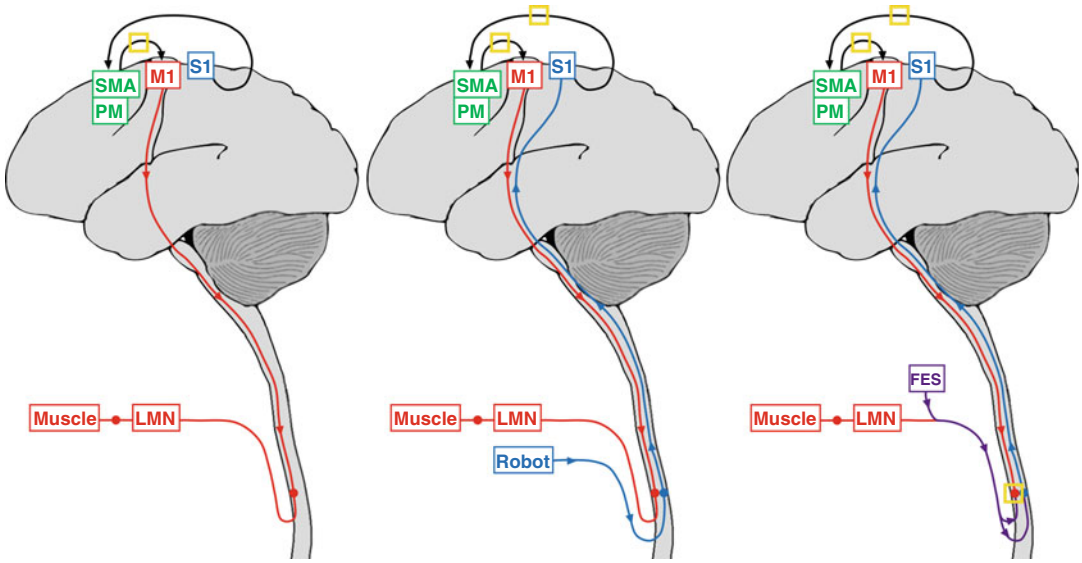

Fig. 30.3 Hypothesized mechanisms of poststroke motor recovery using BCI systems. Here the lower motor neuron (LMN) output and subsequently the muscle output are severely impaired. (**a**) MI- and ME-based BCIs may elicit cortical changes (*yellow square*) between the primary motor cortex (M1) and the supplementary motor area (SMA), premotor cortex (PM), and even the prefrontal and posterior parietal areas (not shown). (**b**) MI- and ME-based BCIs that provide robotic assistance may additionally stimulate dorsal sensory pathways and subsequently facilitate neuroplastic changes between the primary somatosensory cortex (S1) and the non-primary motor areas. (**c**) BCIs that deliver MI- or ME-controlled FES may also promote changes in the anterior horn of the spinal cord at the level of the antidromically activated LMN

physiotherapy in three chronic stroke patients. Patients attempted either elbow flexion or extension or MI, while the BCI would detect their intention to move and then initiated active robotic assistance. Ang et al. [48] studied the effect of MI-based BCI with haptic feedback in 21 chronic stroke patients in a controlled trial. Subjects participated in 18 therapy sessions in which grasping and knob manipulation tasks were carried out using MI-BCI with robotic assistance. Note that all of the above studies were conducted using noninvasive EEG-based BCIs.

In addition to delivering proprioceptive feedback, BCI can also control functional electrical stimulation (FES) systems as another potential means to drive neuronal plasticity processes (see Fig. 30.3). Using FES with MI- and ME-based BCIs not only activates afferent sensory pathways but also lower motor neurons. Compared to proprioceptive feedback alone, this mechanism may further enhance neural plastic changes, especially in sensorimotor areas [38, 40, 49, 50]. Additionally, the coincident activation of upper and lower motor neurons may induce Hebbian learning via long-term potentiation at their synapse in the spinal cord [50, 51]. Initial evidence from Hara et al. [52] supports the use of therapies that coactivate upper and lower motor neurons. Here, it is suggested that an EMG-controlled FES therapy, in which motor intention is coupled with FES, may be more beneficial than either attempted movement or FES alone.

