# Contents

**Neural Rehabilitation: Action and Manipulation**  
*Maurizio Corbetta and Susan M. Fitzpatrick*  
Page 3S

**Neurological Principles and Rehabilitation of Action Disorders: Computation, Anatomy, and Physiology (CAP) Model**  
*Scott H. Frey, Leonardo Fogassi, Scott Grafton, Nathalie Picard, John C. Rothwell, Nicolas Schweighofer, Maurizio Corbetta, and Susan M. Fitzpatrick*  
Page 6S

**Neurological Principles and Rehabilitation of Action Disorders: Common Clinical Deficits**  
*K. Sathian, Laurel J. Buxbaum, Leonardo G. Cohen, John W. Krakauer, Catherine E. Lang, Maurizio Corbetta, and Susan M. Fitzpatrick*  
Page 21S

**Neurological Principles and Rehabilitation of Action Disorders: Rehabilitation Interventions**  
*Valerie Pomeroy, Salvatore M. Aglioti, Victor W. Mark, Dennis McFarland, Cathy Stinear, Steven L. Wolf, Maurizio Corbetta, and Susan M. Fitzpatrick*  
Page 33S
Neurorehabilitation and Neural Repair (NNR) serves clinicians and researchers with an interest in the clinical science and practice of neurological rehabilitation. Neurologists, physiatrists, neurosurgeons, clinical and basic scientists working on neural regeneration and plasticity, rehabilitation nurses, physical, speech, and occupational therapists, neuropsychologists, and engineers. NNR is an international, peer-reviewed publication sponsored by the American Society of Neurorehabilitation and the World Federation for NeuroRehabilitation with its component national societies. The journal features original clinical and basic research articles, brief communications, reviews, points of view about controversial issues, and book reviews. Examples of topics covered include neural reorganization, synaptogenesis, neurogenesis and axon regeneration associated with gene expression, biological interventions, and training paradigms; neurophysiological probes of activity-dependent plasticity such as fMRI and TMS; well-designed pilot studies of physical, cognitive, language, neuropsychological, pharmacological, neurostimulation, and other potential approaches to lessen disability; controlled clinical trials of interventions; useful research designs, statistical procedures, and outcome measures for neurological rehabilitation; bioengineered, assistive, and robotic devices for training and care.

Neurorehabilitation and Neural Repair (ISSN 1545-9683) (J534) is published nine times a year—in January, February, March/April, May, June, July/August, September, October, November/December—by SAGE Publications, 2455 Teller Road, Thousand Oaks, CA 91320. Send address changes to Neurorehabilitation and Neural Repair, c/o SAGE Publications, 2455 Teller Road, Thousand Oaks, CA 91320.

Copyright © 2011 by The American Society of Neurorehabilitation. All rights reserved. No portion of the contents may be reproduced in any form without written permission of the publisher.

Disclaimer: The authors, editors, and publisher will not accept any legal responsibility for any errors or omissions that may be made in this publication. The publisher makes no warranty, express or implied, with respect to the material contained herein. Advertisements in NNR for products, services, courses, and symposia are published with a “caveat emptor–buyer beware” understanding. The authors, editors, and publisher do not imply endorsement of products, nor quality, validity, or approval of the educational material offered by such advertisements.

Subscription Information: All subscription inquiries, orders, back issues, claims, and renewals should be addressed to SAGE Publications, 2455 Teller Road, Thousand Oaks, CA 91320; telephone: (800) 818-SAGE (7243) and (805) 499-0721; fax: (805) 375-1700; e-mail: journals@sagepub.com; http://www.sagepub.com. Subscription Price: Institutions: $1,393; Individuals: $258. For all customers outside the Americas, please visit http://www.sagepub.co.uk/customerCare.nav for information. Claims: Claims for undelivered copies must be made no later than six months following month of publication. The publisher will supply replacement issues when losses have been sustained in transit and when the reserve stock will permit.

Member Subscription Information: American Society of Neurorehabilitation member inquiries, change of address, back issues, claims, and membership renewal requests should be addressed to American Society of Neurorehabilitation, 5841 Cedar Lake Road, Suite 204, Minneapolis, MN 55416; telephone: (952) 545-6324; fax: (952) 545-6073; Web site: http://www.asnr.com; e-mail: asnr@llmsi.com. At the request of the American Society of Neurorehabilitation, the publisher will supply missing copies when losses have been sustained in transit and when the reserve stock will permit.

Abstracting and Indexing: Please visit http://nnr.sagepub.com and, under the “More about this journal” menu on the right-hand side, click on the Abstracting/Indexing link to view a full list of databases in which this journal is indexed.

Copyright Permission: Permission requests to photocopy or otherwise reproduce material published in this journal should be submitted by accessing the article online on the journal’s Web site at http://nnr.sagepub.com and selecting the “Request Permission” link. Permission may also be requested by contacting the Copyright Clearance Center via their Web site at http://www.copyright.com, or via e-mail at info@copyright.com.

Advertising and Reprints: Current advertising rates and specifications may be obtained by contacting the advertising coordinator in the Thousand Oaks office at (805) 410-7772 or by sending an e-mail to advertising@sagepub.com. To order reprints, e-mail reprint@sagepub.com. Acceptance of advertising in this journal in no way implies endorsement of the advertised product or service by SAGE, the journal’s affiliated society(ies), or the journal editor(s). No endorsement is intended or implied. SAGE reserves the right to reject any advertising it deems as inappropriate for this journal.

Change of Address: Six weeks’ advance notice must be given when notifying of change of address. Please send the old address label along with the new address to the SAGE office address above to ensure proper identification. Please specify the name of journal.
Neural Rehabilitation: Action and Manipulation

Maurizio Corbetta, MD¹, and Susan M. Fitzpatrick, PhD¹,²

Introduction

Taking a Cognitive Neuroscience Approach to Neurorehabilitation

Stroke and other neurological injuries and diseases are a leading source of death and disability worldwide. In the United States alone, 6 million people live with the consequences of stroke-related disability (http://www.strokecenter.org/patients/stats.htm). Improved medical care and increased public awareness of the need to respond swiftly to the signs of a possible stroke have reduced deaths. Similarly, individuals with traumatic brain injury and other insults disrupting brain function are also benefitting from improved acute care. The increasing numbers of survivors, many of whom must learn to cope with impairments and disabilities, are placing an increasing demand on the field of neurorehabilitation to do more to help individuals recover as much function and resume as much of their prestroke life as possible. Moreover, in industrialized countries, more and more people will need rehabilitation services as the general population grows older, and neurodegenerative conditions such as Alzheimer’s or Parkinson’s diseases become more prevalent. In developing countries, there is a critical need for rehabilitation services, both neurological and nonneurological, especially in countries devastated by natural disasters, ongoing armed conflicts, and wars. The need for rehabilitation is also increasing in countries in which the use of personal motorized transportation has led to sharply increasing rates of traumatic injuries.

The reasons behind the likely expansion of the field of neurorehabilitation are not only social but also scientific. Over the past 3 decades, many studies have challenged the traditional notion that the brain cannot change once development is completed. There is now compelling evidence that the adult brain retains the ability to modify anatomical and functional connections as a result of learning or injuries. Some of these changes have been associated with recovery of function, especially when coupled with behavioral training. This is good news for rehabilitation because it provides strong scientific bases for the use of exercises and behavioral interventions to promote recovery after injuries of the nervous system.

However, these opportunities are overshadowed by a number of theoretical and practical issues that could lead to the marginalization of this field of medicine. First, at present, neurorehabilitation is not built on solid scientific and theoretical foundations. Most current interventions have not been validated scientifically or are based on concepts of brain function that are outdated. Even when certain interventions have been shown to yield better clinical outcomes in randomized-controlled trials, as in the case of admission to specialized stroke rehabilitation units leading to better outcomes than admission to general medicine wards, it is not known what factors or combination of factors (specialized personnel, environment, intensity or type of therapy, or multidisciplinary approach) actually contribute to this effect.

Second, the efficacy of rehabilitation interventions is likely overestimated because of the way in which rehabilitation teams operate. Typically, a therapist is responsible for both treating patients and evaluating their progress. This dual responsibility of therapists introduces bias, which would be unacceptable in a randomized-controlled study on the efficacy of a drug, and is compounded by institutional pressure to obtain positive results because third-party payers (insurance companies, national health agencies, etc) often “weight” or make decisions regarding payments based on indices related to patients’ progress in therapy.

Third, although more and more randomized-controlled trials are being performed, philosophically, the field of rehabilitation embraces a holistic view of disease processes in which physical and psychological deficits are considered jointly with their impact on everyday function and disability, individual by individual. Hence, treatments and protocols are traditionally tailored to a single patient, often based on a therapist’s or physician’s own personal preference and experience, with little pressure to follow protocols in a consistent manner within or across patients. A final problem for the field is the steady decrease in health care funds, especially for those branches of medicine that do not rely on procedures or high-tech devices. This issue is most severe in the United States where, as competition for funds increases, so does the pressure for each field of medicine to demonstrate the

¹Washington University in St Louis, St Louis, MO, USA
²James S. McDonnell Foundation, St Louis, MO, USA

Corresponding Authors:
Maurizio Corbetta. Washington University School of Medicine, 660 South Euclid, Campus Box 8111, St. Louis, MO 63110, USA
Email: mau@npg.wustl.edu
Susan M. Fitzpatrick, James S. McDonnell Foundation, 1034 S. Brentwood Blvd Ste 1850, St Louis, MO 63117, USA
Email: susan@jsmf.org
scientific value, efficacy, cost-effectiveness, and perceived social value of its interventions based on evidence.

We think that neurorehabilitation might be at a crossroads. One path may lead to the development of a mature clinical-behavioral science grounded in the principles of psychology and neuroscience. The other path is continuing the status quo, which, in the current environment of strong economic pressure, might lead to marginalization of the field. This trend would not only cause severe difficulties to hundreds of thousands of brain injury and stroke victims and their families but would, at the same time, promote an already existing trend in social policies whereby people of more modest economic means and new disabilities after brain injury would be left to their own destiny.

The McDonnell Project Rationale

Cognitive neuroscience defines the study of the relationships between behavior and brain systems. This field has grown greatly over the past 20 years, and accordingly, significant progress has been made in defining, at least in broad strokes, some of the computational, anatomical, and physiological principles that mediate specific behaviors. Much of what we now know, and are continuing to learn about the relationship between neural structure and observable behavior, has been derived from studying individuals with intact nervous systems in comparison to individuals with nervous system injuries. What has not yet happened, in any widespread systematic way, is using the knowledge of cognitive neuroscience to guide and inform interventions designed to minimize or reverse the impairments resulting from neural injury and disease.

The 3 manuscripts in this special issue are the first to appear from a series of workshop and panel activities organized by the editors and supported by the James S. McDonnell Foundation. It is not a novel idea that cognitive neuroscience could serve as a foundational science for neurorehabilitation. Several excellent monographs and edited series have been recently published in this area, and private and public funding agencies have promoted programs to foster collaborations in these 2 areas. These domains of knowledge are conceptually adjacent to each other and could profitably share concepts and principles and even a common language. Cognitive neuroscience has matured into a scientific discipline with an internally consistent set of principles based on the idea that complex behavior can be described as a collection of simpler task processes using task analysis and that these processes are implemented in specialized brain systems.

There are already several reference books for experts and academics, engaged predominantly in research, at the interface of cognitive neuroscience and rehabilitation. An excellent example is the book by Stuss et al. At the clinical end, there have been a number of books, predominantly written by neurologists and psychologists, to relate concepts in basic cognitive neuroscience with syndromes observed in behavioral neurology. An excellent example is the book by Feinberg and Farah. From the neurological perspective, an excellent monograph on the scientific basis of brain rehabilitation is the volume by the editor of Neural Rehabilitation and Repair, Bruce Dobkin.

In the McDonnell Project, our (the editors’) goal is not to produce yet another scholarly article or book primarily serving academic interests. Rather, we are interested in producing practical manuscripts written primarily for clinicians and clinical trainees in the field of neurorehabilitation (physiatrists, neurologists, neuropsychologists, therapists, and nurses). We believe that it is only by engaging a widening circle of hands-on practitioners and providing them with cogent summaries of what is relevant to clinical practice from the rapidly expanding and highly specialized research literature will it be possible to move the fields of neurorehabilitation and cognitive neuroscience closer together.

Our project involved enumerating a set of functions. A function is defined as a set of behaviors that share a common goal. Seeing, walking, speaking, feeling your body, and reaching to grasp a desired object are examples of functions. These distinctions have ecological significance, but they also have clinical significance because, when damaged, these functions cause limitations in the performance of everyday activities and result in disability. Generally, in practice, it is in terms of the ability, or lack of ability, to carry out these functions that rehabilitation professionals think about their patients. We deliberately chose not to divide functions based on neural systems but rather to invoke the interconnected neural systems that contribute to performance. The chapters appearing here deal with “actions” of the upper limb and hand, such as reaching, grasping, manipulating, and pointing.

Once the functions were determined, the next step was assembling a panel of experts for each function. The panels were charged with reviewing the current state of knowledge and creating a framework whereby findings and principles from basic cognitive neuroscience could translate to clinical problems. The panels then began the task of generating a series of articles using a consensus-building process. A chair, appointed for each panel, accepted the responsibility of shepherding the panel discussions and guiding the manuscript preparation to completion. Bridging levels of analysis from cognitive neuroscience to rehabilitation is important and necessary if we are to make progress building the science of “neuro-rehabilitation,” but it is also intellectually and practically difficult as anyone engaged in such efforts can attest.

It is important to note that the material summarized in the 3 chapters does not probe the bleeding edge of scientific controversy but rather represents an expert view of the field. Each of the 3 chapters represents a consensus document written by the panel. The chair of each panel is the first author of each of the 3 chapters. The names of panel members are then listed in alphabetical order. Author order should not be used to interpret the degree to which any one individual contributed.
his or her expertise to the final documents; rather, the chapters represent the collective expertise. They are not heavily referenced; citations are limited to review articles or to book chapters that could serve as additional sources of information. The 3 panels of experts, and the chapters that resulted from their discussions, are organized by 3 subtopics (basic science, clinical diagnostics, and treatment interventions) within the overall topic of this special issue.

The editors asked the first group of experts (see Frey et al5) to use a computational–anatomical–physiological (CAP) framework for developing a set of principles about upper-extremity actions. At the computational level (C), we consider the following: What is the goal of a certain function? How is this function performed at the behavioral level? What are the elementary behavioral components? We then consider how these processes are implemented in terms of anatomy (A) and physiology (P). What principles of anatomical organization have important behavioral consequences? What physiological signals underlie specific processes?

Although we strive for simplicity, a certain degree of complexity is indispensable: we cannot treat effectively one of the most sophisticated and complicated machines of the universe without knowing some of its inner workings. Diagrams and figures are used across the chapters to illustrate difficult concepts. Critically, as we go forward with this project, each CAP chapter will contain a small set of heuristics that distill what is most important from a cognitive neuroscience perspective and what is important to know about that specific function.

The second group of experts (see Sathian et al5) produced the second chapter in the series discussed the most common action disorders resulting from neurological damage. The goal was 2-fold. The first goal was to describe in a fairly practical way how to test a function based on the principles established in the first chapter. A second goal was to give a description of the most common syndromes in light of the CAP framework, if possible, or otherwise, to note relevant discrepancies. The general idea is to provide clinicians with a principled and scientifically oriented way to think about sensory, motor, and cognitive impairments in light of the current state of knowledge in cognitive neuroscience. For instance, what are the processes and neural systems that may be affected when someone is unable to grasp a desired object or turn a key in a lock after brain injury? How does one separate purely sensorimotor from higher-level planning deficits?

The third group of experts (see Pomeroy et al6) addressed current interventions. The emphasis was on evidence-based interventions: How do they relate to the theoretical principles stated in the CAP model? What experimental or clinical results support the use of one intervention over another? What is the best way to provide the interventions keeping in mind our understanding of dose, frequency, and intensity of treatment? What novel ideas or strategies of intervention could stem from the CAP model and its application to clinical problems?

By reading the 3 chapters, a rehabilitation professional—physician, nurse, or therapist—can acquire a theoretical framework and some working principles on how to think about the behavioral deficits and underlying dysfunction of brain systems, which an individual with brain injury may present with. Additionally, the practitioner will gain knowledge about how to prioritize interventions based on evidence-based principles. Ideally, we hope that rehabilitation professionals will use these manuscripts as a training tool and as a clinical practice reference. We also hope that the manuscripts will encourage clinicians to think critically about the rationale, application, and assessment of established and novel interventions as well as test some of the predictions of the CAP model in their own patients. In the end, the success or failure of cognitive neuroscience will be measured by its potential for uncovering mechanisms of brain diseases and improving human brain health. Finally, we hope that this project will stimulate the development of novel strategies either in the form of formal clinical trials or everyday practice. We believe that there are both nonscientific and scientific ways to practice rehabilitation, and we hope, through this effort, to foster the latter approach.

Acknowledgments
The editors and the contributors thank Brent Dolezalek of the James S. McDonnell Foundation for his dedication and commitment to this project. Without the contribution of his organizational expertise, the panel discussions and subsequent publications would not have succeeded.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Funding
The author(s) received no financial support for the research and/or authorship of this article.

References
Neurological Principles and Rehabilitation of Action Disorders: Computation, Anatomy, and Physiology (CAP) Model

Scott H. Frey, PhD¹, Leonardo Fogassi, PhD², Scott Grafton, MD³, Nathalie Picard, PhD⁴, John C. Rothwell, PhD⁵, Nicolas Schweighofer, PhD⁶, Maurizio Corbetta, MD⁷, and Susan M. Fitzpatrick, PhD⁷,⁸

This chapter outlines the basic computational, anatomical, and physiological (CAP) principles underlying upper-limb actions, such as reaching for a cup and grasping it or picking up a key, inserting it into a lock, and turning it.

Introduction

One of the most remarkable aspects of human behavior is the seemingly effortless manner in which everyday activities involving the upper extremities are successfully achieved. This apparent ease, however, masquerades the underlying functions of a truly complex biological system. In their attempts to understand brain functions, neuroscientists have found it useful to seek explanations at several different levels of analysis.¹ This strategy can be particularly useful in our quest to discern how sensorimotor systems respond to brain injury and rehabilitative interventions.

Levels of Analysis

A helpful starting point in analyzing any complex system is to ask what are the problems that this system must solve and why? In the broadest sense, we use our upper extremities to accomplish goal-directed actions—actions that are driven by our motivational states. For instance, our thirst may drive us to seek out a drink. Then, we have to solve the problems of finding a source to quench our thirst and carrying out the actions that allow us to achieve our goal (see Box 1). Our environment may present us with a variety of potential paths from which to select, and achieving each goal may require distinctly different sets of actions that vary in their costs. We might opt to reach out for the cup of water on the table in front of us, rather than walking down the hall to the drinking fountain or locating the change we would need to use the nearby soda machine. Having settled on the water cup, we now face additional choices of how to get it to our mouth. By default, we might opt to use the dominant hand to reach for, grasp, and transport the cup to the mouth. If the preferred hand is preoccupied with another task (e.g., holding a telephone, or shaking hands), we can (at the increased risk of spilling) switch to the nonpreferred side. For an individual with impaired upper-extremity function, the range of potential solutions is obviously restricted, and the costs associated with various goal-directed actions are considerably different. A moderately hemiparetic patient might, for instance, decide to rely exclusively on their less-affected limb. In the moment, this choice may provide a more efficient solution to the problem of getting the cup to the mouth (low immediate costs). Yet the choice to avoid using the impaired limb may have distinctly undesirable longer-term costs that include further weakening of an already compromised system (or learned disuse), eventually leading to a dramatic restriction of the range of available actions (high long-term cost). Conversely, opting to use the affected limb will provide a less efficient solution that is costlier in the short term but that may hold potential for longer-term gains, including improved strength and dexterity. Motivating patients to make such trade-offs consistently can be a major challenge for rehabilitation specialists because costs are also influenced by individuals' emotional and energetic states and also change along with functional status. Strategies such as constraint-induced movement therapy (Pomeroy et al) can be thought of as a way of

¹University of Oregon, Eugene, OR, USA
²University of Parma and Italian Institute of Technology, Parma, Italy
³University of California–Santa Barbara, Santa Barbara, CA, USA
⁴University of Pittsburgh, Pittsburgh, PA, USA
⁵University College London, London, United Kingdom
⁶University of Southern California, Los Angeles, CA, USA
⁷Washington University in St. Louis, St. Louis, MO, USA
⁸James S. McDonnell Foundation, St. Louis, MO, USA
Box 1. Motor goals and apraxia

Actions are normally organized in terms of desired outcomes. To make a cup of coffee requires the organization of a broad range of subgoals such as boiling water, measuring the coffee grounds, and so on. Subgoals in this task need to be sequenced in a sensible order. For example, the water needs to be hot before it is poured. This capacity to organize complex serial behavior is uniquely human. There are multiple cognitive models of how the human brain accomplishes this. At the one extreme are planning models that propose that the brain learns how to set up the subgoals within a logical hierarchy. For example, picking up a spoon is subordinate to scooping the sugar, which is subordinate to making the coffee sweater. One can readily construct a complex contingency table for getting the entire task organized. At the opposite extreme are associative models that link percepts (a coffee cup) and stereotypical actions (grasp the cup to take a drink). Through experience, we learn the links between these typical motor programs and different situations. It is likely that both these extremes are needed in real life. The system must be able to organize complex sequences of actions in a task space but also perform some of the subgoals such as shaping the hand to fit an object in a direct way. Lesions in the brain can damage the organization of these sequences and lead to deficits of motor action selection known as apraxias. Retraining subgoals via verbal or visual inputs is the basis of the strategy training approach, the only method that has been shown to improve activities of daily living (ADLs) in individuals with apraxia.

Artificially rebalancing the costs associated with using the affected versus the less affected limb.

Finally, we can ask how these actions are organized and produced by the brain—what are the biological mechanisms that implement these computational processes? What specific neural mechanisms are involved, and how do they change in response to injury or rehabilitation? Given the central role of manual behaviors in our lives, it should come as no surprise that many regions of the human brain are involved. As will be reviewed below, however, a number of organizing principles have emerged regarding how the brain produces upper-extremity functions. In this chapter, we introduce a conceptual framework for organizing and integrating knowledge gained from studies of functional neuroscience over the past 3 decades that can inform and influence approaches to neurorehabilitation. We refer to this framework as the CAP model because it draws on developments in computational, anatomical, and physiological research.

Computational Principles

Although central to the topic of human actions, our knowledge of the complexities of motivation, intention, and goal formation is relatively sparse. Therefore, we begin our discussion further downstream, with what is currently known about the processes involved in the planning and execution of manual behaviors. We begin by considering some of the processing steps that lead to the generation of a motor command, which is the initial step illustrated in Figure 1. Note that the separation between goal establishment, planning or action selection, and execution relate to the clinical separation between disturbances of motivation (motor neglect, akinetic mutism, others), planning/selection (the apraxias), and execution (hemiparesis) as discussed in the second chapter in this series by Sathian et al.

Computing the Initial Motor Command to the Internal Model and Spinal Cord

One way to appreciate the complexity of upper-extremity functions is to try to program a robot to undertake these behaviors. This exercise is useful in identifying the particular problems that must be solved and in suggesting possible solutions that might also be used by the brain. This task requires solving a number of nontrivial problems. The processes involved in these solutions can be thought of as computations or operations that are performed on incoming information (input) to transform it into output that is useful to the system. For example, an adding machine applies the addition computation to numerical inputs and outputs the sum. As a starting point, consider again the task of reaching for a cup. As a first pass, we can perform a task analysis to decompose this action into 5 basic steps. (1) Assuming that one is motivated to drink and that the cup of water located nearby is the goal, then, a critical first step is to precisely determine the position of the cup in the environment, often through vision. (2) Next, the current state of the system (position of the arm) must be estimated, a process that may draw both on visual and proprioceptive input as well as prediction (a concept that is developed further below). (3) To compute the spatial relationship between the cup and hand, sensory information must be transformed into a common frame of reference. This is analogous to the importance of locating both one’s current location and desired destination on a single map when navigating. (4) A plan can then be formed that specifies the direction and distance from the current position of the hand to the cup’s location. (5) Finally, motor commands can be issued that cause the hand to reach the cup with sufficient precision to accomplish the goal within a reasonable period of time. These motor commands are generated in the primary motor cortex and then sent to the spinal cord where they activate circuits that generate the final commands to individual muscles. We will return to a more detailed discussion of the motor cortex shortly.
As summarized above, the steps that lead from the motivation to drink to the motor commands to grasp the cup seem rather simple and intuitive. However, it is important to recognize that mechanical properties of the limbs and body introduce a very high level of complexity into this task. The musculoskeletal system possesses a very high degree of redundancy, which means that the number of combinations of joint angles and muscle contractions that can successfully bring the hand to a particular location in space is extremely large. Consequently, an enormous number of different movements can be used to achieve the very same end—that is, grasping the cup. Precisely how the nervous system selects the particular joint and muscle combinations to be used for a given action remain a mystery. Moreover, our system must also cope with relatively long conduction delays in neurons and large amounts of noise. As detailed below, feedback and feed-forward control mechanisms appear to play important roles in coping with these challenges.

**Feedback and Feed-Forward Control**

What computational processes are used to generate the motor commands? Computational neuroscientists, robotics experts, and engineers distinguish between 2 general types of control—feedback and feed-forward—each with its own unique advantages and drawbacks. In feedback control, signals that carry information about the discrepancies (error) between the desired movement and the actual sensory consequences associated with its execution are used to generate subsequent motor commands. The performance of systems that rely exclusively on feedback is limited by delays in sensory and motor pathways, which in biological nervous systems can be as long as a few
hundred milliseconds. Although that may not sound like much, delays of this magnitude often approximate the duration of the movements themselves. The consequence is a system that develops large oscillations as it attempts to self-correct. We have all experienced this phenomenon when trying to control the water temperature of an unfamiliar shower located at some distance from the water heater based on perceived temperature alone. You first turn the shower faucet, but after some delay, the temperature is hotter than you wish. You then attempt to adjust the temperature by increasing the flow of cold water, but shortly, the temperature becomes colder than you wish. With some luck, you may be successful on the third trial, but 2 or 3 more iterations may be needed to achieve the perfect mixture. In other words, obtaining the goal will be relatively inefficient and time-consuming. The difficulty here is that the change in water temperature (the consequence) is delayed relative to the time at which your movements occurred. The same thing occurs in the nervous system where, as a result of the time needed for signal transmission, the sensory consequences are delayed relative to our movements. As a result, discrepancies can develop between our motor plans and the actual sensory consequences of our actions. Feed-forward control provides a potential solution to this dilemma.

In feed-forward control, motor commands are generated directly from the goal of the action (eg, grasping the cup) and other internal signals. To achieve a high level of accuracy, feed-forward controllers require learning from experience, just as you will (perhaps following somewhat jolting experiences) eventually learn to rotate the faucet to the exact position necessary to produce the ideal water temperature. Although feed-forward control does not suffer from the delay problem (because there is no need to wait for sensory information), a purely feed-forward approach does require 3 conditions: a perfectly learned controller, a static (ie, not changing) environment, and the absence of noise in the motor command. Because none of these conditions is ever realized in the real world of biological systems, movements resulting from a purely feed-forward motor command will differ from what was planned, and as a consequence, we may fail to grasp the desired cup. By combining both feed-forward and feedback control, however, the nervous system can overcome these challenges and generate a motor command that gets the job done. It is believed that the brain uses feed-forward control to produce fast movements in the face of long delays in neural transmission, whereas feedback control enables correction of these movements when they deviate from the intended goal. Figure 1 presents a schematic of how these 2 types of controllers might work together to control movements of the hand.

**Internal Models**

An important concept related to feed-forward control is that of the internal model. Like models of other complex systems, internal models capture important features of the systems that they mimic (eg, the muscle properties, biomechanics, and dynamics of the arm and hand). However, internal models are implemented in the brain. Feed-forward control relies on 2 flavors of internal models: forward and inverse. Given the motor command, the forward model predicts the sensory consequence of this command, in effect mimicking the movements of the body in parallel with actual movements. A dramatic example of error in a forward model is the weird feeling of lifting an object that we expect to be heavier than it actually is (eg, an empty soda can that is believed to be full). Because forward models are implemented within the brain (see section on functional neuroanatomy below), the sensory consequences of the movements are predicted in advance of the actual sensory feedback that accompanies movement. The reason for this is that actual sensory feedback experiences more significant delays in neural transmission from the peripheral nervous system and spinal cord. Outputs of the forward models, if they are well learned, can thus be used to alleviate the delay problem faced by feedback control. Figure 1 shows the forward model is represented by the computations that start with a copy of the motor command and end with a prediction of the estimated position.

An inverse model can be conceptualized as an inverted forward model. Given the desired sensory consequence (grasping the cup), and the current state of the body and environment, the inverse internal model computes the motor command to be sent to the body. For movements to achieve the desired plan, the inverse model must faithfully capture the characteristics of the actual physical systems (muscle properties, arm dynamics, etc) it represents.

There are important clinical implications to the concept of internal models. Internal models must undergo experience-dependent change or learn to accommodate changes associated with alterations that accompany development, senescence, and injury. This ability to adjust, even in the adult brain, is exemplified by amputees who relearn to walk with a prosthetic leg in a matter of days. An even more striking example is the capacity to learn to control, by intention alone, a peripheral device (eg, a mouse). Indeed, some patients who lack the capacity for voluntary movements (eg, those with high-level spinal cord injury and amyotrophic lateral sclerosis), appear to retain motor planning functions. In some patients with stroke and motor deficits, internal models may be damaged but in theory can be relearned.

An interesting possibility to consider is that a well-learned forward model might be used in the mental rehearsal of movements or motor imagery. If you imagine reaching to grasp the cup without actually moving, it is possible that a motor command is generated but is only sent to activate the forward model and not the body. This would result in a prediction of the sensory feedback that would likely accompany the movement but in the complete absence of any actual feedback. Such mental rehearsal has been shown to activate some of the same brain areas as actual movements and may be useful therapeutically.
in patients with limited mobility. However, because of the absence of an error signal, it remains uncertain how such activation can be used to tune the motor system. One ought always to consider the importance of sensory feedback in shaping actions and internal models because they provide the signal to update forward models. Accordingly, restoration of motor function is typically more complete in the case of pure motor deficits as compared with combined motor plus sensory deficits.

We conclude this section with a brief discussion of noise—variation in neural activity that is not carrying information about the task. Noise in the motor system is known, at least in part, to be signal dependent: that is, the greater the motor signal, the greater the noise. Therefore, the faster you reach for the cup, the greater the uncertainty in the final position of your hand. It has been proposed that the nervous system minimizes movement variability by generating smoothly varying motor commands; this reduces the need for brusque accelerations and decelerations in activity and minimizes the amplitude of the noise generated. The presence of noise in the motor command, however, contributes to the inaccuracy of purely feed-forward movements, and visual and proprioceptive feedback signals are often critical for correcting for these inevitable deviations.

**Principles of Functional Anatomy**

Having established a computational framework consisting of various processing components that are critical to upper-extremity control, we now turn our attention to what is currently known about how these functions are implemented in the brain. Despite the complex and distributed nature of the brain systems involved in upper-extremity functions, it is possible to distinguish several principles of functional organization within the cerebral cortex and in the descending pathways to the spinal cord that have direct relevance to understanding the effects of brain injury. Although there are many ways to slice the pie, we have identified 6 principles that we find are of particular relevance. Generalizations about the relationship between processes and brain anatomy always come at the cost of some details. However, they can be very helpful in capturing the larger organizing principles and are useful for interpreting clinical syndromes and planning treatment for functional restoration.

An important caveat is that most of the information we have about anatomical connections and the response of neurons in different circuitries comes from studies in nonhuman primates, but there is increasing evidence from functional neuroimaging that a similar organization exists in humans.

**Principle I: Anatomical Gradients in the Parietal and Premotor Cortices**

Anatomical connections are organized in the brain according to patterns or trends that relate to function. These patterns do not change abruptly between different regions but gradually. Three main organizational principles have been identified in the cortical areas involved in motor planning and control, and these have important functional implications for understanding the brain mechanisms of action.

**From Goal to Action: Anterior-to-Posterior Gradient in the Frontal Lobe.** The neural processes that are involved in moving from an action’s intended goal (eg, grasping the cup) to generation of a motor command can be mapped onto an anatomical gradient running along the anterior–posterior axis of the frontal lobe (Figure 2). The goal emerges from motivational influences on the activity of associative areas in the prefrontal cortex located at the very front of the brain (gray). Prefrontal regions receive inputs from areas like the amygdala, hypothalamus, and the ventral striatum that code primary impulses like fear, hunger, and reward. Goals are translated into action selection, for example, reach for a cup to drink, and into more specific movement plans and execution for moving the arm and shaping the hand in the right posture. The premotor areas (red), located more posteriorly in the
frontal lobe, are pivotal for action selection and serve as the interface between the prefrontal and parietal (blue) association areas and the primary motor cortex.

One organizational principle is that the more abstract and time-removed processes (eg, action selection and planning) tend to involve more anterior areas of the frontal cortex, whereas increasingly more specific and immediate requirements for movement execution are represented more posteriorly in the frontal lobe. It is important to recognize that it is an oversimplification, however, to assume that the computations performed in the frontal lobe occur in a strictly serial (step-by-step) fashion as information moves along the anterior–posterior gradient. On the contrary, like most brain systems, the regions of the frontal lobe form a highly interconnected network, and this enables a parallel flow of information through the system. It might be helpful to think of the system less as a superhighway and more as the complex grid of city streets.

**From Sensory to Motor and Back: Parallel Parieto-Frontal Circuits.** A second organizational principle is the existence of parallel pathways that reciprocally interconnect distinct regions of the parietal and premotor cortices (see Figure 2). Earlier, we introduced the idea that our ability to prepare and control goal-directed actions depends on visual information about the external scene and somatosensory (and also often visual) information regarding the state of our body (Figure 1): Where is the cup in the environment, and how is this location related to the current state of the hand?

The posterior parietal areas are important for coding the location of the stimulus (eg, the cup) and forming an estimate of the body’s state, for example, the relative position of the gaze, trunk, arm, and hand in relation to the stimulus prior to the movement. The right parietal cortex is particularly important for representing the spatial aspects of movements, whereas the left appears to be more heavily involved in planning familiar actions. Information from parietal areas flows into premotor regions in the frontal lobe where information about stimulus and body position is combined with goal representations. Put differently, parietofrontal circuits participate in the transformation of sensory information into motor commands (sensory-to-motor transformations). The parietal cortex is also critical for adjusting these estimates based on incoming information during the movement (sensory feedback; compare Figures 1 and 2).

Although it is often taught that sensory processing for action is accomplished in parietal areas and that motor signals originate in frontal regions, this is not correct. As illustrated in Figure 2, these regions are in fact reciprocally interconnected, and both frontal and parietal areas are endowed with motor and sensory properties. Because of this reciprocity, areas within parietofrontal circuits not only transform sensory input in the motor programs for specific goal-directed movements but are also directly involved in motor plan selection. Furthermore, as alluded to earlier, parietal regions are involved in calculating the sensory effects of an intended movement (motor-to-sensory transformations). As shown in Figure 1, intended movements generate predicted sensory feedback, which is a key component of the forward plan. It is important to highlight that this basic computational, anatomical, and physiological architecture is replicated several times in different parietofrontal circuits, each specialized for a different body part and/or set of movements, as described in the following sections.

**Superior parietal lobule to dorsal premotor cortex (SPL-PMd).** Circuits connecting these regions of the cortex appear to be important for the control of goal-directed upper-limb movements on the basis of visual and/or proprioceptive feedback (Figure 2). In SPL, there are some areas (eg, PE) that are activated only by stimulation of the joints and skin, whereas other areas (eg, MIP, V6A) also receive input arising primarily from peripheral vision (ie, extrafoveal visual space). The former nonvisual processing areas are linked with a sector of the PMd involved in reaching movements, whereas the latter visual processing centers are connected with a different sector of PMd that contributes to both reaching and grasping movements. These latter regions monitor visual and somatosensory feedback to ensure that the trajectory of the arm and shape of the hand is appropriate for achieving the desired goal (eg, stably grasping the cup). If not, then this information is critical in specifying any corrective adjustments that might be necessary (see Figure 1). Patients with damage in this circuit may suffer from optic ataxia, a disturbance in which movements of the upper extremity are inaccurate when trying to make contact with visual objects (see accompanying chapter by Sathian et al).