Several preliminary studies have demonstrated the feasibility of BCI-FES systems for physiotherapy. Daly et al. [25] combined BCI and FES for motor learning in a single chronic stroke patient who was unable to perform isolated finger movements. Visual cues were provided to the subject to relax or move her paretic fingers, and ME- or MI-based motor intention (via the BCI) triggered FES-induced index finger extension. After a small number of training sessions, volitional motor control over the index finger was obtained. McCrimmon et al. [45] utilized a similar paradigm for lower extremity rehabilitation. Nine chronic stroke subjects with foot drop each participated in 12 sessions, in which they followed visual cues and attempted either ankle dorsiflexion or relaxation, while FES was either supplied or withheld, respectively. Gait function improved in several subjects (details discussed further below).

30.4.2 BCI-Based Stroke Physiotherapy in Clinical Applications

The BCI systems presented above have led to an increasing number of clinical studies that examined the feasibility and outcomes of BCI-based therapies for stroke rehabilitation. However, among these studies, formal clinical trials are sparse, and the rest are proof of principle, small case series, or other uncontrolled studies. At the time of this review, there was one Phase I clinical trial [45] and two Phase II clinical trials [33, 48] on BCI-based physiotherapies. Given the absence of any definitive Phase III clinical trials regarding the efficacy of BCI-based physiotherapy, it is currently not possible to determine whether these approaches are beneficial. In addition, there is also little existing research that elucidates the underlying mechanism of any improvements seen in stroke patients who underwent BCI-based physiotherapies.

As discussed above, stroke patients are generally able to operate EEG-based BCIs that are designed for rehabilitation purposes. The existing case reports and series that employed a before-and-after comparison in a small number of stroke subjects suggest that motor outcomes improved after BCI-based physiotherapy. These outcomes include upper and lower extremity motor function and other physiological measures. However, outside of demonstrating that BCI-based physiotherapy is technically feasible, no safety or efficacy conclusions can be drawn from these studies.

McCrimmon et al. [45] have conducted a Phase I trial examining the safety of a BCI-FES dorsiflexion therapy in chronic stroke patients with gait impairment due to foot drop. It was found that none of the participants ($n=9$) experienced any deterioration, hence indicating preliminary safety of this approach. Post hoc analysis

also revealed that 66.6 % of subjects experienced a significant increase in either their gait velocity or 6-min walk distance at 1 month after the completion of the intervention. Five out of these six subjects with gait velocity or 6-min walk distance improvement also experienced changes in the magnitude of alpha and beta band ERD and ERS at the end of the study. This was not observed in any of the subjects with no gait velocity improvement. These observations provide preliminary evidence that BCI-FES dorsiflexion therapy is safe and are promising to explore in a Phase II clinical trial.

Ramos-Murguialday et al. [33] described a randomized Phase II trial which examined the potential efficacy of BCI-controlled robotic orthosis therapy for the upper extremity in chronic stroke survivors. In this study, subjects were randomized to either BCI-controlled robotic orthosis therapy or sham therapy. All subjects also received concurrent physiotherapy. The treatment group had a 3.416 ± 0.563-point difference in the Fugl-Meyer upper extremity motor score compared to the control group ($p < 0.018$).

Ang et al. [48] reported a randomized Phase II trial on BCI-controlled haptic feedback therapy in chronic stroke survivors. Study subjects were randomly assigned to one of three treatment groups: (1) BCI-controlled haptics knob paired with conventional physiotherapy, (2) haptics knob therapy paired with conventional physiotherapy, and (3) conventional physiotherapy. All three treatment groups received the same dose of therapy. A total of 22 subjects were recruited (after excluding 921 patients). All groups had significant improvement in the upper extremity FM motor score, but there were no significant intergroup differences.

Based on the current clinical trial literature, there is some evidence to suggest that BCI-based physiotherapies may be safe and promising enough to warrant further clinical investigations. However, no clinical practice recommendations can be made regarding BCI-based physiotherapies. Given the paucity of data, researchers in the field of BCI-based physiotherapies must ultimately pursue formal evaluation pathways that culminate in large definitive Phase III clinical trials to determine whether these approaches are safe and efficacious. There are many outstanding clinical questions that must be answered along this pathway. First, it is notable that there is very little interest in the safety of BCI-based physiotherapies among the research community, yet there is no clear evidence that indicates whether these approaches can cause adverse events, e.g., worsening of function due to maladaptive behaviors or other negative forms of neural plasticity. In addition, the complexity of BCI systems also raise many comparison questions that affect how BCI-based physiotherapies may be adopted or applied clinically even if they prove to be safe and efficacious. For example, it is unknown how the effects of BCI-based therapies compare to those of other physiotherapies (i.e., do they surpass standard physical and occupational therapy, or are they simply equivalent?). Are there particular characteristics of stroke patients who will respond best to BCI-based physiotherapy? Will the approaches be relevant to the stroke population at large, or can they only be applied to a small proportion of patients (e.g., [48])? The answers to these questions have implications for the future justification of BCI-based therapies, particularly if existing dose-matched therapies turn out to be cheaper and just as efficacious. Finally, given the conflicting results of Ang et al., Ramos-Murguialday et al., and McCrimmon et al., it remains unclear which BCI-based physiotherapy mechanisms are most effective for poststroke therapy.

In addition to the above scientific questions, many practical issues related to the implementation of BCI-based physiotherapies need to be addressed. Since these therapies currently require extensive setup, it is unclear how they will be efficiently and effectively delivered in clinical practice. Are there ways to drastically reduce the setup time of such BCI systems? Additionally, will BCI-based therapies be provided by the physical and occupational therapists in the community? Will they be time and resource efficient? Will the associated equipment and training costs be acceptable to practicing clinicians? Will patients be interested in such therapies? Since this research field is still in early development, the medical device industry has yet to streamline these systems. As the field

matures, it can be expected that BCI-based physiotherapy studies will transition toward large clinical trials. At that time, significant research and development must be performed to understand and address these market issues that may ultimately affect the success of BCI-based physiotherapies.