**Inferior parietal lobule to ventral premotor cortex (IPL-PMv).** These regions of the brain are connected by at least 3 separate circuits. The first connects the ventral intraparietal areas (VIP) and a division of the PMv (known as PMvc or area F4). This circuit is involved in actions such as feeding or avoiding objects approaching the face. These actions involve objects in the environment or within our work space that eventually make contact with our body and that are coded both by visual and somatosensory information. The VIP is located in the depths of the intraparietal sulcus (IPS), a deep fold that separates the IPL and SPL (Figure 2). Neurons in VIP become active during tactile stimulation of different body parts, particularly the face. Some of them are bimodal (ie, they respond to both vision and touch) and increase their activity when moving visual objects come within reach. The interconnected PMvc (or F4) also contains bimodal neurons that respond to tactile stimulation of the face, arm, or body and to visual stimulation from objects introduced in the peripheral space near the tactile receptive field (RF). Furthermore, in this area, there are neurons showing increased responses during the execution of reaching and approaching/avoidance movements directed toward objects.

A second circuit in the IPL transforms objects’ visual features into appropriate grasping postures. If, for instance, you want to pick up the water cup by the rim when cleaning up the table, its visual attributes (shape, orientation, size, etc) are
transformed into a precision grip. However, visual features may be transformed into a power grip if your intention is to grasp a large water glass and take a drink. This visual-to-motor transformation is accomplished in a circuit connecting the anterior part of the IPS (AIP) and an area located in the rostral part of the PMv (known as F5 or PMvr). Neurons in both areas show increased activity when target objects (e.g., the water cup) are grasped and manipulated. In some cases, this is true regardless of whether grasping involves the hands, mouth, or even a tool. That is, some of these neurons appear to be concerned with the act of grasping independent of the effector used. AIP also contains visual neurons that increase their activity when individuals observe graspable objects of specific sizes, shapes, or orientations. By contrast, PMvr (area F5) contains neurons that show selective changes in activity when performing specific types of grasps (e.g., precision vs power). Patients with damage in this circuit have problems shaping their hands to grasp objects (see accompanying chapter by Sathian et al).

A third circuit links the IPL (area PFG) with areas PMvr (F5) and the cortical area 44. In the left hemisphere, this latter region may be the precursor of what in humans is classically defined as Broca’s speech production center. Of considerable relevance to those working in rehabilitation is evidence indicating that the parietal node of this circuit receives visual information about motor acts performed by other individuals. There is a growing body of evidence that we may achieve an understanding of others’ actions by matching them with our own internal motor representations (probably stored in the frontal node of this circuit). What is interesting is that this circuit shows increased activity not only when we observe others’ actions but also when we attempt to imitate them. Because of these joint properties, such cells have been named mirror neurons. As discussed in Pomeroy et al in the third chapter, there have been some recent attempts to develop rehabilitative interventions based on the effects of action observation on motor system activity.

**Internally Versus Externally Cued Movements: Medial-to-Lateral Gradient in Premotor Areas.** A third gradient of functional organization can be defined along the mediolateral dimension of the premotor areas (Figure 2). Premotor areas on the medial wall are particularly involved in the planning and generation of internally guided actions like imagining oneself playing a musical piece from memory. They also participate in initiating voluntary movements that are not driven by sensory stimuli such as walking, speaking, or pointing. Premotor areas on the lateral surface of the cerebral cortex are particularly active for actions made in response to sensory stimuli, like braking at a red traffic light, and object-oriented actions, like grasping a cup to get a drink (Figure 1). As with the anterior–posterior gradient, this functional distinction is also relative. It has nevertheless proven important to evaluate whether patients have more problems planning internally versus externally driven movements. Motivational syndromes (e.g., abulia, akinetic mutism, or motor neglect) may be attributable to difficulties with more internally driven actions, whereas deficits of motor planning in response to sensory stimuli (e.g., optic ataxia) may reflect more a problem with externally driven actions. Rehabilitation protocols might be devised that tap into one or the other mechanism.

**Principle II: Overlapping Synergies in the Primary Motor Cortex**

Several principles of functional organization within the primary motor cortex are relevant to rehabilitation. Zones within the primary motor cortex that project to the spinal cord are organized topographically by body segments such as the hand, face, or foot—a feature called somatotopy (see Box 2). A less clearly differentiated somatotopic organization is also found in the premotor areas. The coarse segmental somatotopy of the primary motor cortex masks its fine-grained organization. Cells connected to motoneurons controlling a particular muscle are widely distributed within a patch of cortex representing that particular body part and intermingled with other cells influencing the activity of different muscles within the same segment (e.g., the hand or face). This is an important difference with the primary sensory cortex where, for example, regions receiving inputs from individual digits can be identified within the hand map. Also, neurons in the primary motor cortex typically influence the activity of several muscles that may act at different joints. The activity of a single neuron in the primary motor cortex may produce a mixture of facilitation and suppression of the activity of its target muscles. This organization suggests that the primary motor cortex represents overlapping synergies (coordinated patterns) of muscle activations rather than individual muscles or movements. It is interesting to note that recent electrical stimulation studies of the motor cortex indicate that these muscle synergies are not random, but they resemble simple mini-actions (e.g., grimacing or withdrawal) of naturalistic, more complex actions. This is directly relevant to understanding why rehabilitation strategies just based on training non-goal-directed movements may be less effective than training based on task-specific exercises. A further discussion of this point is found in Pomeroy et al in this issue.

The primary motor cortex makes the most direct and powerful connections with spinal motor neurons controlling the distal muscles of the hand. However, as will be discussed below (Principle V), in truth, multiple movement-related cortical areas project onto the spinal cord either directly or indirectly through the brainstem. Direct connections to motor neurons are essential for the fractionation of movements such as those seen in the independent keystrokes performed by a typist (see Case A in the accompanying chapter by Sathian et al). The primary motor cortex is particularly concerned with the precise patterning of muscle activity. It may achieve this patterning by selective recruitment and weighing of synergies. This also contributes to the fine control of force (e.g., at the fingertips when grasping). Clinically, testing fine finger movements, especially those involving fractionation of movements at 1 joint, for example, wiggling the distal phalanx of your thumb, strongly relies on the primary motor cortex.
The somatotopic organization of the motor cortex reflects the somatosensory input that a patch of cortex receives and the group of muscles that its output influences. At the macroscopic level, the primary motor cortex contains an orderly representation of body segments along the central fissure and precentral gyrus illustrated by Figure 3A. The lower extremity, the upper limb, and the face are represented in sequence from superior–medial to inferior–lateral regions. A similar arrangement is found in the postcentral somatosensory cortex. The body representation appears distorted because larger areas of the brain control the most dextrous (and sensitive) body parts like the fingers and mouth. Lesions affecting a small part of the primary motor cortex impair the function of the corresponding body segment but spare the function of other segments represented at distant sites. Like the primary motor cortex, all premotor areas are somatotopically organized to some degree. The somatotopic organization of the primary motor cortex appears more detailed than that of the premotor areas. This is partly a result of the large size of the primary motor cortex, which allows a better resolution of separate representations with exploratory techniques such as electrical stimulation. For example, a pulse stimulation at a site in the hand representation (yellow arrow) might cause a small deviation at the wrist (Figure 3B). More complex gestures can be evoked from longer trains of stimulation that activate a larger network. In the primary motor cortex, the topography of representations decays from the segmental level to that of its constitutive parts. For example, within the representation of the upper limb, regions of the cortex that control the musculature of the shoulder or elbow partially overlap with regions that control the wrist and fingers. This overlap is one reason why a cortical lesion rarely impairs the function of individual joints in isolation. At the level of small groups of cells or single neurons projecting to the spinal cord, it becomes apparent that the representation of individual muscles is diffused over a large expanse of cortex and intermixed with other muscle representations. In addition, cortical neurons projecting to the spinal cord typically influence the activity of multiple muscles sometimes acting at different joints. Thus, the coarse somatotopy masks the distributed and mosaic-like nature of the organization of the motor cortex that is present on a fine scale.

**Box 2. Somatotopy in the motor cortex**

The somatotopic organization of the motor cortex reflects the somatosensory input that a patch of cortex receives and the group of muscles that its output influences. At the macroscopic level, the primary motor cortex contains an orderly representation of body segments along the central fissure and precentral gyrus illustrated by Figure 3A. The lower extremity, the upper limb, and the face are represented in sequence from superior–medial to inferior–lateral regions. A similar arrangement is found in the postcentral somatosensory cortex. The body representation appears distorted because larger areas of the brain control the most dextrous (and sensitive) body parts like the fingers and mouth. Lesions affecting a small part of the primary motor cortex impair the function of the corresponding body segment but spare the function of other segments represented at distant sites. Like the primary motor cortex, all premotor areas are somatotopically organized to some degree. The somatotopic organization of the primary motor cortex appears more detailed than that of the premotor areas. This is partly a result of the large size of the primary motor cortex, which allows a better resolution of separate representations with exploratory techniques such as electrical stimulation. For example, a pulse stimulation at a site in the hand representation (yellow arrow) might cause a small deviation at the wrist (Figure 3B). More complex gestures can be evoked from longer trains of stimulation that activate a larger network. In the primary motor cortex, the topography of representations decays from the segmental level to that of its constitutive parts. For example, within the representation of the upper limb, regions of the cortex that control the musculature of the shoulder or elbow partially overlap with regions that control the wrist and fingers. This overlap is one reason why a cortical lesion rarely impairs the function of individual joints in isolation. At the level of small groups of cells or single neurons projecting to the spinal cord, it becomes apparent that the representation of individual muscles is diffused over a large expanse of cortex and intermixed with other muscle representations. In addition, cortical neurons projecting to the spinal cord typically influence the activity of multiple muscles sometimes acting at different joints. Thus, the coarse somatotopy masks the distributed and mosaic-like nature of the organization of the motor cortex that is present on a fine scale.

**Principle III: Critical Role of the Cerebellum in Motor and Cognitive Predictions**

While the cerebral cortex often grabs most of the attention, many critical aspects of movement control are performed by structures that are positioned below the cerebral hemispheres—hence subcortical. There are several structures of which the most important are the cerebellum and the basal ganglia (BG).

**A common circuit throughout the cerebellum.** Let us first consider the cerebellum, or “small brain” in Latin, which contains about 50% of all neurons in the brain despite occupying only 10% of its volume. A first important, and rather surprising, fact is that despite the large number of cells, the cerebellum contains a very simple anatomical circuitry that is the same throughout its cortex. The cerebellum receives input from the spinal cord and the cerebral cortex via the mossy fibers that in turn project to numerous and tiny granule cells in the cerebellar cortex (Figure 4A). The axons of the granule cells (called parallel fibers because of their long T-shape parallel to the surface of the cerebellar cortex) in turn project to the Purkinje cells, the sole output cell out of the cerebellar cortex. The Purkinje cells, which inhibit the deep cerebellar neurons, also receive major inputs from the climbing fibers. The latter are the axons of a group of neurons within the brainstem nucleus called the inferior olive, a nucleus known to carry error signals in relation to the execution of movements. The deep cerebellar neurons do not project to the spinal cord directly but instead send large projections to the brainstem and to the cerebral cortex via the thalamus (Figure 5).

In summary the cerebellar cortex (Purkinje cells) is in the optimal position to compare different kinds of signals: signals from the cerebral cortex related to the planning of movement, feedback signals about limb position from the spinal cord, and error signals during movement execution. The output of the cerebellum in turn modulates the cerebral cortex and the brainstem. It is interesting to note that although traditionally the cerebellum is considered a structure for monitoring and correcting ongoing movements, a number of recent studies show that cerebellar neurons respond in anticipation of a movement rather than during execution as previously believed (see section of forward models). This fact has important implications for understanding its functions, as described below.

Another important fact is that the cerebellum is amenable to learning. Granule cell/Purkinje cell synapses are plastic and are modified when the parallel fiber inputs fire at approximately the same time as the climbing fiber inputs, that is, when the input from the cerebral cortex or spinal cord is synchronized with that from the inferior olive. The inferior olive is thought to tune the cerebellar output such that the movements become more accurate with practice (by virtue of more precise predictions) or are better adapted to new environmental conditions (such as the sudden introduction of a force field). It is likely that this mechanism may also be critical in adaptation to control of an upper extremity whose functions have been impaired by stroke or degenerative disease.

**The functional-anatomical organization of the cerebellum.** Despite regularity in its circuitry, it is important not to think of the cerebellum as a homogeneous structure. Different parts of the cerebellum through their input/output connections with different parts of the cerebral cortex contribute in different ways to brain functions. The phylogenetically oldest part of
The cerebellum is the vestibulocerebellum located anteriorly, just behind and lateral to the brainstem. This part is strongly connected with the vestibular nuclei, and it is important for balance and interactions between the eyes, head, and body. The spinocerebellum, so called because of its massive input from the spinal cord, involves the vermis, central and dorsal part of the cerebellum, and the intermediate cerebellum located between the vermis and the cerebellar hemispheres. This region contains maps of the body, is strongly connected with motor and premotor cortices, and is important for coordination of balance and gait as well as movements of the trunk and proximal limbs (Figure 4B). Phylogenetically, the most recent portion, the neocerebellum or lateral cerebellum, includes the cerebellar hemispheres. These have greatly expanded in primates in parallel with the development of the frontal, temporal, and parietal cortices, regions involved in sensory and cognitive functions. The neocerebellum is important for the coordination of hand movements (grip and manipulation) as well as of cognitive functions. Recent studies suggest a lateralization of function. Consistent with its preferential connections to the left hemisphere language regions, the right neocerebellum appears to be specialized for verbal selection and working memory, whereas the left neocerebellum (connected with the right cerebral hemisphere) may be more involved in spatial working memory and nonverbal reasoning.

Motor and cognitive function of the cerebellum: prediction and internal models. The role of the cerebellum in motor control is still not fully understood despite more than half a century of theories and experiments. The dominant idea has been that the cerebellum participates in motor feedback and error correction; however, more recent findings indicate that it is critically involved in the prediction of sensory consequences of motor commands, as discussed earlier (see Figure 1).

The cerebellum presumably acts in concert with the parietal cortex where information about the state of the body (e.g., trunk and limb positions) as well as information about spatial environment are stored. It appears to be ideally suited to acquire new, and adapt existing, internal models. Indeed, experimental evidence suggests that the cerebellum acquires both forward and inverse models. Lesions of the cerebellum prevent adaptation to environmental changes, probably because the internal models cannot be modified via the errors between intended and realized movements. For instance, patients with ataxia caused by cerebellar disease or profound loss of proprioception from large-fiber sensory neuropathy are unable to properly anticipate interaction torques—they cannot send predictive signals that correct for errors before they occur. Consequently, trajectories are curved, lack smoothness, and overshoot the target. Cerebellar patients also have trouble performing overhead throws—they seem unable to coordinate opening of the hand and release of the ball at the right point along the arm’s trajectory, which is required to make an accurate throw. In both reaching and throwing, the abnormalities arise because the patients do not seem to have the ability to anticipate forces acting at the joints and, therefore, how the limb position will change over time. These deficits in anticipation prevent cerebellar patients from learning novel actions. Multiple studies have shown that this is indeed the case: patients with cerebellar damage, either from stroke or neurodegenerative disease, are impaired in their ability to adapt to prisms, visuomotor rotations, and force fields.

In summary, the cerebellum provides predictive state estimates that allow feed-forward coordination between agonist and antagonist muscles and between limb segments in anticipation of the movement. This accounts for its early recruitment in the planning phase of a movement. Similar predictions are
likely to occur in more cognitive functions such as verbal selection or nonverbal decisions that also require anticipation of sensory consequences.

**Principle IV: Basal Ganglia—Movement Selection and Reward**

As illustrated in Figure 5, the BG are a set of nuclei located in the center of the brain adjacent to the thalamus. These nuclei receive inputs from a broad expanse of the frontal and parietal cortices, as discussed earlier, that extend beyond the classic motor areas. Within the BG, there is a complex network of excitatory and inhibitory pathways that modulate information propagation. The main output nucleus sends inhibitory projections to the thalamus. The thalamus in turn sends excitatory projections back to the cortex. This inhibitory output to the thalamus has been used to explain some of the motor features observed in certain movement disorders. Hypokineti(c movement disorders, such as Parkinson’s disease, are caused in part by excessive BG output, leading to inhibition of the thalamus and a lack of cortical recruitment to initiate or appropriately scale movements. In contrast, hyperkinetic movement disorders such as Huntington’s chorea or drug-induced dyskinesias are caused by a loss of...
BG output, a lack of thalamic inhibition, and the release of cortically derived movements.

An important organizational principle is the existence of segregated BG-cortical loops through the BG (Figure 5). For example, a projection into the BG from the prefrontal cortex will stay segregated from a projection arising in the premotor cortex. This segregation will persist through the thalamus and back to the originating cortex. This anatomical pattern suggests that the BG are not designed for mixing information between different cortical areas. Instead, the anatomy suggests that the BG are involved in modifying local areas of the cortex. Within the premotor and motor cortex loops of the BG, there is strong evidence that the network is necessary for the scaling of force, amplitude, and acceleration of both simple and complex movements. Abnormalities in these loops help explain the bradykinesia observed in Parkinson’s disease.

In sum, there are several cortico-BG loops (motor, oculomotor, executive, and motivational), each involving different regions in the prefrontal cortex and segregated regions in the BG. This explains why lesions in the BG can give rise to cortical deficits such as aphasia, neglect, and akinetic mutism.

A second essential role of the BG is in reward-mediated learning. The BG have the highest density of dopamine-containing neurons in the brain. These neurons fire in anticipation of an upcoming reward. Pathology of reward circuits can lead to increased reward-seeking behavior, as in drug addiction. Reward circuits may also be needed for normal skill learning as well as motor recovery after brain injury. Finally, harkening back to our discussion of computational principles, it has been proposed that the BG are needed for automatically selecting one motor program from among many possible alternatives.