30.5 Conclusion and Future Directions

In recent years, BCI-based physiotherapies have garnered increasing interest as a means of substituting for lost motor functions or for improving poststroke motor outcomes. Neuroprosthetic BCIs have been designed primarily for SCI, but can be extended to poststroke paralysis. Significant engineering challenges must still be overcome before these systems can be used in the clinic in a robust and practical manner. BCI systems for physiotherapy may be applied as a novel means of facilitating Hebbian learning mechanisms, which can be elicited by two major strategies. One involves providing BCI-controlled proprioceptive sensory feedback to upregulate the connection between sensory and motor cortices and subsequently cause increased motor output to the lower motor neurons. The second strategy employs BCI-controlled electrical stimulation to simultaneously activate the poststroke motor areas and the lower motor neurons, thereby increasing their connectivity over time. Both of these strategies can potentially promote motor recovery. In fact, these strategies have already been realized in BCI-controlled robotic and FES therapies. Existing case reports and series and clinical trials suggest that these strategies are promising. However, many questions still remain regarding the safety and efficacy of BCI-based physiotherapies and whether they can be practically applied in the clinical setting.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2–220.
2. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, et al. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011;364(21):2026–36.
3. Jørgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Støier M, Olsen TS. Outcome and time course of recovery in stroke. Part I: outcome. The Copenhagen stroke study. Arch Phys Med Rehabil. 1995;76(5):399–405.
4. Nakayama H, Jørgensen H, Raaschou H, Olsen T. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1994;75(4):394–8.
5. Hendricks HT, van Limbeek J, Geurts AC, Zwarts MJ. Motor recovery after stroke: a systematic review of the literature. Arch Phys Med Rehabil. 2002;83(11):1629–37.
6. Lord SE, McPherson K, McNaughton HK, Rochester L, Weatherall M. Community ambulation after stroke: how important and obtainable is it and what measures appear predictive? Arch Phys Med Rehabil. 2004;85(2):234–9.
7. Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. Stroke. 1995;26(6):982–9.
8. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362(19):1772–83.
9. Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. Clin Neurophysiol. 2002;113(6):767–91.
10. Pfurtscheller G, Neuper C. Future prospects of ERD/ERS in the context of brain-computer interface (BCI) developments. Prog Brain Res. 2006;159:433–7.
11. Miller K, Zanos S, Fetz E, Den Nijs M, Ojemann J. Decoupling the cortical power spectrum reveals real-time representation of individual finger movements in humans. J Neurosci. 2009;29(10):3132–7.
12. Schalk G, Kubanek J, Miller K, Anderson N, Leuthardt E, Ojemann J, et al. Decoding two-dimensional movement trajectories using electrocorticographic signals in humans. J Neural Eng. 2007;4(3):264.
13. Georgopoulos AP, Kalaska JF, Caminiti R, Massey JT. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. J Neurosci. 1982;2(11):1527–37.
14. Georgopoulos AP, Schwartz AB, Kettner RE. Neuronal population coding of movement direction. Science. 1986;233(4771):1416–9.
15. Scherberger H, Jarvis MR, Andersen RA. Cortical local field potential encodes movement intentions in the posterior parietal cortex. Neuron. 2005;46(2):347–54.
16. Pfurtscheller G, Müller GR, Pfurtscheller J, Gerner HJ, Rupp R. Thought–control of functional electrical stimulation to restore hand grasp in a patient with tetraplegia. Neurosci Lett. 2003;351(1):33–6.

17. Do AH, Wang PT, King CE, Chun SN, Nenadic Z. Brain-computer interface controlled robotic gait orthosis. J Neuroeng Rehabil. 2013;10(1):111.
18. King CE, Wang PT, McCrimmon CM, Chou CCY, Do AH, Nenadic Z. The feasibility of a brain-computer interface functional electrical stimulation system for the restoration of overground walking after paraplegia. J Neuroeng Rehabil. 2015;12(80):1–11.
19. Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature. 2006;442(7099):164–71.
20. Hochberg LR, Bacher D, Jarosiewicz B, Masse NY, Simeral JD, Vogel J, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature. 2012;485(7398):372–5.
21. Collinger JL, Wodlinger B, Downey JE, Wang W, Tyler-Kabara EC, Weber DJ, et al. High-performance neuroprosthetic control by an individual with tetraplegia. Lancet. 2013;381(9866):557–64.
22. Aflalo T, Kellis S, Klaes C, Lee B, Shi Y, Pejsa K, et al. Decoding motor imagery from the posterior parietal cortex of a tetraplegic human. Science. 2015;348(6237):906–10.
23. Wang W, Collinger JL, Degenhart AD, Tyler-Kabara EC, Schwartz AB, Moran DW, et al. An electrocorticographic brain interface in an individual with tetraplegia. PLoS One. 2013;8(2):e55344.
24. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol. 2009;8(8):741–54.
25. Daly JJ, Cheng R, Rogers J, Litinas K, Hrovat K, Dohring M. Feasibility of a new application of noninvasive Brain Computer Interface (BCI): a case study of training for recovery of volitional motor control after stroke. J Neurol Phys Ther. 2009;33(4):203–11.
26. Daly JJ, Wolpaw JR. Brain–computer interfaces in neurological rehabilitation. Lancet Neurol. 2008;7(11):1032–43.
27. Pfurtscheller G, Muller-Putz GR, Scherer R, Neuper C. Rehabilitation with brain-computer interface systems. Computer. 2008;41(10):58–65.
28. Ang KK, Guan C, Chua KSG, Ang BT, Kuah C, Wang C, et al. A clinical study of motor imagery-based brain-computer interface for upper limb robotic rehabilitation. In: Proceedings of 31st annual international conference engineering in medicine and biology society, IEEE, Piscataway, New Jersey, USA 08854, 2009. p. 5981–4.
29. Teasell RW, Kalra L. Advances in stroke 2003-what's new in stroke rehabilitation. Stroke. 2004;35(2):383–5.
30. Belda-Lois JM, Mena-del Horno S, Bermejo-Bosch I, Moreno JC, Pons JL, Farina D, et al. Rehabilitation of gait after stroke: a review towards a top-down approach. J Neuroeng Rehabil. 2011;8(1):66.
31. Ramos-Murguialday A, Schürholz M, Caggiano V, Wildgruber M, Caria A, Hammer EM, et al. Proprioceptive feedback and Brain Computer Interface (BCI) based neuroprostheses. PLoS One. 2012;7(10):e47048.
32. Ang KK, Guan C. Brain-computer interface in stroke rehabilitation. J Comput Sci Eng. 2013;7(2):139–46.
33. Ramos-Murguialday A, Broetz D, Rea M, Läer L, Yilmaz Ö, Brasil FL, et al. Brain-machine interface in chronic stroke rehabilitation: a controlled study. Ann Neurol. 2013;74(1):100–8.
34. Wang C, Phua KS, Ang KK, Guan C, Zhang H, Lin R, et al. A feasibility study of non-invasive motorimagery BCI-based robotic rehabilitation for Stroke patients. In: Proc 31st Ann Int Conf Eng Med Bio Soc. IEEE; 2009. p. 271–4.
35. Kaiser V, Kreilinger A, Müller-Putz GR, Neuper C. First steps toward a motor imagery based stroke BCI: new strategy to set up a classifier. Front Neurosci. 2011;5:86.
36. Broetz D, Braun C, Weber C, Soekadar SR, Caria A, Birbaumer N. Combination of brain-computer interface training and goal-directed physical therapy in chronic stroke: a case report. Neurorehabil Neural Repair. 2010;24:674.
37. Takeuchi N, Izumi SI. Rehabilitation with poststroke motor recovery: a review with a focus on neural plasticity. Stroke Res Treat. 2013;2013:128641.
38. Meng F, Tong KY, Chan ST, Wong WW, Lui KH, Tang KW, et al. BCI-FES training system design and implementation for rehabilitation of stroke patients. In: Proceedings of international joint conference on neural networks, IEEE, Piscataway, New Jersey, USA 08854, 2008. p. 4103–6.
39. Varkuti B, Guan C, Pan Y, Phua KS, Ang KK, Kuah CWK, et al. Resting state changes in functional connectivity correlate with movement recovery for BCI and robot-assisted upper-extremity training after stroke. Neurorehabil Neural Repair. 2013;27(1):53–62.
40. Saito K, Sugawara K, Miyaguchi S, Matsumoto T, Kirimoto H, Tamaki H, et al. The modulatory effect of electrical stimulation on the excitability of the corticospinal tract varies according to the type of muscle contraction being performed. Front Hum Neurosci. 2014;8:835.
41. Mohapp A, Scherer R, Keinrath C, Grieshofer P, Pfurtscheller G, Neuper C. Single-trial EEG classification of executed and imagined hand movements in hemiparetic stroke patients. Proceedings of international BCI workshop & training course; Graz University of Technology, Graz, Austria, 2006.
42. Bai O, Lin P, Vorbach S, Floeter MK, Hattori N, Hallett M. A high performance sensorimotor beta rhythm-based brain-computer interface associated with human natural motor behavior. J Neural Eng. 2007;5(1):24–35.
43. Buch E, Weber C, Cohen LG, Braun C, Dimyan MA, Ard T, et al. Think to move: a neuromagnetic Brain-Computer Interface (BCI) system for chronic stroke. Stroke. 2008;39(3):910–7.