An example would include choosing among all the actions taken in the morning prior to work that are given no thought, such as dressing, brushing, eating, and so on. An important caveat is that there is little evidence that motor skills such as dressing, brushing, or eating are actually “stored” in the BG. Rather, the BG may be used to release these behaviors given the proper environmental cues. There is also evidence that the BG interact with the prefrontal cortex for the selection of novel, not habitual, actions.

**Principle V: Parallel Pathways From the Cortex to the Spinal Cord—Alternative Routes for Motor Commands**

Having discussed both cortical and subcortical contributions to upper-extremity functions, we are now in a position to consider the variety of ways in which motor commands reach the body.

*Multiple cortical areas output to the cord.* An important, and often overlooked, fact is that the corticospinal tract, the main output pathway from the cortex, is not limited to descending fibers from the primary motor cortex but includes a number of parallel pathways to the brainstem and spinal cord that originate in premotor and even parietal cortices. As we will see, this has important implications for the prognosis and treatment of patients with motor deficits. The large majority of projections to the spinal cord come from the frontal lobe (80%). These include, but are not limited to, projections from the primary motor cortex (Figure 6A). In fact, when considered together, 6 premotor areas actually make a larger contribution (60%) to the corticospinal projections from the frontal lobe than the primary motor cortex (40%). The rest of the corticospinal system originates from the SPL (20%). All considered, a substantial chunk of the cerebral cortex has the capacity to influence muscle activity through direct input into the spinal machinery (a topic discussed in detail shortly).

As reviewed earlier, outputs from the primary motor cortex are involved in the control of the distal musculature of the hand, whereas outputs from the superior parietal cortex and some premotor areas are more involved in guiding limb movements in space (kinematics). Still other descending pathways (eg, from the brainstem) are more involved in the maintenance of posture and whole-limb movements.

The multiple descending pathways from the brain convey largely parallel signals that shape the activity of spinal networks for movement generation and control. Some signals establish the functional set in anticipation of movement execution; that is, they prepare the appropriate segmental networks in the spinal cord for the upcoming job. Other signals regulate the activity of axial and proximal muscles for postural support and appropriate limb positioning, and still other signals trigger the sequence of muscle activity to accomplish the goal.

Descending signals and aspects of motor performance may be disrupted by either cortical lesions that interfere with specific computations (see case B in the chapter by Sathian et al), or by white matter lesions that block the results of these computations from reaching the spinal cord (see case A in Sathian et al). White matter fibers coming from the cortex (the corona radiata) bundle together near the middle of the brain to form the internal capsule (Figure 6B) and continue on to the spinal cord. Interruption of these long fiber tracts deprives the spinal cord of its normal cortical input (see case A). Functional recovery after a cortical or fiber tract lesion often involves a shift in the balance of function to intact motor areas of the same or opposite hemisphere that retain access to the spinal cord. The 2 hemispheres are heavily interconnected, and each has a small number of fibers (10%) that reach the spinal cord on the same side of the body (ie, uncrossed pathways). As a result, motor areas in the right hemisphere can influence the activity of muscles on the right side of the body that have lost their dominant input from the left hemisphere, for example. Another route is through connections to brainstem regions that in turn connect to the spinal cord.

*Brainstem—spinal pathways: additional routes from the brain to the spinal cord.* Though often overlooked, the organization of pathways that project from the brainstem to the spinal cord
Figure 6. Descending pathways to the spinal cord: (A) Large portions of the frontal and parietal lobes contribute to the corticospinal system. In addition, several pathways to the spinal cord originate from brainstem nuclei. All pathways can influence muscle activity by acting on the rich network of spinal interneurons. Fibers from the primary motor cortex and premotor areas terminate in or near the ventral horn on the opposite side of the body. This pathway controls the activity of limb muscles by activating motoneurons directly or through local interneurons. A small contingent of fibers innervates the ventral horn on the same side of the body. This pathway is primarily involved in the control of proximal muscles. Fibers originating from the parietal cortex terminate mainly in the dorsal horn of the spinal cord. These fibers can influence muscle activity only through spinal interneurons. (B) Descending fibers from the cortex form the internal capsule on their way to the spinal cord or other lower brain structures. The anterior limb of the internal capsule arises from anterior parts of the frontal lobe (prefrontal cortex). Fibers originating from the premotor areas, the primary motor cortex and parietal regions occupy successively more posterior locations (with partial overlap) in the posterior limb of the internal capsule. Because of this arrangement, lesions affecting parts of the internal capsule may block descending influences from particular cortical areas and may have differential effects on motor and cognitive functions. Brain section adapted with permission from the Talairach daemon (http://www.talairach.org, Lancaster JL, Woldorff MG, Parsons LM, et al. Automated Talairach atlas labels for functional brain mapping, Hum Brain Mapp. 2000;10:120-131).

has important implications for recovery of functions following brain injury. Notably, these pathways provide additional avenues for a diversity of regions within the contralesional and ipsilesional hemispheres to influence movements of the affected upper extremity.

Several motor pathways originate in the brainstem and project to the spinal cord (Figure 7). The largest of these are the reticulospinal tracts (RSTs) that arise from cells in the pons and medulla. The axons of the latter lie close to the corticospinal tract in the lateral columns of the spinal cord, whereas axons from the pons run in the ventromedial portion of the cord. Their terminations are mainly onto interneurons in the spinal gray matter, which then activate spinal motor neurons; however, direct monosynaptic inputs to motor neurons also exist. There are extensive inputs to the RSTs from wide areas of the cerebral cortex, including the primary and all premotor areas of the cortex, many of which are branches from corticospinal axons that traverse this region on their way to the spinal cord. Other inputs come from spinal afferents and from the fastigial nucleus of the cerebellum.

It is important to note that reticulospinal neurons are thought to receive input from both hemispheres; they then project ipsilaterally or bilaterally to the spinal cord. This organization, which is quite different from the predominantly crossed corticospinal projection, has an important implication for functional recovery. Specifically, it means that after a hemispheric stroke, the nonstroke hemisphere has intact projections to both sides of the spinal cord via the RST and hence
Figure 7. The reticulospinal tract: large regions of the cortex project to groups of nuclei in the brain stem where several pathways to the spinal cord originate. The reticulospinal tract is composed of the pontine (blue) and medullar (orange) divisions, which originate from nuclei located in the pons and medulla, respectively. The reticulospinal tract differs from the corticospinal tract (see Figure 6) in the larger cortical territory that contributes to it and the course and termination of fibers in the spinal cord.

Principle VI: The Complex Roles of the Spinal Cord—Shaping the Consequences of the Motor Command

Although some descending commands from the CST have monosynaptic connections with (particularly) distal hand motor neurons, the majority of both CST and RST projections synapse on the interneurons of the intermediate zone of the spinal gray matter. It is critical to appreciate that the spinal gray matter is not a passive conduit for cortical inputs to reach motor neurons; it is a complex piece of computational circuitry where descending commands interact with sensory reflex pathways before producing movement. Essentially, the descending inputs can set the excitability of reflex pathways and modulate their effectiveness during different types of movement. In turn, the reflex inputs can modulate the descending motor commands to muscle.

The final processing of the motor command occurs at the motor neurons themselves. Although often thought of as summing synaptic inputs to reach a firing threshold, these neurons have several active membrane properties that allow them to adjust the “gain” of the input–output relation. Plateau

potentials have been described in cat motor neurons that are caused by the activation of persistent inward Na⁺ and Ca²⁺ currents. They are activated when the neuron is depolarized beyond a certain potential. Their effect is to maintain the depolarization even when the original driving input is no longer present. In this way, they can effectively amplify the action of synaptic inputs and produce sustained firing of motor neurons in the absence of large inputs.

**Reflex pathways.** Descriptions of reflex pathways can be found in many textbooks. Here, it is interesting to ask how much of the excitatory drive during muscle contraction is provided by reflex inputs versus descending signals from the cortex. Experiments with peripheral anesthesia suggest that in leg muscles, about 30% to 40% of the force output during a volitional contraction is supported by reflex inputs. This means that without reflex support, maximum voluntary strength is reduced by 40%; conversely, a good deal more descending drive is needed to start off a contraction in the first place. Not all this support need necessarily occur through sensory interactions at the spinal cord, although in simple tests of muscle strength, this is thought to be the case. Reduced sensory input to the brain may also contribute.

The converse question is what happens to spinal circuitry when deprived of supraspinal motor input, as in the case of cortical or subcortical stroke or high-level spinal cord injury? With a complete spinal transection, there is a sudden loss of all descending excitation to the spinal circuits, and they become unable to respond to any sensory inputs with a reflex output (spinal shock). However, over time, there are adjustments in the excitability of neural circuits that gradually raise excitability so that responses can occur again, although no longer under the control of central commands. One factor that might contribute to the gradual adaptation to loss of descending drive is an increase in the role of plateau potentials; indeed, by increasing motor neuronal excitability, they may contribute to muscle spasms that can often be easily triggered in spinal cord patients.

**Conclusions**

The CAP model described in this chapter highlights the main computational, physiological, and anatomical principles that we can use to think about movement in the healthy brain and in patients with movement deficits secondary to brain injuries. It is important to have in mind a few key simplifying principles. The goal or desire of moving originates in the more anterior part of the frontal (or prefrontal) cortex from signals that relate to internal states (hunger, thirst, fear, motivation, memory, etc). This initial goal is transformed into an intention to move one or more body parts. We know that signals related to the intention or motor plan are maintained in specific circuits—some for moving the eyes and others for moving the head or the arm—that involve premotor and posterior parietal cortices. Accordingly, damage to anterior (and medial) prefrontal regions impair the goal, giving rise to problems with initiation such as abulia, whereas lesions in the premotor and posterior parietal cortices give rise to problems with intention and motor plans, or apraxias.

Movements are furthermore context dependent, and different regions are recruited depending on whether the movement is guided by sensory information, as when reaching for an object, and/or by internal information, as when we “search” for food when hungry. Most movements involve both sensory and internally driven plans. As we get closer to the actual execution of the movement, motor plans code the actual combination of body parts to be moved. For example, in the motor cortex, moving the hand activates a different subregion of the motor cortex than that activated while speaking or walking. This segregation of body parts in the cortex, or somatotopy, is present not only in the primary motor cortex but also in other parts of the cortex, the cerebellum, and in the organization of descending fibers to the spinal cord. Notably, not all descending motor fibers come from the primary motor cortex. Other premotor and parietal regions directly project to the spinal cord and brainstem.

Whereas the traditional view is that the motor cortex generates the commands to activate the spinal cord and that signals from the spinal cord are relayed back to the cortex to control the movement (feedback), an important and novel concept is that motor control involves both feedback and feedforward control. Parallel to the generation of the descending motor signal, a copy (like a backup on your computer) travels to sensory regions “anticipating” where the body part will be at the end of the movement. This “forward model” is important to accommodate sensory changes induced by the movement itself. For example, in the absence of a forward model of an intended eye movement, our retinal image would appear to jump every time we move the eyes. Instead, this mechanism allows rapid calculation of the retinal displacement produced by the movement and enables us to accommodate for it. Forward models are also essential for smooth movements and fill the time before feedback sensory signals from the peripheral receptors activated by the movement itself (cutaneous, joint, and tendons) return to the cortex. When the forward model is broken, as in the case of cerebellar injuries, movements are very irregular (ataxic) because they primarily depend on the sensory feedback.

Another important aspect of movement is the association with reward and habits. Useful actions tend to be more common and are carried out more automatically. In contrast, novel tasks require more control and need to be reinforced to become habitual. The BG are important for integrating reward with action and also for shifting from one action to another. Lesions in the BG lead to rigidity both in movement and cognition. Finally, although we think of the cortex as the structure generating all the movements, in reality, many postures and movements are controlled unconsciously by the brainstem and the
spinal cord via sensorimotor reflexes. The brainstem and spinal cord are sophisticated devices that hold our body upright, maintain common postures in our limb segments, and allow us to walk. They also determine the level of excitability of our muscles through the interaction with the cortex.

References

Neurological Principles and Rehabilitation of Action Disorders: Common Clinical Deficits

K. Sathian, MD, PhD¹, Laurel J. Buxbaum, PsyD², Leonardo G. Cohen, MD³, John W. Krakauer, MD⁴, Catherine E. Lang, PhD⁵, Maurizio Corbetta, MD⁶, and Susan M. Fitzpatrick, PhD⁶,⁷

In this chapter, the authors use the computation, anatomy, and physiology (CAP) principles to consider the impact of common clinical problems on action. They focus on 3 major syndromes: paresis, apraxia, and ataxia. They also review mechanisms that could account for spontaneous recovery, using what is known about the best-studied clinical dysfunction—paresis—and also ataxia. Together, this and the previous chapter lay the groundwork for the third chapter in this series, which reviews the relevant rehabilitative interventions.

Paresis

Phenomenology

The most common motor disorder experienced by individuals after central nervous system damage is paresis. In the strictest sense, paresis is the reduced ability to voluntarily activate the spinal motor neurons. Total paresis is called plegia, reflecting a complete inability to voluntarily activate the motor neurons. In the human experience, however, paresis is more appropriately viewed as a syndrome, that is, a collection of impairments that coexist in most patients.¹ The impairments that typically make up the paretic syndrome are weakness, spasticity, a decreased ability to fractionate movement, and an often subtle, higher-order planning deficit. Paresis can result from a wide range of neurological diseases and conditions such as stroke, multiple sclerosis, cerebral palsy, amyotrophic lateral sclerosis, traumatic brain injury, and spinal cord injury. The disease or condition may define the distribution of the paresis, such as hemiparesis seen after stroke and paraparesis seen after spinal cord injury.²

When a person with paresis reaches out to grasp a cup or pick up a key, the result is movement differs from that performed by a person with an intact nervous system. Paretic movements are slower, less accurate, and not as efficient as normal movements. A person with paresis often makes multiple attempts to position the hand near the desired object and to open the fingers wide enough to grasp it. Particularly when grasping a small object such as a key, the fingers may touch and retouch the object multiple times to accomplish a successful precision grasp. Forces produced by the fingers to lift an object are not as well coordinated in people with paresis compared with neurologically intact individuals. Fingertip forces can be poorly timed and of inappropriate magnitude and direction such that, even if successfully lifted off the table, a cup may tilt as it is raised or a key may fall from the fingers. Once the object is in hand, a person with paresis has difficulty moving it to some locations. Lifting the cup to the mouth, where the arm movement is close to and directly in front of the body, is usually much easier than lifting the cup to a shoulder-height shelf on the opposite side of the body. Reaching movements where the hand moves to locations further away from the body are often accomplished via compensatory trunk movements rather than the normal rotations at the shoulder and elbow. Because of the difficulty in controlling the reaching movement, the hand may not be appropriately oriented to grasp or to release an object. Letting go of a grasped object is often as difficult as grasping an object for people with paresis. It can take multiple attempts and extra time to open the hand and leave the object on the table. Finally, increased efforts to move, especially in those individuals with more severe paresis, often results in associated movements of other body parts. For example, when a person with stroke tries to grasp the key with the paretic hand, the ipsilesional, nonparetic hand may also extend at the wrist and flex at the fingers, or the patient may even extend the knee. As will be discussed later, this reflects activation of the hemisphere opposite the lesion when the weak limb tries to move.

¹Emory University. and Rehabilitation R&D Center of Excellence, Atlanta VAMC, Atlanta, GA, USA
²Moss Rehabilitation Research Institute, Philadelphia, PA, USA
³NINDS, NIH, Bethesda, MD, USA
⁴Johns Hopkins University, Baltimore, MD, USA
⁵Washington University School of Medicine, St Louis, MO, USA
⁶Washington University School of Medicine, St Louis, MO, USA
⁷James S. McDonnell Foundation, St Louis, MO, USA
Mechanisms of Paresis

Paresis can be largely considered a problem of movement execution. The primary mechanism underlying paresis is damage to the corticospinal system—that is, the cortical motor areas and the corticospinal tract that connect the cerebral cortex to the spinal cord (Figure 1). Figure 2 illustrates how the disruption of the corticospinal system input alters the activation of motor units, the activation of muscles and sets of muscles, and the ability to move. Paresis reflects a problem in transferring the motor commands from the cortex to the spinal cord (red line from the motor cortex to the hand). Together, these changes in the ability to volitionally activate motor units, muscles, and sets of muscles can explain much of the impairments of weakness and reduced fractionation of movement. Spasticity is largely a result of loss of supraspinal inhibition to the spinal cord, causing the response to afferent input (eg, input from muscle spindles or cutaneous receptors) to be abnormally large.

It is important to note that higher-order planning deficits can be superimposed on impairments of motor execution. Excessive activation of the motor cortex to try to overcome the interruption of motor commands can lead to abnormalities of the motor command (efference) copy and thus of the forward model, causing inappropriate estimation of the movement parameters and joint positions needed to efficiently execute the movement (refer to Figure 2). These include difficulties with anticipating the correct force with which to grip an object or anticipating the consequences of a selected movement.

A clinical example of an abnormal forward model is the phenomenon of past-pointing after oculomotor palsy. Patients with a partial sixth nerve palsy and weakness of abduction on lateral gaze tend to overshoot a target when pointing to it with the hand while looking. The explanation is that excessive activation of oculomotor plans to overcome the partial paralysis of eye muscles spills over to motor commands for the hand that incorrectly predict the new hand position despite normal visual information. Paresis and difficulty with fractionation can also be made worse by concurrent deficits in the perception of limb position (proprioception), tactile properties of objects (touch, surface texture, etc), or by pain. Abnormal sensory feedback (blue line from hand to sensory cortex and position feedback in Figure 2) can worsen an already abnormal forward model.

Examination of the Paretic Patient

Items from the normal clinical exam are used to determine if the patient has a paretic syndrome and to rule out other disorders of movement. Weakness is one of the more salient impairments of paresis and is the one most easily tested. Standard muscle strength testing using the Medical Research Council (MRC) rating scale (0-5) allows clinicians to determine the severity and distribution of the weakness. If patients are unable to maintain a position against gravity (<3 on the scale), then an alternate means to quantify weakness is to measure the active range of motion (AROM) at that joint. AROM and strength can be considered indirect measures of the ability to volitionally activate the spinal motor neuron pools. AROM measures may be better able to capture deficits at the lower end of the spectrum—that is, whether the muscles can be activated enough to move the joint through the range. Strength measures may be better able to capture deficits at the higher end of the spectrum—that is, whether the muscles can be activated sufficiently to produce force against externally imposed loads.