44. Prasad G, Herman P, Coyle D, McDonough S, Crosbie J. Applying a brain-computer interface to support motor imagery practice in people with stroke for upper limb recovery: a feasibility study. J Neuroeng Rehabil. 2010;7(1):60.
45. McCrimmon CM, King CE, Wang PT, Cramer SC, Nenadic Z, Do AH. Brain-controlled functional electrical stimulation therapy for gait rehabilitation after stroke: a safety study. J Neuroeng Rehabil. 2015;12:57.
46. Caria A, Weber C, Brötz D, Ramos A, Ticini LF, Gharabaghi A, et al. Chronic stroke recovery after combined BCI training and physiotherapy: a case report. Psychophysiology. 2011;48(4):578–82.
47. Gomez-Rodriguez M, Grosse-Wentrup M, Hill J, Gharabaghi A, Schölkopf B, Peters J. Towards brainrobot interfaces in stroke rehabilitation. In: Proceedings of international conference rehabilitation robotics IEEE, Piscataway, New Jersey, USA 08854, 2011. p. 5975385.
48. Ang KK, Guan C, Phua KS, Wang C, Zhou L, Tang KY, et al. Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke. Front Neuroeng. 2014;7:30.
49. Everaert DG, Thompson AK, Chong SL, Stein RB. Does functional electrical stimulation for foot drop strengthen corticospinal connections? Neurorehabil Neural Repair. 2010;24(2):168–77.
50. Takahashi M, Takeda K, Otaka Y, Osu R, Hanakawa T, Gouko M, et al. Event related desynchronization-modulated functional electrical stimulation system for stroke rehabilitation: a feasibility study. J Neuroeng Rehabil. 2012;9(1):56.
51. Rushton D. Functional electrical stimulation and rehabilitation – an hypothesis. Med Eng Phys. 2003;25(1):75–8.
52. Hara Y, Obayashi S, Tsujiuchi K, Muraoka Y. The effects of electromyography-controlled functional electrical stimulation on upper extremity function and cortical perfusion in stroke patients. Clin Neurophysiol. 2013;124(10):2008–15.

Epilogue: What Lies Ahead?

In the relatively short period that has elapsed since the publication of our previous volume (*Neurorehabilitation Technologies, 1st Edition*), there have been rapid shifts in technology applied to rehabilitation, and a number of novel technical approaches have emerged that show promise for transforming the ways in which neurologic rehabilitation will be provided in the future.

Shifts in Advanced Technology

There has been a continuing growth in the use rehabilitation robots for therapy, although the growth appears to have slowed to some degree. This is potentially because of the continuing high cost of most robotic systems, coupled with the rather demanding level of technical sophistication required to manage these systems. As a result, they have had limited impact on clinical rehabilitation practice of neurologic disorders.

While cost and complexity appear to be important, as listed above, there remain significant technical limitations in robotic technology that are equally important. In particular, there is increasing emphasis on high-intensity gait training after stroke or spinal cord injury, once the acute period of injury has passed. Most of the robotic systems cannot yet allow, let alone actively support, the capacity of a recovering patient to generate large forces that move the robot, or allow the person to impose rapid motion. Until these robotic designs are able to match ongoing therapeutic needs, it is less likely that there will be much new penetration into regular clinical practice.

There is also an increasing need for a rational analysis of interaction between robots and humans. Currently, most robotic systems are used to impose presumptively useful patterns of motion, especially in the lower extremity, or to facilitate game playing in the upper extremity, which is believed to improve visually guided hand use. There is as yet no global theory based on identified mechanisms of motor learning and activity-dependent neuroplasticity that motivates or drives the use of many robotic systems for rehabilitation.

Rise of the Exoskeletons

As described in the new Chap. 24, there are currently under development or in active use somewhere around ten different commercial lower extremity exoskeletal systems. Most of these are used to support locomotion in patients with complete spinal cord injury. One of the earlier systems, ReWalk™ from Argo, has been able to demonstrate the ability to support effective locomotion in certain patients with complete spinal injury, allowing them to walk in a community setting or at home for long periods of time. Although it is worth noting that successful use of these devices requires considerable upper extremity strength combined with a degree of athleticism, limiting widespread application of the devices. It is also worth noting that there are many fewer commercial exoskeletons available for upper extremity retraining, again perhaps of

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the uncertainty about therapeutic objectives for these devices.