Spasticity is traditionally defined as a velocity-dependent resistance to movement. Spasticity can be assessed by passively moving the affected limb through its available range of motion and then by varying the speed at which it is moved. Spasticity is present if there is increasing resistance as the limb is moved faster. The resistance is often stronger in one direction than in the other (eg, greater during passive elbow extension vs flexion), typically being most pronounced in antigravity muscles. Spasticity can be differentiated from rigidity: the latter is not velocity dependent (resistance is the same regardless of the speed of passive movement) and is less likely to be directionally dependent (feels the same during flexion and extension). Unlike spasticity, rigidity is believed to stem from altered basal ganglia function (for a review of rigidity see Delwaide or Hallett). The underlying neuropathology affects the severity and pattern of spasticity. For example, people with spinal cord injury often experience greater levels of spasticity than people with stroke. Following stroke, the severity of spasticity matches the severity of weakness reasonably well. Spasticity may contribute to problems such as being unable to release a grasped object.

Fractionation of movement is a critical part of our ability to use our upper extremities for many different movements. Along with spasticity and weakness, there is frequently a reduced ability to fractionate movement in people with paresis. The ability to fractionate movement can be assessed by asking the patient to move 1 segment in isolation and keep other, adjacent segments still. Assessment of fractionation is most common at the fingers, where patients are asked to touch the tip of the thumb to the tip of each of the other fingertips. Loss of fractionated movement also occurs at more proximal segments and can be determined by asking a patient to flex the shoulder alone. The reduced fractionating can be seen as the patient flexes and abducts the shoulder while simultaneously flexing the elbow and wrist and pronating the forearm. This reduction in fractionated movement, particularly in patients with stroke, has the same origins as the abnormal movement synergies originally observed by Twitchell and categorized by Brunnstrom. Like spasticity, the degree of...
Figure 1. Lesions to the corticospinal system causing paresis: the small lesion in the motor cortex (leftmost panel) resulted in paresis only to the contralateral upper limb, whereas the other 3 lesions resulted in paresis affecting the contralateral face, upper limb, and lower limb.

Figure 2. Effects of damage to the corticospinal system on movement generation and feed-forward computations. (A) In the intact system, the motor command for elbow flexion, for example, computed in the motor areas is sent to the spinal cord motoneurons (MNs) and interneurons (red line). The command results in agonist contraction (biceps), antagonist relaxation (triceps), and the generation of force. A copy of the motor command is input to an internal model of limb position computed centrally (for details, see Frey et al.). (B) After damage to the corticospinal system, the generation of movement is compromised both by reduced descending commands to the spinal cord (dotted red line) and by interference with feed-forward computations of the internal model. Some descending effects illustrated here are the following: reduced spinal MN (and muscle motor units) activation, decreased agonist drive, increased coactivation of antagonist muscles, and altered sensory input as a result of loss of supraspinal inhibition of sensory afferents. As a consequence, activation and termination of muscle activity are delayed, force production and its rate are decreased, and muscle activation is less selective. Movements are slower and less accurate, leading to repeated attempts or compensatory strategies and, overall, less functionality. Centrally, compensatory increase in movement plans (or effort) and irregular sensory feedback and proprioception may lead to the formation of an abnormal internal model and erroneous feed-forward computations.
loss in movement fractionation is related to the degree of weakness. Patients with more severe paresis and spasticity typically have less ability to fractionate movement, whereas those with milder paresis and minimal spasticity can make well-fractionated movements. (For experimental data on weakness, spasticity, and fractionation and their relationship to hand function poststroke, see Lang and Beebe).

Higher-order planning deficits (including those attributable to the apraxia syndrome) can be superimposed on the impairments discussed above. They include difficulties with anticipating the correct force with which to grip an object or anticipating the consequences of a selected movement. Whether higher-order planning deficits are present in an individual patient is difficult to assess early after neurological injury because the deficit can be masked by weakness and loss of fractionation. Additionally, one should always test for deficits in limb position or abnormal tactile discrimination that can amplify difficulty with planning more complex movements. For patients with severe paresis, the presence or absence of higher-order planning deficits may be harder to detect because of the diminished ability to execute volitional action. For those with milder paresis, planning deficits are usually identified by patients’ reports of difficulties with challenging activities requiring high levels of dexterity (eg, skilled tool use and typing) as they return to jobs and other daily activities. Specific testing of the higher-order deficits may best be done within the evaluation for apraxia (see section below and Box 1).

Finally, it is important to evaluate secondary impairments that may arise from paresis. The most common secondary impairments in the upper extremity are contracture and atrophy. The presence and severity of secondary impairments may affect the process of selecting the most appropriate treatment for an individual patient and the anticipated prognosis.

Quantitative Measurement

Quantitative measures of motor impairment, motor function, and motor disability seen with paresis are provided in Table 1. For the upper-extremity function measures, data from people with stroke indicate that the measures are strongly related to one another. Quantitative scales are important to initially measure impairment, function, and disability; they should be repeated regularly (eg, monthly) for clinical decisions to continue, switch, or interrupt a treatment, ideally by personnel not involved in the patients’ rehabilitation (to avoid bias). Scales with continuous variables (eg, AROM in degrees) are preferable to interval scales (eg, MRC scale for motor strength).

Apraxia

Phenomenology

Apraxia is a common clinical disorder affecting complex, skilled movements that may result from stroke, traumatic brain injury, or degenerative dementias, including Alzheimer’s disease and corticobasal ganglionic degeneration (CBD). It is particularly common after dominant (usually left) hemisphere stroke and can be observed in both contralesional and ipsilesional limbs. There are several major apraxia syndromes, all of which frequently co-occur with the components of the paretic syndrome—weakness, spasticity, and impaired fractionation (see above sections)—rendering diagnosis difficult, particularly in the contralesional limb.

When a person with apraxia attempts to use a key (even with the ipsilesional hand), there may be inaccuracy in the direction, amplitude, and timing of movement and/or posture of the arm and hand. For example, rather than exhibiting a clear turning movement at the wrist, the patient may attempt to slide the wrist to the side or may attempt to turn at the shoulder rather than at the wrist joint. Alternatively (and less frequently), the patient may attempt to use the key as if it were another object.

Early anecdotal observations suggested that apraxia is evoked only in the context of specialized, abstract tests, with little functional impact. It is now widely recognized that, to the contrary, apraxia is a major predictor of poor functional performance on everyday tasks and of increased dependence on caregivers. However, for the purpose of diagnosis, the disorder is most clearly evoked on tests of gesture to the sight of objects and on so-called multiple objects tests. We will describe apraxic patterns of performance on these tests next.

---

**Box 1. Motor neglect**

One relatively common impairment of movement not directly related to motor execution or planning deficits is motor neglect. Patients tend to ignore their affected arm and appear weak or clumsy on examination; surprisingly, however, their strength and dexterity improve dramatically when they are cued to pay attention to the arm. This failure in attending to and moving the affected arm is often present in the absence of any sign of spatial neglect or of impaired attention to sensory stimuli. Motor neglect can reflect a problem of motor activation without specific spatial impairment, or it can also take the form of a specific deficit in moving toward contralesional space (directional hypokinesia). Lesions that cause motor neglect are typically anteriorly located in the frontal white matter or the basal ganglia.
The taxonomy of apraxia subtypes is confused by a number of different conventions in labeling and diagnosis. Recent investigations indicate that there are reliable differences in 2 major subtypes of apraxia.

**Ideational/conceptual apraxia.** Ideational/conceptual apraxia refers to the impaired ability to carry out multiple-step actions with objects, such as making a sandwich or lighting a candle. Patients with ideational/conceptual apraxia may substitute inappropriate actions, mis-sequence actions, or omit action steps. For example, an ideational apraxia might spread butter on bread before placing it in the toaster, or use a spoon to cut food in the close proximity of a visible knife.

Ideational/conceptual apraxia may be conceptualized as an inability to select or sequence the appropriate motor programs for completing a temporally extended sequence of meaningful actions. This problem can be exacerbated by problems of executive control, loss of knowledge about objects (object semantics), and impairments in arousal and attention.

Ideational apraxia is most frequently induced by large strokes, moderate-to-severe traumatic brain injury, or...
degenerative dementia. It tends to diminish over time after stroke or brain injury. Although ideational apraxia was previously associated with frontal-subcortical lesions, recent investigations indicate that large lesions at many brain loci may result in the disorder.  

**Ideomotor apraxia (IMA)**. This refers to the impaired ability to plan and recognize complex motor actions especially when they rely on stored (semantic) knowledge. Patients with IMA can have trouble in carrying out skilled, object-related motor actions with either hand and may also be deficient with actions that convey a symbolic meaning, like saluting. Recent investigations suggest that IMA reflects damage at 2 major levels (see below). The complexity of the underlying mechanisms is a major cause of the confusion that has characterized the literature in this area for many years (Figure 3).  

One computational deficit in IMA is reduced ability to program movements using an intrinsic spatial coordinate frame, with relative preservation of coding in extrinsic spatial coordinates. An intrinsic spatial coding scheme is used to calculate the positions of body parts with respect to one another, possibly partly in terms of joint angles. For example, while reaching to a cup, calculation of the positions of the hand and fingers with respect to the shoulder is an intrinsic computation. This computation corresponds to the development of a forward model based on estimation of body state described in the accompanying chapter by Frey et al. Extrinsic spatial coding is used to calculate the positions of the body and its parts with respect to the external world. For example, calculation of the positions of the hand and fingers with respect to a cup is an extrinsic computation. Clearly, most actions in the world require both types of calculation. However, pantomimed actions (see examination) are actions performed without any external referent, and this is thought to explain why pantomimes are so difficult for ideomotor apraxics.

The second major deficit in IMA is reduced activation of stored representations of skilled object-related actions to the sight of objects (ie, with visual input) or to command (ie, with auditory input). Instead, there is overreliance on somatosensory information—particularly information gleaned from object structure (shape, size, weight, and possibly texture). This helps explain why many ideomotor apraxics perform better when actually holding objects rather than mimicking their function (see examination and Box 2).

Unlike ideational apraxia, IMA is a syndrome with relatively clear brain localization, most frequently because of left inferior parietal and left premotor cortical damage following middle cerebral artery stroke, Alzheimer’s disease, or CBD. Frequently, both ideational apraxia and IMA may occur in the same patient; however, these subtypes also dissociate.

**Examination of the Apraxic Patient**

Ideational/conceptual apraxia is diagnosed on the basis of action errors in everyday activities, including omissions...
of key steps (e.g., wrapping a gift while the wrapping paper is still on the roll), substitutions of erroneous objects (use of juice rather than milk in cereal), reversal of steps (spreading butter and jelly, then toasting bread), and other more flagrant errors (using a yellow marking pen to color bread rather than spreading yellow mustard on bread). Few formal tests for ideational apraxia have been developed. One is the Naturalistic Action Test, which assesses the ability to perform a number of everyday tasks, such as packing a lunchbox and making toast while ignoring distractor objects. Errors of a number of types are quantified, and the performance is compared with normative scores. The Test for Upper Limb Apraxia (TULIA) is a brief bedside examination with good reliability. Testing for IMA frequently includes gesture to command or imitation of the examiner for transitive (object-related) movements, such as hammering, cutting, brushing teeth and the like, and intransitive (symbolic) movements, such as waving goodbye or signaling stop. It is also useful to ask the patient to gesture in response to seeing and holding actual tools. The Florida Apraxia Battery assesses gesture production in a number of different conditions and provides standardized guidelines for scoring (L. J. G. Rothi, A. M. Raymer, C. Ochipa, L. M. Maher, M. L. Greenwald, K. M. Heilman, Florida Apraxia Battery [experimental edition], unpublished data, 1992). Kinematic analyses have revealed that IMA patients pantomime skilled tool use movements with abnormal joint angles and limb trajectories and uncoupling of the spatial and temporal aspects of movement. Spatiotemporal errors persist to a lesser degree with actual tool use.

Ataxia

Phenomenology

Ataxia results from damage to the cerebellum, its input and output pathways in the brainstem, the spino-cerebellar tracts or posterior columns in the spinal cord, or large fibers in peripheral sensory nerves. For the sake of brevity, the term cerebellum will be used to include the cerebellum and its brainstem connections. The term ataxia is sometimes used in a specific sense to refer to impaired spatial and temporal coordination of movements or sometimes more generally as a catch-all term for poor coordination, inaccurate and variable movements, dysmetria, and intention tremor.

A patient with ataxia may present with balance and gait problems, depending on what components of the input/output pathways to/from the cerebellum are compromised. Patients are unable to maintain a standing and/or a sitting posture and may show violent oscillations of the trunk laterally or anteriorly and posteriorly, as if trying to catch themselves. Balance and posture difficulties are typically exacerbated while standing up. Walking abnormalities are characterized by difficulties in coordinating a correct stepping sequence with 1 foot hitting the ground either early or late, typically with inaccurate force and placement. The result is a stepping gait in which the legs seem to advance chaotically forward while the patient’s trunk may be leaning in the wrong direction. In severe bilateral ataxia, patients cannot walk if not fully supported. There can also be problems in the use or coordination of the arms and hands. Patients may reach inaccurately and may be unable to grasp with precision because tremor interferes with a smooth action. Tremor typically increases when the hand is approaching the target. Speech can be also affected by tremor, which makes it sound scanning, in a very characteristic manner. Finally, cognitive deficits in verbal production, timing, and nonverbal decision making have also been reported (see below).

Mechanisms of Ataxia

Current theories lead to the idea that the cerebellum provides predictive state estimates that allow feed-forward coordination between agonist and antagonist muscles and between limb segments. When there is cerebellar damage, patients are forced to rely more on delayed sensory feedback and respond with reactive rather than predictive control. Some of the jerkiness and slowness in movements (ataxia) can represent this attempt at catchup with feedback adjustments, but errors accumulate because of feedback delays. Prediction here does not seem to be based on some internal clock that anticipates the timing of events, but instead on an internal simulation or model of the limb system that receives an efference copy of the command and can predict the consequence of that command on kinematic and dynamic variables (state variables); predicted states can then be sent to motor areas to send anticipatory commands for feed-forward control. For an illustration of this model, please refer to Figure 1 in the chapter by Frey et al.

If cerebellar patients have persistent inability to anticipate the consequences of their motor commands, then it must mean that they are unable to learn the internal model (forward model in the CAP framework) of their limb needed to anticipate errors. This leads to a very interesting question: can cerebellar patients be rehabilitated if they cannot learn? We address this later in this consensus chapter.

Examination of the Ataxic Patient

It is important that ataxia be distinguished from weakness, loss of fractionated movements, hyperreflexia or hypertonia, and higher-order motor abnormalities such as apraxia. Unfortunately, this can be difficult when the cerebellum and noncerebellar structures are damaged together. For example, in certain brainstem strokes, cerebellar connections and the corticospinal tract can both be affected. In addition, damage to the corticospinal tract can also lead to poor multijoint coordination and inaccurate movements, leading to overlap in clinical signs and psychophysical findings. Nevertheless, careful examination of limb movements will usually reveal cerebellar involvement, or its absence, with a good deal of accuracy.
Hypermetria. From the Greek hypermetros, meaning "beyond measure," hypermetria refers to the tendency for patients with cerebellar disease to fail to properly terminate fast movements, so that they overshoot the target. Hypermetria is usually assessed in 2 ways. (1) Finger–nose–finger test: The patient first holds up the arm so that the elbow and shoulder are in more or less the same horizontal plane. The patient is instructed to make rapid out-and-back movements with the arm and shoulder in the plane, then back to the nose. Rotation of both shoulder and elbow joints is required here to make the pointing movement because multijoint movements accentuate cerebellar abnormalities. Speed is important because the errors are velocity dependent, and patients often slow down to compensate for their errors. Patients tend to overshoot the examiner’s finger and then attempt to correct the overshoot. The initial overshoot and subsequent wayward corrections are collectively called dysmetria. (2) Finger chase: here, the patient holds the forefinger in front of and in near contact with the examiner’s forefinger. The examiner then moves his finger rapidly up, down, and sideways with a pause between each movement, instructing the patient to track his finger with his own finger. The cerebellar patient will show marked overshoots with each movement. This test is more challenging and can elicit dysmetria in those with milder ataxia.

Failure of check. This test, like those above, un masks the inability to properly decelerate the limb. In the first part, the patient is asked to flex the elbow against the examiner’s attempt to extend it. The examiner then lets go suddenly. The ataxic patient is unable to stop abruptly and overshoots.

Excessive rebound. The patient is asked to hold the arms out in front, palms down. The examiner then quickly and gently displaces 1 arm downward, looking for excessive upward displacement, termed rebound.

Dysdiadochokinesis. Patients are asked to rapidly tap 1 hand on the other, alternating between palm up and palm down. Patients with cerebellar disease are slower, are unable to maintain a steady rhythm, and show a variable contact point (slippage between palms). This test un masks acceleration and deceleration abnormalities as well as timing abnormalities (see later).

Tremor. The archetypal cerebellar tremor is an oscillation of 3 to 5 Hz that tends to be accentuated at the end point of a movement—for example, during the deceleration phase of the finger–nose–finger test.

Hypotonia. The traditional teaching is that hypotonia is a classic cerebellar sign. Transient hypotonia may be seen after large acute cerebellar lesions and some of the spinocerebellar ataxias. However, otherwise, tone tends to be normal in cerebellar disease, and this is therefore neither a sensitive nor specific finding. Hypotonia can be tested for by shaking the limb and noting excessive flappiness about the wrist.

Two tests mistakenly thought to test the cerebellum. (1) Rapid alternating or sequential finger movements: slowing may be a result of cerebellar disease but is much more common after corticospinal tract damage, and it is hard to distinguish between them. Thus, this test should be avoided for determining cerebellar involvement. (2) Past-pointing: here patients are asked to place the extended index finger on the examiner’s forefinger, then raise the arm above the head, and then, with the eyes closed, bring the forefinger down (without bending the arm) onto the examiner’s finger. The abnormality that is sought is a systematic directional bias. This is not a particularly sensitive test because it can be compensated for and corrected after a few attempts. The important point is that this tests for vestibular imbalance caused by unilateral vestibular disease, with a directional error toward the side of the vestibular lesion. This is not seen with cerebellar lesions.

Recovery of Function, Its Neural Basis, and Implications for Rehabilitation

Recovery From Paresis

Predictors of recovery. After a central nervous system injury, recovery of paresis occurs along a fairly predictable time course. Figure 4 illustrates the time course of recovery from paresis at the impairment and at the functional levels, as derived from epidemiological data after stroke. In general, most motor recovery occurs within the first 3 months, with stronger recovery occurring in the first 4 to 8 weeks and eventually reaching a plateau at around 12 weeks. Several large, longitudinal studies show that initial severity is one of the best predictors of final impairment and function. For example, 50% to 80% of patients with mild motor deficits (MRC scale 4–5) can expect full recovery, whereas only 10% to 25% with severe deficits (MRC scale 1–2) can expect full recovery at 3 months. Another way to express the same concept is that patients with mild paresis are 2 to 8 times more likely to recover than patients with severe paralysis. Another sensitive measure of chronic recovery at the acute stage is the presence/absence of motor evoked potentials (MEPs) measured by magnetically stimulating the affected hemisphere and recording muscle responses. Patients with MEPs present in the first few days are 20 to 100 times more likely to recover than patients with absent MEPs. A third important concept is that patients with more mild deficits recover more quickly and completely than patients with more severe deficits. For the purpose of predicting recovery of individual
patients, it is important to appreciate that this is the general pattern of recovery and that most, but not all, patients follow similar time courses. There are several consistent predictors of poor outcomes poststroke that are useful to look for when evaluating individual patients. First, the greater the nonmotor impairments (e.g., somatosensory loss or visual field loss) that accompany the motor deficits, the less likely the person is to return to functional independence. Second, earlier improvements in motor deficits indicate that a person is more likely to reach higher levels of independence. And, third, individuals with minimal grip strength and/or minimal active movement at the shoulder at 30 days postinjury are unlikely to regain functional use of the hand and arm. Recovery of function typically lags recovery of motor deficits by about 1 week, but the shapes of the 2 recovery curves are very similar. The reason for the lag and the similar shape may be because as the motor ability emerges, movement practice is required to capitalize on the motor recovery and incorporate it into daily function. These principles are important to decide whether and when to switch the emphasis of rehabilitation from restorative to compensatory techniques. For instance, in the case of a patient with a nonfunctional hand at 3 months, the chance of regaining function is very small, even with prolonged restorative intervention, at least based on current methods.

Mechanisms of recovery from paresis. It is important to recognize that the brain regions mediating performance of a particular task are not, as often taught, discrete or unique single anatomical sites. Any complex motor behavior is the consequence of activity in a distributed network of regions or nodes, often in both cerebral hemispheres, that contribute, perhaps in differentiated but also possibly in overlapping ways, to motor control. Understanding of this principle is important because it explains the relative similarity of clinical signs elicited by lesions in different locations as well as the difficulties in trying to assign unique brain regions to single behaviors. From a neurorehabilitative point of view, it raises the possibility of accessing a specific network through different nodes, as discussed below.

The process of recovery of motor function after stroke represents a relative continuum from the initial hours after the actual event to the chronic stage years later. Early recovery in the hours or first few days following a stroke is likely to reflect...
improvement of hemodynamic and metabolic factors in the area of injury or surrounding tissue. For instance, early recanalization of an obstructed blood vessel or relative increases in blood pressure can improve the metabolic function of an ischemic area and therefore its neuronal function. At the cellular level, in the first few weeks following a stroke, a number of genetic, cellular, and neuronal changes occur both near the lesion and in the regions connected to it. For instance, increments in excitability in contralateral homologous zones and decreases in excitability near the lesion have been described. Synaptic sprouting from the contralateral homologous cortex to the site of a lesion has been demonstrated to occur in rats. In monkeys, changes in physiological organization of cellular responses near the lesion as well as sprouting of new connections between distant cortical areas have been demonstrated. It is interesting to note that some of these changes are modulated by rehabilitation. Whether and how these neural changes are relevant to patients remains unclear and deserves study.

In humans, neuroimaging and neurophysiological studies are beginning to provide a few general principles on neurological reorganization after stroke. First, after subcortical lesions involving descending fibers from the primary motor cortex, cortical activity moves toward anterior premotor areas likely involved in driving brainstem and spinal mechanisms through different parts of the corticospinal tract. Second, patients after stroke tend to recruit more areas than healthy persons when moving their paretic limb. This relative overactivation seems to be inversely correlated with level of function—that is, more spread of activation across cortical regions equals lower function—and longitudinal normalization of activation patterns seems to correlate with better recovery. Third, an important emerging physiological principle is the importance of balanced activity between the 2 hemispheres for normal function. Unbalanced activation or excitability seems to be associated with greater impairment. This principle has important rehabilitative applications (see Box 3).

**Recovery From Apraxia**

There have been few investigations of recovery from apraxia. The available evidence suggests that IMA after left-hemisphere stroke is persistent, with only mild improvement over time. Patients with less severe apraxia at initial testing, not surprisingly, are most likely to recover.15

**Recovery From Ataxia**

Compared with paresis, far less is known about the time course of recovery from ataxia and the factors that influence this recovery. In humans, substantial recovery can occur in the first 3 months after cerebellar stroke, and it proceeds through a series of stages that can be mapped onto characteristic changes in the triphasic electromyographic (EMG) response.

---

**Box 3. Interhemispheric interactions in motor control**

Neuroimaging studies have consistently documented enhanced activity in motor areas of both cerebral hemispheres, associated with movements of the paretic hand. Patients with stroke experience changes in motor cortical excitability and an abnormally high interhemispheric inhibition from contralesional to ipsilesional M1 when attempting to move the paretic hand. These changes are more prominent in those with more substantial motor impairment. What is interesting is that these abnormalities may be task dependent because they may not be present when patients are at rest. These findings give rise to the hypothesis that targeted modulation of excitability in motor regions of the intact and affected hemispheres, through either somatosensory or motor cortical stimulation, could potentially contribute to improvements in motor function.20

Somatosensory input is required for accurate motor performance and skill acquisition. Reduction of such input by local anesthesia impairs motor control, as shown in patients with large-fiber sensory neuropathy who display characteristically abnormal motor behavior. In stroke patients, somatosensory deficits are associated with slower recovery of motor function. It has been proposed that somatosensory stimulation, which enhances motor cortical excitability, could operate as an adjuvant to rehabilitative treatments. Indeed, application of somatosensory stimulation to an affected body part can facilitate motor function in patients with stroke. It is interesting to note that anesthesia of body parts contralateral to the paretic side can influence motor function in the paretic hand, perhaps through modulation of interhemispheric inhibitory interactions. For example, anesthesia of 1 hand results in facilitated motor function in the other hand in healthy persons and in stroke patients.

Noninvasive brain stimulation represents a useful tool to modulate human brain function.21 Three techniques have been the most commonly tested in the framework of recent neurorehabilitative studies. Transcranial magnetic stimulation (TMS), a procedure that modulates cortical excitability, has contributed significantly to the understanding of mechanisms underlying cognitive and sensorimotor processes. Depending on stimulation parameters, TMS can enhance or decrease excitability in the neural structures under the stimulating coil. Transcranial direct current stimulation (tDCS) is a procedure used to polarize brain regions through the noninvasive, transcranial application of weak direct currents that can also enhance or decrease cortical excitability depending on the polarity with which it is applied. Both techniques, recently tested after stroke, are able to modulate brain function, are painless in addition to being noninvasive.

(continued)
and can be used in the setting of double-blind experimental designs. Additionally, based on studies in animal models, recent studies attempted to facilitate motor function after stroke by stimulating perilesional areas on the cortex through epidural electrodes. Cortical stimulation has been applied with the purpose of either facilitating activity in the ipsilesional M1 or downregulating activity in the contralesional M1, consistent with the notion of interhemispheric inhibitory interactions between motor cortical regions.

**Box 3. (continued)**

as it converges toward the normal pattern. Recovery from hypermetria in humans can be unmasked by increasing the inertial load of the moving hand with weights. This interesting finding suggests that spontaneous recovery from hypermetria is incomplete and may not be mediated through learning.

**Mechanisms of recovery from ataxia.** Recovery from ataxia after a stroke affecting the cortex or the output nuclei can occur quickly within 2 to 3 weeks in monkeys because of adjustment of activity in the opposite normal cerebellum. This is also commonly observed in human patients, in whom the prognosis after a single cerebellar stroke is generally good. However, a second lesion in the opposite cerebellum reinstates the original deficits and produces novel deficits in the other arm. Recovery in monkeys in this case is much longer and incomplete and is likely dependent on other regions like the somatosensory cortex. In fact, damage to the somatosensory cortex can also reinstate deficits that have recovered after a single cerebellar lesion.

These results have important implications for neurorehabilitation and are further discussed in the accompanying chapter by Pomeroy et al. First, in the monkey experiments, recovery occurred in the setting of daily practice, which means that recovery required interaction of a learning process with spontaneous biological recovery processes. It is doubtful that similar degrees of recovery would have been seen if the monkeys had not been made to practice. Second, faster and more complete recovery occurs early (within 1 month), which means that practice protocols may need to be initiated early after injury. Third, the anatomical loci and physiological processes mediating recovery are multiple, and each may be targeted in different ways. For example, noninvasive cortical stimulation over the sensory cortex might enhance recovery from ataxia and should be studied.

**Illustrative Case B: Apraxia**

BO is a 52-year-old, right-handed male who suffered a cerebrovascular accident affecting the territory of the left middle cerebral artery and resulting in a large frontotemporoparietal lesion. His speech production and comprehension are mildly impaired, and he has a distal hemiparesis on the contralesional side (intact shoulder shrug only). When reaching to grasp objects, the patient has no difficulties in bringing the hand to the correct location in space or in shaping, orienting, and preshaping the grip. However, apraxia testing revealed significant difficulties with common skills. When asked to demonstrate how to use a spoon to eat a bowl of soup, BO instead pantomimmed the action of brushing his teeth (content error). When asked to prepare a letter for mailing, he sealed the envelope before inserting the note (sequencing error). BO is, however, able to correctly recognize and name familiar objects and also identify their common uses and functions. Likewise, he performs at low-normal levels on tests of both working memory and executive function.

**Illustrative Case A: Hemiparesis**

RV is a 70-year-old, right-handed woman with a left-hemisphere stroke, with damage extending subcortically into the corona radiata. Her clinical presentation includes some voluntary activation of the contralesional shoulder, elbow, and wrist (grade 2) but no individuated movements of the digits. Mild tactile and proprioceptive deficits are noted on the affected side as well as some weakness in the contralesional face and leg. She has no aphasia or neglect, and ipsilesional hand function is unimpaired. RV’s ability to imagine movements was evaluated by asking her to determine whether images depicted left or right hands appearing in different orientations. Despite the paralysis, her performance on this task was within the normal range and did not differ between hands. Though by no means atypical, this case illustrates several key concepts. Involvement of the contralesional face and leg, in addition to the hand, reflects damage to adjacent regions of the descending motor fibers organized in a somatotopic fashion. In terms of the model discussed, this hemiparesis can be thought of as a difficulty in computing the proper motor command. This may be a result of either the direct insult to regions of the left prefrontal, premotor, and/or primary motor cortex or damage to the descending white matter tracts that carry commands from these regions to the brainstem and spinal cord. The ability of RV to shrug the shoulder may reflect contributions from the motor areas of the intact cerebral hemisphere to control of proximal muscles via uncrossed pathways. Depending on the posterior extent of the lesion within the internal capsule, parietal output to the spinal cord may also still be intact. One challenge will be how to engage these routes. One possibility may be to augment standard therapies with motor imagery (mental rehearsal exercises). As noted above, RV appears to be capable of these behaviors, and evidence from neuroimaging indicates that such tasks consistently increase activity within parietal as well as frontal regions.
The difficulties that this apraxic patient is experiencing may be a result of deficits in the integrity or selection of stored representations of functional use actions. His ability to produce coordinated reaching-to-grasp movements with the intact hand suggests that he can form an accurate internal model of prehensile actions. Yet it appears that he has difficulties retrieving the correct functional use action program in response to the object stimulus. Testing with an action recognition task requiring distinctions between correctly and incorrectly performed functional actions would help distinguish deficits in the integrity of functional use representations from action selection/retrieval deficits.

References
Neurological Principles and Rehabilitation of Action Disorders: Rehabilitation Interventions

Valerie Pomeroy, PhD1, Salvatore M. Aglioti, MD2, Victor W. Mark, MD3, Dennis McFarland, PhD4, Cathy Stinear, PhD5, Steven L. Wolf, PhD6, Maurizio Corbetta, MD7, and Susan M. Fitzpatrick, PhD7,8

This third chapter discusses the evidence for the rehabilitation of the most common movement disorders of the upper extremity. The authors also present a framework, building on the computation, anatomy, and physiology (CAP) model, for incorporating some of the principles discussed in the 2 previous chapters by Frey et al and Sathian et al in the practice of rehabilitation and for discussing potentially helpful interventions based on emergent neuroscience principles.

Introduction

Much of the evidence-based body of knowledge informing upper-limb rehabilitation has been generated from research with patients recovering from stroke. It is not surprising, given the number of affected individuals worldwide, that stroke would serve as the dominant model. However, many principles informing neurorehabilitation interventions can be translated from stroke into interventions for other neurological conditions when appropriate.

Whenever possible, our recommendations are based on randomized clinical trials (RCTs). Unfortunately, there have been only a handful of RCTs, most of them carried out with small sample sizes. Hence, current recommendations could be overturned by a relatively small number of robust trials (ie, with a larger sample size).1 If evidence from RCTs is not available, we refer the reader to current evidence-based guidelines developed in different countries (Box 1). These guidelines also take into consideration interventions for which the evidence is preliminary, based on nonrandomized trials or case series. Finally, we present a framework for thinking about potentially helpful interventions based on emergent neuroscience principles, as outlined in the chapters by Frey et al and Sathian et al.

It is important to keep in mind that not all movement disorders are amenable to therapy interventions alone. Some individuals will benefit from pharmacological, surgical, or orthotic interventions to reduce impairment that limits functional ability. Persistent pain can interfere with the motivation and the ability of individuals to participate in rehabilitation and pain management should take clinical priority.

General Principles for Delivery of Therapy Interventions

Delivery of therapy interventions is multifaceted, and certain general principles should be considered in each patient:

1. The establishment of a ‘contract’ between people with neurological deficits and their therapy team.
2. Analysis of behavioral deficits in relation to known principles of brain organization.
4. Whether the aim of intervention is to restore neurological function or to adapt to its loss, and more generally the prognosis after the intervention.
5. The amount of therapy provided over what time period (dose).

1University of East Anglia, Norwich, UK
2Sapienza University of Rome and Fondazione Santa Lucia, IRCCS, Rome, Italy
3University of Alabama at Birmingham, Birmingham, AL, USA
4Wadsworth Center, Albany, NY, USA
5University of Auckland, Auckland, New Zealand
6Emory University School of Medicine, Atlanta, GA, USA
7Washington University in St Louis, St Louis, MO, USA
8James S McDonnell Foundation, St Louis, MO, USA
Neurological rehabilitation is an active participatory process involving a dynamic interaction between the person with neurological deficits and the health professional members of the team. Appreciating the amount of effort required to achieve agreed-on functional goals and establishing a framework for the interaction among everyone participating is necessary to obtain an ideal balance concerning perceived effort (both the patient’s and therapist’s viewpoint), maintenance of attention and motivation, and expectation of the rewards and benefits of and satisfaction with rehabilitation. Frey et al discuss at least 3 mechanisms through which reward interacts with movement. Interactions between the basal ganglia and the prefrontal cortex are important for goal selection on the basis of expected or predicted reward, to reinforce movements based on expected reward, and for switching to novel actions. Although there is no direct evidence that establishing a rehabilitation contract taps into any of these mechanisms, it is important to realize that setting the right expectations will ultimately affect the perceived success or failures of therapy, and this will in turn lead to stronger or weaker learning of compensatory movement or strategies.

Underpinning agreement of goals are 2 key areas of understanding that (1) the therapist is aware of what is important for the patient and (2) the patient appreciates the mechanisms of recovery, the need to maintain ability, and the need to prevent secondary complications. Active communication is therefore a prerequisite for active participation. It is important to use enhanced communication strategies, including the following: chunking information into small bits; using diagrams, facial expressions, or gestures; and frequent checking for understanding of key messages conveyed by all conversation partners.

The setting of goals must be consistent with the likely outcome expected for that patient. Sathian et al review a number of variables that allow some “average” prediction of motor outcome. Although average estimates may not apply to specific individuals, it is important for the therapist to set realistic expectations. For instance, in a patient with no voluntary movements of the hand at 1 month poststroke, it is not realistic to set up full recovery of hand function as a goal (please refer to detailed discussions of this point in Sathian et al). Great care is required to ensure that the provision of information does not diminish motivation for participation in rehabilitation. Indeed, preliminary evidence indicates that signing a rehabilitation contract is associated with improved functional recovery and, simultaneously, increased cortical grey matter.

Analysis of Deficits and Pathophysiology

Based on the CAP principles established in Frey et al and the diagnostic examinations described in Sathian et al, it is important that the clinician (rehabilitation physician or therapist) develops an understanding of the neurological mechanisms of the patient’s observed impairment. Does the motor deficit reflect primarily an output, planning, or sensory feedback problem? Is there any problem with ataxia? Do the deficits primarily involve skilled or gross movements?

Ideally a behavioral analysis should be complemented by anatomical information about lesion location and size. For example, the presence of a small lesion in the subcortical white matter that damages only some of the corticospinal tract may be expected to be associated with greater recovery than a lesion in the brainstem that completely severs descending fibers. Similarly, a small lesion in the motor cortex may be expected to produce some clumsiness early on but good recovery overall, given compensation from other premotor regions. Bilateral lesions in the cerebellum are expected to cause more long-lasting ataxia than unilateral lesions. Although formal neuroscience-based principles for assessment and planning of therapy are not yet established, it is important that therapists begin to incorporate some of the principles discussed above as they plan their therapy. In the near future, it is expected that as neural analyses of functional recovery improve, more specific parameters based on imaging or other methods will become more clinically applicable.