Because of constraints imposed by the Food and Drug Administration in the USA and by other agencies in Europe, the role of these robots has been blurred by the perceived need to also show therapeutic benefit during rehabilitation. This task has proved much more difficult to accomplish than anticipated, mainly because the robots are not well suited to achieve this objective.

If a person can walk, they would probably be best suited to be walking in a safety harness on a treadmill or over ground, not necessarily supported by an exoskeleton. If they cannot walk independently at all, then the question arises as to whether there is long-term benefit from the use of the exoskeletons as therapy devices, or alternatively whether one of the established robotic gait systems would serve the patient's needs better. This question of optimal application of exoskeletons is a pressing one.

A different but equally important issue is the question of safety. Given that many patients with spinal cord injury have lost sensation as well as voluntary strength, it would seem that falls are inevitable, and these falls may be dangerous because of their potential to produce fracture of long bones. Long bones in spinal cord injured patients are known to lose bone mass quite quickly and can therefore become quite fragile. Most importantly, it is well known that femoral or tibial fracture in persons with spinal cord injury can constitute a risk to life. Currently, none of the major commercial vendors of exoskeletons have developed a coherent approach towards minimizing the risk of falls. Most rely on education and on the use of family or other support staff to minimize the risk of falls, but if these systems are to achieve widespread use in the community, then a more rigorous approach to safety will need to be developed.

Cost Benefit of Robotic Technologies

On a different theme, the most advanced exoskeleton technologies have achieved limited penetration in clinical practice. Partly this is because the technology is still relatively new and there are relatively few published examples where it has made a material difference to outcomes. One other equally compelling reason, shared with other established rehabilitation robots, is their cost. Many of the machines remain extremely expensive, and that has an adverse impact in this era of constrained resources. In this regard, the expectation in our field that we will be able to achieve economies of scale once robots became more prevalent and popular has not been sustained. This is because (in part) the numbers of systems being constructed and sold remains relatively small (the most successful companies have sold in the hundreds of devices), but also because there is continuing evolution and improvement of the systems, which has meant that many companies maintain cost at a relatively constant level, but advance the quality and sophistication of the embedded technology. Whatever the primary reason, the machines remain very expensive and most lie well beyond the typical budget of a physical or occupational therapy clinic. Non-robotic technologies, as described in the new section "Other Promising Technologies," which implement the same features as robotic technologies, but with lower cost and greater simplicity, may become increasingly important.

Wearable Sensors

The final novel feature that has burgeoned in the last few years is the emerging use of wearable sensors, as described in the new Chap. 29. These range from accelerometers to force sensors to inertial measurement devices. There are often associated GPS systems that allow tracking the location of the user. There is also widespread use of smart phones in which many of them have embedded sensors that can be used as an alternative way of tracking patient performance when other kinds of sensors are impractical or too costly.

The major constraints in this field are linked to the question of how to deal with the staggering amounts of data that are generated by the sensors.

Most clinicians do not have the time or the sophistication to evaluate and absorb large data sets that describe subjects' use of technologies, and/or their performance at home or in the workplace. In short, what is needed is a way to collapse down the critical piece of information derived from the use of these sensors into a compact form that most clinicians can understand and use readily.

Conclusion

There are clearly challenges emerging in the application of advanced technologies in rehabilitation, and predictably, the cost and complexity of many of the devices, as well as their limited therapeutic benefit, continue to impose constraints on their widespread use. What may ultimately be the most pressing challenge, however, is to find ways for clinicians to apply these devices more broadly, and to find ways to reach out to neurologically injured persons who may have had limited or no access to even simple forms of rehabilitation therapy.

If this is to happen, then machines will have to be far simpler, far cheaper, and much easier to use by all concerned, including clinicians and patients.

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