Sensitive and Objective Measurements of Motor Impairment and Function

The chapter by Sathian et al provides a number of scales describing the motor status of a patient before and during rehabilitation. The key point we are adding is that measurements should be objective and free of bias, ideally performed at the beginning of the intervention and at the end by therapists who are not primarily treating the patient.

Restorative Versus Adaptive Emphasis, and Outcome

Restorative interventions are thought to improve impairment of function and to work directly on modifying the underlying neural mechanisms. Adaptive interventions provide an
alternative strategy to perform the same task. For instance, whereas task-oriented repetitive training is a restorative intervention, training to use an assistive device, for example, a tool to grasp, may be considered adaptive.

An important consideration in deciding what rehabilitation to use is the likely outcome of a patient with a neurological injury. Clinical assessment and outcome analysis as described in the chapter by Sathian et al are necessary to decide if the planned intervention should be restorative or adaptive. From a neural perspective, the potential for reorganization is maximal early on after injury; hence, as a general principle, restorative methods should be offered to acute patients. Motor function improves rapidly in the first 6 to 8 weeks poststroke and reaches a plateau around 3 months. At the chronic stage, a key element for deciding the approach to be taken is to consider prognostic factors on recovery of function. Although these factors are average, that is, apply to a group of patients as a whole, and cannot be precisely applied to individual patients, they do provide a framework to think about what is feasible in a specific patient at a specific stage. On the other hand, there is growing evidence that even at the chronic stage, restorative interventions can be beneficial. For instance, constraint-induced movement therapy (CIMT) has been shown to work in selected groups of chronic stroke patients.

A final point to judge the feasibility of restorative interventions is the presence of any voluntary motor output irrespective of its normalcy. Traditional theories (eg, neurodevelopmental theories) emphasize the quality of movement as a prerequisite before pushing more active or intense restorative training. However, work in animals indicates that even small lesions in the motor cortex compromise the normality of movement dynamics and that any motor “recovery” should be considered actually a “reorganization” of function. Hence, modern therapy strategies emphasize that any voluntary movement, even if highly abnormal in its dynamic, should be reinforced toward improving function.

A possible strategy at the chronic stage is to attempt a restorative intervention if there are elements in the clinical examination suggesting promise. For instance, the presence of wrist extension or voluntary finger movements in 1 patient at 6 months may be used to motivate a restorative intervention for the hand. After a few weeks of intense therapy, if no improvement is detected, then, one may consider switching to more adaptive or conservative therapy, for example, range of motion, stretching, and so on, for prevention of complications.

**Dose**

Amount of therapy (dose) is of primary importance for outcome. Dose can be thought of in terms of intensity (number of repetitions or time per session), frequency (eg, 5 sessions a week), and duration (eg, for 6 weeks). A Cochrane review reported that in a large meta-analysis of repetitive task training for the upper or lower extremity, the amount of therapy in number of hours was positively related to effect size. For both the upper extremity and lower extremity, it was necessary to train for more than 20 hours to have a significant change in function. It is likely that higher doses may be more effective. In general, one explanation for why it is often difficult to demonstrate the benefit of rehabilitative interventions may very well be because they are routinely delivered at suboptimal doses.

Experimental studies with animal models suggest that 300 to 400 repetitions of a task are required to learn a motor skill and to change the patterns of brain activity. This intensity is not currently achieved in clinical practice. A recent multicenter observational study in North America showed that fewer than 30 repetitions per session are currently achieved in rehabilitation practices. Indeed, the mean number of repetitions of an active exercise and functional activity during rehabilitation sessions is low both after stroke and after traumatic brain injury and is probably dependent on the experience of the therapists. However, the findings of an early phase trial indicate that it is possible to achieve a mean of 322 repetitions of task-oriented training for the upper extremity in a 60-minute session and that delivery of high-repetition therapy was sustained 3 times a week over a 6-week period. An early concern regarding high-dose therapy was the observation that high levels of physical activity in rats, early poststroke, were associated with a poorer functional outcome. However, a recent clinical trial did not find a relationship between lesion volume and high-dose-activity rehabilitation.

**Therapeutic Environment for Motor Learning**

People with neurological deficits need to learn to move again in the most energy-efficient way possible within the confines of the damage sustained. The therapist is therefore a mediator in each individual’s motor learning process. Motor learning is defined here as follows: a change in the capability of a person to perform a skill as a result of practice or experience.

Although an extensive discussion of learning is outside the scope of this chapter, some general principles can be quickly reviewed. All models of motor learning include the need for the detection of errors and production of appropriate corrective adjustments in different environmental contexts. For instance, during a reaching task, one needs to vary the features of the object to be reached (size, shape, etc.), which determine the shaping of the hand and sensory feedback; the position of the object, which determines the trajectory of the movement; and the possibility to see the arm/hand before/during movement, which affects the estimation of initial state and forward models (please refer to Figure 1 in Frey et al and Figure 1 in Sathian et al).

Errorless performance leads to slower improvement than performance with a small number of errors. At the same time, an excessive number of errors leads to frustration and potentially negative feedback, which impairs optimal learning. A rule of thumb is to have patients work at 80% to 90% accuracy of their maximal capacity. Part of the role of a therapist is to provide extrinsic feedback to enhance motor learning.
A final important aspect is assessment of motor learning capacity, such as capacity for sustained attention, communication ability, and problem-solving ability. In the future, therapists might also need to consider that damage to different brain areas may affect motor learning differentially. For instance, patients with cerebellar lesions may not benefit as much from performance feedback, given their inability to learn from their errors. In this case, a more implicit strategy may be more beneficial.

Content of Rehabilitation Interventions: Specific Techniques
At present, techniques (components of interventions) used to treat different patients vary considerably across different geographical locations. This range of techniques provided in current clinical practice have, historically, been described according to different conceptual approaches. There is, however, an urgent need to validate the efficacy of this wide range of techniques and develop treatment algorithms that stack interventions and component techniques based on the level of evidence. This is critical to make the practice of rehabilitation more evidence based and less subjective.

Unfortunately, current recommendations in rehabilitation are based on relatively weak evidence that could be easily overturned by a few well-done RCTs. Each technique has been tested only by a small number of trials—typically, only 3 per method; furthermore, these trials have been underpowered, with an average of only 70 patients per trial; finally, the methodology used so far has not been optimal in terms of making the trials more objective and less prone to statistical biases. Nonetheless, there is a strong theoretical framework and several solid findings that can be used to select the most appropriate intervention. A final caveat that should be considered when reading the following section is that there is much more evidence for improving arm function than hand function. In fact, interventions to improve hand coordination and dexterity have yielded very disappointing results overall.

Specific Techniques to Reduce Paresis
The paretic upper limb is typically weak, slow, and lacking in coordination and dexterity. Spasticity may be a feature. These symptoms can appear alone or in combination. Paresis involves difficulty with or inability to modulate the production of appropriate force in the right muscles at the right time to produce a movement or perform a functional task deftly, accurately, and in an energy-efficient manner. Paresis that follows cerebral injury reflects difficulty with motor outflow either from damage to the cortical neurons or damage to the white matter fibers projecting to the spinal cord.

Based on principles developed in the first 2 chapters by Frey et al and Sathian et al, 3 principles for treatment can be defined:

1. priming techniques to increase the excitability of the stroke-affected motor system and promote plastic reorganization in response to subsequent practice of physical activity;
2. augmenting techniques applied during physical practice to enhance their effects by boosting voluntary activation of paretic muscles (in the following section, we will describe some of these interventions emphasizing those methods that have received support in RCTs); and
3. practice of task-specific exercises.

Box 2 provides a vignette to illustrate the application of some of these techniques.

Priming Techniques. Priming interventions may prepare the sensorimotor system for subsequent motor practice, thereby enhancing its effects. Brief details are given here, with a fuller version provided in Box 3.

Motor and visual imagery. These techniques can be used to internally generate somatosensory and visual input to the motor system. There is strong evidence from neuroimaging studies that mental practice and imagery can activate regions in the motor system. These signals can be conceptualized as motor plans without execution. Repetitive generation of motor plans may promote physiological patterns of activation in motor cortical circuitries that are either directly damaged or functionally impaired because of impaired outflow after damage of the corticospinal tract, abnormal forward models, or decreased activation by sensory feedback because of lack of movement. Four RCTs have shown that the addition of mental practice to physical practice can have a beneficial effect on motor performance. In one of these studies, chronic stroke patients (≥12 months) were randomized to 2 groups: (1) mental + physical practice, in which twice a week for 6 weeks they participated in a 30-minute physical therapy session centered on activities of daily living (ADL) followed by a 30-minute mental practice session in which they mentally rehearsed the exercises just performed; (2) relaxation + physical practice, in which the therapy sessions were followed by a 30-minute session of mental relaxation. At 1 week postintervention, motor impairment and functional scores for the upper extremity were significantly improved in the mental practice group as compared with the relaxation group. Although the effect size is relatively robust, only a small number of patients have been tested so far (about 70 till March 2010). The duration of the intervention effect is also unknown because most postintervention measurements were obtained shortly after the end of the trial (typically 1 week).

Tactile stimulation, soft tissue mobilization, and passive movements. These methods provide sensory input that engages the patient’s attention and orients the individual to the paretic limb. Passive movement has similar effects while also providing sensory feedback to the motor system.
Box 2. Vignette illustrating the use of emergent neuroscience principles to inform choice of interventions for paresis

Mrs X is a 70-year-old woman with a stroke and a paresis of the right hand (dominant) resulting from an infarct in the territory of the middle cerebral artery in the left hemisphere. Neuroimaging indicates that the infarct is subcortical in the corona radiata.

At 3 days after stroke, Mrs X is alert and has no evidence of either aphasia or visuospatial neglect, and sensorimotor function of her left upper limb is essentially normal. The right upper limb is paretic with the following characteristics: mild sensory deficit (both tactile and proprioception) and grade 2 voluntary muscle activity (able to produce muscle contraction but not against gravity) around the shoulder, elbow, and wrist. However, she is unable to produce any fractionated movement of her fingers.

Functionally, she is able to reach for a key by sliding her upper limb across a table but is unable to grasp it and use it to unlock a door. This impairment pattern is consistent with the location of the lesion.

Initially, the primary focus of therapy is restorative—that is, to facilitate biological recovery and improve upper-limb functional ability. Mrs X is able to produce some voluntary muscle activity for reaching but is unable to grasp objects. Key interventions provided are the following: therapist-assisted repetitive practice of reaching, electromyographic biofeedback of muscle activation (visual display of wrist extension activity) during reaching, tactile stimulation and mobilization of soft tissues of the hand, passive movements of the paretic hand while encouraging Mrs X to join in the movement, motor imagery training of both reaching and grasping, and functional electrical stimulation of grasp/release as the ability to voluntarily activate paretic muscle improves. As she gains the ability to contract paretic muscles in an appropriate temporal-spatial pattern, resistive training is added to practice of reaching. Throughout this intensive treatment period, which may last for approximately 6 weeks, Mrs X is given the rationale for interventions and encouraged to pursue self-directed activities.

At 3 months after stroke, Mrs X has sufficient fractionation of fingers to reach to a shelf at eye level and pick up the key, albeit abnormally, but is unable to insert it into the lock. A rehabilitation service may or may not be available as provision varies across the globe. On the assumption that rehabilitation is available, testing indicates that improvement in the paretic upper limb has slowed down and is more evident in hand than in arm function. The primary focus of therapy therefore changes from facilitating recovery (restorative) to enabling Mrs X to

(continued)

Box 2. (continued)

compensate for hand paresis. Strategies could include signing documents with her left hand (nondominant) and providing adaptations to a key to reduce grasp requirements. Such strategies provide the benefits of increasing independence but could lead to learned nonuse of the paretic upper limb. These strategies therefore need to be used judiciously.

Mrs X is therefore introduced to constraint-induced movement therapy to ensure that she continues to use her paretic upper limb for functional activity as part of a planned program. Again, as in the earlier rehabilitation phase, Mrs X is given information about the rationale for intervention and is encouraged to undertake self-directed motor activities. It should be appreciated that in some health care settings very few stroke survivors receive any therapy after the initial rehabilitation period.

Box 3. Priming techniques to reduce paresis

Tactile stimulation and soft tissue mobilization provide sensory input that engages the patient’s attention to their paretic limb. Passive movement has similar effects while also providing a sensory template for desired movements. There is preliminary evidence for this module of conventional therapy.

Motor imagery and visual imagery can be used to internally generate somatosensory and visual input to the motor system. During mental practice, the patient rehearses the planning and preparation components of activities of daily living, particularly when actual practice may be limited by impairment or fatigue. Imagining the somatosensory consequences of movement (motor imagery) has been shown to activate the motor cortex and may serve to reinforce the sensorimotor templates of desired movements. There is some evidence that mental practice can improve upper-limb function, but further studies are needed to determine the optimal dose and characterize the patients most likely to benefit.

Action observation and mirror therapy use visual input for priming. The patient observes specific movements or tasks performed by the therapist or by their nonparetic limb reflected in a mirror placed at the body’s midline. By placing the paretic limb behind the mirror, the reflected movements of the nonparetic limb appear to be performed by the paretic limb. Both these techniques are thought to activate the motor system and prepare it to perform the observed actions with the paretic limb. Mirror therapy can also be

(continued)
Box 3. (continued)

used as an augmenting technique during practice. Studies of healthy adults suggest benefit, and there is preliminary evidence that they improve upper-limb function following stroke.

Some priming techniques specifically aim to alter neurotransmission, balance motor cortex excitability between the 2 hemispheres, and enhance neural plasticity. This balance can be achieved with stable movement patterns, such as active-passive bilateral therapy (APBT). During APBT, the patient produces rhythmic flexion-extension of a nonparetic joint in a mechanical device that produces passive mirror-symmetric flexion-extension of the corresponding paretic joint. Preliminary studies of wrist APBT performed prior to motor practice found lasting reductions in impairment and balancing of motor cortex excitability. These effects are most likely a result of the mirror-symmetric movement pattern and the number of passive movement repetitions being much greater than could be achieved actively in each session. Further studies are required to determine the optimal dose and characterize those most likely to benefit.

Magnetic stimulation techniques can be used to alter motor cortex excitability prior to practice. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique that delivers brief magnetic stimuli over the scalp, activating the underlying cortex, at a low frequency (1 Hz) for up to 15 minutes or at higher frequencies (10-50 Hz) for as little as 3 s. rTMS can either increase or decrease the excitability of the underlying cortex, depending on the frequency and pattern of stimuli. It has been used to increase ipsilesional motor cortex excitability and decrease contralesional motor cortex excitability in stroke patients. These effects appear to improve functioning of the paretic upper limb, particularly when delivered prior to motor practice.

It should be noted that rTMS is more suitable for patients with a largely intact motor cortex and is contraindicated in patients with cardiac pacemakers or a history of seizures.

Transcranial direct current stimulation (TDCS) is another noninvasive technique for stimulating the cortex of the brain. It involves passing a low current (1 or 2 mA) between 2 electrodes on the scalp for 10 to 30 minutes. The underlying neurons are polarized and become more or less excitable, depending on the polarity of the overlying electrode. As with rTMS, TDCS has been used to increase ipsilesional excitability or decrease contralesional excitability in stroke patients. There is preliminary evidence that these effects are associated with improved function of the paretic upper limb. TDCS can be applied before and during motor practice, making it both a priming and augmenting technique. Similar benefits may be produced by stimulating the cortex with implanted electrodes, and this technique is being developed. As with rTMS, these techniques are more suitable for patients with a largely intact motor cortex.

Pharmacological agents can be used to alter neurotransmission and the excitability of the motor cortex. It is possible that drugs such as amphetamines and dopamine agonists improve motor function when administered prior to therapy to both prime and augment the effects of motor practice. Selective serotonin reuptake inhibitors may have beneficial effects on the motor system, distinct from their antidepressant actions. Further clinical trials are needed to draw definite conclusions, and it should be noted that unlike other priming and augmenting techniques, drug actions are not hemisphere specific.

Action observation, mirror therapy. These techniques use visual input for priming. The patient observes specific movements or tasks performed by the therapist or by their nonparetic limb reflected in a mirror placed at the body’s midline. In the first chapter in this series, we discussed frontoparietal circuitry that respond not only during one’s own movement but also during the observation of others’ movements. Observation may promote activation of these circuits. A recent RCT of mirror therapy demonstrated improvement in motor function.\(^3\)

Repetitive transcranial magnetic stimulation (rTMS). rTMS noninvasively delivers brief magnetic stimuli over the scalp, activating the underlying cortex, at a low frequency (1 Hz) for up to 15 minutes or at higher frequencies (10-50 Hz) for as little as 3 s. rTMS can either increase or decrease the excitability of the underlying cortex depending on the frequency and pattern of stimuli. One possible future application of rTMS is to prime the excitability of the motor cortex prior to rehabilitation.

Transcranial direct current stimulation (TDCS). TDCS is another noninvasive technique for stimulating the cortex of the brain. TDCS involves passing a low current (1 or 2 mA) between 2 electrodes on the scalp for 10 to 30 minutes. The underlying neurons are polarized and become more or less excitable, depending on the polarity of the overlying electrode.

Pharmacological agents. Drugs like methylphenidate or dextroamphetamine have been tried alone or in combination with motor rehabilitation to enhance recovery.

Augmenting Techniques. Augmenting techniques are thought to enhance aspects of sensorimotor function during practice. Brief details are given here with a fuller version provided in Box 4.
Therapist- or robot-assisted movement of the paretic upper limb provides the motor system with the sensory feedback it would receive if it were able to move normally. This sensory feedback is thought to facilitate the motor system and provide a template of desired movement patterns. Robotic devices can also be used to guide voluntary movements along optimal trajectories to reinforce desired movements. There is some evidence that robotic devices can reduce shoulder and elbow impairment, and their impact on wrist and hand function may increase with further developments in their design.

Biofeedback provides patients with visual and/or auditory feedback of the timing and strength of their muscle activation. This approach is directed at helping individuals to gain greater conscious control over components of the practiced movement, although at present, there is no clear evidence of its efficacy.

Functional electrical stimulation (FES) and transcutaneous electrical nerve stimulation (TENS) can be used to activate muscles and generate sensory input. In particular, FES can be used to enhance the voluntary activation of elbow, wrist, and finger extensors during reach-to-grasp and other functional tasks. There is some evidence that these techniques can reduce impairment, but further research is required to confirm this and establish the optimal dose.

Some augmenting techniques specifically aim to alter the balance of excitability between the 2 hemispheres during practice. Generally, the aim is to increase ipsilesional excitability and/or decrease contralesional excitability. One example is TDCS, which can be used for both priming and augmenting and which has been described earlier.

Bilateral training involves performing activities such as reaching and grasping with both arms simultaneously. This approach may improve task performance with the paretic upper limb because of the facilitation of paretic muscle representations in the motor system by their healthy counterparts on the opposite side. Although the evidence for bilateral training to date is mixed, those patients with greater impairment, who are more likely to recruit contralesional motor cortex activity in the brain during paretic limb movement, may benefit the most.

Constraint-induced movement therapy (CIMT) involves therapist-directed practice and self-directed motor activity with the paretic arm while the opposite arm is restrained. CIMT aims to rebalance motor cortex activity by increasing the activity of the paretic arm with massed practice while restricting the activity of the opposite limb. There is strong evidence that this approach is beneficial, particularly for patients at least 3 months after stroke with at least 10° of active wrist and finger extension. Further study is required to determine the optimal dose in terms of contact hours and their distribution.

**Box 4. Augmenting techniques to reduce paresis**

**Constraint-induced movement therapy**. CIMT is the only intervention that has been validated by many different trials (21 with more than 500 patients enrolled) and in a prospective multicenter RCT. It should therefore be considered as the first choice for patients who qualify.6 CIMT therapy is based on the notion that brain injury leads not only to structural damage but also to physiological impairment of motor pathways/regions. Specifically, injury leads to depression of neural excitability near the lesion, which, coupled with negative feedback from unsuccessful attempts, leads to further decrement of excitability and, secondarily, a learned nonuse of the paretic arm. There is also evidence of impaired interhemispheric interaction with increased excitability in the contralesional (normal) motor cortex that can exacerbate the learned nonuse. It is indeed a common clinical observation that patients after a stroke tend to use their paretic arm less and less over time. The intervention is based on constraining movements in the normal arm, for example, by asking patients to wear a mitten during waking hours while intensely training the weak arm. There are other important elements to CIMT, such as the execution of task-specific exercises (eg, reaching, turning, opening, etc), the high dose (4-6 h/d), and “shaping.” This involves a complex set of interactions in which the therapist both sets the difficulty of the exercises to a level that the patient can successfully perform most of the time while at the same time providing feedback and encouragement on the errors. As discussed earlier, errors are necessary to learn as they provide a training signal for change. It is currently unknown which combination of factors is most important. The value of CIMT has been demonstrated in chronic patients, whereas in subacute patients (1-3 weeks poststroke), a recent study did not show a differential effect above standard therapy. Another strong limitation is that only patients who have 10° to 20° of wrist flexion can benefit from this therapy; unfortunately, this group represents only a minority of all stroke patients (about 20%).

**Electromechanical or robotic-assisted therapy**. A number of different devices have been designed for aiding the movement of the paretic upper extremity during tasks such as reaching for a visual target. These systems provide the motor system with the sensory feedback it would receive if it were able to move normally, which, in turn, may increase excitability in motor pathways. Vision of the arm in movement may also activate circuits related to action observation. The interest in robotic-assisted movements is also instrumental to the notion of providing high doses of therapy in a relatively inexpensive way. Although early generation robots provided assistance with a fixed torque, that is, the same torque irrespective of the patients’ voluntary contraction, more recent models can “feel” the patient’s movement and adjust the degree of assistance. In 1 meta-analysis (10 trials with about 200 patients), a moderate overall size effect was obtained, but the small sample size of each study prevented stronger conclusions. A recent meta-analysis compared numerous RCTs of robotic-assisted
movement therapy (11 studies with more than 300 patients and fewer than 50 patients per trial) with other methods (standard physical therapy, free reaching, electrical stimulation-triggered movement, and resistive robotic therapy) while matching the dose of the intervention. A typical training schedule consists of a 30- to 90-minute session 5 days/week for 3 to 12 weeks (ie, about 15-60 hours of training). Whereas weak effects were demonstrated on ADL and only for patients less than 3 months poststroke, robust effects were found on motor strength and function. This intervention may therefore be an important adjuvant to standard physical therapy, but again, dose effects may be of utmost importance.

Electromyographic (EMG) biofeedback. This set of methods provides patients with visual and/or auditory feedback of the timing and strength of their muscle activation recorded via a surface EMG electrode. Although the putative neural mechanisms behind this method are unknown, recent evidence indicates that patterns of cortical activity can be modulated with biofeedback. This method has been tested in a small number of RCTs (4 trials, <150 patients) and has been shown to have a small to moderate effect overall. In a few studies, robust effects on range of motion and strength were obtained.

Functional electrical stimulation (FES) and transcutaneous electrical nerve stimulation (TENS). FES and TENS can be used to activate muscles and generate sensory input. This technique has been studied in a fair number of RCTs (13 trials on >250 patients), and its effects on movement are small to moderate overall. From a physiological standpoint, it appears that the ability to facilitate voluntary movements generated by the patient through electrical stimulation (FES) would be much more desirable than electrically inducing movements. Natural movements are produced by delicate and complex patterns of muscle activity that are not reproduced by the nonspecific and massive activation produced by TENS. In the near future, it will be possible to interface brain signals recorded, for instance, through EEG during movement planning, imagery, or execution and use those signals to drive peripheral devices or for enhancing movements of the affected arm. Closing the loop with the brain will allow a more specific and timely form of functional stimulation.

Bilateral training. Bilateral training involves performing activities such as reaching and grasping with both arms simultaneously. It is based on the notion of disrupted interhemispheric interactions (see Box 3 in Sathian et al, this issue). This technique has been tested in a small number of trials (2 RCTs and 122 patients), and its effectiveness is unknown.

Task-Specific Practice. In addition to specific methods, a more general set of principles that are thought to be essential in rehabilitation includes the notion of task-specific practice. Practice is the core of therapy. The repeated performance of a specific movement or task can produce meaningful improvements in function. Practice improves performance by providing the central nervous system with repeated opportunities to estimate the body's state and integrate this with a movement goal; produce appropriately sequenced, timed, and scaled motor commands; and adjust motor output on the basis of sensory feedback.

The strongest scientific rationale at present is for task-specific practice based on principles of experience-dependent motor cortex plasticity. Task-specific practice can include shaping of the patient's performance by identifying key components of the task (such as movement speed or distance) and providing positive verbal feedback with each small improvement in these components while progressively increasing the task demands. Task-specific practice elements are present in most of the techniques described above and intersect strongly with the issue of dose discussed above. A recent meta-analysis compared repetitive task training with either no intervention or other training (attention and strength; 13 RCTs and >600 patients) with a variable amount of practice (from <10 hours to >40 hours) and for periods of 2 to 6 weeks. Overall, a trend of a positive effect for arm function was found, but there was no effect for hand function. However, when the efficacy was compared as a function of dose, it was found that the effect was nearly double in patients with more than 20 hours of practice as compared with patients with 0 to 20 hours of practice.

Specific Techniques to Reduce Apraxia and Motor Neglect

Apraxia. Apraxia reflects a problem with high-level motor planning and the retrieval of stored knowledge for the generation of actions. Historically, it was believed that limb apraxia had little if any impact on everyday activity. Now, it is widely held that limb apraxia is an important determinant of dependence in activities of daily living after stroke. For example, limb apraxia (ideational and ideomotor) may increase clumsiness in object manipulation and be detrimental to daily life activities. Therefore, during the initial assessment of patients, the presence and severity of limb apraxia should be determined.

Standardized testing batteries derived from cognitive models of limb apraxia are currently available. However, for clinical practice, it is important for the clinician to understand if the patient suffers from apraxia in addition to motor deficits per se. Observing whether a patient uses tools correctly or pantomimes their use correctly during ADL training is sufficient to screen for the presence/absence of ideomotor apraxia. Ideational apraxia can be screened by asking the patient to execute or pantomime a complex sequence of actions (eg, striking a match to light a candle or making coffee).

There is a paucity of systematic research into therapeutic techniques for treating apraxia. Evaluations of the reduction in specific movement errors have been undertaken in individuals by using verbal or physical cues on how to position specific upper-limb segments during action execution. Breaking the task into different components or systematic withdrawal of facilitation cues have also been tested. All these approaches, however, have been carried out in single case
subjects, and no generalization effects or influence on daily life activities have been investigated.

Thus far, a small number of systematic treatment approaches to apraxia rehabilitation have been evaluated in groups of patients. One of these is the strategy training approach developed specifically as a compensatory technique for patients in whom apraxia negatively influences ADL. This method is based on the notion that goals and actions are composed of subgoals and that these subgoals can be accessed by a variety of inputs (verbal or pictorial; see Box 1 in Frey et al). This method focuses on the use of internal (eg, patients use language to describe the task and reinforce themselves) or external strategies (eg, use of pictures). This approach was found to be more effective than standard occupational therapy in improving ADL. The beneficial effects were maintained 5 months after stroke and to some extent generalized to untrained everyday activities.

Another approach is the errorless completion method in which patients imitate the activity performed by the examiner. This aims to reduce the errors made by the patient with the rationale that errors do not help patients relearn but introduce further noise. This technique was compared with the exploration training method that is not based on direct practice but on perceptual attention to the functional significance of details and critical features of the action to be performed. Hence, in one case, the patient directly practices, whereas in the other case, the patient attentively observes. These 2 methods were applied to 2 different ADLs performed by patients with chronic limb apraxia. Although the exploration method was ineffective, the errorless completion method had a lasting facilitation effect. However, this did not generalize to untrained everyday activities.

The reported findings that action observation and action execution are based on largely overlapping neural networks in the ventral parietal and frontal cortex (as described in Frey et al) have inspired the development of novel intervention techniques. The training consists of 3 progressive phases, each of which is characterized by an increasing degree of difficulty. For example, in phase 1 of gestures training, patients were shown the use of common tools and then requested to imitate the examiner. In phase 2, patients had to perform a given gesture after having seen a depiction of part of the same gesture. In phase 3, patients had to perform the gesture corresponding to the object shown in a picture. Measures were made to determine whether a given action was performed correctly. This type of treatment was found to be effective as compared with standard apraxia treatment, although it required up to 35 sessions. What is of importance is that both subjective and objective improvements in ADLs were found 2 months and 2 weeks after treatment, respectively. Box 5 provides a vignette to illustrate the application of some of these techniques.

Motor neglect. No study to date has tested rehabilitation techniques specifically designed for improving upper-limb action in motor neglect, defined as the failure to initiate limb movement on one side because of an attentional deficit rather than a motor one

| Box 5. Vignette illustrating the use of emergent neuroscience principles to inform the choice of interventions for apraxia |

Mr Y has sustained a stroke in the left hemisphere resulting from an infarct in the middle cerebral artery. Neuroimaging indicates that the lesion extends through the frontal-parietal-temporal area. He is 52 years old and is a plumber. At 3 days after stroke, Mr Y has evidence of aphasia (mild anomia and mild comprehension impairment) and mild/moderate paresis in his right upper limb. During the day, it is noticed that he mixes up objects on his food tray and makes sequence errors (open/pour cereal) but has intact object recognition.

In terms of our target behavior, he is able to reach and grasp the key using his right hand but with a variety of abnormal grips, attempts to turn it before approaching the lock, and then makes clumsy attempts to place the key, held in various orientations, into the lock. Similar problems are observed when using the left hand. Clinical examination reveals difficulty in both action production and perception. Defective performance involves pantomime execution as well as recognition and identification of transitive and intransitive pantomimes. Gesture production in response to seeing and/or holding actual tools or the objects on which the tools act is also impaired.

Initially, the primary focus of therapy is restorative and aims to facilitate recovery of both conceptual and execution aspects of gesture production and comprehension. The key intervention provided consists of a therapist-assisted behavioral training program consisting of gesture production and gesture recognition exercises. Training of both transitive and intransitive gestures is contemplated. Increasing complexity of the training tasks is obtained by a phased reduction of facilitation cues as performance improves. The treatment period may last for approximately 4 to 5 weeks (this is influenced by different health care delivery systems). Mr Y is given the rationale for interventions and encouraged to pursue self-directed activities.

At 3 months after stroke, Mr Y shows improvement in the ability to perform gestures in response to specific verbal and also visual requests. Comprehension of conceptual and executive aspects of gestures is improved. Crucially, performance of daily living activities is also improved. Mr Y is encouraged to undertake self-directed gestural production and motor planning activities. Beyond 3 months, intermittent therapy sessions are delivered on request from Mr Y or his family if and when they notice that ADL problems reappear. In these later stages after stroke, it is recognized that rehabilitation services may or may not be available and that this varies with geographical location.
than because of an impairment to primary motor systems or learned nonuse. The lack of a gold standard test for assessing motor neglect has made it difficult to test techniques specifically designed for treating motor neglect. It is worth noting, however, that CIMT or possibly bilateral arm training could be of benefit.\textsuperscript{14}

**Specific Techniques to Reduce Ataxia**

Ataxia is often associated with damage to the cerebellum or its connections. Ataxia caused by disruption of cerebellar input includes loss of proprioception as a result of dysfunction of spinal dorsal columns or vestibular dysfunction. In terms of the CAP model, this produces a disturbance in forward modeling of intended movements. The result is uncoordinated movements. A large variety of pharmacological treatments have been tried (eg, isoniazid, pyridoxine, and baclofen) but have not shown consistent results. Preliminary research suggests that CIMT may improve reaching kinematics and real-world limb use among individuals who have developed poststroke ataxia.\textsuperscript{15}

Tremor and other involuntary hyperkinetic limb motor disorders after brain injury are associated both with cerebellar and basal ganglia dysfunction. Drugs are often used for management (eg, propranolol, primidone, and sertraline). More recently, tremor has been successfully treated with deep-brain stimulation of sites in the basal ganglia and thalamus. Preliminary research has suggested that adopting rhythmic limb movements during physical therapy can reduce involuntary limb movements after stroke and thus may allow improved treatment participation.\textsuperscript{16}

Because ataxia and tremor interfere with normal limb use, teaching patients strategies to cope with these deficits can be useful.

**Specific Techniques to Maintain Integrity of Effectors**

An important part of neurorehabilitation is the use of techniques that are designed to maintain or protect the integrity of upper-limb joints and muscles during periods of suboptimal movement performance. For example, in the presence of paralyzed muscle early after stroke, there is a risk of shoulder pain and/or glenohumeral dislocation. Another example is the development of muscle hypertonicity and/or contractures in the presence of permanent CNS damage. These techniques include those described below.

Exercise and stretching are used in the first instance to reduce spasticity. For people with constant focal spasticity in the absence of contracture, botulinum toxin is used intra-muscularly. For those people experiencing generalized spasticity, antispastic drugs, for example, baclofen, can be given. All drugs should be administered within an expert neurorehabilitation setting and accompanied by specific techniques (outlined earlier in this chapter) designed to gain motor function as spasticity subsides. If contractures develop or are likely to develop, then a program of stretching and splinting should be considered.

To prevent and treat shoulder pain and glenohumeral subluxation, considerable attention is provided to positioning of the upper limb 24 hours a day, which is accompanied by expert moving and handling techniques. Particular positioning and moving and handling techniques are specified for each individual and used by each member of the neurorehabilitation team, including the patient and their informal careers. There is, therefore, an emphasis on education personalized for each individual that centers on the normal anatomy of the shoulder complex, the disruption caused by neurological damage, and the specific techniques to minimize disruption and prevent further damage. Specific supports, for example, foam wedges, may be used for the upper limb. Simple analgesia may be given regularly. For individuals with troublesome pain, the neurorehabilitation team will consider use of shoulder strapping, high-intensity transcutaneous nerve stimulation, or FES.

**Future Clinical Directions**

Recent advances in the scientific rationale and evidence base for neurological rehabilitation have, over the past 10 years, changed the clinical emphasis from that of treatment approaches to specific techniques for particular aspects of upper-limb movement dysfunction. This change has accompanied an exponential increase in research over the last 20 years.\textsuperscript{17}

Most interventions that have been proposed and tested have typically concentrated on improving 1 specific mechanism (learned nonuse, decreased excitability, disrupted interhemispheric interactions, etc). However, the principles discussed in the CAP show that motor deficits can arise from different computational problems and that a single lesion is likely to cause multiple problems both through direct structural damage and impaired function of distant and connected regions. In an ideal future, a patient would receive in-depth assessments that quantify his or her motor deficits through careful behavioral testing; neuroimaging measures of structure, function, and connectivity; and computational modeling. This assessment would allow the characterization of the patient’s deficit with a small number of different parameters that ideally would be sensitive to changes over time and final outcome. For argument’s sake let us assume that 3 parameters (intactness of output, normalcy of forward models, and sensory feedback) describe the great majority of behavioral variance of a normal movement. And, let us also assume that these parameters provide a good description of an individual’s hemiparesis. For example, in the case of a lesion interrupting the corticospinal tracts, output parameters will be prominently affected, whereas forward models and sensory feedback would be less affected. With time, all 3 parameters may worsen because an attempt by the cortex to overcome the bottleneck caused by the lesion will generate more errors in the forward
model that will accumulate over time. Accordingly, therapies should be first aimed at improving the motor outflow through, for example, excitatory stimulation of the damaged motor cortex. At the same time, however, other methods can be applied to improve the other parameters. A decrement in sensory feedback could be helped by robotic therapy, whereas a problem in the forward model could be lessened by motor imagery exercises. Critically, which cocktail or dosing of treatments to apply will depend on a deeper understanding of the system, its abnormal output after lesions, and its response to therapy. It is very likely that targeted interventions will be more likely to produce positive results than single-mode treatments. It will be important to develop prognostic models also to avoid the “one model fits all” approach currently used in rehabilitation. As resources in health care are limited, identifying patients with a good chance for recovery is as important as identifying patients with a poor chance of recovery in whom compensatory strategies or orthotic devices should be tried earlier. Moreover, improvements in technology that are already being tried will profoundly modify the assisting devices that we will be able to provide. Whether this vision will be realized in 10 years or never will be a matter of persistence, money, and the intellectual discipline to continue pursuing a science of rehabilitation.

References